Diagnostic efficacy of gadoxetic acid-enhanced MRI for the detection and characterisation of liver metastases: comparison with multidetector-row CT

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Objectives: We compared the diagnostic performance of gadoxetic acid-enhanced MRI and 16-slice multidetector CT (MDCT) with respect to their abilities to detect hepatic metastases and differentiate hepatic metastases from hepatic cysts and haemangiomas.

Methods: 67 patients with 110 liver metastases (size 0.3–2.5 cm), 33 haemangiomas (size 0.5–1.5 cm) and 17 cysts (size 0.3–1.0 cm) underwent 4-phase MDCT and gadoxetic acid-enhanced MRI, including early dynamic phases, post-contrast T_2 weighted turbo spin echo sequences and 20 min hepatocyte-selective phases. Two observers independently analysed each image in random order. Sensitivity and diagnostic accuracy for lesion detection and differentiation for MDCT and gadoxetic acid-enhanced MRI were calculated using receiver operating characteristic analysis.

Results: For both observers, the Az values of gadoxetic acid-enhanced MRI (mean, 0.982 and 0.981) were significantly higher than the Az values of MDCT (mean, 0.839 and 0.892) ($p < 0.05$) for the detection of metastases and for the differentiation of metastases from haemangiomas and cysts. Sensitivities of gadoxetic acid-enhanced MRI with regard to the detection and characterisation of liver metastases (mean, 96.9% and 96.0%) were significantly higher than those of MDCT (mean, 78.7% and 75.0%) ($p < 0.05$).

Conclusion: Gadoxetic acid-enhanced MRI showed higher diagnostic accuracy and sensitivity than did MDCT for the detection of hepatic metastases and for the differentiation between hepatic metastases and hepatic haemangiomas or cysts.

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The early detection and precise characterisation of liver metastases are crucial factors in liver imaging because the success of surgery and ablation therapy depends on the knowledge of the precise number and locations of metastatic lesions [1–4]. Multidetector-row CT (MDCT) has been widely used as a primary imaging modality for evaluating liver metastases because of its wide availability. However, there has been some concern that MDCT images may not accurately characterise small hepatic nodules that are “too small to characterise”, and may not sufficiently differentiate small hepatic metastases from small hepatic cysts or haemangiomas, which are the most frequently encountered causes of focal liver lesions on CT [5–7]. Furthermore, MDCT is less able to detect liver metastases than MRI using liver-targeted agents, such as superparamagnetic iron oxide [8–13]. Thus, with the advent of new MR contrast agents for liver imaging, considerable attention has been focused on the ability of MR contrast agents to detect and characterise small focal liver

lesions relative to the conventional imaging modality or previously existing MR contrast agents.

Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA, gadoxetic acid disodium, Primovist®; Bayer HealthCare, Berlin, Germany) is a recently introduced dual-acting MR contrast agent that combines the properties of an extracellular space contrast (ECS) agent and a liver-specific agent [14–19]. The combination of these properties enables the acquisition of the early vascular-interstitial phase, which provides haemodynamic information, and the hepatocyte phase, which detects liver malignancies. Thus, gadoxetic acid has a potency to fulfil the dual requirements for early detection and accurate characterisation of focal liver lesions. To the best of our knowledge, no previous study has evaluated the diagnostic capability of gadoxetic acid-enhanced MRI to detect and characterise liver metastases compared with MDCT. In this study, we retrospectively compared the diagnostic performance of gadoxetic acid-enhanced MRI and 16-slice MDCT in detecting small hepatic metastases and in differentiating hepatic metastases from hepatic haemangiomas and cysts, using alternative free-response receiver operating characteristic (ROC) analysis.

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Methods and materials

We retrospectively reviewed our institutional database for liver MRIs and MDCTs conducted on patients suspected of having liver metastases that were performed at our institution, a tertiary referral hospital, between June 2007 and August 2009. According to our current institutional guidelines, patients being considered for surgical resection for primary cancer with CT scans suspicious for hepatic metastases are referred for liver MRI for further evaluation of the suspected liver lesions when the exact number and location of possible metastatic lesions is needed for treatment planning. Our search yielded 88 patients, 21 of whom were excluded because of lack of histological evidence of liver metastases, lack of sufficient follow-up or because too many nodules were found (>15 lesions). Hence, 67 patients (38 males, 29 females; age range, 31–73 years; mean age, 56 years) were included in this study. Our hospital's institutional review board approved this retrospective study.

A total of 160 focal hepatic lesions were either histologically or clinically confirmed in all 67 of the study patients. These lesions consisted of 110 hepatic metastases, 33 hepatic haemangiomas and 17 hepatic cysts. 37 patients had only metastases, 12 had both metastases and haemangiomas or cysts ($n=14$) and 18 patients had only haemangiomas or cysts ($n=36$). The primary cancer sites of patients exhibiting liver metastases included colorectal ($n=33$), stomach ($n=8$), breast ($n=6$) and lung ($n=2$). The size of the lesions ranged from 0.3 to 2.5 cm (mean, 1.3 cm) for metastases, 0.5 to 1.5 cm (mean, 1.2 cm) for haemangiomas and 0.3 to 1.0 cm (mean, 1.3 cm) for cysts. Of 110 metastases, 87 lesions were ≤ 10 mm in diameter. None of the study patients had liver masses other than hepatic metastases or haemangiomas or hepatic cysts. The final diagnosis and determination of the total number of metastases was confirmed by histopathological analyses of the surgical specimens as well as intra-operative sonography for 30 patients (39 metastases). For the remaining 19 patients with 71 liver metastases, a combined interpretation of all imaging modalities was used including MDCT, MRI and at least 6 month follow-up CT or MRI (rapid progression of disease). Cavernous haemangiomas and hepatic cysts were diagnosed based on a consensual interpretation of findings by two experienced radiologists from the available diagnostic procedures, including MDCT and MRI, stability for at least 6 months' follow-up, as well as intra-operative sonography findings in the patients who underwent surgery.

Multidetector-row CT examination

CT examinations were performed on a 16-MDCT scanner (Sensation 16; Siemens HealthCare, Erlangen, Germany). MDCT was performed first in all patients, followed by MRI. The images were acquired through the liver in a craniocaudal direction, with a 1.5×16 beam collimation. The other scanning parameters used were as follows: 160 mAs, 120 kVp, 1.5 mm detector collimation, 24 mm per rotation table speed and a 0.5 s gantry rotation time. A reconstruction slice thickness of 3.0 mm and a reconstruction interval of 3.0 mm were also established.

Unenhanced MDCT was initially performed starting from the top of the liver and continuing in a cephalocaudal direction. After the acquisition of unenhanced liver imaging, a contrast medium with an iodine (I) concentration of 370 mg ml^{-1} (Ultravist 370; Schering, Berlin, Germany) was administered with a power injector (Multilevel CT; Medrad, Pittsburgh, PA). The contrast medium was then injected at 3 ml s^{-1} through an 18 gauge plastic intravenous catheter positioned in the antecubital vein. The volume of contrast medium delivered varied according to the body weight of each patient (2 ml kg^{-1} of body weight); therefore, the total contrast medium volume administered ranged from 110 to 150 ml (mean 120 ± 10 ml). Scanning for the dynamic three-phase images, including the hepatic arterial phase, the portal venous phase and the equilibrium phase, began at 35, 70 and 180 s, respectively, after the initiation of the contrast medium injection.

MRI examination

All MRIs were performed using a 1.5 T superconducting imager (Magnetom Symphony; Siemens HealthCare) with a combination of a phased-array body coil and spine-array coil for signal reception. The interval between MDCT and gadoteric acid-enhanced MRI ranged from 2 to 11 days (mean interval, 6 days).

A transverse volumetric three-dimensional fat-suppressed spoiled gradient-echo acquisition (volumetric interpolated breath-hold examination, VIBE; Siemens HealthCare) with mSense was performed using the following parameters: repetition time (TR)/echo time (TE) of 4.3/2.0, 12° flip angle, 450 Hz/Px bandwidth, 256 (read) $\times$ 135 (phase) $\times$ 40–46 (partition) matrix, 2.5–3.0 mm effective slice thickness and a field of view of 32–35 cm. After the unenhanced images were acquired, patients received a dose of 0.25 mol l^{-1} gadoteric acid disodium solution based on their body weight ($0.025 \text{ mmol kg}^{-1}$ of body weight, volume range, 6–9 ml), administered intravenously at a rate of 1 ml s^{-1} , followed by a 20 ml saline flush. The MR fluoroscopic bolus detection technique (CARE Bolus; Siemens HealthCare) was used to determine the timing for the dynamic arterial phase imaging. The mean delay time (time interval between bolus administration and the start of image acquisition) for the arterial, portal and equilibrium phases were 20, 60 and 180 s, respectively. 5 min after the injection of the contrast media, a respiratory-triggered T_2 weighted turbo spin echo (TSE) sequence was obtained with and without chemically selective fat suppression using the following parameters: TR/TE of 3378–4800/68–76, an echo train length of 13, a 150° flip angle, a matrix of 225×384 , 6 mm slice thickness and an average scan time of 3 min for 20 slices. Finally, a hepatocyte-specific phase image was acquired at 10 min and 20 min after the contrast medium was administered.

Imaging analysis

All of the MR images were evaluated independently and separately by two gastrointestinal radiologists, both of whom were experienced in the interpretation of liver MRI in their daily clinical practice. All of the acquired

images were reviewed using a 2000 × 2000 picture archiving and communication systems [PACS: Marosis Workgroup; Marotech, Seoul, Republic of Korea] monitor. The readers were free to alter the window level and window width at their discretion. Two separate sets of images were analysed in random order, including the MDCT set (pre-contrast, arterial, portal and equilibrium phases) and the gadoxetic acid set (pre-contrast, arterial, portal, 3 min delay, and 10 and 20 min hepatocyte phases of three-dimensional MR images plus T_2 weighted images). In order to minimise any learning biases, there was a 3 week interval between the blinded interpretations.

Each of the observers recorded the presence and location of the lesions, assigning each of them a confidence level scored on a four-point scale. The four-point scale consisted of a score of 1, meaning "probably not present", 2, meaning "possibly present", 3, meaning "probably present", and 4, meaning "definitely present". A score of 0 was recorded for lesions missed during the reviews. Each of the observers also indicated the possibility of malignancy, assigning each of the lesions a confidence level on a five-point scale (1, definitely benign; 2, probably benign; 3, possibly benign; 4, probably malignant; and 5, definitely malignant). Lesions not detected on CT or MRI were given a rating of 1. The observers made their decisions of benign *vs* malignant lesions based on the subjective features of the lesions (including the margin sharpness, shape, homogeneity, attenuation and the presence of enhancement), the diagnostic criteria for a cyst (including smooth margins, homogeneous low attenuation similar to that of water and no enhancements during contrast-enhanced CT) and the diagnostic criteria for hepatic haemangiomas (including centripetal enhancement during dynamic CT or MRI and bright hyperintensity similar to cysts on T_2 weighted images). Prior to the interpretation, the two observers were aware that all of the hepatic lesions included only metastases, cysts and haemangiomas. To achieve an accurate correlation between the findings of the scored lesions and the findings of the reference standard, each observer made markings at all lesions with arrows on the PACS monitor. After the two reviewing sessions were completed by the two observers, the study co-ordinator and another radiologist not involved in previous image interpretation compared the scoring results of the two observers with a reference standard and then devised a possible explanation for the false-positive and false-negative findings of each observer.

Based on the reviews submitted by the two observers, an alternative free-response ROC curve analysis was performed on a lesion-by-lesion basis [20]. For each imaging set, an alternative free-response ROC curve was fitted to each observer's confidence rating data, using a maximum likelihood estimation program (ROCKIT 0.9B; CE Metz and University of Chicago, Chicago, IL) [21]. 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 mean Az for the imaging sets were compared using the two-tailed Student's *t*-test for paired data. The sensitivities for lesion detection on a per-lesion (all lesions and metastases alone) and a per-patient basis for each of the image sets were then calculated. The sensitivity of each observer and each set of images was evaluated according to the number of lesions assigned

confidence levels of 3 or 4 from among the 160 lesions. Prior to image analysis, the observers were aware that only those lesions that had been assigned confidence levels of 3 or 4 would be included in separate sensitivity calculations. The sensitivity of the presence of hepatic lesions on a per-patient basis was calculated according to the number of patients who had liver lesions that were assigned confidence levels of 3 or 4. We also determined the sensitivity and specificity of each set of images regarding the characterisation of metastases. The sensitivity regarding the positive diagnoses for metastasis was calculated according to the number of metastases assigned confidence levels of 4 or 5. The sensitivities of the MR and CT images were then compared using the McNemar test. A two-tailed $p < 0.05$ was considered to be a significant difference. In order to report a range of plausible sensitivity differences, we also calculated the 95% confidence intervals (CIs) [22].

In order to assess interobserver agreement for the evaluation of the two imaging modalities, we calculated the κ statistic for multiple observers [23]. Agreement between the blinded observers is reported below in terms of κ -values, with those values greater than 0 indicating positive correlations. κ -values of less than 0.20 indicated positive but poor agreement, those of 0.21–0.40 indicated fair agreement, those of 0.41–0.60 indicated moderate agreement, those of 0.61–0.80 indicated good agreement and those greater than 0.81 indicated excellent agreement. The significance of the difference between the κ -values assigned to the two imaging modalities was then tested using *z*-tests. The statistical significance level was set at $p < 0.05$. All statistical analyses were calculated with the SPSS 8.0 program [IBM Corporation (formerly SPSS Inc.), Armonk, NY].

Results

Of the 49 patients with hepatic metastases, 25 had solitary lesions, 5 had 2 lesions, 5 had 3 lesions, 10 had 4 lesions and 4 had 5 lesions. Table 1 shows the Az value for each of the observers with each image set for detecting all 160 lesions, including the 110 hepatic metastases. For the detection of all lesions and metastases, the Az values in the gadoxetic acid set were significantly higher than those in the MDCT set for both observers (mean Az in MDCT set, 0.889 for all lesions, 0.839 for metastases; mean Az in gadoxetic acid set, 0.988 for all lesions, 0.982 for metastases) ($p < 0.05$) (Figure 1).

The sensitivities for lesion detection from each observer, according to each image set, are shown in Table 2. Overall, there was a trend towards an increased sensitivity on a per-lesion and per-patient basis for the gadoxetic acid set compared with the MDCT set, and the sensitivities of the gadoxetic acid set from both observers were significantly higher than those from the MDCT set for all 160 lesions and for the 110 hepatic metastases as well as for a per-patient basis (Figure 2) ($p = 0.0001$). Among the 110 hepatic metastases, MDCT allowed for the identification of 84 lesions (sensitivity, 76.4%; 95% CI: 67.3–83.9%) by Observer 1 and 89 lesions (sensitivity, 80.9%; 95% CI: 72.3–87.8%) by Observer 2. However, the gadoxetic acid MRI allowed for the identification of 106 lesions (sensitivity, 96.4%; 95% CI: 90.9–99.0%) by Observer 1 and 107

Table 1. Az and *p*-values for gadoxetic acid-enhanced MRI and 16-slice MDCT for revealing 110 metastases, 33 haemangiomas and 17 cysts in 67 patients

Imaging modality	Observer 1		Observer 2	
	Total lesions	Metastases	Total lesions	Metastases
Gadoxetic acid-enhanced MRI	0.984±0.011	0.977±0.017	0.991±0.008	0.986±0.012
MDCT	0.884±0.055	0.832±0.086	0.894±0.051	0.845±0.081
<i>p</i> -value	0.032	0.047	0.032	0.049

MDCT, multidetector CT.

lesions (sensitivity, 97.3%; 95% CI: 92.2–99.4%) by Observer 2. In a per-patient analysis, the gadoxetic acid set depicted metastases in 45 out of 49 patients with metastases for Observer 1 (sensitivity, 91.8%; 95% CI: 80.4–97.7%) and in 46 patients for Observer 2 (sensitivity, 93.9%; 95% CI: 83.1–98.6%). MDCT depicted metastases in 32 patients for both observers (sensitivity, 67.3%; 95% CI: 52.5–80.0%). There were three surgically confirmed lesions (0.3, 0.5 and 0.8 cm in diameter) in three patients that could not be verified with either imaging technique. During the retrospective review of these lesions, all three were seen as subtle and hypointense upon gadoxetic acid-enhanced hepatocyte-phase imaging. There were 15 metastases (0.3–1.0 cm) in 12 patients that were not detected by either observer using MDCT but were clearly revealed using the gadoxetic acid set (Figures 1 and 2),

with a confidence rating of 3 or 4 by both observers constituting clear identification. 9 of these 15 lesions were confirmed after surgery. On the retrospective review of the MDCT images, six lesions were not identified and nine lesions appeared with faint low attenuation (Figures 1 and 2). In contrast, all lesions detected by MDCT were also not verifiable using the gadoxetic acid set. Neither image set gave false-positives at the confidence level of 3 or 4.

The calculated Az values for each observer using MDCT *vs* gadoxetic acid in differentiating liver metastases from cysts and haemangiomas are shown in Table 3. For both observers, the Az values for the gadoxetic acid set were significantly higher than those for MDCT (mean Az on gadoxetic acid set, 0.981; mean Az on MDCT, 0.892) ($p=0.0001$). Regarding the sensitivity for the positive

Figure 1. Liver metastases in a 57-year-old male with rectal carcinoma. The presence of liver metastases was confirmed at surgery. (a) An axial arterial-phase image of multidetector row CT scanning with 1.5 mm collimation and 3 mm reconstruction interval showing no visible liver masses. (b) An axial portal venous-phase image of multidetector row CT scanning with 1.5 mm collimation and a 3 mm reconstruction interval shows suspicious tiny low attenuation (arrow), which is not a definitive result. (c) An axial equilibrium-phase image of multidetector row CT scanning with 1.5 mm collimation and a 3 mm reconstruction interval showing no visible liver mass. (d) An axial portal phase of a three-dimensional MR image after the administration of gadoxetic acid (4.3/2.0) showing a small hypointense mass (arrow). (e) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) clearly showing a hypointense liver mass (arrow).

Table 2. Sensitivities of gadoxetic acid-enhanced MRI and 16-slice MDCT for revealing 110 metastases, 33 haemangiomas and 17 cysts in 67 patients

Imaging modality	Observer 1		Observer 2	
	Total lesions	Metastases	Total lesions	Metastases
Gadoxetic acid-enhanced MRI	96.9 (155)/94.0 [63]	96.4 (106)/91.8 [45]	98.1 (157)/95.5 [64]	97.3 (107)/93.9 [46]
MDCT	83.8 (134)/74.6 [50]	76.4 (84)/65.3 [32]	86.9 (139)/74.6 [50]	80.9 (89)/65.3 [32]
<i>p</i> -value	0.0001		0.0001	

MDCT, multidetector CT.

Data are presented as values on a per-lesion/per-patient basis. Data in parentheses represent the number of true-positive lesions.

Data in square brackets represent the number of patients with true metastases.

diagnoses for metastasis, the gadoxetic acid set [sensitivity, 96.4%; (95% CI: 90.9–99.0%) for Observer 1; sensitivity, 95.5%; (95% CI: 89.7–98.5%) for Observer 2] was also better than MDCT for both observers [sensitivity, 70.9%; (95% CI: 61.5–79.2%) for Observer 1; sensitivity, 74.5%; (95% CI: 65.4–82.4%) for Observer 2] ($p=0.0001$). Specificity for both image sets were similar as 98.0 % of the gadoxetic acid set for both observers and MDCT for Observer 1 and 96.0 % of MDCT for Observer 2. 20 metastases (0.3–1.0 cm) were misinterpreted as benign lesions on the MDCT images by both observers but were accurately characterised by both observers on the gadoxetic acid set (Figure 3). Three

metastases were misinterpreted as benign lesions on the MDCT and gadoxetic acid set by both observers. There was one haemangioma that was misinterpreted as a metastasis in both image sets (Figure 4).

For lesion detection, the κ -value for the gadoxetic acid set (0.822) was significantly higher than that of the MDCT images (0.718) ($p<0.05$), which indicated good-to-excellent interobserver agreement. However, the κ -value of MDCT (0.824) was significantly higher than that of the gadoxetic acid set (0.768) ($p<0.05$) for the differentiation of benign *vs* metastatic lesions, which also indicated good-to-excellent interobserver agreement.

Figure 2. Liver metastases in a 56-year-old male with rectal carcinoma. The presence of liver metastases was confirmed at surgery. (a) An axial arterial-phase image of multidetector row CT scanning with 1.5 mm collimation and 3 mm reconstruction interval showing no visible liver mass. (b) An axial portal venous-phase image of multidetector row CT scanning with 1.5 mm collimation and 3 mm reconstruction interval showing no visible liver mass. (c) An axial portal-phase of three-dimensional MR image after the administration of gadoxetic acid (4.3/2.0) showing subtle low attenuation in the right hepatic lobe (arrow). (d) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) clearly showing a hypointense mass in the right hepatic lobe (arrow).

Table 3. Az and sensitivity for gadoxetic acid-enhanced MRI and 16-slice multidetector (MDCT) for the differentiation of metastases from haemangiomas or cysts

Imaging modality	Observer 1	Observer 2
Gadoxetic acid-enhanced MRI	0.980 ± 0.010/96.4	0.982 ± 0.009/95.5
MDCT	0.889 ± 0.025/70.9	0.894 ± 0.024/74.5
<i>p</i> -value	0.0001	0.0001

Data represent Az/sensitivity.

Discussion

This study investigated three issues that need to be addressed when using gadoxetic acid for a liver metastasis work-up. First, we needed to determine the level at which gadoxetic acid-enhanced hepatocyte-phase imaging could detect liver metastases compared with MDCT. Second, we needed to determine whether the capability of the gadoxetic acid-enhanced early vascular interstitial phase is similar to that of MDCT in providing haemodynamic information for small haemangiomas. Finally, we needed to determine whether T_2 weighted images acquired after the contrast medium was administered could still offer useful information for differentiating solid masses from benign lesions, as pre-contrast T_2 weighted

images provide information to allow such differentiation. Also, we wanted to evaluate the additional benefit of hepatocyte-phase imaging to differentiate between hepatic metastases and haemangiomas. Most of our study samples were less than 2.0 cm in diameter, for both benign lesions and metastases. Our findings reflect the actual clinical practice of using imaging modalities to detect and characterise small liver metastases, so our study results should be reproduced, as we expect them to have a significant impact on current clinical practice.

Our study has revealed the superior capability of gadoxetic acid-enhanced MRI to detect hepatic metastases compared with MDCT. It evidenced qualitatively in terms of both diagnostic accuracy and sensitivity that the gadoxetic acid set was significantly better than MDCT

Figure 3. Multiple liver metastases in a 60-year-old male with colon carcinoma. (a) An axial arterial-phase image of multidetector row CT scanning with 1.5 mm collimation and a 3 mm reconstruction interval showing pinpoint bright enhancement in the left hepatic lobe (arrow). (b) An axial portal venous-phase image of multidetector row CT scanning with 1.5 mm collimation and 3 mm reconstruction interval showing a small, hypoattenuated lesion with peripheral nodular enhancement (arrow). (c) The lesion is shown as an isoattenuation on an axial equilibrium-phase multidetector row CT image with 1.5 mm collimation and a 3 mm reconstruction interval. This was interpreted as a haemangioma by both observers. (d) An axial portal-phase of three-dimensional MR image after the administration of gadoxetic acid (4.3/2.0) showing a subtle hypointense lesion in the left hepatic lobe (arrow). (e) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) clearly showing a hypointense mass in the left hepatic lobe (arrow). (f) The lesion is seen as a subtle hyperintensity (arrow) on a fat-suppressed axial respiratory-triggered T_2 weighted turbo spin echo image (4300/78). This was correctly characterised as a metastasis by both observers.

Figure 4. Hepatic haemangioma in a 61-year-old male with gastric carcinoma. (a) An axial portal phase of three-dimensional MR image after the administration of gadoxetic acid (4.3/2.0) showing a hypointense round lesion in the hepatic dome (arrow). (b) The lesion is seen as a round hypointensity with rim enhancement (arrow) on an axial 3 min late-phase three-dimensional MR image after the administration of gadoxetic acid (4.3/2.0). (c) An axial gadoxetic acid-enhanced 20 min hepatocyte-phase image (4.3/2.0) clearly showing a hypointense mass in the hepatic dome (arrow). (d) The lesion is seen as a hyperintensity (arrow) on a fat-suppressed axial respiratory-triggered T_2 weighted turbo spin echo image (4300/78). This lesion was misinterpreted as a metastasis by both observers.

for both of the study's observers. However, there was no difference between the gadoxetic acid set and the MDCT set in the detectability for cysts and haemangiomas. There were 15 metastases in 12 patients that were not detected by either observer on MDCT, but were clearly revealed on the gadoxetic acid set by both observers. Six of these lesions were not identified, even on the retrospective reviewing of the MDCT images. However, there were no lesions that were detected with MDCT but were undetected using the gadoxetic acid set. Three of the lesions not identified by MDCT that were also not identified by gadoxetic acid MRI by either observer were seen as tiny low attenuations on hepatocyte-phase images upon retrospective review. These lesions were probably missed during imaging analysis because small, hypointense liver lesions are similar to the end-on of a vessel upon hepatocyte-phase imaging.

During a work-up to search for possible metastases, the accurate differentiation of small metastases from small haemangiomas or cysts is important, as these lesions can appear similar upon dynamic CT or MRI, particularly in cases of slowly enhancing haemangiomas. In our study of the differentiation of liver metastases from cysts or haemangiomas, we found that gadoxetic acid showed superior diagnostic capabilities to MDCT. This finding was partly attributable to the lower detectability of MDCT than gadoxetic acid, as missed lesions were regarded as

benign during the image review process. Given that the gadoxetic acid dosage is lower than that of other conventional gadolinium-based agents ($0.025 \text{ mmol kg}^{-1}$ vs 0.1 mmol kg^{-1}), there has been concern that this agent would be less able to differentiate between small metastases and haemangiomas in early dynamic phases. Although we did not create a separate analysis for the enhancement patterns of haemangiomas during the early dynamic phases of both image sets, most haemangiomas showed a similar enhancement pattern on dynamic phases of both images. Therefore, the better diagnostic capability of gadoxetic acid than that of MDCT could be attributable to the differentiation between solid and non-solid lesions added by the T_2 weighted image. Despite the theoretical T_2 shortening effect of gadoxetic acid on post-contrast T_2 weighted images [24, 25], the majority of haemangiomas preserved bright high-signal intensity, even on post-contrast T_2 -TSE sequences. There was only one haemangioma that was misinterpreted by both observers as a metastasis using the gadoxetic acid set. This misinterpretation could be explained by the partial volume-averaging effect on the T_2 -TSE sequence, which may have mimicked a solid liver mass.

In this study, hepatocyte-phase imaging showed no benefit in characterising haemangiomas. Although the signal intensity of haemangiomas tended to be slightly higher than that of hepatic cysts, we did not find any

differential feature between the haemangiomas and metastases, as both were seen as clear hypointensity on hepatocyte-phase imaging. In addition, the signal intensity of metastases on the TSE sequence tended to be bright, making them appear similar to haemangiomas. This tendency probably occurred because within the metastatic tumours were areas of tumour necrosis or increased interstitial space, which generally contain more free water than solid masses, such as hepatocellular carcinomas [26, 27]. Actually, three metastases were misinterpreted as haemangiomas upon MRI by both observers. In our study, only four of the metastases showed a target appearance composed of a central round enhancing area and peripheral hypointense rim on hepatocyte-phase imaging, which is a well-established imaging feature for liver tumour with abundant fibrous stroma at the delayed phase of conventional gadolinium chelate-enhanced MRI or gadobenate dimeglumine-enhanced hepatocyte phase [28, 29]. Homogeneous hypointensity of haemangiomas or metastases on the hepatocyte-selective phase could be explained by the weak and short-acting properties of gadoxetic acid as an ECS agent compared with conventional ECS agents or gadobenate dimeglumine [28, 29]. However, these properties could be beneficial in the detection of lesions because of their higher lesion-to-liver contrast. Although we did not perform a separate analysis to determine the diagnostic capability between 10 min and 20 min hepatocyte-phase images, we found no difference between the two images in terms of detection and characterisation of lesions. Therefore, based on our findings in this study, we could adopt a shortened protocol with a total study duration of approximately 10 min, which would be more clinically applicable. This would require introducing the T_2 -TSE sequence during the wait time between the 3 min late phase and the hepatocyte phase and acquiring a hepatocyte-selective image at 10 min instead of at 20 min after contrast media administration.

Our study has recognised limitations. First, not all of the lesions analysed were confirmed surgically, which may have resulted in a lower number of falsely negative lesions, resulting in a possible overestimation of the actual sensitivity of both image modalities. Second, selection bias may exist as the majority of the patients referred to and included in our study were already suspected of having hepatic metastases, as evidenced by MDCT images taken during routine pre-operative diagnostic work-ups in these patients. Therefore, lesions not apparent upon MDCT may have been under-represented in our study. Third, 12 patients had hepatic cysts or haemangiomas concomitantly with metastases, which might have introduced a bias resulting in poorer performance in lesion characterisation. However, we did not identify any noticeable patterns, clustering of false-negative lesions or misinterpreted lesions among patients. Instead, there was a relatively even distribution of false-negatives and misinterpretations. Fourth, as for the inherent methodological limitations, the lesions that were missed during the image analysis for assessing lesion detectability were regarded as definitively benign lesions on the image analysis that was done for lesion characterisation because the effect of the diagnosis as a missed lesion might be similar to the effect of the diagnosis as definitively benign. We believe that our categorisation method seemed

to closely approximate real clinical practice. Finally, the image analysis in this study utilised only two observers. Further, the confidence level scoring system could be quite a subjective outcome measure since it would be influenced by the reviewer's *a priori* opinions about the different imaging techniques. However, they were both faculty-level gastrointestinal radiologists experienced in interpreting liver MRIs in their daily clinical practice for at least 8 years. In addition, our calculated interobserver agreement was good despite the large study population, thus suggesting the reproducibility of our results.

In conclusion, gadoxetic acid-enhanced MRI showed higher diagnostic accuracy and sensitivity than did MDCT for the detection of hepatic metastases and for the differentiation between hepatic metastases and hepatic haemangiomas or cysts.

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