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Delay before the hepatocyte phase of Gd-EOB-DTPA-enhanced MR imaging: Is it possible to shorten the examination time?

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Abstract Aim: To examine if it is possible to shorten the examination time of gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB)-enhanced MRI by omitting hepatocyte-phase images of 20-min delay time (Im-20) for detecting focal liver lesions. Materials and methods: Four hundred ninety-five malignant focal liver lesions observed on Im-20 in 265 patients were included. The hepatocyte phase was obtained 10 min (Im-10) and 20 min (Im-20) after Gd-EOB injection. Liver enhancement was evaluated using a 4-point scale [excellent/good/poor/non-diagnostic; visual liver-spleen contrast (V-LSC)] and a quantitative liver–spleen contrast ratio (Q-LSC). Two radiologists evaluated lesion conspicuity for assessing the sensitivity of lesion detection. As Im-20 was used as the standard of reference for the lesions, Im-20 artificially had 100% sensitivity. Results: The results showed that although sensitivities and Q-LSC significantly increased from Im-10 to Im-20 (sensitivity/mean Q-LSC: Im-5, 81%/1.4 Im-10, 96%/1.7: Im-20, 100%/1.9), the sensitivity of Im-10 achieved 100% (the same as Im-20) in patients with good/excellent V-LSC or Q-LSC of more than 1.5. On Im-10, 202 patients (77%) were assigned as having good/excellent V-LSC (78%), and 161 (61%) were assigned as having Q-LSC of more than 1.5. Conclusion: We concluded that Im-20 can be omitted in at least 61% of the patients.

Keywords Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid · MR imaging · Hepatocyte-phase images · Liver

Introduction

Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB) is one of the commercially available hepatobiliary magnetic resonance (MR) contrast materials in the world. Gd-EOB, a liver-specific hepatobiliary contrast agent, offers both the potential of dynamic imaging and liver-specific static MR imaging of hepatocytes with accurate delineation, classification and characterisation of liver tumours [1, 2].

During an MR examination using Gd-EOB, it is important to wait until the contrast agent is taken up by the hepatocytes to obtain adequate liver parenchymal enhancement, i.e. good lesion–liver contrast. A 20-min duration is the recommended delay time according to the package insert and has been widely accepted as an adequate delay time for the hepatocyte phase in past reports [1–7]. However, a 20-min wait is too long considering that other MR sequences, such as precontrast T1-weighted, T2-weighted, balanced steady-state free precession sequence and diffusion-weighted images, are available within 15 min. The total examination time should be reduced without compromising the quality of images, not only increasing patient comfort, but also reducing medical costs.

Although some studies have suggested that decreasing the delay time for the hepatocyte phase to 10 min is sufficient to detect liver lesions, there has been no

research focusing on the reduction of the examination time thus far [7, 8].

The purpose of this study was to compare lesion detectability of hepatocyte-phase images obtained 10 and 20 min after contrast material injection (Im-10 and Im-20) and examine if it is possible to shorten the examination time by omitting Im-20 on Gd-EOB-enhanced MR imaging.

Materials and methods

Patients

This study was performed in accordance with the principles of the Declaration of Helsinki [9]. The ethics committee at our institution deemed that approval of this study was unnecessary. From January 2008 to July 2008, 265 patients (173 men and 92 women) with a mean age of 66 years (range: 37–85 years) underwent MR imaging with Gd-EOB for the evaluation of liver diseases. Of the 265 patients, 164 had chronic liver diseases as a result of hepatitis B (n=24) and C (n=130) virus infection, primary biliary cirrhosis (n=3), autoimmune hepatitis (n=1), alcoholic chronic hepatitis (n=2) and liver cirrhosis without hepatitis virus infection or alcohol abuse (n=4).

Inclusion criteria for lesions

As this study was aimed at assessing whether reduction of the examination time was possible or not, the lesions detected on the Im-20 were included in the study. The study coordinator (L.T.) retrospectively reviewed the radiological reports of the patients and found 520 focal potentially malignant lesions seen on Gd-EOB-enhanced MR images. On the basis of the patients' charts, histopathological reports and image findings of dynamic contrast-enhanced multidetector-row CT (dynamic CT), abdominal ultrasound (AUS) and follow-up dynamic CT obtained more than 3 months later, the 495 lesions were diagnosed as hepatocellular carcinoma (HCC; n=412), intrahepatic cholangiocarcinoma (ICC; n=5) or metastatic liver tumour (metastasis, n=78). Twenty-one lesions were excluded because they were diagnosed as haemangioma by follow-up dynamic CT and AUS. Another four lesions were also excluded because the size of the lesions did not change on the follow-up dynamic CT and the diagnoses were not confirmed. Finally, 495 lesions diagnosed as malignant liver lesions were included. All the Gd-EOB-enhanced MR images were assessed by a study coordinator, and it was confirmed that all 495 lesions were visualised as hypointense lesions on images obtained 20 min after injection. The mean diameter of all the lesions was 12.5 mm (range: 4–83 mm), and those of HCC, ICC and the metastases were 12.2 mm, 30.0 mm and 13.0 mm, respectively. As the lesions were selected using Im-20, the sensitivity of Im-20 was artificially set as 100%.

MRI

MRI was performed for all patients by using a superconducting magnet operating at 1.5 T (Signa EXCITE HD, GE Medical Systems, Milwaukee, WI) and an eight-channel phased-array coil. After the pre-contrast T1-weighted fast spoiled gradient echo imaging, T2-weighted first spin echo images and diffusion-weighted single-shot spin-echo echo-planar images were obtained; dynamic images using fat-suppressed T1-weighted gradient-echo images with 3D acquisition sequence [liver acquisition with volume acceleration (LAVA)] were obtained before (pre-contrast) and 20 s, 60 s, 2 min, 5 min, 10 min and 20 min after IV administration of Gd-EOB (0.025 mmol/kg body weight). The images obtained 5 min (Im-5), 10 min (Im-10) and 20 min (Im-20) after the injections were used for evaluation in this study. The Gd-EOB was administered intravenously as a bolus at a rate of 3 ml/s through an IV cubital line (20–22 gauge), which was flushed with 20 ml saline using a power injector. The images were acquired in the transverse plane with a section thickness of 5 mm and a 2.5-mm overlap. The repetition time (TR; ms)/echo time (TE; ms) was 3.8/1.9; flip angle (FA), 12°; number of signals acquired (NSA), 1; field of view, 40×40 cm; matrix, 320×192; acquisition time, 18 s.

Lesion detectability

Two radiologists (H.S. and K.S.) independently evaluated 495 lesions on Gd-EOB-enhanced MR images obtained 5 min (Im-5), 10 min (Im-10) and 20 min (Im-20) after injection by using a 4-point confidence scale, on which a score of 1 indicated that the lesion was definitely absent; 2, that the lesion was probably absent; 3, that the lesion was probably present; 4, that the lesion was definitely present. The evaluation was performed on a lesion-to-lesion basis. During the scoring, the readers were allowed to refer to Im-20 and T2-weighted images for identifying the lesions scored. They were not blinded to which phases the images were. The readers were aware that the sensitivity was calculated, i.e. the lesion was considered to be "detected" only if it was assigned a confidence score of 3 or 4 by both of them.

Visual liver-spleen contrast (V-LSC)

The two radiologists were also asked to evaluate the degree of liver parenchymal enhancement by comparing it with the enhancement of the spleen using a 4-point scale (excellent, good, poor and non-diagnostic). The score was

said to be excellent if sufficient liver–spleen contrast was obtained and the spleen was barely enhanced; good when sufficient liver–spleen contrast was obtained, but the spleen was slightly enhanced, poor when there was slight liver–spleen contrast and non-diagnostic when there was no liver–spleen contrast (Fig. 1). When the evaluations of the two readers were different, a third reader (T.I.) was consulted to decide the patient's visual liver–spleen contrast (V-LSC). The V-LSCs of Im-5, Im-10 and Im-20 were compared with each other. We also compared the V-LSC observed for patients with and without chronic liver diseases.

Quantitative liver–spleen contrast ratio (Q-LSC)

The signal intensities of the liver and spleen were measured on Im-5, Im-10 and Im-20, and the ratio of the signals was calculated in terms of the quantitative liver–spleen contrast ratio (Q-LSC). The equation used for the calculation is as follows: Q-LSC = signal intensity of the liver/signal intensity of the spleen. The mean values of the Q-LSC of Im-5, Im-10 and Im-20 were calculated and compared with each other. We also compared the mean values of the Q-LSC of the patients with and without chronic liver diseases.

Statistical analysis

The statistical significance of any differences among the sensitivities of Im-5, Im-10 and Im-20 was examined using the McNemar test. To assess the statistical significance of the differences among the V-LSCs and Q-LSCs, we used the chi-square test and *t*-test, respectively. A *P* value of less than 0.01 was considered to indicate a statistically significant difference.

Results

V-LSC

Forty-seven percent of the patients were classified as having reliable liver–spleen contrast on Im-5 (V-LSC score of good, 44%; V-LSC score of excellent, 3%). A fraction of patients with reliable liver–spleen contrast significantly increased to 77% on Im-10 (good, 35%; excellent, 42%) and to 88% on Im-20 (good, 23%; excellent, 65%). There were significant differences among the V-LSCs on Im-5, Im-10 and Im-20 ($P<0.001$).

The V-LSC scores on Im-5, Im-10 and Im-20 were significantly better in patients without chronic liver diseases than in those with chronic liver diseases (Fig. 2). Sufficient liver–spleen contrast (V-LSC score of good or excellent) was achieved in 92% of the patients without chronic liver diseases and in 70% of those with chronic liver diseases on Im-10.

Q-LSC

The mean values of the Q-LSC for Im-5, Im-10 and Im-20 were 1.4 (±0.27), 1.7 (±0.36) and 1.9 (±0.46), respectively.

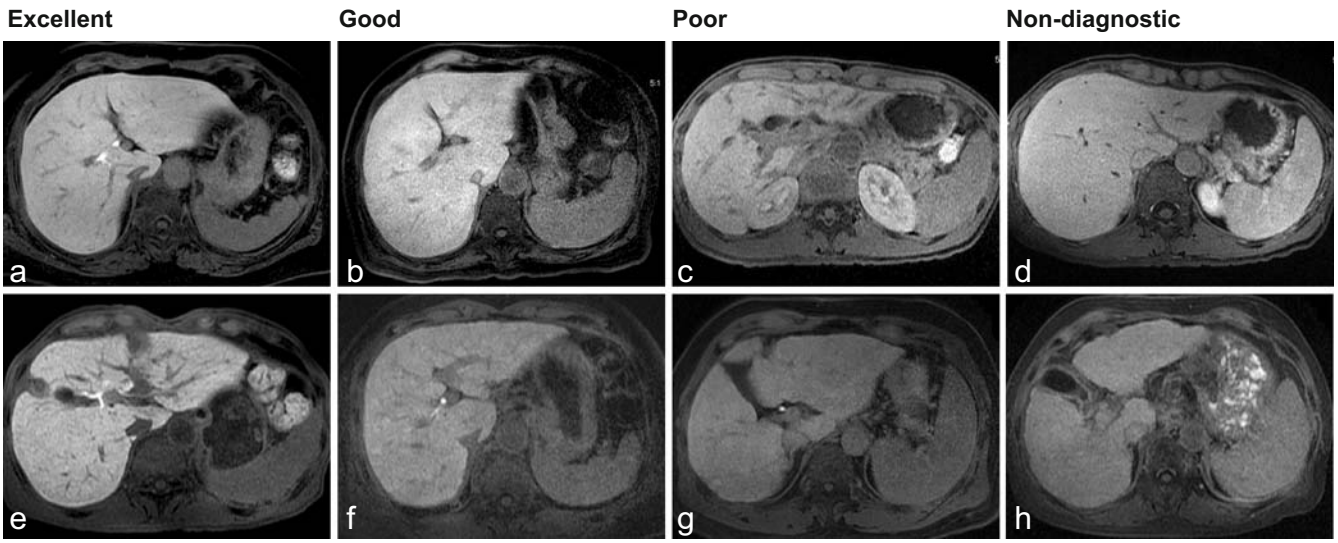

Fig. 1 Hepatocyte-phase images of Gd-EOB-enhanced MR imaging. The examples of images that were classified as having excellent, good, poor and non-diagnostic V-LSC in patients without chronic liver disease (a-d) and with chronic liver disease (e-h). The score was excellent if the spleen was barely enhanced and the liver parenchyma was well enhanced (a and e), good when the spleen was slightly enhanced with sufficient lesion–liver contrast (b and f), poor when there was slight spleen enhancement and slight liver–spleen contrast (c and g) and non-diagnostic when no liver–spleen contrast was observed (d and h)

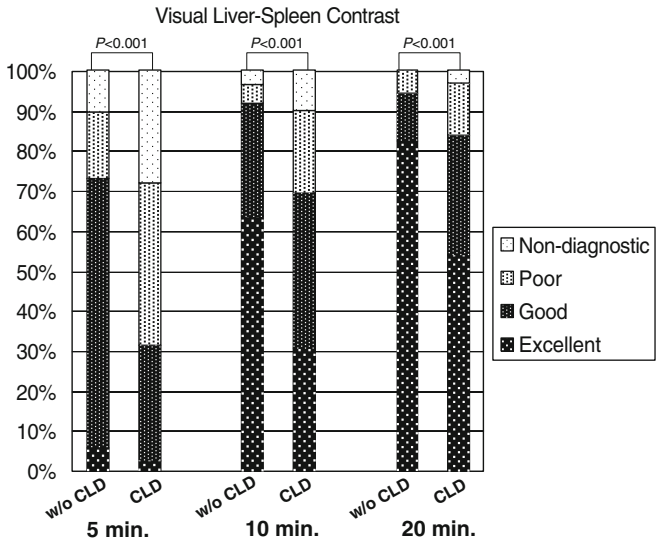

Fig. 2 Visual liver–spleen contrasts of the patients with chronic liver diseases (CLD) were significantly inferior to those of patients without chronic liver diseases (w/o CLD) on any of the images obtained 5, 10 and 20 min after the injection of Gd-EOB. Adequate liver–spleen contrast was obtained in more than 90% of the patients without chronic liver diseases on images obtained 10 min after the injection

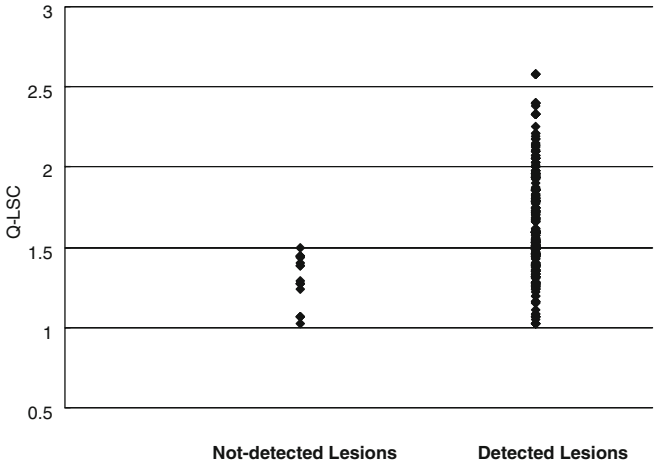

Fig. 3 Scatter plot of values of quantitative liver–spleen contrast ratio (Q-LSC) on the basis of whether livers with lesions were detected on hepatocyte-phase images obtained 10 min after injection. All lesions were detected in the liver with a Q-LSC score of more than 1.5

There were significant differences among the Q-LSCs of Im-5, Im-10 and Im-20 ($P<0.001$).

The mean Q-LSC values of patients without chronic liver disease were significantly higher than those of patients with chronic liver diseases on Im-5, Im-10 and Im-20 (Im-5, 1.6±0.3 vs. 1.4±0.3; Im-10, 1.9±0.4 vs. 1.6±0.3; Im-20, 2.2±0.4 vs. 1.8±0.4).

Sensitivities

The sensitivities of Im-5 and Im-10 were 81% (400/495) and 96% (478/495), respectively. There were significant differences between any two phases (Im-5, Im-10 and Im-20) ($P<0.001$) (Table 1). However, when only the lesions in the livers with a V-LSC score of good or excellent were considered, the sensitivity of Im-10 was the same as that of Im-20 (100%) (bold text in Table 1). On the other hand, for the lesions in the liver with a V-LSC score of good, the sensitivity of Im-5 was 91% (not 100%).

The values of Q-LSC on Im-10 ranged from 1.0 to 1.5 among the livers with undetected lesions (Fig. 3). In other words, all lesions were detected in the liver with a Q-LSC of more than 1.5 on Im-10. The rate of patients with Q-LSC of more than 1.5 was 61% (161/265) on Im-10 (52% and 83% for those with and without chronic liver disease, respectively). All V-LSC scores of patients with Q-LSC of more than 1.5 were good or excellent (Figs. 4 and 5).

Discussion

Gd-EOB is reported to be one of the most reliable contrast media used not only for the detection of small hepatic lesions, but also for tumour tissue characterisation [7, 10–14]. The most important objective is to obtain good hepatocyte-phase images for evaluating the results of abdominal MR examination using Gd-EOB. However, considering the recent advances in rapid MR imaging, radiologists and radiological technologists find it stressful to wait for 20 min for the hepatocyte phase.

Table 1 Sensitivities based on visual liver-splenic contrast (VLSC)

VLSC	5 min	10 min	20 min
Excellent	26/26 (1.00)	187/187 (1.00)	311/311 (1.00)
Good	136/148 (0.91)	199/199 (1.00)	136/136 (1.00)
Poor	180/227 (0.79)	65/77 (0.84)	37/37 (1.00)
Non-diagnostic	58/94 (0.62)	27/32 (0.84)	11/11 (1.00)
Total	400/495 (0.81)	478/495 (0.96)	495/495 (1.00)

$P<0.001$, $P<0.001$

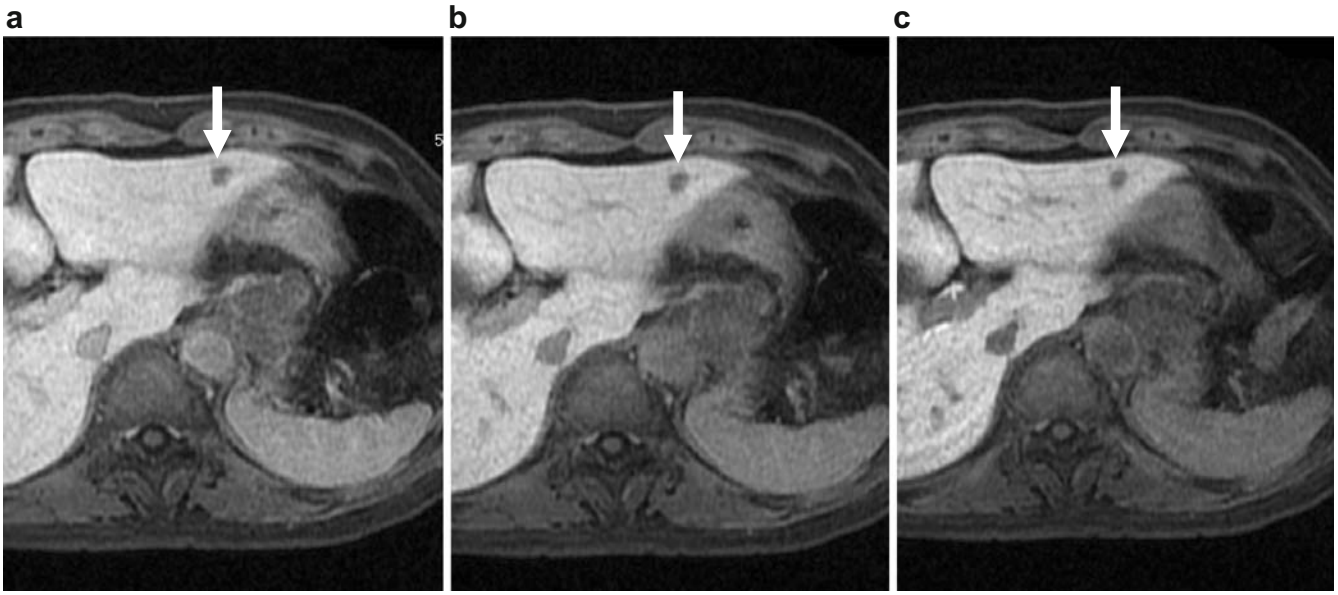

Fig. 4 Gd-EOB-enhanced T1-weighted image obtained 5 (a), 10 (b) and 20 min (c) after injection. The visualised liver–spleen contrast was assigned 'good' for all images. Q-LSC was 1.38, 1.68 and 1.95 in the images obtained 5, 10 and 20 min after injection, respectively. The lesion (metastasis from colon carcinoma) of the lateral segment was clearly visualised with excellent lesion–liver contrast on all images

In the 1990s, a delay of 20 min for the hepatocyte phase after injection was proposed as appropriate and included in the imaging protocol for a preliminary evaluation of Gd-EOB [1, 3, 5]. Most subsequent reports have followed this protocol [2, 4, 6, 7, 11, 15]. Only one report described that although lesion–liver contrast was higher on the images obtained 20 min after injection than on those obtained after 10 min, the difference was not significant [8].

As previously reported, the quantitative and qualitative liver enhancement was significantly higher on Im-20 than on Im-10, and the sensitivity of Im-20 was significantly higher than that of Im-10 in this study (Table 1 and Fig. 2)

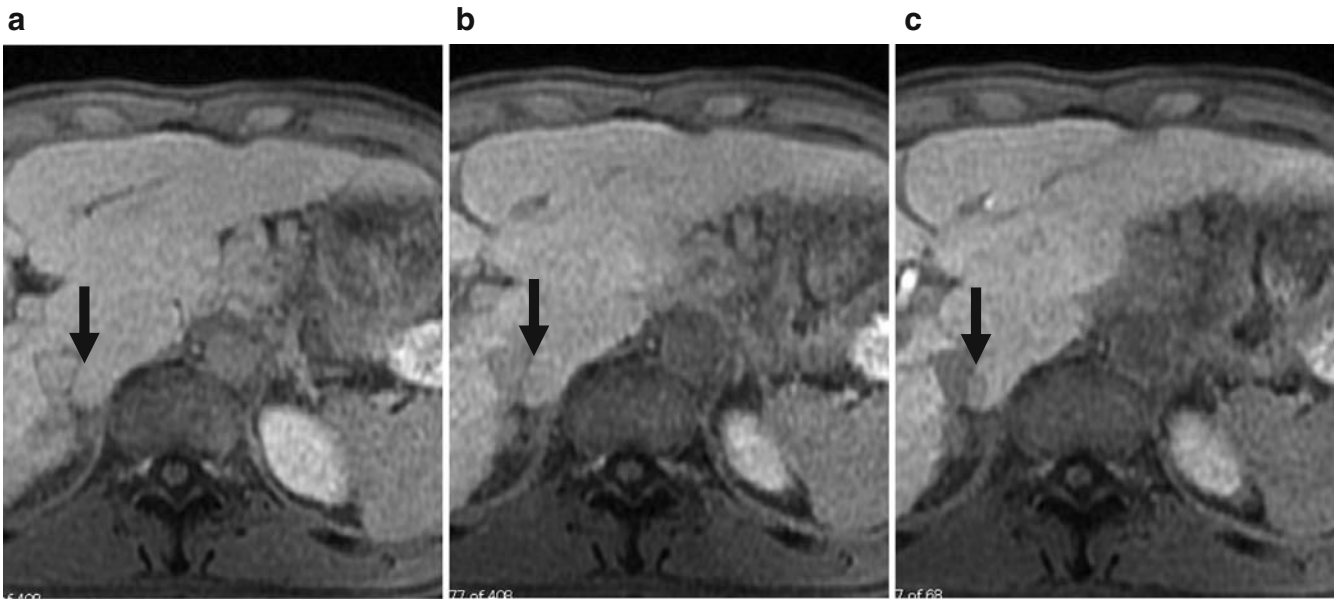

Fig. 5 Gd-EOB-enhanced T1-weighted images obtained 5 (a), 10 (b) and 20 min (c) after the injection. The visualised liver–spleen contrast was assigned as non-diagnostic, poor and good, and the Q-LSC was 1.19, 1.23 and 1.39 for (a), (b) and (c), respectively. The lesion (hepatocellular carcinoma) adjacent to the inferior vena cava was unclear on the images 5 and 10 min after injection (a and b)

[1, 5]. However, our results clearly revealed that once the liver parenchyma was sufficiently enhanced 10 min after injection, no more imaging was necessary to detect focal liver lesions. Whether liver enhancement is sufficient should be determined using a visual criterion, i.e. a V-LSC score of good or excellent, or a quantitative criterion, i.e. a Q-LSC of more than 1.5 (Table 1 and Fig. 2). On the basis of the results of this study, 100% sensitivity will be achieved and 10 min of the examination time can be saved at least in 61% of the patients (83% of the patients without chronic liver diseases and 52% of those with chronic liver diseases) when a score of more than 1.5 of Q-LSC is obtained.

The liver intensity might be as useful a measurement as the liver–spleen ratio. Before this study was initiated, a preliminary study was performed using only liver signal intensity, i.e. not using spleen signal; however, the liver signal intensity did not correlate well with sensitivity (data not shown). Contrast material will circulate in the vessels and be excreted via the kidney if it is not taken up to the hepatocytes. The circulating contrast material must enhance the spleen as well as the lesions like other extracellular contrast agents. Thus, contrast materials in the extracellular matrix will decrease lesion-liver contrast during the hepatocyte phases. We supposed that the liver-spleen contrast ratio can represent the lesion-liver contrast more exactly than liver signal intensity alone.

On the images obtained 5 min after injection, the lesion detection rate (sensitivity) was only 91% even when the V-LSC score was good (Table 1), i.e. 8 out of 148 lesions (6 HCCs and 2 metastases) were not detected on the liver images with a V-LSC score of good. The enhancement of HCCs was reported to reach a maximum level within 1 min after Gd-EOB injection, and the signal intensity gradually decreased until about 24 h [1]. We can readily understand why hypervascular tumours, such as HCCs and small metastases not accompanied by necrosis, retain contrast materials and tend to have less lesion–liver contrast on Im-5.

It is empirically well known that the enhancement of the liver is suppressed and delayed in patients with chronic liver disease during the hepatocyte-phase of Gd-EOB-enhanced MR imaging [16, 17]. In this study, the livers of patients with chronic liver diseases were less enhanced than those of patients without chronic liver diseases. In addition, V-LSC scores of Im-20 were more frequently increased from that of Im-10 in patients with chronic liver diseases than in those without chronic liver diseases (Fig. 2). This may indicate that Im-20 will be more useful for patients with chronic liver diseases.

The major limitation of this study is that only lesion detectability was examined for evaluating the usefulness of Im-20. Hepatocyte-phase images are considered to contribute to tissue characterisation of tumours, especially in the case of hepatocellular focal lesions or functional analysis of hepatocytes [12, 14]. Further studies should be performed to evaluate the value of Im-20 in addition to detecting focal liver lesions.

In conclusion, the scoring of sufficient liver–spleen contrast on images 10 min after injection can save 10 min of examination time in at least 61% of patients when detecting focal liver lesions on Gd-EOB-enhanced MR imaging.

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