Comparison of Enhancement Patterns of Histologically Confirmed Hepatocellular Carcinoma Between Gadoxetate- and Ferucarbotran-enhanced Magnetic Resonance Imaging

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Purpose: To compare enhancement patterns of hepatocellular carcinoma (HCC) and dysplastic nodule (DN) between gadoxetate- and ferucarbotran-enhanced MRI.

Materials and Methods: Patients recruited from ultrasound surveillance for HCC in chronic liver diseases were enrolled in this prospective study approved by institutional review board. Thirty-six patients with 37 histologically proven HCC, including 22 well-differentiated HCCs (wHCC), 15 moderately to poorly differentiated HCCs (mpHCCs), and 4 DNs, underwent gadoxetate-enhanced and ferucarbotran-enhanced MRI. We compared hepatobiliary phase image of gadoxetate-enhanced MRI with ferucarbotran-enhanced MR image regarding signal intensity of HCC and DN relative to surrounding liver parenchyma. We calculated contrast ratios between tumor and liver on pre-enhancement, hepatobiliary phase of gadoxetate-enhanced MRI and ferucarbotran-enhanced MRI.

Results: On ferucarbotran-enhanced MRI, all mpHCCs showed hyper-intensity, while 14 wHCCs (14/22;63%) showed iso-intensity. On hepatobiliary phase of gadoxetate-enhanced MRI, 13 mpHCCs (13/15;86%) and 20 wHCCs (20/22;91%) showed hypo-intensity. Two DNs and the other two showed iso- and hypo-intensity, respectively, on gadoxetate-enhanced MRI, whereas all DNs revealed iso-intensity on ferucarbotran-enhanced MRI. Gadoxetate-postcontrast ratio was significantly lower than ferucarbotran-postcontrast ratio in wHCC (P = 0.015).

Conclusion: The uptake function of hepatocytes that are targeted by gadoxetate is more sensitive than that of Kupffer cells targeted by ferucarbotran in stepwise hepatocarcinogenesis.

Key Words: hepatocellular carcinoma; gadoxetate; ferucarbotran; hepatocyte; Kupffer cell

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SPI0-enhanced MR is reported to be sensitive in detecting HCC (7–9). Ferucarbotran can also be used for dynamic liver imaging. In the phantom study with ferucarbotran, T1 relaxivity (R1), T2 relaxivity (R2), and the R2/R1 ratio at 1.5 T were 9.5 L · mmol⁻¹ · sec⁻¹, 230 L · mmol⁻¹ · sec⁻¹, and 24, respectively (10). R1 of ferucarbotran is relatively high, but insufficient enhancement effect is obtained for arterial liver imaging due to small amount of volume in the clinical use. Gadoxetate (gadolinium-ethoxybenzyl-diethylenetriamine; Gd-EOB-DTPA, Primovist®. Bayer Schering Pharma AG) is another liver-specific contrast agent. Because gadoxetate acts as both an extracellular and hepatocyte-specific contrast agent, it allows combined dynamic liver imaging and hepatocyte-specific imaging (11). Functioning hepatocytes take up gadoxetate in the hepatobiliary phase, which occurs approximately 15–20 min after injection. Gadoxetate works as a T1-shortening agent at the hepatobiliary phase after injection. Thus, malignant liver lesions such as liver metastases are spared the contrast uptake that occurs in the surrounding liver parenchyma. Both gadoxetate and ferucarbotran have been designed to overcome the limitations of unspecific tissue uptake of extracellular low-molecular gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (12, 13).

The development of 3-dimensional (3D) T1-weighted sequences enables imaging at high spatial resolution and visualization of fine anatomical structures, and the use of 3D T1-weighted sequences is more suited to gadoxetate-enhanced MRI, because of its higher T1-shortening than ferucarbotran-enhanced MRI.

It remains a point of controversy whether gadoxetate or ferucarbotran is more sensitive as a liver-specific contrast agent for depicting HCC. To the best of our knowledge, only 1 clinical study (14) has assessed MR imaging performance between gadoxetate and ferucarbotran enhancement for patients with pathologically confirmed HCC, and animal studies have been performed with this aim (15, 16). Lee et al (14) recently reported a comparison between ferucarbotran- and gadoxetate-enhanced MRI for the detection of HCC. According to their report, the diagnostic performance of ferucarbotran-enhanced MRI is similar to that of gadoxetate-enhanced MRI in detecting HCC. However, most of the HCCs (34 of 38) were moderately differentiated HCCs. The number of wHCC in their study was too small to be sufficiently evaluated. Thus, we are motivated to compare enhancement patterns between these two agents in histologically proven wHCC.

The goal of the present study was to prospectively compare the enhancement patterns of each histological differentiation of HCC and dysplastic nodule (DN) between gadoxetate- and ferucarbotran-enhanced MRI at the liver-specific phase.

**MATERIALS AND METHODS**

**Patients**

The institutional review board approved this prospective study. The patients with hepatic nodules which were suspicious of HCC at ultrasound surveillance for HCC in chronic liver diseases were included in this study. The patients with cirrhosis classified as Child-Pugh Class C were excluded, because of insufficient enhancement at the liver-specific phase after gadoxetate or ferucarbotran injection (17, 18). After informed consent was obtained from each patient, both gadoxetate and ferucarbotran-enhanced MRI were conducted for further diagnosis of hepatic nodules. Finally, from February 2008 to February 2009, 36 patients (28 men, 8 women; mean age, 69 years) with 37 histologically proved HCCs and 4 DNs were included in this study. This study was conducted at 3 hospitals: 23, 11, and 2 patients for each hospital. Two MR imaging was conducted on separate days (mean interval, 25 days; range, 2–34 days). Gadoxetate-enhanced MRI was performed first in 18 of 36 patients, and ferucarbotran-enhanced MRI was performed first in 18 of 36 patients. Patients had the following diagnoses: 22 wHCCs in 20 patients (13 men, 7 women; mean age, 72 years), 15 moderately to poorly differentiated HCCs (mpHCC) in 14 patients (13 men, 1 woman; mean age, 68 years) and 4 DNs in 2 patients (2 men; mean age 61 years). No patient had undergone previous hepatic or biliary surgery.

Among the 20 patients with wHCC, there were 10 cases of chronic hepatitis C, 1 of chronic hepatitis B, 6 of liver cirrhosis C, 1 of liver cirrhosis B, 1 of chronic hepatitis from nonalcoholic steatohepatitis (NASH), and 1 of liver cirrhosis from NASH. Of these 20 patients, 19 were classified as Child-Pugh class A and 1 as Child-Pugh class B. Serum total bilirubin level and indocyanine green15 min retention test (ICG-R15) were performed in all but 4 patients with wHCC: in the 16 tested patients, mean total bilirubin was 0.8 mg/dL (range, 0.5–1.5 mg/dL) and mean ICG-R15 was 17% (range, 6–35%).

Among the 14 patients with mpHCC, there were 8 cases of chronic hepatitis C, 2 of chronic hepatitis B, 3 of liver cirrhosis C, and 1 of alcoholic liver cirrhosis. Of these 14 patients, 11 were classified as Child-Pugh class A and 3 as Child-Pugh class B. Serum total bilirubin level and ICG-R15 were tested in all but 4 patients with mpHCC; in the 10 tested patients, mean total bilirubin was 1.2 mg/dL (range, 0.6–2.7 mg/dL) and mean ICG-R15 was 22% (range, 0.5–47%).

Among the 2 patients with DN, there were 1 case of chronic hepatitis C and 1 case of liver cirrhosis B. These 2 patients were classified as Child-Pugh class A, and 1 patient with liver cirrhosis B had ICG-R15 test (8%). Another patient with chronic hepatitis C had no ICG-R15 test.

**HCC diagnosis**

The mean size of wHCCs was 14 mm (range, 6–28 mm), while that of mpHCCs was 24 mm (range, 13–46 mm) by sonographic measurement. The mean size of DN was 16 mm (range, 13–22 mm). These measurements were made by 2 readers in consensus.

Tumor specimens for diagnosis were obtained by ultrasound-guided needle core biopsy in 3 mpHCCs, 18 wHCCs and 4 DNs. In the remaining 12 mpHCCs and 4 wHCCs, diagnosis was obtained by surgically
resected specimens. When determination of the exact location for ultrasound-guided needle biopsy was difficult, the biopsy sites were determined by correlation with substantially gadoxetate-enhanced MR. In needle core biopsy, at least 3 samples were taken from each tumor using a 21-gauge needle (Majima needle, Top, Tokyo, Japan) to ensure accurate histological diagnosis. Based on an established reference for pathologic evaluation (19), the diagnosis of HCC and DN was made by two pathologists specialized in liver pathology (Figs. 1, 4, 7).

**MR Examination**

The study was performed in three centers, using the following three different commercially available MR scanners for gadoxetate-enhanced imaging at 1.5 Tesla: Gyroscan Intera Nova (Philips Medical Systems, Best, the Netherlands) for gadoxetate-enhanced MRI and ferucarbotran-enhanced MRI, Signa EXCITE HD version 12 for gadoxetate-enhanced MRI, and Signa EXCITE XL version 11 for ferucarbotran-enhanced MRI (GE Healthcare, Milwaukee, WI, USA). All systems were equipped with high-performance gradient systems and body phased-array coils. For all patients, an MR-compatible power injector (SONIC SHOT 50, Nemoto Kyorindo, Tokyo, Japan or Spectris Solaris EP, Nihon Medrad, Osaka, Japan) was used to deliver bolus injection of gadoxetate at 2 mL/s, at a dose of 25 μmol/kg body weight (0.1 mL/kg), by means of a 20-gauge IV catheter placed in the antecubital vein. A 32- to 35-mL saline flush was administered at 2 mL/s after gadoxetate injection.

Unenhanced scans were obtained using a T1-weighted gradient echo (GRE) sequence (dual echoes; in-phase and opposed-phase) and T1-weighted high-resolution sequence (parameters are shown in Table 1). After injection of gadoxetate, imaging in the arterial (22–35 s postinjection), portal venous (70 s postinjection), and hepatobiliary phases (20 min after injection) were obtained using a T1-weighted high-resolution sequence in a single breath hold (18–20 s).

Ferucarbotran-enhanced MRI was performed using T2*-weighted sequence at the pre-enhancement and Kupffer phase at approximately 15–40 min postinjection, because T2*-weighted sequence is more sensitive than T2-weighted sequence to detect focal liver tumor (20). Ferucarbotran was manually administered at a dose of 0.45 mg of iron/kg body weight, at approximately 1 mL/s, by means of a 20- or 22-gauge IV catheter placed in the antecubital vein. T2*-weighted sequences were obtained in a single breath hold (17–20 s).

Ferucarbotran-enhanced MR examination was performed by a superconducting magnet operating at 1.5 Tesla (Gyroscan Intera Nova or Signa Excite XL version 11) equipped with a body phased-array coil. All images for ferucarbotran-enhanced MR were acquired in the transverse plane with a section thickness of 6–8 mm, intersection gap of 1–2 mm, and field-of-view of 28–35 cm. Presaturation pulses were placed above and below the imaging volume for artifact reduction. After injection of ferucarbotran, we obtained T2*-weighted gradient echo images with a long TE (TR/TE/FA, 150/10–12/60° or TR/TE/FA, 200/14/50°; 256 × 128 matrix).

**Image Review**

The gadoxetate- and ferucarbotran-enhanced MR data were sent to an image viewer (SYNAPSE; FujiFilm Medical, Tokyo Japan or Aquarius Net; TeraRecon Inc., Tokyo, Japan). The combined unenhanced and contrast-enhanced MR images were randomly assigned to 2 observers, and imaging data of all patients were reviewed by both radiologists in consensus. To minimize any learning bias, 1 MR image set was evaluated per session; thereafter, the next session was held more than 1 week later. Two experienced diagnostic radiologists (with at least 10 years experience in clinical body MR) reviewed both the

**Table 1**

| MR Parameter       | Philips Gyroscan Intera Nova | GE Signa EXCITE HD | GE Signa EXCITE XL |
|--------------------|------------------------------|--------------------|--------------------|
| Sequence           | 3D turbo field echo          | LAVA 3D-FSPGR      |                    |
| TR                 | 4 ms                         | 4.3 ms             | 4.8                |
| TE                 | 2 ms                         | 2.1 ms             | 2.2                |
| Flip angle         | 16°                          | 12°                | 12°                |
| SENSE factor       | 2                            | 2                  | 2                  |
| Slice thickness    | 5 mm                         | 5 mm               | 5 mm               |
| Slice interval     | 2.5 mm                       | 2.5 mm             | 2.5 mm             |
| Matrix             | 256 × 320                    | 192 × 320          | 160 × 288          |
| Fat saturation     | +                            | +                  | +                  |
| Field of view      | 390 mm                       | 360 mm             | 350 mm             |
| Breath hold        | 20 sec                       | 18 sec             | 19 s               |

SENSE = sensitivity encoding; 3D turbo field echo = three-dimensional turbo field echo; LAVA = Liver Acquisition with Volume Acceleration; 3D-FSPGR = three-dimensional fast spoiled gradient recalled acquisition in the steady state.
gadoxetate-enhanced T1-weighted images and ferucarbotran-enhanced T2*-weighted images using a DICOM viewer in consensus (alternating gadoxetate- and ferucarbotran-enhanced MRI). We analyzed the signal intensity of HCC and DN relative to the surrounding liver parenchyma in the hepatobiliary phase for gadoxetate-enhanced MRI and in the Kupffer phase for ferucarbotran-enhanced MRI.

**Image Analysis**

Signal intensity characteristics were compared between the lesion and the surrounding liver parenchyma on the precontrast T1-weighted and T2*-weighted images and classified as iso-intense, hypo-intense, or hyper-intense. 3 dimensional Fourier transformation (3DFT) T1-weighted high-resolution sequence (parameters are shown in Table 1) was used as image analysis of T1-weighted images. In addition, dual echo sequence (in-phase / opposed-phase) as pre-contrast T1-weighted image was used to investigate whether hepatic nodule includes fat. The signal reduction from in-phase to opposed-phase was investigated by visual and intense-measured evaluation. Similar signal between the lesion and surrounding liver parenchyma was classified as iso-intensity. Higher or lower signal compared with surrounding liver parenchyma was defined as hyper- or hypo-intensity, respectively. Unenhanced T2*-weighted images were not obtained for 3WHCCs and 3mpHCCs.

The gadoxetate- and ferucarbotran-enhanced MRI data were classified into the 4 signal intensity patterns relative to the surrounding liver parenchyma, inferior vena cava and intrahepatic vessels (Tables 2 and 3).

Signal intensities of tumor and liver parenchyma were measured as quantitative analysis for precontrast and postcontrast MR images in both gadoxetate- and ferucarbotran enhanced MRI. We measured signal intensities of the tumorous and liver parenchymal areas directly from a monitor (Aquarius Net) by using an operator-defined region of interest (ROI), which was specified as around area up to 10 mm in diameter. 1 area of the tumorous lesion and 3 areas of adjacent liver parenchymal regions without visible vascular structures were analyzed. The mean of the latter 3 points was used as the signal intensity of the liver parenchyma. To evaluate the uptake of gadoxetate and ferucarbotran by HCC and DN, we calculated contrast ratios between tumor and liver on the hepatobiliary phase image for gadoxetate-enhanced MRI and Kupffer phase image for ferucarbotran-enhanced MRI, as well as those on unenhanced images. The contrast ratio between tumor and liver on gadoxetate-enhanced MRI (gadoxetate-contrast ratio) was defined as follows; Gadoxetate-contrast ratio (precontrast ratio or postcontrast ratio) = tumor signal intensity / liver parenchymal signal intensity.

The contrast ratio between tumor and liver on ferucarbotran-enhanced MRI (ferucarbotran-contrast ratio) was defined as the reciprocal of measured signal intensity (because ferucarbotran acts as a positive

| Table 2 | Definitions for Signal Classification of the Hepatic Nodules on Hepatobiliary Phase of Gadoxetate-Enhanced MRI |
|--------|---------------------------------------------------------------|
| Signal intensity of the nodule | Definition |
| Iso-intense: | The nodule is invisible, indicating similar intranodular hepatocyte function to that of surrounding liver parenchyma. |
| Slightly hypo-intense: | The signal intensity of the nodule is higher than that of the intrahepatic inferior vena cava in which no contrast agent was seen in the hepatobiliary phase, but lower than that of the surrounding liver parenchyma. This indicates a decrease in, but not absence of, intranodular hepatocyte function. |
| Clearly hypo-intense: | The signal intensity of the nodule is similar to that of the intrahepatic inferior vena cava, indicating an absence of intranodular hepatocyte function. |
| Hyper-intense: | The signal intensity of the nodule is more hyper-intense than that of the surrounding liver parenchyma, indicating increased intranodular hepatocyte function. |

| Table 3 | Definitions for Signal Classification of the Hepatic Nodules on Kupffer Phase of Ferucarbotran-Enhanced MRI |
|--------|---------------------------------------------------------------|
| Signal intensity of the nodule | Definition |
| Iso-intense: | The nodule is not visualized, indicating similar intranodular Kupffer cell function to that of the surrounding liver parenchyma. |
| Slightly hyper-intense: | The signal intensity of the nodule is lower than that of the intrahepatic vessels in which no contrast agent is seen at the Kupffer phase, but higher than that of the surrounding liver parenchyma, indicating a decrease in, but not absence of, intranodular Kupffer cell function. |
| Clearly hyper-intense: | The signal intensity of the nodule is similar to that of the intrahepatic vessels, indicating an absence of intranodular Kupffer cell function. |
| Hypo-intense: | The signal intensity of the nodule is more hypo-intense than that of surrounding liver parenchyma. |

To avoid artifact of inferior vena cava on ferucarbotran-enhanced MR, we preferred to compare signal between the nodule and the intrahepatic vessels rather than with the inferior vena cava.
contrast agent, although gadoxetate acts as a negative contrast agent) as follows:

Ferucarbotran-contrast ratio (precontrast ratio or postcontrast ratio) = 1/(Tumor signal intensity/liver parenchymal signal intensity)

**Evaluation of Tumor Vascularity**

The dynamic phase of gadoxetate for each patient was analyzed by the other 2 diagnostic radiologists (with at least 10 years experience in clinical body MR) in consensus; these data were then used to discuss for the histological diagnosis of HCC. If tumor enhancement was observed on arterial phase images of gadoxetate-enhanced MR imaging, the tumor was classified as hyper-vascular. Other tumors were classified as iso-vascular (as well as surrounding liver parenchyma) and hypo-vascular (lower enhancement than that of surrounding liver parenchyma). The tumor enhancement on arterial phase images of gadoxetate-enhanced MR and ferucarbotran-enhanced MR was determined visually in most nodules. If the hepatic nodule was minimally enhanced, the image was evaluated by subtracting precontrast image from arterial image.

**Statistical Analysis**

Statistical analysis was performed by SPSS version 11.0 software (SPSS Inc., Chicago, IL, USA). Statisti-

### Table 6
Comparison of Enhancement Patterns Between Hepatobiliary Phase of Gadoxetate-Enhanced MRI and Kupffer Phase of Ferucarbotran-Enhanced MRI in Well-Differentiated Hepatocellular Carcinoma

| MRI        | Gadoxetate-enhanced MRI | Ferucarbotran-enhanced MRI |
|------------|-------------------------|---------------------------|
| Hyper      | 6                       | 1                         |
| Iso        | 13                      | 1                         |
| Hypo       | 1                       | 0                         |

There was a difference in enhancement patterns of well-differentiated hepatocellular carcinoma between gadoxetate-enhanced MR and ferucarbotran-enhanced MR ($P = 0.001$).

Hypo = hypo-intense, Iso = iso-intense, Hyper = hyper-intense.

### RESULTS

**Unenhanced MRI**

On unenhanced MRI, most wHCCs showed iso-intense (14 of 22; 64%) (Fig. 2a) on T1-weighted high-resolution imaging and iso-intense (13 of 19; 68%) (Fig. 3a) on T2*-weighted imaging. All iso-intense nodules were small (<2 cm in size), in addition, capsule and mass effect were not detected on MRI, although sonography allowed to detect the nodules. In contrast, mHCCs showed hypo-intense (11 of 15; 73%) (Fig. 5a) and iso-intense (4 of 15; 27%) on T1-weighted high-resolution imaging and mHCCs showed iso-intense (6 of 12; 50%) and hypo-intense (6 of 12; 50%) (Fig. 6a) on T2*-weighted imaging. On T1-

### Table 7
Comparison of Enhancement Patterns Between Hepatobiliary Phase of Gadoxetate-Enhanced MRI and Kupffer Phase of Ferucarbotran-Enhanced MRI in Moderately to Poorly Differentiated Hepatocellular Carcinoma

| MRI        | Gadoxetate-enhanced MRI | Ferucarbotran-enhanced MRI |
|------------|-------------------------|---------------------------|
| Hyper      | 13                      | 1                         |
| Iso        | 0                       | 0                         |
| Hypo       | 0                       | 0                         |

There was no difference in enhancement patterns of moderately to poorly differentiated hepatocellular carcinoma between gadoxetate-enhanced MR and ferucarbotran-enhanced MR.

Hypo = hypo-intense, Iso = iso-intense, Hyper = hyper-intense.
weighted high-resolution imaging, 5 of 22 wHCCs (23%), 2 of 15 mpHCCs (13%) and none of DNs (0%) showed hyper-intense in comparison to surrounding liver. Five hyper-intense wHCCs and 2 hyper-intense mpHCCs had no apparent change of tumor intensity decreased from in-phase to opposed-phase of T1-weighted imaging by both visual and intense-measured evaluation. All DNs showed iso-intense (4 of 4; 100%) (Fig. 8a) on unenhanced T1-weighted high-resolution imaging, and iso-intense (4 of 4; 100%) (Fig. 9a) on unenhanced T2*-weighted image.

Gadoxetate-enhanced MRI Versus Ferucarbotran-enhanced MRI

Tables 4 and 5 show the correlation between the histologic types of the hepatic nodules and the findings on gadoxetate- and ferucarbotran-enhanced MRI. On gadoxetate-enhanced MRI, wHCC appeared hypo-intense (slightly and clearly hypo-intense, 20 of 22; 91% in Table 4) (Fig. 2b) relative to surrounding liver, and there was a higher tumor to liver contrast compared with ferucarbotran-enhanced MR imaging, on which the lesion appeared hyper-intense (slightly and clearly hyper-intense, 7 of 22; 32% in Table 5). The distribution of enhancement pattern of wHCC was different from that of mpHCC in both gadoxetate- and ferucarbotran-enhanced MRI ($P < 0.001$ for both)

**Table 8**

| Gadoxetate-enhanced MRI | Hypo | Iso | Hyper |
|-------------------------|------|-----|-------|
| Ferucarbotran-enhanced MRI | Hyper | 19 | 2 | 1 |
|                       | Iso  | 13 | 1 | 0 |
|                      | Hypo | 1 | 0 | 0 |

There was a difference in enhancement patterns of hepatocellular carcinoma between gadoxetate-enhanced MR and ferucarbotran-enhanced MR ($P = 0.013$).

Hypo = hypo-intense, Iso = iso-intense, Hyper = hyper-intense.

Tables 4 and 5 show the correlation between the histologic types of the hepatic nodules and the findings on gadoxetate- and ferucarbotran-enhanced MRI. On gadoxetate-enhanced MRI, wHCC appeared hypo-intense (slightly and clearly hypo-intense, 20 of 22; 91% in Table 4) (Fig. 2b) relative to surrounding liver, and there was a higher tumor to liver contrast compared with ferucarbotran-enhanced MR imaging, on which the lesion appeared hyper-intense (slightly and clearly hyper-intense, 7 of 22; 32% in Table 5). The distribution of enhancement pattern of wHCC was different from that of mpHCC in both gadoxetate- and ferucarbotran-enhanced MRI ($P < 0.001$ for both)

**Table 9**

| Gadoxetate-Precontrast and Postcontrast Ratios Between Tumor and Liver Parenchyma for DN and HCC on Hepatobiliary Phase of Gadoxetate-Enhanced MRI |
|---------------------------------|-----------------|-----------------|
| Gadoxetate-enhanced MRI         | DN              | wHCC            | mp HCC           |
| precontrast ratio               | 1.00 ± 0.00     | 1.01 ± 0.17$^a$ | 0.85 ± 0.14$^a$  |
| postcontrast ratio              | 0.93 ± 0.08$^b$ | 0.76 ± 0.15$^a$ | 0.59 ± 0.27$^{a,b}$ |

$^a$Significant difference is seen in comparison between wHCC and mpHCC.

$^b$Significant difference is seen in comparison between DN and mpHCC.

**Table 10**

| Ferucarbotran-Precontrast and Postcontrast Ratios Between Tumor and Liver Parenchyma for DN and HCC on Kupffer Phase of Ferucarbotran-Enhanced MRI |
|---------------------------------------------------------------------------------|-----------------|-----------------|
| DN                      | wHCC            | mp HCC           |
| precontrast ratio       | 1.00 ± 0.00     | 0.98 ± 0.05      | 1.00 ± 0.15     |
| postcontrast ratio      | 1.00 ± 0.00$^b$ | 0.93 ± 0.26$^a$ | 0.60 ± 0.20$^{a,b}$ |

$^a$Significant difference is seen in comparison between wHCC and mpHCC.

$^b$Significant difference is seen in comparison between DN and mpHCC.

DN = Dysplastic nodule, Well HCC = Well-differentiated hepatocellular carcinoma, Moderate-poor HCC = Moderately to poorly differentiated hepatocellular carcinoma.

Figure 2. Gadoxetate-enhanced MR images of a well-differentiated HCC in a 69-year-old woman (same patient as in Fig. 1). **a:** Unenhanced T1-weighted image (Liver Acquisition with Volume Acceleration: LAVA) shows a lesion in liver segment 3 (arrow) that is almost iso-intense compared with surrounding liver parenchyma. **b:** Gadoxetate-enhanced MR image with LAVA obtained at the hepatobiliary phase. The lesion showed slightly hypo-intense than surrounding liver parenchyma at 20 min after gadoxetate injection (arrow; 1 cm in diameter; signal intensity in the nodule was lower than surrounding liver, but slightly higher than that in the intrahepatic inferior vena cava).
Tables 4 and 5). Thirteen (93%) of the 14 iso-intense wHCCs (Fig. 3b) on ferucarbotran-enhanced MRI were classified as hypo-intense relative to surrounding liver on gadoxetate-enhanced MRI. There was a difference in enhancement patterns of wHCC between gadoxetate- and ferucarbotran-enhanced MRI ($P = 0.001$, Table 6). Even for all HCCs (wHCC + mpHCC), there was a clear difference between gadoxetate as hypo-intense (slightly and clearly hypo-intense; 89% in Table 4) and ferucarbotran as hyper-intense (slightly and clearly hyper-intense; 59% in Table 5).

Thirteen (59%) of the 22 wHCCs were hypo-intense on gadoxetate-enhanced MRI and iso-intense on ferucarbotran-enhanced MRI (Table 6); in contrast, 13 (87%) of the 15 mpHCCs were hypo-intense on gadoxetate-enhanced MRI (Fig. 5b), and all mpHCCs appeared hyper-intense on ferucarbotran-enhanced MRI (Fig. 6b). In addition, 1 mpHCC (1 of 15; 7%) was hyper-intense on gadoxetate-enhanced MRI (Table 4), and 1 wHCC (1 of 22; 5%) was hypo-intense on ferucarbotran-enhanced MRI (Table 5).

As shown in Table 8, 13 of 14 HCCs (93%) in gadoxetate-enhanced MRI showed hypo-intense, whereas these 14 HCCs showed iso-intense in ferucarbotran-enhanced MRI. There was a significant difference in enhancement patterns of wHCC and mpHCC between gadoxetate- and ferucarbotran-enhanced MR ($P = 0.013$).

Four DNs showed hypo-intensity in 2 nodules (Fig. 8b) and iso-intensity in the other 2 nodules after gadoxetate injection. On the other hand, all DNs showed iso-intensity (Fig. 9b) after ferucarbotran injection.

### Contrast Ratios Between Tumor and Liver for HCC and DN: Quantitative Analysis

Gadoxetate-precontrast and postcontrast ratios on hepatobiliary phase of gadoxetate-enhanced MRI and ferucarbotran-precontrast and postcontrast ratios on Kupffer phase of ferucarbotran-enhanced MRI for HCC and DN (defined in the Materials and Methods) are shown in Tables 9 and 10. In gadoxetate-precontrast and ferucarbotran-postcontrast ratios, a significant change was observed only between gadoxetate-precontrast ratio of wHCC (1.01 ± 0.17) and that of mpHCC (0.85 ± 0.14) (Table 9).

On hepatobiliary phase of gadoxetate-enhanced MRI, gadoxetate-postcontrast ratio of mpHCC (0.59 ± 0.27) was significantly lower than those of wHCC (0.76 ± 0.15) and DN (0.93 ± 0.08) (Table 9). These results were consistent with the qualitative analysis of Table 4. On Kupffer phase of ferucarbotran-enhanced MRI, ferucarbotran-postcontrast ratio of mpHCC (0.60 ± 0.20) was significantly lower than those of wHCC (0.93 ± 0.26) and DN (1.00 ± 0.00) (Table 10).

![Figure 3. Ferucarbotran-enhanced MR images of a well-differentiated HCC in a 69-year-old woman (same patient as in Fig. 1). a: Unenhanced T2*-weighted gradient-echo (Three dimensional fast spoiled gradient recalled acquisition in the steady state = FSPGR) image shows a lesion (arrow) in liver segment 3 that is iso-intense compared with surrounding liver parenchyma, which could not be detected. b: Ferucarbotran-enhanced MR image with FSPGR obtained at the Kupffer phase. The lesion showed iso-intensity (arrow; 1 cm in diameter) compared with surrounding liver parenchyma at approximately 15 min after the ferucarbotran injection. Non-visualization of the nodule indicates the similarity of intranodular Kupffer cell function between the nodule and the surrounding liver parenchyma.](image1)

![Figure 4. Histology of a moderately differentiated HCC in a 75-year-old woman. Hematoxylin and eosin staining.](image2)
These findings were also compatible with the results of Table 5. Gadoxetate-postcontrast ratio was significantly lower than ferucarbotran-postcontrast ratio in wHCC ($P=0.015$). This result was consistent with the qualitative analysis of Table 6.

**DISCUSSION**

The results revealed a tendency for wHCC to appear hypo-intense on T1-weighted high-resolution images (91%) after gadoxetate-injection, and indicate a great advantage for the detection of wHCC because 63% of wHCC showed iso-intense on $T2^*$-weighted imaging in size, and as heterogeneous enhancement in all 3 mphHCCs more than 2.5 cm in size. Whereas, hyper-vascularity of 3 wHCCs was obtained as entire nodular enhancement (homogeneously).

All DN showed iso-vascularity, and were not detected in the arterial phase alone after gadoxetate injection.

**Arterial-dominant Phase in Gadoxetate-enhanced MRI**

In the arterial-dominant phase after gadoxetate injection, all mphHCCs were shown as hyper-vascular tumors, while among the 22 wHCCs, 2 (9%) were shown as hyper-vascular, 17 (77%) as iso-vascular, and 3 (14%) as hypo-vascular tumors. Hyper-vascularity of mphHCCs was clearly detected as homogeneous enhancement in all 4 mphHCCs less than 1.5 cm.
after ferucarbotran injection. Thus, we have clearly demonstrated that wHCC rarely takes up gadoxetate (Fig. 2), whereas there is a range of enhancement patterns in wHCC on ferucarbotran-enhanced MR imaging (Fig. 3), as previously reported (3). However ferucarbotran-enhanced MRI may be more useful than gadoxetate-enhanced MRI for the differentiation of mpHCC from wHCC (3). Regarding DNs, all 4 DNs showed iso-intensity on ferucarbotran-enhanced MRI, whereas 2 DNs showed hypo-intensity on gadoxetate-enhanced MRI in this study. These findings were consistent with the previous reports that some DNs revealed hypo-intensity on T1-weighted high-resolution image of hepatobiliary phase of gadoxetate-enhanced MRI similar to HCCs (21) and that none of the DNs were depicted as a hyper-intense nodule on ferucarbotran-enhanced MRI (3). Accordingly, these results suggest that reduced uptake of gadoxetate by HCCs and DNs appears earlier than reduction or impaired function of Kupffer cells in them as assessed by ferucarbotran uptake during multistep hepatocarcinogenesis. Taken the previous report (3) and this study together, it seems likely that DNs are iso-intense on ferucarbotran-enhanced MRI. On the other hand, uncertainties might exist in differentiation between HCCs and DNs by hepatobiliary phase of gadoxetate-enhanced MRI, although only small number of DN was studied. Further study is needed to confirm our observation in diagnosis of DN by gadoxetate-enhanced MRI.

In the hepatobiliary phase with gadoxetate of a rat study conducted by Ni et al (22), stronger enhancement was observed in wHCCs than in the surrounding liver. In another rat study, Fujita et al (23) stated that positive enhancement occurred independently of cellular differentiation after gadoxetate injection. According to another experimental study using rats, gadoxetate-enhanced T1-weighted imaging showed the same performance as SPIO-enhanced T2-weighted imaging in detecting liver cancer (16). The results of the present study differ from these previous reports possibly because our study was performed in human cases.

According to a recently published study, Lee et al state that ferucarbotran-enhanced MRI and gadoxetate-enhanced MRI show a similar diagnostic performance for the detection of 38 HCCs (3 wHCCs and 35 mpHCCs) (14). Patient population between the study by Lee et al and our study shows difference, because our study consisted of 22 wHCCs and 15 mpHCCs. Regarding the patient population, our study is more appropriate than the study by Lee et al for the comparison of wHCCs between gadoxetate- and ferucarbotran-enhanced MRI.

Fourteen of 22 (63%) wHCC showed iso-intense on ferucarbotran-enhanced MRI in our study. On the other hand, 5 of 17 (29%) showed iso-intense in another study (24). Kim et al also stated that a total of 13 (15%) of 84 wHCCs were not hyper-intense on T2* or T2 weighted image of ferucarbotran-enhanced MRI (25). More than 90% of wHCC in our study were iso- or hypo-vascular suggesting that most of them might be iso-intense on ferucarbotran-enhanced MRI.

**Figure 7.** Histology of a dysplastic nodule in a 76-year-old woman. Hematoxylin and eosin staining.

**Figure 8.** Gadoxetate-enhanced MR images of a dysplastic nodule in a 76-year-old woman (same patient as in Fig. 7). a: Unenhanced T1-weighted image (Liver Acquisition with Volume Acceleration: LAVA) shows a lesion in liver segment 8 (arrow) that is almost iso-intense compared with surrounding liver parenchyma. b: Gadoxetate-enhanced MR image with LAVA obtained at the hepatobiliary phase. The 1-cm lesion showed slightly hypo-intense (arrow; 1.3 cm in diameter) than surrounding liver parenchyma at 20 min after gadoxetate injection (arrow; signal intensity in the nodule was lower than surrounding liver, but higher than that in the intrahepatic inferior vena cava).
early HCC. We speculate that our study may include more early HCCs, which usually have normal Kupffer cell function and counts (3), than previous studies. Most mpHCCs are shown as hyper-vascular tumors (26,27). Gadoxetate acts as both an extracellular and a hepatocyte-specific contrast agent, and has blood pool properties as an extracellular contrast agent in the arterial phase. Thus, early scanning with dynamic features is required for patients with lesions highly suspicious of mpHCC. When MR imaging is performed in the dynamic liver phase, gadoxetate may potentially be used in diagnosis of mpHCC as well as mpHCC. In the present study, gadoxetate-enhanced MR showed hyper-vascularity in all mpHCCs (100%). This result also indicates a requirement for assessing the enhancement pattern of lesions in arterial phase for the diagnosis of mpHCCs, using gadoxetate-enhanced MR. In contrast, only 9% of wHCCs were shown as hypervascular tumors. It is noted that some wHCCs are hyper-vascular on dynamic CT (28), but our results showed wHCCs to be substantially iso-vascular (77%) in the arterial phase after gadoxetate administration. Thus, the hepatobiliary phase plays a more important role in the detection and characterization of wHCC than does the dynamic arterial phase. From the present results, we expect that gadoxetate-enhanced MR could be effective in wide-ranging histological differentiation of HCC using both the dynamic liver and hepatobiliary phases.

Put simply, SPIO particles are taken up by reticulo-endothelial cells where they cluster in the lysosomes (29). Tanimoto et al (30) found statistically significant differences in the observed change in mean hepatic signal-to-noise ratio between the cirrhotic group and noncirrhotic group in late-phase T2*-weighted imaging. This finding was more likely due to Kupffer cell dysfunction than to Kupffer cell depletion. In contrast, gadoxetate accumulates in hepatocytes with hepatocytic function (31), making it possible to assess liver function on gadoxetate-enhanced MR imaging (32). Finally, the uptake of SPIO or gadoxetate depends on the status of background liver. In the present study, most patients (25 of 34; 74%) were Child-Pugh class A, for which enhancement of liver parenchyma is expected to be homogeneous on both SPIO- and gadoxetate-enhanced MR imaging. Moreover, the diagnosis of HCC was made by experienced pathologists based on the histological criteria of International Consensus Group for Hepatocellular Carcinoma (33). Biopsy is not typically needed for diagnosis of hypervascular HCC such as mpHCC; therefore, our study population included a high number of wHCCs, which may have introduced selection bias into our study.

Second, the majority of patients in our study were Child-Pugh class A. The results of detection for HCC may be affected in patients with severe liver dysfunction, as has been shown in rat livers (32); this may be a key point with regard to enhancement in the hepatobiliary phase after gadoxetate injection. Liver parenchymal background is important in assessing the liver-specific phase, for both gadoxetate and SPIO. In patients with liver cirrhosis, MR imaging after SPIO injection results in an unwanted inhomogeneous decrease in signal intensities (30). Because the cirrhotic liver shows less uptake of gadoxetate and SPIO particles than does normal liver, HCC detection in

Figure 9. Ferucarbotran-enhanced MR images of a dysplastic nodule in a 76-year-old woman (same patient as in Fig. 7). a: Unenhanced T2*-weighted gradient-echo (Three dimensional fast spoiled gradient recalled acquisition in the steady state = FSPGR) image shows a lesion (arrow) in liver segment 8 that is iso-intense compared with surrounding liver parenchyma, which could not be detected. b: Ferucarbotran-enhanced MR image with FSPGR obtained at the Kupffer phase. The lesion showed iso-intensity (arrow) compared with surrounding liver parenchyma at approximately 15 min after the ferucarbotran injection. Nonvisualization of the nodule indicates the similarity of intranodular Kupffer cell function between the nodule and the surrounding liver parenchyma.
patients with liver dysfunction may be limited (34). In addition, as mentioned above, our study population substantially consisted of patients with chronic hepatitis or cirrhosis due to hepatitis C virus infection; other types of chronic hepatitis or cirrhosis may show a different enhancement pattern with ferucarbotran and gadoxetate.

Third, the enhancement patterns of DN on gadoxetate-enhanced MRI was not sufficiently investigated, because the number of DN was very small in this study. A further study on DNs by using gadoxetate-enhanced MR imaging should be conducted.

In conclusion, the uptake function of hepatocytes that are targeted by gadoxetate is more sensitive than that of Kupffer cells targeted by ferucarbotran in step-wise carcinogenesis of HCC.

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