

Original

**Chemical-shift Magnetic Resonance Imaging Performed after
Chemoembolization of Hepatocellular Carcinoma
—Signal Evaluation of Oil-based Contrast Agent—**

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Abstract : We investigated whether the Lipiodol-derived signal accumulated in hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization (TACE) using Lipiodol (oil-based contrast agent) mixed with an anticancer agent, known as Lp-TACE, could be evaluated with chemical-shift magnetic resonance imaging (MRI). The subjects were 25 HCC patients (n = 45 tumors) who had undergone Lp-TACE and chemical-shift MRI of the abdominal region from April 1, 2000 to March 31, 2012. The regions of interest (ROIs) were set as large as possible to include the Lipiodol accumulation region on computed tomography (CT) images and the hyperintense signal region in double-echo fast low-angle shot (FLASH), automatic-subtracted images on MRI. We then used both modalities to measure the CT value and signal intensity for each specimen. The MRI signal intensity was calculated by subtracting the background signal intensity from the measured value. The mean CT value for the 45 tumors in the 25 patients of 710 Hounsfield units (HU ; range, 139–3,062 HU) was positively correlated with the mean MRI signal intensity of 43.5 (0–212). Tumors with a diameter ≥ 2 cm exhibited a stronger correlation between CT values and MRI signal intensity in areas of Lipiodol accumulation than tumors smaller than 2 cm. A weaker correlation was observed between the CT values and MRI signal intensity in areas of Lipiodol accumulation when the period from Lp-TACE to MRI was shorter than a week compared to one week or over. Our findings suggest that chemical-shift MRI can detect Lipiodol accumulation in HCCs and could therefore be useful in evaluating such types of accumulation.

Key words : Lp-TACE, HCC, chemical-shift magnetic resonance imaging

Introduction

Transcatheter arterial chemoembolization (TACE) using Lipiodol (oil-based contrast agent) mixed with an anticancer agent is known as Lp-TACE, and is a widely used treatment for hepatocellular carcinoma (HCC) ¹⁻³⁾. However, many questions exist regarding the effects of Lipiodol accumulation on the magnetic resonance imaging (MRI) signal obtained from HCC after Lp-TACE. A number of studies have indicated that high signal intensity on T1-weighted images in HCC after Lp-TACE is caused by hemorrhagic necrosis ⁴⁻⁶⁾, while other studies concluded that

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Lipiodol affects the MRI signals themselves^{7,8)}. By contrast, a few studies found only slight effects of Lipiodol on MRI signal intensity⁹⁻¹²⁾.

Computed tomography (CT) readily detects Lipiodol accumulation in HCC due to its high-resolution imaging, with CT after an intra-arterial injection of Lipiodol from the hepatic artery able to diagnose small hepatomas^{13, 14)}. CT is also useful in the post-Lp-TACE management of HCCs^{15, 16)}. However, once a high density of Lipiodol has accumulated in the tumor, evaluating whether tumor-enhancing effects are present by contrast-enhanced CT and diagnosing residual or recurrent tumors can be difficult^{17, 18)}. It is also worth noting that artifacts are created when Lipiodol exhibits markedly high attenuation, and that these artifacts make recurrence evaluation in the area around the tumor difficult¹⁹⁾. Some studies have reported (in cases such as this) that MRI is very useful in determining treatment effects and assessing recurrence in HCCs after Lp-transcatheter arterial embolization (TAE). This is because artifacts are less likely to be present when the evaluation of contrast effects is easy and not affected by the presence of Lipiodol¹⁷⁻¹⁹⁾.

In recent years, chemical-shift images, which are obtained using a type of MRI that has the ability to detect trace amounts of fat as signal, have been clinically applied in a range of fields. A few studies have reported that this new technology makes it possible to discriminate the signals obtained in Lipiodol accumulation in HCCs²⁰⁻²²⁾. In the present study, we therefore investigated whether chemical-shift MRI could be used to evaluate the signal derived from Lipiodol accumulation in HCCs after Lp-TACE.

Subjects and methods

All study procedures were performed in accordance with the Declaration of Helsinki.

Patients

Subjects were patients with HCC who had undergone Lp-TACE and chemical-shift MRI of the abdominal region. Only patients ($n=25$) who had undergone simple CT performed for comparison at roughly the same time as the MRI testing (within 24 h) were included in this study. The study period was April 1, 2000 to March 31, 2012. The mean patients age was 66.5 years (range: 46–78 years) and the ratio of men to women was 18:6. We evaluated 45 tumors that had been rendered on pre-TACE MRI.

MRI imaging

MRI was performed using a whole-body, super-conductive MRI (1.5 T) (Siemens Magnetom Vision) and torso-array coils. T2-weighted images were repetition time (TR) /echo time (TE) = 3000–4200/92–138 and field of view (FOV) 320–380 × 232–272 mm, and the slice thickness was 5 mm.

Chemical-shift MRI

Chemical-shift images were taken using double-echo fast low-angle shot (FLASH) (TR = 100,

TE = 2.3/4.7, Flip Angle 30, FOV 350×256 , matrix 256×256). In-phase images (TR/TE = 100/2.3) and opposed-phase images (TR/TE = 100/4.7) were taken simultaneously. We created subtraction images by subtracting opposed-phase images from in-phase images. For T1-weighted images, we used the chemical-shift, in-phase images.

CT imaging

CT imaging was performed using a whole-body multidetector CT (GE-Yokogawa: Proseed SA or Siemens: Somatom plus) ; the reconstruction slice thickness was 5 mm.

Chemoembolization

Chemoembolization was performed by mixing and emulsifying 5 ml of 300 mg/ml iodine contrast medium, 1 ml of distilled water, 40 ~ 60 mg of adriamycin, and 10 ml of Lipiodol. We then injected this mixture intra-arterially into the hepatic artery and performed embolization with Gelfoam particles.

Imaging analysis and statistical analysis

We compared the automatically subtracted double-echo FLASH MRI images and CT images taken at approximately the same time. For CT, we set the regions of interest (ROIs) within the tumor as large as possible, including the area of Lipiodol accumulation. For MRI, we also set ROIs within the tumor as large as possible, including the high-signal areas. MRI signal intensity was calculated by subtracting the value of background signal intensity from the measured value. Statistical package for social science (SSPS) version 21 was used for statistical analysis and a *P*-value of < 0.05 was considered statistically significant.

Results

MRI signal intensity and CT values of Lipiodol in HCCs

The mean T1-weighted image signals in the 45 preoperative tumors were of a lower intensity than those of the surrounding liver parenchyma. After Lp-TACE, we noted a change in the tumor area in that 32 tumors showed high-intensity signals and 13 tumors showed isointense signals. For the T2-weighted images, the preoperative tumor-signal intensity in all subjects was higher than in the liver parenchyma. After Lp-TACE, the signals of 30 tumors remained at a higher intensity, whereas isointense signals were noted in 3 tumors, and 12 tumors showed lower signal intensity lower than the liver parenchyma (Table 1).

The mean CT value for the 45 tumors in the 25 patients was 710 Hounsfield units (HU ; range, 139–3,062 HU), and the mean MRI signal intensity of the double-echo FLASH, automatic subtracted images was 43.5 (0–212), revealing a strong positive correlation ($r = 0.862$, $P < 0.0001$) between the CT values and MRI signal intensity (Fig. 1).

Comparison according to tumor diameter

We classified the tumors with HCC staging according to tumor diameter. We found that 26

Table 1. Tumor intensity before Lp-TACE and after Lp-TACE (n=45)

(signal intensity)	T1WI			T2WI		
	low	iso	high	low	iso	high
before TACE	45	0	0	0	0	45
after TACE	0	13	32	12	3	30

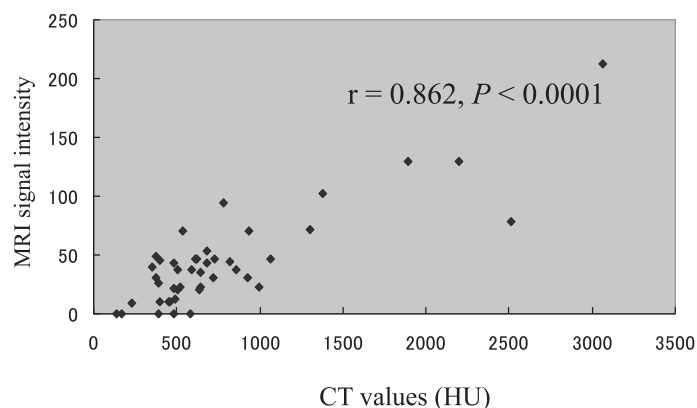


Fig. 1. CT values and MRI signal intensity of Lipiodol accumulation in HCCs

A positive correlation was observed between CT values and MRI signal intensity

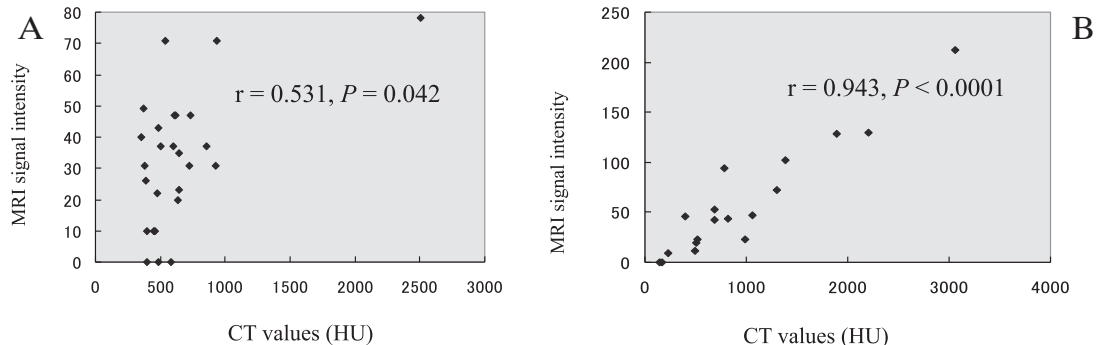


Fig. 2. CT values and MRI signal intensity of Lipiodol accumulation in HCCs and comparison according to tumor diameter

Tumors with a diameter ≥ 2 cm exhibited a stronger correlation than those with a diameter < 2 cm

nodules had a diameter of < 2 cm and 19 nodules had a diameter of ≥ 2 cm, and the larger tumors exhibited a stronger correlation ($r = 0.943$, $P < 0.0001$) between Lipiodol CT values and MRI signal intensity (Fig. 2) than the smaller group ($r = 0.531$, $P = 0.042$). This discrepancy in diameter occurred because some tumors may have been too small to set ROIs.

Comparison according to the period after Lp-TACE

The period from the Lp-TACE to the MRI was < 1 week for 12 nodules, 1 week to < 1 month for 22 nodules, and ≥ 1 month for 11 nodules. A weaker correlation (moderate cor-

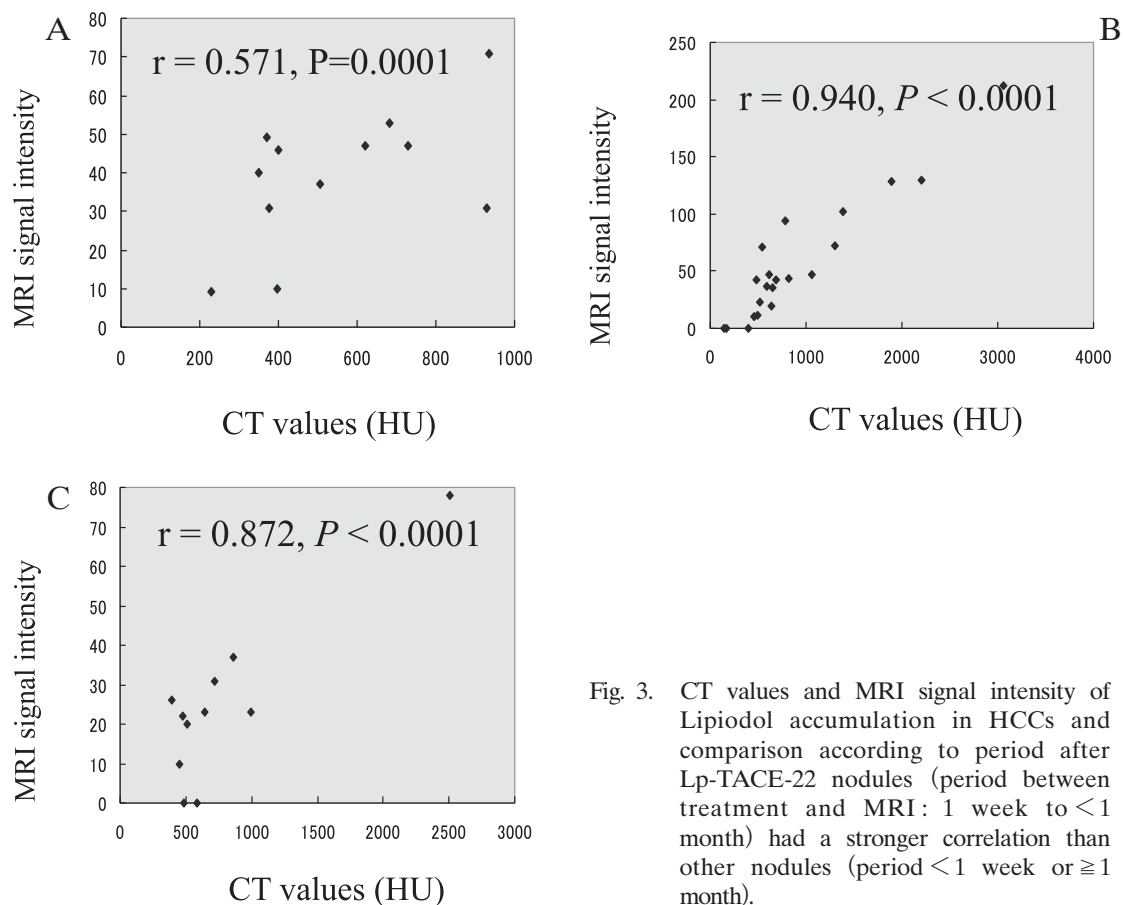


Fig. 3. CT values and MRI signal intensity of Lipiodol accumulation in HCCs and comparison according to period after Lp-TACE-22 nodules (period between treatment and MRI: 1 week to <1 month) had a stronger correlation than other nodules (period <1 week or \geq 1 month).

relation: $r = 0.571$) between CT values and MRI signal intensity was observed for the areas of Lipiodol accumulation when the period from the Lp-TACE treatment to the MRI was < 1 week than when this period was \geq 1 week (See Fig. 3. 1week to < 1month: $r = 0.840$, \geq 1month: $r = 0.872$).

Visually, the extent of CT high attenuation and MRI high-signal intensity brought about by Lipiodol accumulation in the tumor were almost identical (Fig. 4, 5). However, hyperintense signals could not be visually detected on the subtraction images in five cases.

Discussion

HCCs are thought to develop coagulation necrosis after TACE, and MRI findings may also reflect coagulation necrosis⁴⁻⁶⁾. However, MRI signals in such tumors are diverse because of HCC hemorrhage, necrosis, and the timing of these events. MRI signals appear to intricately reflect the process from the appearance of pathological changes, which are thought to be coagulation necrosis to the completion of these changes. Because the signal intensity of Lipiodol itself may affect the results of MRI findings in cases that have undergone Lp-TACE, making the MRI signal intensities even more diverse.

Because Lipiodol is an oil-based, iodine contrast medium, it absorbs X-rays and exhibits high-

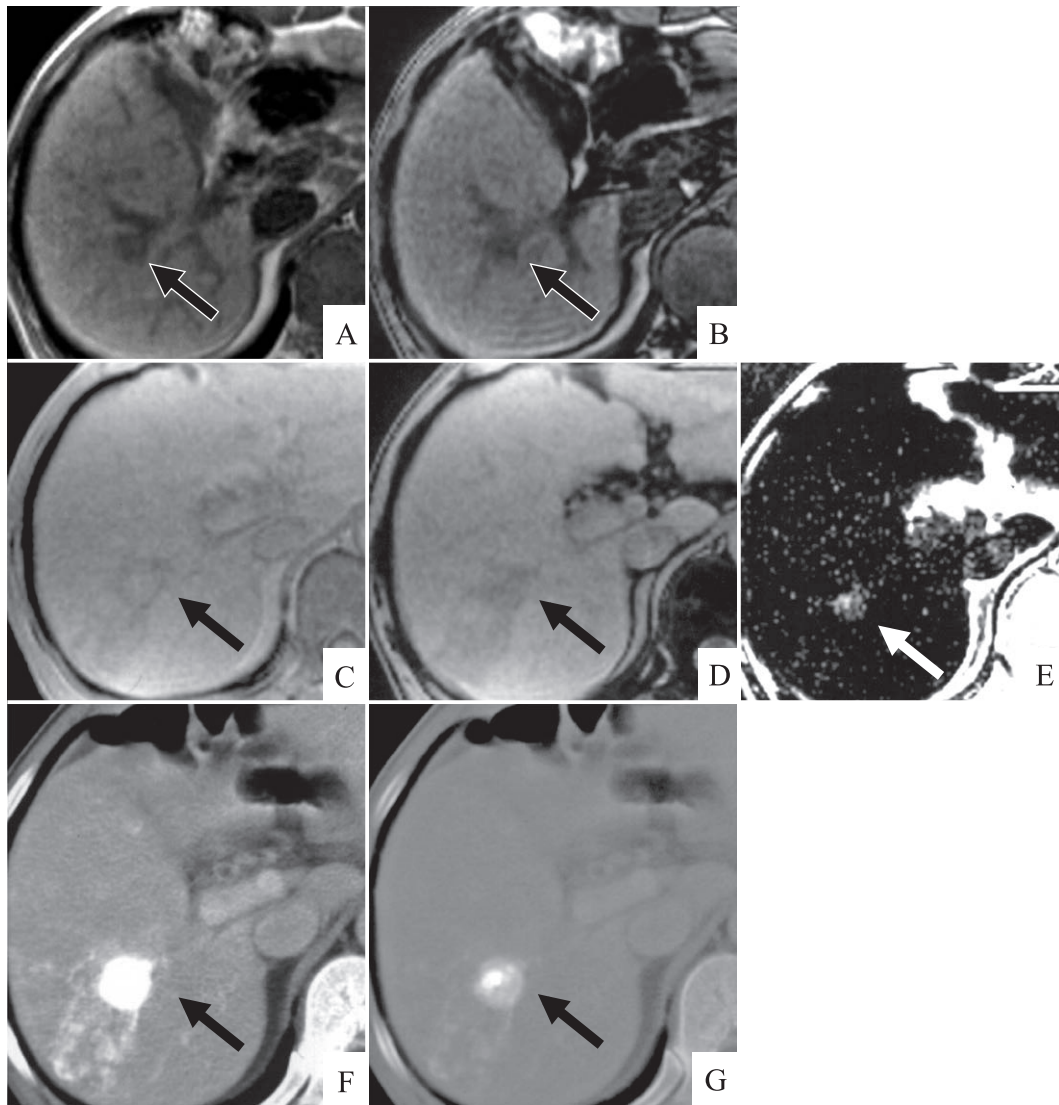


Fig. 4. 46-year-old male

Hypointense signals (arrows) observed on both FLASH in-phase (A) and opposed-phase images (B) before TAE. The MRI performed 27 days after TAE showed signal intensity in the HCC that was slightly higher or identical to that in the liver parenchyma on in-phase images (C). On opposed-phase images (D), the HCC area exhibited hypointense signals. On the subtraction images (E), a hyperintense signal region was noted in the HCC that was composed of both strong and weak hyperintense signals.

CT performed 26 days after TAE indicated Lipiodol accumulation in the HCC, and the HCC exhibited high attenuation. CT performed under normal conditions indicated uniform, markedly high attenuation (F) for the Lipiodol area. CT imaging with the window width expanded (G) showed Lipiodol accumulation coinciding with that in the non-uniform hyperintense signals area seen on the post-TAE subtraction image (E).

density resolution on X-ray images. In turn, because CT obtains high-density resolution, it can diagnose even a slight accumulation of Lipiodol in HCCs and is thus normally used to evaluate Lipiodol accumulation in HCCs following Lp-TACE^{15, 16)}. However, high-density accumulation of Lipiodol in tumors makes the diagnosis of residual or recurrent tumors difficult. Therefore, MRI

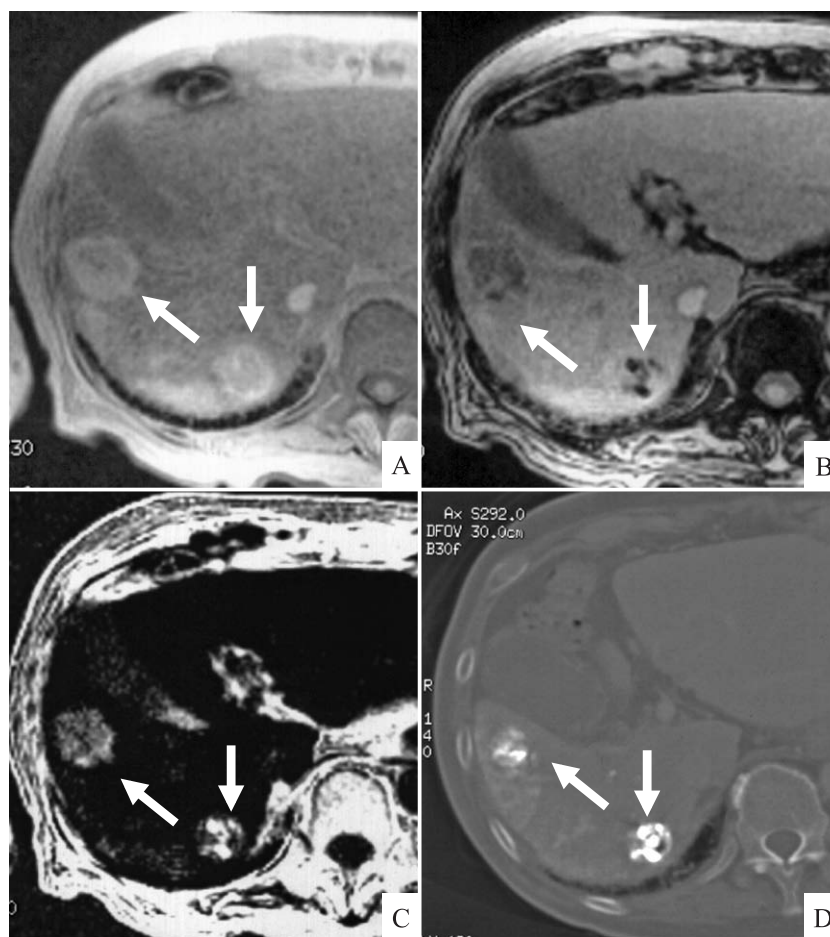


Fig. 5. 74-year-old male

An MRI performed 14 days after TAE indicated hyperintensity in the HCC (arrows) on in-phase images (A) and hypointensity on most of the opposed-phase images (B). The hyperintensity observed on the subtraction images (C) almost completely coincided with that in the high attenuation region on CT (D).

is useful for diagnosing residual and recurrent tumors in HCC cases after Lp-TACE, because Lipiodol has been thought not to affect MRI signal intensity¹⁷⁻¹⁹). However, some studies have suggested that Lipiodol itself induces MRI signal changes with normal imaging methods, possibly due to its oil-based nature^{7, 8)}, while other reports indicate that Lipiodol hardly affects MRI signals⁹⁻¹²).

There is a method of MRI imaging based on the chemical shift of differences in the resonance frequencies of water and fat, called chemical-shift MRI, that can be used to obtain in-phase and opposed-phase data from water and fat protons. This method is useful in detecting trace amounts of fat^{23, 24}). Images created by subtracting chemical-shift, opposed-phase images from in-phase images can accurately detect microscopic levels of fat and are highly useful for this purpose²⁵). In the present study, we found a strong, positive correlation between the CT values and MRI signal intensity of the subtraction images of HCCs with accumulated Lipiodol.

We therefore believe that these subtraction images can reflect Lipiodol signals. The somewhat weak correlation observed between CT and MRI values for accumulated Lipiodol in HCCs of < 2 cm in diameter might have occurred due to the partial volume effect or because early HCCs, especially those tumors < 1 cm in diameter, are occasionally well differentiated pathologically²⁶⁾. Because such tumors often contain fat and portal components²⁶⁾, they can show peculiar signal intensity. Generally, advanced HCC is regarded as hepatic-artery dominated, while early HCC less than 2 cm in diameter is dominated by both the hepatic artery and portal vein, possibly accounting for the weak correlation observed in early HCC.

Moreover, the weak correlation between CT values and MRI signals for the areas of Lipiodol accumulation when measured < 1 week after Lp-TACE might have been affected by signals caused by intratumoral hemorrhage or coagulation necrosis that is commonly found directly after TACE. In fact, even if the CT and MRI testing were performed within 24 h of each other, with 1 week or less after Lp-TACE, it is still likely that a washout of Lipiodol from the HCCs could have occurred. Although the Lipiodol signal appeared visually similar on CT and MRI images, no signals were detected on MRI in five tumors. This discrepancy may have reflected a low accumulation of Lipiodol in those HCCs that were under the MRI detection limit, which is not as low as that for CT. However, because Lipiodol accumulation appeared almost identical on the CT and MRI images, we believe that Lipiodol accumulation can be detected on MRI in many cases and that changes over time such as in signal intensity could be used to evaluate such accumulation by MRI alone. In other words, this method is thought to be useful for avoiding radiation exposure. Furthermore, because hyperintense signals on T1-weighted images can be distinguished as either hemorrhagic necrosis or Lipiodol, we believe that MRI could be useful in determining treatment effects after Lp-TACE.

In conclusion, our results suggested that chemical-shift MRI can detect Lipiodol accumulation in HCCs and could be useful for the evaluation of such types of accumulation.

Conflict of interest disclosure

The authors have declared no conflict of interest.

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