Assessment of ablative margin by MRI with ferucarbotran in radiofrequency ablation for liver cancer: comparison with enhanced CT

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Objectives: Our aim was to determine whether ablated liver parenchyma surrounding a tumour can be assessed by MRI with ferucarbotran administered prior to radiofrequency ablation (RFA) compared with enhanced CT.

Methods: 55 hepatocellular carcinomas (HCCs) in 42 patients and 5 metastatic liver cancers in 3 patients were treated by RFA after ferucarbotran administration. We then performed T_2^* weighted MRI after 1 week and enhanced CT after 1 month. T_2^* weighted MRI demonstrated the ablated parenchyma as a low-intensity rim around the high intensity of the ablated tumour in these cases. The assessment was allocated to one of three grades: margin (+), high-intensity area with continuous low-intensity rim; margin zero, high-intensity area with discontinuous low-intensity rim; and margin (–), high-intensity area extending beyond the low-intensity rim.

Results: Margin (+), margin zero and margin (–) were found in 17, 35 and 5 nodules, respectively. All 17 nodules with margin (+) and 13 of those with margin zero were assessed as having sufficient ablative margins on CT. The remaining 22 nodules with margin zero had insufficient margins on CT. The overall agreement between MRI and CT for the diagnosis of the ablative margin was moderate ($\kappa=0.507$, $p<0.001$). No local recurrence was found in 15 HCC nodules with margin (+), whereas local recurrence was found in 4 (11.8%) out of 34 HCC nodules with margin zero.

Conclusion: Administration of ferucarbotran before RFA enables the ablative margin to be visualised as a low-intensity rim, and also enables the evaluation of the ablative margin to be made earlier and more easily than with enhanced CT.

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Radiofrequency ablation (RFA) has become a widely used treatment for hepatocellular carcinoma (HCC) [1], with some studies reporting significant long-term survival results [2, 3]. One of the most difficult and troublesome issues in RFA is the lack of a reliable method for confirming that complete necrosis has been achieved in the treated lesion. CT and MRI are commonly used to evaluate the therapeutic response in the ablated tumours. The imaging hallmark of successful treatment is a lack of enhancement in the index tumour on CT or MRI [4, 5]. However, previous pathological examination has demonstrated the presence of micro-satellite nodules around the original tumour [6, 7]. Therefore, it is necessary to ablate liver parenchyma surrounding the original tumour, as well as the tumour itself, and the ablation zone of the surrounding normal tissue needs to be recognised.

In fact, several studies [8–10] have reported that the local recurrence rate in nodules with sufficient ablative margin is lower than that in those without sufficient ablative margin. The ablative margin is conventionally assessed by comparing enhanced CT images before and after RFA for HCC tumours.

Mori et al [11] reported a new method of evaluating the ablative margin using ferucarbotran (Resovist; Bayer Schering Pharma, Berlin, Germany), and demonstrated that the ablative margin is easily assessed by MRI. Ferucarbotran is a clinically approved superparamagnetic iron oxide (SPIO) that is liver specific on MRI. It is composed of SPIO microparticles (γ - Fe_2O_3) coated with carboxydextran. After intravenous administration, ferucarbotran is phagocytosed by Kupffer cells and equally distributed throughout the entire liver [12]. Kupffer cells are much more dominant in hepatic parenchyma than in cancer tissue. Therefore, the signal intensity from cancer in T_2^* weighted sequences becomes relatively high compared with that from hepatic parenchyma. Ferucarbotran in ablated hepatic parenchyma would remain after ablation, showing low intensity around high-intensity cancer on post-ablational MR images.

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The aim of this study was to determine the usefulness of ablative margin assessment by enhanced MRI using ferucarbotran administered before RFA in patients with liver cancer in comparison with post-ablation enhanced CT images after 1 month.

Methods and patients

From January 2008 to January 2009, we studied 42 consecutive patients with 55 HCCs and 3 patients with 5 metastatic liver cancers (2 originated from breast cancer, 2 from gastrointestinal stromal tumour and 1 from colon cancer) who were treated with percutaneous RFA at our hospital. The pre-operative clinical features of these 45 patients are listed in Table 1. Three patients with metastatic liver cancer had normal liver and 42 patients had underlying chronic liver disease: chronic hepatitis in 9 patients and cirrhosis in 33. The study was approved by the ethics committee of our institution (number 1186) and performed prospectively. The nature of the study was fully explained to the patients, and informed consent was obtained.

Prior to RFA, all patients underwent ultrasound, enhanced CT, enhanced MRI and/or CT scan under angiography. On enhanced CT or MRI, hyperenhancement in the arterial phase with washout in the portal phase was diagnosed as HCC. For each case of iso- or hypoenhancement in the arterial phase with hypoenhancement in the portal phase, diagnosis was obtained by percutaneous tumour biopsy. All metastatic liver cancers were diagnosed by percutaneous tumour biopsy.

We performed transcatheter arterial chemoembolisation (TACE) in 18 of 60 nodules prior to RFA. TACE was performed by selectively introducing a catheter into the segmental branch or subsegmental branch of the hepatic artery and injecting a mixture of an iodised oil and epirubicin hydrochloride (Farmorubicin; Pharmacia, Tokyo, Japan), followed by gelatin sponge (Gelpart; Astellas Pharma Inc., Tokyo, Japan).

Table 1. Baseline characteristics of the 45 patients (60 nodules)

Mean age (range), years	67.8±8.9	(51–85)
Male/female	35/10	
HCC	55 nodules	42 patients
Metastatic liver cancer	5 nodules	3 patients
Aetiology of HCC		
Hepatitis B	15 nodules	12 patients
Hepatitis C	31 nodules	24 patients
Hepatitis B+C	2 nodules	1 patient
Alcohol	4 nodules	3 patients
Cryptogenic	3 nodules	2 patients
Underlying liver disease		
Normal		3 patients
Chronic hepatitis		9 patients
Cirrhosis		33 patients
Pugh A		23 patients
Pugh B		10 patients
Tumour size (range), mm	16.8±5.9	(6.5–32.0)
Tumour number (range)	1.3±0.7	(1–4)
Combination of TACE	18 nodules	

HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolisation.

Study design

Ferucarbotran (0.016 ml kg⁻¹ body weight) was injected intravenously 20–60 min before RFA. We performed MRI in all patients 7 days after RFA to evaluate the ablative margin. MRI was performed with a 1.5T magnet (Magnetom Symphony; Siemens, Erlangen, Germany) using the following imaging protocol: T₂* weighted fast low-angle shot (FLASH); repetition time, 150–200 ms; echo time, 8.5 ms; flip angle, 60°; section thickness, 3 mm; bandwidth, 400 Hz per pixel.

For post-treatment evaluation, helical multiphase CT examinations were performed 1 month after RFA using a 64 channel multidetector scanner (Aquilion 16; Toshiba Medical Systems, Tochigi, Japan) with the following imaging protocol: tube voltage, 120 kV; tube current, automatic mA setting; reconstruction section and interval thickness, 3 mm; detector configuration, 32×1 mm; pitch, 27; and gantry speed, 0.5 s per rotation. Unenhanced CT images were acquired, followed by triple-phase contrast-enhanced images during power injection of 100 ml of iopamidol (Iopamiron; Nihon-Schering, Osaka, Japan) at a rate of 2.7 ml s⁻¹. The entire liver was scanned three times. Early arterial phase imaging was initiated at 10 s, late arterial phase imaging at 20 s and portal venous phase imaging at 120 s after initiation of the injection. All scans were obtained with 3 mm slice pitch. Two patients with iodine hypersensitivity were evaluated by enhanced MRI rather than enhanced CT following RFA.

RFA protocol

RFA therapy was performed under sonographic guidance using a real-time convex scanner with 3.75 MHz probes (SSA-340A; Toshiba, Tokyo, Japan) and a biopsy guide device. We used two RFA systems: the RF3000 generator system on 40 nodules (67%) and the Cool-tip RF system (Radionics, Burlington, MA) on 20 nodules (33%).

In the RF3000 generator system, we used a 17 or 16 gauge expandable RFA device with 10 solid retractable curved electrodes with array diameters of 2–3.5 cm (LeVeen Needle Electrode; Boston Scientific Corporation, Natick, MA). The LeVeen needle was positioned in the tumour and the array was then expanded in three to five steps. The diameter of the array at each step was 10, 15, 20, 25, 30 and 35 mm. In the first step, hooks were deployed at an array diameter of 10 mm and RF power was initially applied at 30 W, which was increased by 10 W min⁻¹ until it impeded out. The second step was begun at the RF power level reached in the first step, and RF power was increased by 10 W min⁻¹ until it impeded out. This cycle was repeated at each step to full extension of the array. Additional ablation was applied at 70% of maximum power until it impeded out or for 15 min.

In the Cool-tip RF system, RF power was increased by 20 W min⁻¹ from 40 W for a 3 cm exposed tip or 10 W min⁻¹ from 30 W for a 2 cm exposed tip until maximum power was reached or it impeded out. After it impeded out three times, the power was decreased by 20 W for a 3 cm exposed tip or by 10 W for a 2 cm exposed tip and ablation was continued for 12 min.

Image analysis

MRI studies were reviewed on a computer workstation by two abdominal imaging radiologists (TK and ST, who had 12 and 11 years' experience, respectively). The reviewers knew the diagnosis of HCC or metastatic liver cancer but were blinded to other clinical data. Discrepancies between the two readers were resolved by discussion to reach consensus. On post-ablational MRI, we defined ablated surrounding hepatic parenchyma as a low-intensity rim around a central high-intensity area.

To evaluate whether the size of a high-intensity area on MRI agreed with the tumour size, we compared the tumour size on enhanced CT before treatment with the size of the high-intensity area on post-ablational MRI. The size was defined as the average of the major and minor axes; the size difference was measured for each tumour as the size of the high-intensity area on MRI minus the tumour size on enhanced CT.

We classified treatment efficacy on MRI into the following three grades (Figure 1). (1) Margin (+): a high-intensity area with a continuous low-intensity rim. The high-intensity area does not extend beyond the low-intensity rim, and a continuous rim is seen around the nodule on multidirectional MR images. (2) Margin zero: a high-intensity area with a discontinuous low-intensity rim. The high-intensity area does not extend beyond the rim, and the low-intensity rim is partially discontinuous. (3) Margin (-): the high-intensity area extends beyond the rim, with tumour protrusion.

We took tumour necrosis into account in defining treatment efficacy, using dynamic enhanced CT or MRI at 1 month after RFA. No residual tumour was defined as the absence of enhanced tumour areas, indicating complete tissue necrosis. The ablative margin was defined as ablated normal parenchyma surrounding the tumour, lying beyond the previously estimated tumour borders.

Sufficient ablative margin was defined as the presence of ablative margin (at least 2 mm) on all sides of the tumour in all CT slices. Insufficient ablative margin was defined as the partial absence of the ablative margin.

Patients with HCC were followed up every 3 months with measurement of serum α -fetoprotein (normal $<12 \text{ ng ml}^{-1}$) and des-gamma-carboxyprothrombin (normal $<40 \text{ mAU ml}^{-1}$) levels, and enhanced CT or enhanced MRI. When recurrence was suspected, diagnosis of intrahepatic recurrence was made when there were positive findings in at least two of the following: CT, MRI, sonography, angiography and needle biopsy. Detection of local recurrence was defined as a recurrent tumour within or adjacent to the treated tumour.

Statistical analysis

The agreement between post-ablational MRI and enhanced CT for the diagnosis of the ablative margin was expressed by the κ coefficient (poor agreement, $\kappa=0$; slight agreement, $\kappa=0.21-0.40$; moderate agreement, $\kappa=0.41-0.60$; good agreement, $\kappa=0.61-0.80$; excellent agreement, $\kappa=0.81-1.00$). The Kaplan-Meier method was used to calculate the cumulative rate of local recurrence and the log-rank test was used for statistical analysis.

Results

Comparison between tumour size before treatment and the size of the high-intensity area on post-ablational MRI

We compared the tumour size on enhanced CT before treatment with the size of the high-intensity area on post-ablational MRI in 57 nodules, except for 3 nodules

Figure 1. Grades of radiofrequency ablation treatment efficacy by post-ablational MRI. (a) Margin (+): high-intensity area (HIA) is contained within the low-intensity rim (LIR) and a continuous LIR is seen around the nodule. (b) Margin zero: HIA does not extend beyond the LIR, but the LIR is partially discontinuous (arrow). (c) Margin (-): discontinuous LIR with protrusion of HIA (arrow).

in which no high-intensity area was found. The size difference was within ± 5 mm in 32 nodules (56.1%), within 5–10 mm in 13 (22.8%), within 10–15 mm in 11 (19.3%), and within 15–20 mm in 1 (1.8%) (Figure 2). Thus, the size of the high-intensity area on MRI was equal to or larger than the tumour size on enhanced CT. Figure 3 shows the presence of a high-intensity band on the outer side of an actual nodule on MRI after RFA. From these results, we consider that a high-intensity area seen after RFA consists of the tumour itself and a part of the ablated surrounding hepatic parenchyma.

Assessment of ablative margin on post-ablational MRI

We estimated the ablative margin of 60 nodules by MRI. Three nodules had no high-intensity area in the index tumours and were assessed as undeterminable. These three nodules were 10, 12 and 16 mm in size, and two nodules showed isoenhancement in the arterial phase with washout in the portal phase. Margin (–) was found in five nodules, two of which were retreated immediately. Of the remaining 52 nodules, 17 (32.7%) demonstrated margin (+) and 35 (67.3%) demonstrated margin zero; of these, 16 were located at the surface of the liver (Figure 4) and 2 were in contact with vessels.

Comparison of the assessment of ablative margin by post-ablational MRI with that by enhanced CT

Table 2 compares the ablative margin determined by MRI after 7 days with that by enhanced CT after 1 month. No nodule assessed as margin (+) or margin zero on MRI was assessed as having residual tumour on enhanced CT. All 17 nodules assessed as margin (+) on MRI were demonstrated as having sufficient ablative

margin on enhanced CT. Of 35 nodules assessed as margin zero on MRI, 13 (37%) showed sufficient ablative margin and 22 (63%) showed insufficient ablative margin on enhanced CT. When enhanced CT is used as the gold standard, the sensitivity of MRI for sufficient margin was 56.7% (17/30) and the specificity was 100% (25/25). In one of three nodules assessed as margin (–) on MRI, enhanced CT after 1 month demonstrated local residue. The remaining two nodules were evaluated as having no residual tumour with insufficient ablative margin on enhanced CT (Figure 5). The overall agreement rate between post-ablational MRI and enhanced CT for the diagnosis of ablative margin was 73%. The κ coefficient was 0.507 ($p < 0.001$), indicating moderate agreement.

Comparison of local recurrence rates in HCC nodules

During the observation periods (mean 20 ± 5 months) after RFA in patients with HCC, local recurrence was detected in 4 (11.8%) of the 34 nodules that were assessed as margin zero; these nodules showed insufficient margin by enhanced CT and were retreated. No local recurrence was found in the 15 nodules assessed as margin (+). The cumulative detection rates of local recurrences were lower in the margin (+) nodules than in the margin zero nodules ($p = 0.079$) (Figure 6).

Discussion

Treatment efficacy and ablative margin after RFA are conventionally evaluated by enhanced CT or MRI with dynamic study. Enhanced CT or MRI performed after RFA have some limitations. First, early assessment may be flawed by vascular abnormalities related to inflammatory change or microsurgical fistula. A thin rim of enhancement may be seen at the early stage, which is transient and commonly resolves over subsequent follow-up examinations [5, 13]. This area of benign periablational enhancement is likely to be due to inflammation and hyperaemia, may last nearly 1 month in some cases, and usually measures 1–2 mm in thickness, but may approach 5 mm. It is difficult to distinguish this appearance from residual tumour enhancement [14]; therefore, we perform enhanced CT at least 1 month after treatment, thus delaying the identification of treatment failure.

Second, the ablative margin is measured by comparing pre- and post-enhanced CT/MRI images by superimposition of hepatic anatomic landmarks; however, it is not easy to measure the acquired ablative margin because pre- and post-CT cross-sectional images are not perfectly reproducible. Nishijima et al [15] reported on the measurement of the ablative margin using iodised oil accumulation within HCCs as an index of HCC. The advantage of this method is to enable evaluation of both the ablative area and the index tumour on identical images, but it has two limitations: it requires arterial infusion of iodised oil prior to RFA, and iodised oil accumulation does not always reflect tumour size. Contrast-enhanced ultrasound can evaluate loss of

Figure 2. Frequency distribution of size difference (size of high-intensity area on post-ablational MRI minus the tumour size on pre-treatment enhanced CT).

Figure 3. A 72-year-old male with an 8 mm hepatocellular carcinoma in liver segment V. (a) Transverse plane and (b) sagittal plane ferucarbotran-enhanced MRI before radiofrequency ablation (RFA) demonstrates a high-intensity tumour (arrow). (c) Transverse plane and (d) sagittal plane MRI after RFA shows three layers (low–high–low) around the index tumour. Part of the ablative margin was demonstrated to have become a high-intensity band (arrowhead).

Figure 4. A 71-year-old male with a 21 mm hepatocellular carcinoma in liver segment VI. (a) Enhanced CT (arterial phase) reveals a hypervascular tumour (arrow). (b) Post-ablational MRI (coronal plane) reveals interruption of the rim at the liver surface (arrow). This tumour was evaluated as margin zero. (c) Enhanced MRI (arterial phase) 1 month after radiofrequency ablation reveals no hypervascular area (arrow). This tumour was evaluated as having no residue with insufficient ablative margin.

Table 2. Comparison of ablative margin by post-ablational MRI with that by enhanced CT

			Ferucarbotran-enhanced MRI			
			Margin (+)	Margin zero	Margin (-)	Total
Enhanced CT	No residual tumour	Sufficient margin	17	13	0	30
		Insufficient margin	0	22	2	24
	Residual tumour		0	0	1	1
	Total		17	35	3	55

Except for two nodules which were evaluated as tumour residue and treated by radiofrequency ablation before CT examination.

tumour stain and detect residual HCC, as in dynamic CT, but cannot confirm the presence of an ablative margin because contrast-enhanced ultrasound in most cases cannot distinguish tumour from ablated areas [16, 17].

Mori et al [11] have proposed a new method with ferucarbotran to assess the ablative margin. Ferucarbotran, which is administered intravenously, is phagocytosed by Kupffer cells. The signal from liver parenchyma in T_2^* weighted sequences markedly decreased on MRI [18]. The number of Kupffer cells in cancerous tissues is significantly lower than in liver parenchyma, and decreases with decreasing histological grade [19]. Imai et al [20] demonstrated that ferucarbotran-enhanced MRI reflects Kupffer cell numbers in HCCs and dysplastic nodules; therefore, HCC is imaged as an area of high intensity within low-intensity liver.

Mori et al [11] demonstrated that the ablative margin appears as a low-intensity rim surrounding a high-intensity area including a tumour by administration of ferucarbotran prior to RFA. In the present study, we confirmed that a low-intensity rim is visualised around an ablated tumour. We compared the size of the high-intensity area on post-ablational MRI and the tumour size on pre-treatment enhanced CT in all tumours except for three nodules without any high-intensity area and found that the size of the high-intensity area on MRI was approximately equal to or larger than the actual tumour size on CT. We cannot explain why the high-intensity area on MRI after RFA was larger than the tumour size on

enhanced CT in some cases. One possibility is that the degree of ablation may alter the signal intensity on MRI. In fact, a high-intensity band around a tumour was found, as shown in Figure 3. Because the magnetic susceptibility effect of ferucarbotran observed on MRI depends on cluster size [21], alterations in the signal intensity may result when the cluster size is changed by the extent of ablation. These findings indicate that the acquired ablative margin is larger than the low-intensity rim on MRI.

No areas of high intensity were seen in the ablated area of three nodules, although enhanced CT confirmed that these tumours had been completely ablated. The absence of a high-intensity area may be caused by these tumours having the same number of Kupffer cells as surrounding liver tissue. In fact, some well-differentiated HCCs are reported to contain as many Kupffer cells as surrounding liver tissue [20]. Because these three nodules were small and two nodules were iso-enhanced in the arterial phase, it is highly possible that they are well-differentiated HCCs; however, we cannot confirm this finding because we did not examine ferucarbotran-enhanced MRI before RFA in these cases.

We compared the ablative margin on post-ablational MRI with that on enhanced CT. All nodules assessed as margin (+) or margin zero on MRI were demonstrated as having no residual tumour on enhanced CT. All nodules of margin (+) and 37% of those of margin zero had sufficient ablative margin on enhanced CT. The sensitivity of MRI for sufficient margin was 56.7%, while the specificity for sufficient margin was 100%. Furthermore,

Figure 5. A 65-year-old male with a 12 mm hepatocellular carcinoma in liver segment VIII. (a) Enhanced CT (arterial phase) reveals a hypervascular tumour (arrow). (b) Post-ablational MRI demonstrates obvious discontinuity of the low-intensity rim with tumour protrusion [margin (-)] (arrow). (c) Enhanced CT (arterial phase) 1 month after radiofrequency ablation reveals no residue with insufficient ablative margin.

Figure 6. Comparison of the detection rates of local recurrences between the margin (+) nodules and the margin zero nodules on post-ablational MRI. It tended to be lower in margin (+) nodules than in the margin zero nodules ($p=0.079$).

the overall agreement between post-ablational MRI and enhanced CT for the diagnosis of ablative margin was moderate ($\kappa=0.507$). MRI may provide more accurate criteria for the assessment of the ablative margin than enhanced CT because MRI using ferucarbotran enables both the ablative margin and the index tumour to be visualised in the same image. At the least, margin (+) on MRI is a sufficient condition for sufficient ablative margin.

We classified 16 nodules located at the liver surface as margin zero; in these cases, the ablative margin could not be acquired anatomically at the surface site. A recent study found no difference in local tumour progression, distant intra- and extrahepatic tumour recurrence or major complication rate between tumours on the surface and those beneath the surface of the liver [22]. Therefore, we consider that the lack of an ablative margin in tumours located on the surface has no bearing on treatment efficacy. If these nodules are evaluated as having sufficient ablative margin, 33 nodules should be classified as margin (+) on MRI and sufficient margin on CT, and 6 nodules should be classified as margin zero on MRI and insufficient margin on CT.

We also classified two nodules in contact with large vessels as margin zero. The heat sink effect that occurs when a large vessel (more than 3 mm in diameter) abuts a tumour becomes an obstacle to achieving complete ablation [23]. Furthermore, the presence of large abutting vessels is a high-risk factor for major complications such as a biliary stenosis and portal thrombus [24]. We consider, therefore, that nodules in contact with large vessels should be classified as margin zero.

Of three nodules assessed as margin (-) on MRI, two were evaluated as having no residual tumour with insufficient margin on enhanced CT. As shown in Figure 5, although MRI showed that the index nodule lay beyond the ablated area, enhanced CT revealed that the area including the index nodule had become an avascular lesion. It is possible that projecting portions should also be considered ablated because of the so-called oven effect [25]. In essence, this effect involves the capsule of the tumour or cirrhotic tissue surrounding the tumour behaving as a thermal insulator, increasing heat retention within the tumour. Because ferucarbotran-enhanced MRI cannot distinguish between viable and non-viable HCC, we could not evaluate the viability of a portion projecting beyond the low-intensity rim on MRI.

We attempted to investigate the local recurrence rate in HCC nodules without residual tumours (margin (+) and margin zero). The cumulative detection rates of local recurrences were lower in the margin (+) nodules than in the margin zero nodules ($p=0.079$), although the difference was not significant statistically because of the small numbers of nodules. In particular, no local recurrence was found in the margin (+) nodules. Longer observation periods and larger numbers of nodules are necessary to evaluate local recurrence rates.

From these results, we recommend the following. Patients evaluated as margin (+) on post-ablational MRI have been treated completely. Patients with margin zero and margin (-) should undergo enhanced CT and, if a sufficient ablative margin is obtained, treatment has been successful. If an insufficient ablative margin and/or tumour residues are found, retreatment is required.

In conclusion, MRI using ferucarbotran is an easily performed, helpful method of evaluating the ablative margin in RFA. Further study with a large number of patients and long-term observation is needed to investigate its usefulness for predicting the occurrence of residual or recurrent tumours after RFA.

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