Original Research

Tumor-Liver Contrast and Subjective Tumor Conspicuity of Respiratory-Triggered T2-Weighted Fast Spin-Echo Sequence Compared With T2*-Weighted Gradient Recalled-Echo Sequence for Ferucarbotran-Enhanced Magnetic Resonance Imaging of Hepatic Malignant Tumors

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Purpose: To compare respiratory-triggered T2-weighted fast spin-echo (RTT2W-FSE) and gradient T2*-weighted recalled-echo (T2*W-GRE) images for visualization of malignant hepatic tumors using ferucarbotran-enhanced magnetic resonance (MR) imaging.

Materials and Methods: Ferucarbotran-enhanced RTT2W-FSE and breath-hold long-TE 2D-fast spoiled gradient recalled acquisition in the steady state (FSPGR) images as T2*W-GRE were used to evaluate 128 malignant hepatic tumors (77 metastases, 37 hepatocellular carcinomas, 14 other) in 62 patients. Tumor-to-liver contrast (TLC) was quantitatively compared using the paired Student’s t-test, and the score of lesion conspicuity was qualitatively compared using Wilcoxon’s signed rank test.

Results: The mean TLC of RTT2W-FSE was significantly higher than that of FSPGR (1.10 ± 0.82 vs. 2.54 ± 1.42) in all malignant tumors. The score of lesion conspicuity of RTT2W-FSE was significantly higher than that of FSPGR (4.84 ± 0.52 vs. 4.52 ± 0.99) in all malignant tumors.

Conclusion: For ferucarbotran-enhanced MR imaging, compared to FSPGR images, RTT2W-FSE images provide greater TLC and subjective conspicuity for malignant tumors.

Key Words: liver neoplasm; iron; magnetic resonance (MR); contrast media; ferucarbotran

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SUPERPARAMAGNETIC IRON OXIDE (SPIO) agents are currently used to improve the detection and characterization of focal hepatic lesions in hepatic magnetic resonance (MR) imaging examinations (1–7). Numerous investigators have adapted various pulse sequences for SPIO-enhanced MR imaging and have compared imaging sequences. Many previous studies report that gradient T2*-weighted recalled-echo (T2*W-GRE) images are superior to T2-weighted spin-echo (SE) or fast spin-echo (FSE) images on SPIO-enhanced MR imaging (4,8–12), whereas few reports describe the advantages of T2-weighted FSE over T2*W-GRE images for detecting hepatic tumors (13).

A previous study reported that respiratory-triggered T2-weighted FSE (RTT2W-FSE) images are superior to breath-hold T2-weighted (BHT2W) FSE images (14,15) on nonenhanced MR imaging. If RTT2W-FSE images are clearly superior to BHT2W for hepatic MR imaging, the same results should be expected for enhanced MR imaging with SPIO; however, few reports have compared RTT2W-FSE and T2*W-GRE images using SPIO-enhanced liver imaging (12,13) and few studies have reported the superiority of RTT2W-FSE compared to T2*W-GRE using SPIO-enhanced liver imaging (13). The purpose of the present study was to compare RTT2W-FSE and T2*W-GRE images for the detection of malignant hepatic tumors.

MATERIALS AND METHODS

Patients

We performed a retrospective analysis of 75 consecutive patients suspected of having malignant hepatic tumors at previously performed sonography or computed tomography (CT) and who underwent ferucarbotran-enhanced MR imaging at our hospital from December 2003 to August 2006. Thirteen of the patients were diagnosed with no malignancy on MR imaging or clinical follow-up. We evaluated 128 focal malignant hepatic lesions in the remaining 62 patients (44 men and 18 women).
women, mean age 62 ± 11 years; age range, 36–85 years) who underwent MR examination for evaluation of known or suspected hepatic malignancies. The 128 lesions included 77 metastases (46 colorectal cancer, 8 bile duct cancer, 8 renal cell carcinoma, 6 gastric cancer, 6 esophageal cancer, 2 oral cavity cancer, 1 pharyngeal cancer) in 25 patients, 37 hepatocellular carcinomas (HCC) in 28 patients, 12 cholangiocarcinomas (HCC) in 28 patients, 12 cholangiocarcinomas in 1 patient. The mean size of all malignant tumors was 25.7 ± 23.7 (metastases, 21.2 ± 13.9; HCCs, 28.5 ± 24.1; others, 43.1 ± 48.0). In the 25 patients with metastatic liver tumors, 13 of 25 were diagnosed by surgery, while the other 12 were diagnosed by clinical incidence and follow-up for more than 3 months. Of the 28 patients with HCC, 15 of 28 were diagnosed by surgery, which were diagnosed as moderately or poorly differentiated HCC by histopathological examination, while the other 13 were diagnosed by CT imaging and clinical incidence (increase of tumor marker, viral chronic hepatitis or cirrhosis). In 2 of 13 the CT findings were equivocal and they were diagnosed by growth of the tumor with follow-up for more than 3 months. The status of the liver parenchyma for the 28 patients with HCC was as follows: chronic hepatitis, 8; cirrhosis type-B, 9; cirrhosis type-C, 7; alcoholic cirrhosis, 3; and normal liver tissue, 1. In the 7 patients with cholangiocarcinoma, 6 of 7 patients were diagnosed by surgery, while 1 was diagnosed by biopsy. The patient with epithelioid hemangioendothelioma was diagnosed by biopsy.

Informed consent was obtained for the MR examination from each patient prior to MR scanning.

**MR Imaging**

Ferucarbotran (Resovist; Nihon Schering, Osaka, Japan) was administered intravenously as a rapid bolus at a dose of 8 μmol of iron per kilogram of body weight, immediately followed by a 20-mL saline solution flush. There were no adverse effects in any of the patients in this study.

MR imaging was performed with two different 1.5T scanners. In the early group, 48 patients were scanned using a Signa Horizon MR unit (GE Healthcare, Milwaukeee, WI) using a torso phased array coil; in the later group, 14 patients were scanned using a Signa EXCITE HD unit (GE Healthcare) using an 8-channel body coil.

The scanning sequences were as follows: short-TE fast spoiled gradient recalled acquisition in the steady state (FSGR) and RTT2W-FSE before the injection of ferucarbotran, and short-TE FSPGR, long-TE FSPGR, and RTT2W-FSE after injection. Short-TE FSPGR was performed 2 minutes after injection of ferucarbotran. Ten minutes after injection, RTT2W-FSE and long-TE FSPGR were performed in no particular order. RTT2W-FSE was performed prior to FSPGR in 17 patients and FSPGR was performed prior to RTT2W-FSE in 45 patients during postcontrast imaging. The sequences that were evaluated in this study were long-TE FSPGR and RTT2W-FSE after injection of ferucarbotran. All images were acquired in the transverse plane. A rectangular field of view of 35 × 35 cm, adjusted for each patient, was maintained for all sequences. RTT2W-FSE images were obtained with the following parameters: repetition time (TR) range / effective TE, 3157–6666/64–67 msec; number of excitations (NEX), 2; echo train length, 8–16; matrix, 256 × 256; slice thickness, 8 mm; gap, 2 mm; using the array spatial sensitivity technique (ASSET), chemical shift fat suppression, and superior and inferior spatial presaturation. The scanning parameters for long-TE-FSPGR were: TR/TE, 130–185/9.0 msec; flip angle, 45°; slice thickness, 8 mm; gap, 2 mm; matrix, 512 × 192; single breath-hold; using ASSET. The FSPGR acquisition time was 19 seconds (two breath-holds, total time 38 seconds), while that of RTT2W-FSE was 2 minutes 48 seconds ± 1 minute 1 second.

**Image Analysis**

Quantitative analysis was conducted with images obtained using these two pulse sequences and operator-defined region-of-interest (ROI) measurements of the mean signal intensity of both the hepatic lesions and liver tissue adjacent to the hepatic lesions. The signal intensity of the liver adjacent to the hepatic lesions was measured in areas devoid of focal changes in signal intensity, large vessels, and prominent artifacts. To minimize the difference in signal intensity due to the near-field effect when surface coils are used, the ROI for the liver adjacent to the hepatic lesions was located such that the vertical distances from the ventral side surface coils to the ROI were the same for both sequences. For the hepatic lesions a circular ROI was drawn to encompass as much of the lesion as possible. Whenever possible, at least 25 mm² ROIs were used. The tumor-to-liver contrast (TLC) parameter for ferucarbotran-enhanced images was defined using the following formula:

\[
\text{TLC(\%)} = \left(\frac{\text{SIT post} - \text{SIL post}}{\text{SIL post}}\right) \times 100
\]

where SIT post is the signal intensity of tumor after administration of ferucarbotran and SIL post is the signal intensity of liver parenchyma after administration of ferucarbotran.

Two radiologists participated in the qualitative analysis. Image review was conducted for two imaging sequences: RTT2W-FSE and FSPGR. Slices that demonstrated the lesions were saved in advance using a Synapse Workstation (Fuji Medical Systems U.S.A., Stamford, CT) with a bookmarking function. If a patient had more than seven lesions with the same diagnosis in their liver, the number was restricted to six lesions for assessment. The saved slices for each patient were shown in sequence on a 2-megapixel liquid crystal display. The two radiologists viewed the RTT2W-FSE and FSPGR images together by paired slices, recorded the size of the lesions, and assigned one of five confidence levels by consensus as a lesion conspicuity score for each pulse sequence (1, definitely absent; 2, probably absent; 3, equivocal; 4, probably present; 5, definitely present). If the same lesion was assigned a different score for the two sequences, the reason was reviewed and categorized as ghosting, motion, susceptibility ar-
was noted between the group in which RTT2W-FSE was performed prior to FSPGR (34 lesions in 17 patients, 1.06 ± 0.71 vs. 2.02 ± 0.90, \( P < 0.001 \)) and the group in which FSPGR was performed prior to RTT2W-FSE (93 lesions in 45 patients, 1.12 ± 0.86 vs. 2.70 ± 1.59, \( P < 0.001 \)). The mean TLC of RTT2W-FSE was significantly higher when this sequence was acquired after the FSPGR sequence compared to the reverse order (2.70 ± 1.59 vs. 2.02 ± 0.90, \( P = 0.003 \)). The mean TLC of FSPGR was not significantly different when this sequence was acquired after RTT2W-FSE sequence compared to the reverse order (1.12 ± 0.86 vs. 1.06 ± 0.71). In the 11 lesions with noncirrhosis and in the 26 lesions with cirrhosis, RTT2W-FSE was superior to FSPGR (noncirrhosis, 2.57 ± 1.06 vs. 1.25 ± 0.95, \( P = 0.006 \); cirrhosis, 1.74 ± 1.54 vs. 0.97 ± 0.74, \( P = 0.02 \).)

### Qualitative Analysis

Tables 2 and 3 summarize the number or ratings of lesion-conspicuity characteristics for FSPGR compared with RTT2W-FSE. The qualitative lesion-conspicuity score for malignant tumors was significantly higher for RTT2W-FSE (4.84 ± 0.52) than for FSPGR (4.52 ± 0.99) (\( P = 0.00028 \)). The score of RTT2W-FSE was superior to that for FSPGR in 21 lesions of 14 patients. Of the 21 lesions, 18 lesions (12 mets, 1 HCC, 5 cholangiocellular carcinoma) were low TLC, 2 lesions (1 met, 1 HCC) were ghost artifact, and 1 metastatic lesion was absent because the slice gap was extended after mismatching between the two breath-holds. For all metastases, RTT2W-FSE (4.90 ± 0.30) was superior to FSPGR (4.60 ± 0.90) (\( P = 0.002 \)). For all HCCs there was no significant difference between RTT2W-FSE (4.60 ± 0.80) and FSPGR (4.50 ± 1.10). For all others, there was no significant difference between RTT2W-FSE (4.90 ± 0.30) and FSPGR (4.14 ± 1.17). The qualitative score of RTT2W-FSE was inferior to that for FSPGR in three lesions. Two of three patients were classified with
Ferucarbotran-Enhanced MRI of Hepatic Tumor

Figure 1. A 68-year-old man with multiple cholangiocarcinomas in the left lobe of the liver. a: Ferucarbotran-enhanced respiratory-triggered T2-weighted fast spin-echo (RTT2W-FSE) image (TR/TE = 4615/69) shows multiple tumors (arrow) as high intensity without SPIO-uptake. b: Ferucarbotran-enhanced long-TE 2D-fast spoiled gradient recalled acquisition in the steady state (FSPGR) image (TR/TE/FA = 130/9/45°) at the same level as (a) has fewer tumors visible (arrow) in the liver. A tumor-like lesion behind the vena cava is not liver tumor but benign adrenal tumor (arrowhead).

DISCUSSION

The results of this study reveal that for ferucarbotran-enhanced MR imaging, compared to FSPGR images, RTT2W-FSE images provide greater TLC and subjective conspicuity for malignant tumors. The TLC ratio of RTT2W-FSE was significantly higher than that of FSPGR for malignant tumors. In addition, the qualitative score of RTT2W-FSE was significantly higher than that of FSPGR for metastases, but was not significant for HCC or others.

Many previous studies report that T2*W-GRE is better than T2W-FSE for the reasons of malignant hepatic tumors. Ward et al (10) reported that T2*W-GRE is more sensitive than breath-hold T2W-FSE (BHT2W) using ferumoxides, while Kim et al (12) reported that T2*W-GRE is superior to RTT2W-FSE using ferumoxides. Other investigators (6–9) describe the superiority of T2*W-GRE weighted images for the detection of malignant tumor. Kanematsu et al (13) reported that RTT2W is superior to T2*W-GRE for the detection of malignant hepatic tumors; however, they reported that RTT2W and T2*W-GRE had similar contrast-to-noise ratios.

We will now discuss the reasons for the superior detection of malignant tumors demonstrated using RTT2W in the present study. First, the respiratory-triggered method might improve the sensitivity of tumor detection. Many previous reports of SPIO-enhanced MR imaging used BHT2W rather than RTT2W-FSE methods to reduce the acquisition time, while others report the superiority of the respiratory-triggered method compared to the breath-hold method without contrast media for the detection of liver lesions (14–16). To the best of our knowledge, no reports compare RTT2W-FSE and BHT2W for SPIO-enhanced MR imaging. The respiratory-triggered method used in the present study might contribute to improvements in the detection of hepatic malignant tumors.

Second, the contrast material differed considerably in the various studies. Most previous studies that investigated SPIO-enhanced MR imaging comparing T2W-FSE to T2*W-GRE used ferumoxides rather than ferucarbotran. Ferumoxides are administered by slow intravenous drip and require a long time for hepatic distribution. In contrast, ferucarbotran is injected as a bolus and is rapidly distributed to the liver parenchyma. Scan timing differs between ferumoxides and ferucarbotran and may cause differences in detectability.

Third, we considered the possibility that the scan order might affect detectability. In 45 patients we performed scanning after the injection of ferucarbotran in the following order: short-TE FSPGR, long-TE FSPGR, and RTT2W-FSE, while in 17 patients the scanning order was short-TE FSPGR, RTT2W-FSE, and long-TE FSPGR. For each scan order the tumor was visualized significantly better with RTT2W-FSE than with long-TE FSPGR, demonstrating that scan order has no effect on the outcome. In this study the TLC of RTT2W was significantly higher when this sequence was acquired after the FSPGR sequence compared to the reverse order. These data show that the appropriate time delay between contrast administration and data acquisition is needed.

Fourth, it is possible that the use of different scan parameters leads to differences in detectability. Previous studies found the contrast enhancement effect of SPIO to be most dependent on the TE (17–18). In the present study we used a TE of 9.0 msec and flip angle of 45°, which is within the recommended range. The possibility that inadequacies in our protocol could have caused low detectability of FSPGR images is considered unlikely.

A limitation of our study is that some lesions were not pathologically proven. It is well known that well-differentiated HCC and dysplastic nodules are not depicted on SPIO-enhanced MR imaging. Well-differentiated HCC and dysplastic nodules are visualized less frequently on SPIO-enhanced T2W-FSE or T2*W-GRE (17). The subjects in this study did not include patients who were found to have well-differentiated HCC or dys-

Figure 2. A 49-year-old man with multiple liver metastases from colon cancer. a: Ferucarbotran-enhanced RTT2W-FSE image (TR/TE = 3750/64) shows metastases (arrows) as high intensity without SPIO uptake. b: Ferucarbotran-enhanced FSPGR image (TR/TE/FA = 130/9/45°) at the same level shows metastases (arrowheads). Lesion conspicuity is less than that in A.
plastic nodules after surgery; however, we cannot rule out the possibility that these lesions were present in those patients who were diagnosed by clinical incidence and follow-up. If the rates of high-grade HCC and low-grade HCC changed, the results may be different.

A second limitation is that we used consensus interpretation of lesion detection rather than analyzing observer variability. Multiobserver analysis would have better estimated the sensitivity of each technique for depicting lesions and would have more accurately predicted differences between them in clinical practice. Further examinations that include ROC analysis are needed to confirm our results.

A third limitation is that technical parameters introduce biases. In this study the two sequences differ in the use of chemical fat saturation and in voxel size. These might have affected the results.

In conclusion, for ferucarbotran-enhanced MR imaging, compared to FSPGR images, RT2W-FSE images provide greater TLC and subjective conspicuity for malignant tumors.

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