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Reticuloendothelial Negative Contrast Media for Hepatocellular Carcinoma: Initial Comparison of Chondroitin Sulfate Iron Colloid and Ferrixan in Fast T2-Weighted MR Imaging

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Chondroitin sulfate iron colloid (CSIC), a paramagnetic substance, and Ferrixan (SHU555A), a superparamagnetic substance, were administered to 20 patients with 26 nodules of hepatocellular carcinoma, and the visualization of the lesions by fast T2-weighted magnetic resonance imaging (MRI) was quantitatively evaluated. Conventional spin-echo (CSE), turbo spin-echo (TSE), and turbo gradient spin-echo (TGSE) sequences were performed in all patients before and after the administration of the iron colloid preparations. The signal-to-noise ratio (SNR) in the liver decreased significantly after administration of iron colloid preparations by all sequences and at all doses. A reduction in SNR in the liver similar to that obtained with SHU555A could be obtained by increasing the dose of CSIC, which has a weaker T2-shortening effect. In the TSE sequence with a weaker susceptibility effect, the decrease in SNR in the liver tended to be equalized to those in the CSE or TGSE sequences by high dose administration of the iron colloid preparation. We think perhaps that the imaging ability for hepatocellular carcinoma, similar to that of superparamagnetic contrast media, can be obtained with paramagnetic CSIC by administering it at a higher dose.

Key words: fast MR imaging; iron colloid; liver neoplasm

The diagnostic usefulness of magnetic resonance imaging (MRI), which takes time for scanning, has been reduced due to deterioration of the image resolution by artifacts associated with respiration in the abdominal region. Recently, however, fast imaging has become possible due to improvements in the instrument, and the usefulness of techniques such as turbo spin-echo (TSE) sequence has been reported by a number of investigators (Nghiem et al., 1992; Catasca and Mirowitz, 1993; Outwater et al., 1994; Siewert et al.,1994). Iron colloid preparations, which are used in MRI for detection of tumoral lesions of the liver, are incorporated in normal reticuloendothelial cells, reduce signals of normal liver parenchyma by their T2-shortening effects, and increase the liver-tumor contrast, serving as negative contrast media (Stark et al., 1988; Ferruci and Stark, 1990; Yuasa et al., 1992; Reimer et al., 1995; Taylor et al., 1995). We previously evaluated hepatocellular carcinoma by fast T2-weighted imaging using chondroitin sulfate iron colloid (CSIC; Blutal, Dainippon Pharmaceuticals, Osaka, Japan), which is a paramagnetic substance, and reported the usefulness of this contrast media (Sugihara et al., 1996). Generally, iron colloid preparations that have been found to be useful for detection of liver tumors are superparamagnetic substances, but their abili-

Abbreviations: BKG, background; CNR, contrast-to-noise ratio; CSE, conventional spin-echo; CSIC, chondroitin sulfate iron colloid; DR, decrease ratio; DR_{CSE}, DR of CSE; DR_{TGSE}, DR of TGSE; DR_{TSE}, DR of TSE; Ferrixan, SHU555A; FOV, field of view; MR, magnetic resonance; MRI, MR imaging; RDR, relative DR; RDR_{TGSE}, RDR of TGSE; RDR_{TSE}, RDR of TSE; ROI, region of interest; SD_{BKG}, SD of the backgroud; SI, signal intensity; SIL, SI of the liver; SIT, SI of the tumor; SNR, signal-to-noise ratio; TE, echo time; TGSE, turbo gradient spin-echo; TR, repetition time; TSE, turbo spin-echo.

Table 1. Signal-to-noise ratio (SNR) in the liver before and after intravenous injection of iron colloid preparations

	SNR			
	CSIC (μmol Fe/kg)	SHU555A (μmol Fe/kg)		
	23.6 [*n* = 10]	4 [*n* = 4]	8 [*n* = 2]	16 [*n* = 4]
Unenhanced				
CSE	10.4 ± 5.2	10.7 ± 3.5	14.5 ± 2.2	7.0 ± 3.1
TSE	13.4 ± 5.3	10.7 ± 1.6	7.8 ± 0.7	13.0 ± 4.5
TGSE	13.7 ± 3.7	12.9 ± 2.5	14.6 ± 1.3	13.5 ± 4.7
Iron colloid-enhanced				
CSE	5.4 ± 1.7*	6.9 ± 3.2*	7.1 ± 2.0*	2.9 ± 0.5*
TSE	8.7 ± 4.0*	8.0 ± 2.1**	5.0 ± 0.5**	7.1 ± 1.3*
TGSE	7.5 ± 2.7*	8.3 ± 3.0*	7.0 ± 0.3*	4.7 ± 0.2*

CSE, conventional spin-echo; CSIC, chondroitin sulfate iron colloid; TGSE, turbo gradient spin-echo; TSE, turbo spin-echo.
SNR of the liver decreases significantly after administration of iron colloid preparations at all doses and in all image sequences: $*P < 0.01$, $**P < 0.05$.

ties to contrast lesions have not been evaluated comparatively with those of paramagnetic substances. We obtained an opportunity to use Ferrixan (SHU555A; Schering, Berlin, Germany) in a phase II clinical trial. In this study, the abilities to contrast lesions of superparamagnetic SHU555A and paramagnetic CSIC for hepatocellular carcinoma were compared quantitatively in fast T2-weighted imaging.

Subjects and Methods

The subjects were 20 patients (13 males and 7 females; 26 nodules) diagnosed as having hepatocellular carcinoma on the basis of the clinical course and imaging findings. They ranged in age from 42 to 74 years (mean 63.8 years). The tumor size was 1.2 cm to 5.3 cm (mean 2.6 cm). CSIC was administered at 23.6 μmol Fe/kg to 10 patients (13 nodules), and SHU555A was administered at 4 μmol Fe/kg to 4 patients (6 nodules), at 8 μmol Fe/kg to 2 patients (2 nodules), and at 16 μmol Fe/kg to 4 patients (5 nodules). All patients consented to participate in the study after explanation of the intention of the study. MRI was performed using a 1.5 T superconducting MRI system (Magnetom Vision: Siemens, Erlangen, Germany). Conventional spin-echo (CSE) images were obtained with a repetition time (TR) of 1800 ms and an echo time (TE) of 80 ms, with 2 signal excitations. Turbo spin-echo (TSE) images were obtained with a TR of 3500 ms, an effective TE of 99 ms and 11 echo trains, with 5 signal excitations. Turbo gradient spin-echo (TGSE) images were obtained with a TR of 4500 ms, an effective TE of 108 ms and 33 echo trains, with 4 signal excitations. All imaging was performed in the transaxial plane with a slice thickness of 10 mm, gap of 1 mm, and field of view (FOV) of 35–42 cm using a rectangular FOV with a phase encode reduction of 6/8 or 7/8. Also, presaturation pulses were superimposed at the upper and lower imaging limits. Imaging was performed before and after administration of iron colloid preparations, and imaging after administration was started 2 h after intravenous administration of CSIC and 30 min after intravenous administration of SHU555A.

For quantitative evaluation, the region of interest (ROI) containing the liver (L) and the solid portion of the tumor (T) was determined as widely as possible and at the same site by avoiding blood vessels in all imaging sequences. The ROI was determined as widely as possible over the background (BKG) on the abdominal side, which was the phase encode

Table 2. Decrease ratio (DR) and relative DR (RDR) of signal-to-noise ratio (SNR) of the liver caused by administration of iron colloid preparations

	CSIC (μmol Fe/kg)	SHU555A (μmol Fe/kg)		
	23.6	4	8	16
CSE	0.41 ± 0.19	0.36 ± 0.21	0.51 ± 0.12	0.54 ± 0.12
TSE	0.33 ± 0.21	0.24 ± 0.25	0.36 ± 0.00	0.42 ± 0.09
RDR_{TSE}	0.80	0.67	0.71	0.78
TGSE	0.45 ± 0.14	0.37 ± 0.13	0.54 ± 0.02	0.62 ± 0.10
RDR_{TGSE}	1.10	1.03	1.06	1.15

CSE, conventional spin-echo; CSIC, chondroitin sulfate iron colloid; RDR_{TGSE}, RDR of TGSE; RDR_{TSE}, RDR of TSE; TGSE, turbo gradient spin-echo; TSE, turbo spin-echo.
Among imaging sequences, DR of SNR of the liver is the highest in TGSE. RDR_{TSE} tend to be higher in the CSIC group and 16 μmol Fe/kg SHU555A group.

direction. The minimum area of the ROI was 35 pixels, and the mean signal intensity (SI) and SD per pixel were calculated. From these values the signal-to-noise ratio (SNR) in the liver and tumor-to-liver contrast-to-noise ratio (CNR) were calculated as follows. SNR = SIL/SD_{BKG}; CNR = (SIT – SIL)/SD_{BKG}. The decrease rate of SNR in the liver after the administration of the iron colloid preparations, as compared with before, [decrease ratio (DR) = (preSNR – postSNR)/preSNR] was calculated. To compare the DR of the SNR of the liver among imaging sequences at the same dose, the ratios of DRs by TSE and TGSE to DRs by CSE (relative DR, RDR) were calculated (RDR_{TSE} = DR_{TSE}/DR_{CSE}, RDR_{TGSE} = DR_{TGSE}/DR_{CSE}). A paired t-test was used for the comparison of the SNR and CNR between the pre- and post-administration of the contrast media in each imaging sequence. The SNR of the liver and its DR were compared among imaging sequences by Student's *t*-test when the variance was equal but by Welch's *t*-test when the variance was unequal. *P* values less than 0.05 were considered to be significant.

Results

The SNR of the liver decreased significantly after the administration of iron colloid preparations at all doses and in all imaging sequences ($P < 0.01, 0.05$) (Table 1). The DR of the SNR of the liver was highest in the 16 μmol Fe/kg SHU555A group, followed by the 8 μmol Fe/kg SHU555A group, CSIC group, and 4 μmol Fe/kg SHU555A group in all sequences. Among imaging sequences, the DR of the SNR of the liver was highest in TGSE, followed by CSE and TSE at all doses. RDR_{TSE} tended to be higher in the CSIC group and 16 μmol Fe/kg group than in the 4 μmol Fe/kg group or 8 μmol Fe/kg group (Table 2). The tumor-to-liver CNR increased significantly ($P < 0.01, 0.05$) after the administration of the iron colloid preparations in all dose groups except the 8 μmol Fe/kg SHU555A group in all imaging sequences. It showed no significant difference among the dose groups (Table 3). Compared with the images of each sequence in the CSIC group and the 16 μmol Fe/kg group, the tumor-to-liver CNR increases after the administration of CSIC with each sequence and with each dose. Artifacts show markedly in TGSE. Lesion conspicuity is best viewed by TSE both before and after the administration of CSIC (Figs. 1 and 2).

Discussion

Various superparamagnetic substances are being tested clinically as liver-specific MRI contrast media, and many reports have suggested their usefulness (Stark et al., 1988; Ferruci and Stark, 1990; Yuasa et al., 1992;

Table 3. Tumor-to-liver contrast-to-noise ratio (CNR) before and after intravenous injection of iron colloid preparations

	Tumor-to-liver CNR			
	CSIC (μmol Fe/kg)	SHU555A (μmol Fe/kg)		
	23.6	4	8	16
Unenhanced				
CSE	9.2 ± 3.5	5.1 ± 3.0	5.8 ± 5.3	5.4 ± 7.7
TSE	9.0 ± 3.8	5.6 ± 2.7	2.5 ± 2.8	5.8 ± 4.1
TGSE	10.5 ± 3.5	7.9 ± 4.4	4.6 ± 2.1	8.0 ± 8.5
Iron colloid-enhanced				
CSE	12.0 ± 3.4**	10.0 ± 5.3**	8.0 ± 8.0	6.2 ± 7.1**
TSE	13.6 ± 5.1*	9.6 ± 5.1**	5.2 ± 4.3	9.6 ± 2.8**
TGSE	15.4 ± 6.6**	11.1 ± 3.7**	9.8 ± 4.8	11.2 ± 8.6**

CSE, conventional spin-echo; CSIC, chondroitin sulfate iron colloid; TGSE, turbo gradient spin-echo; TSE, turbo spin-echo.
Tumor-to-liver CNR increases significantly after administration of iron colloid preparations in all dose groups expect the 8 μmol Fe/kg SHU555A group in all sequences: $*P < 0.01$, $**P < 0.05$.

Reimer et al., 1995; Taylor et al., 1995). CSIC, which we have used, is a paramagnetic iron colloid preparation in wide and safe clinical use as a treatment for iron-deficiency anemia. Its primary physical properties are: a mean molecular weight of 75,000, a particle size in water solution of 100 nm or above, and T1 and T2 relaxations of 0.44, 2.3 $s^{-1}\cdot mM^{-1}$ (1.5 T spectrometer, 22˚C), respectively (Okuhata, 1992). SHU555A, which was used in this study, is a stable colloid of a complex of superparamagnetic iron oxide particles (bivalent iron content: 5% or less of total iron content) and carboxy dextran (numerical mean molecular weight: 2600 g/mol). Its primary physical properties are: a colloid particle size of 57.4 ± 2.1 nm and T1 and T2 relaxations of 9.48 and 229.5 $s^{-1}\cdot mM^{-1}$ (1.5 T spectrometer, 22˚C), respectively. Its T2 relaxation is about 100 times that of CSIC (Hamm et al., 1994).

In this study, a fast T2-weighted MRI was performed by the administration of SHU555A at 3 doses to patients with hepatocellular carcinoma, and its ability to contrast lesions was quantitatively evaluated in comparison with CSIC.

Among the 3 groups which were administered SHU555A, the DR of the SNR in the liver was greatest in the 16 μmol Fe/kg group, followed by 8 μmol Fe/kg and 4 μmol Fe/kg groups in this order, showing dose-dependence. The DR of the SNR in the liver in the CSIC group was between the values of the 4 μmol Fe/kg and 8 μmol Fe/kg SHU555A groups. We administered CSIC at 23.6 μmol Fe/kg, which was higher than the doses of SHU555A. Therefore, it is expected to be distributed more densely in the reticuloendothelial cells of the normal liver parenchyma than the superparamagnetic contrast media. The T2-shortening effect of an iron colloid preparation is affected by its concentration and distribution density. Its effect is reported to be weaker as its concentration is lower and its distribution is more sparse (Tanimoto et al., 1994). Probably for this reason, a satisfactory DR of the SNR in the liver was obtained with a large dose of CSIC despite its weaker T2-shortening effect.

The fast T2-weighted imaging sequences used in this study were TSE and TGSE. In TSE, fast imaging is made possible by using several 180-degree refocusing pulses per excitation pulse and performing phase encoding for each echo obtained, but the T2-shortening effect is reported to be markedly attenuated by the repeated use of 180-degree refocusing pulses (Hennig et al., 1986; Majumdar et al., 1989; Muller et al., 1991; Tanimoto et al., 1995). In TGSE, gradient echoes are generated on both sides of the spin echoes obtained by TSE with

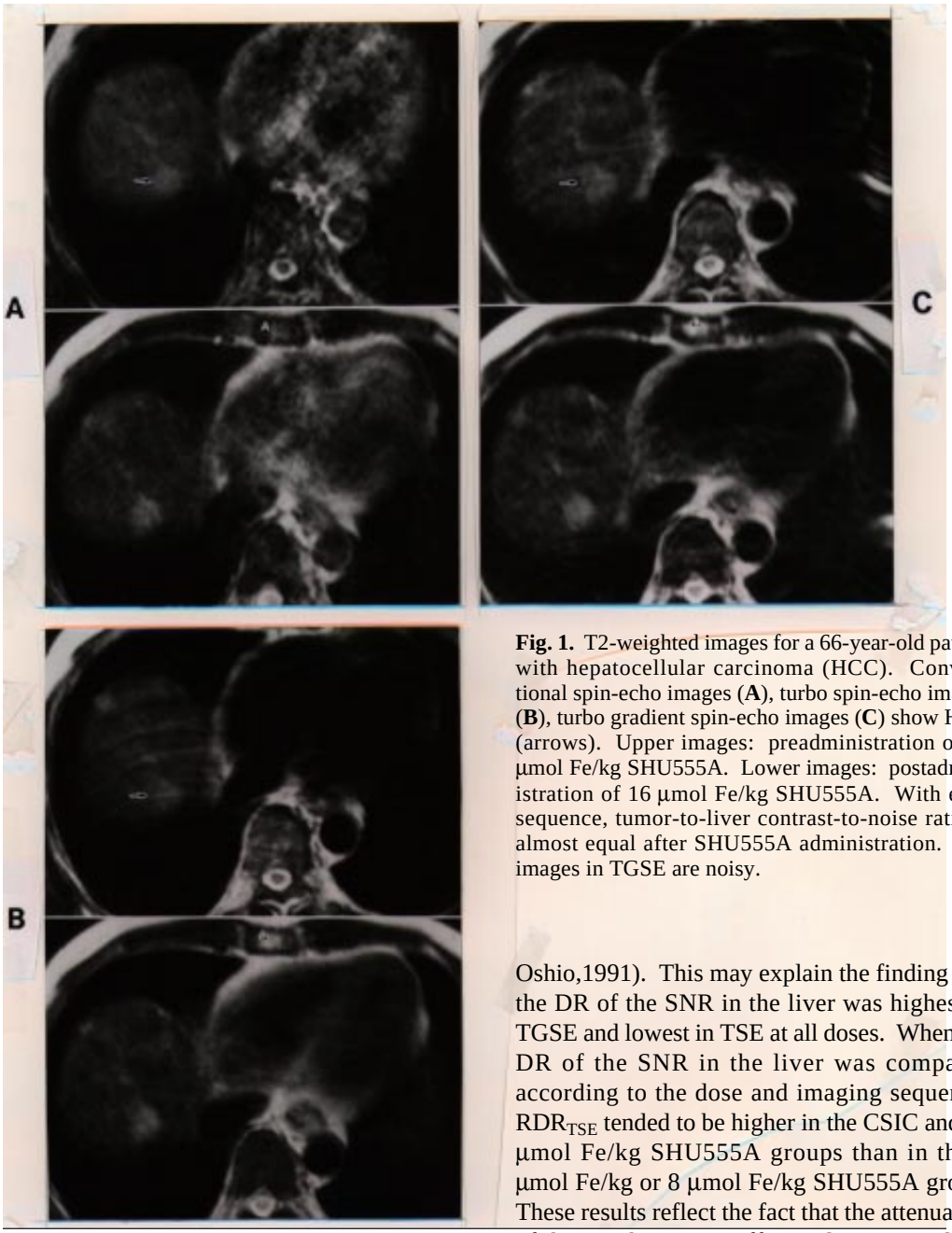

Fig. 1. T2-weighted images for a 66-year-old patient with hepatocellular carcinoma (HCC). Conventional spin-echo images (**A**), turbo spin-echo images (**B**), turbo gradient spin-echo images (**C**) show HCC (arrows). Upper images: preadministration of 16 μmol Fe/kg SHU555A. Lower images: postadministration of 16 μmol Fe/kg SHU555A. With each sequence, tumor-to-liver contrast-to-noise ratio is almost equal after SHU555A administration. The images in TGSE are noisy.

several 180-degree refocusing pulses per excitation pulse by repeatedly inverting the gradient of the magnetic field. As a result, TGSE is reported to allow faster imaging than TSE and to become more sensitive to changes in magnetic susceptibility (Feinberg and Oshio,1991). This may explain the finding that the DR of the SNR in the liver was highest in TGSE and lowest in TSE at all doses. When the DR of the SNR in the liver was compared according to the dose and imaging sequence, RDR_{TSE} tended to be higher in the CSIC and 16 μmol Fe/kg SHU555A groups than in the 4 μmol Fe/kg or 8 μmol Fe/kg SHU555A group. These results reflect the fact that the attenuation of the T2-shortening effect at low iron colloid concentration and density is more striking in TSE (Majumdar et al., 1989; Muller et al., 1991; Tanimoto et al., 1995). Generally, in superparamagnetic substances, temporary hypotension and bradycardia were noted as side effects after administration at 15 μmol Fe/kg (Gandon et al., 1991), and their safety in large

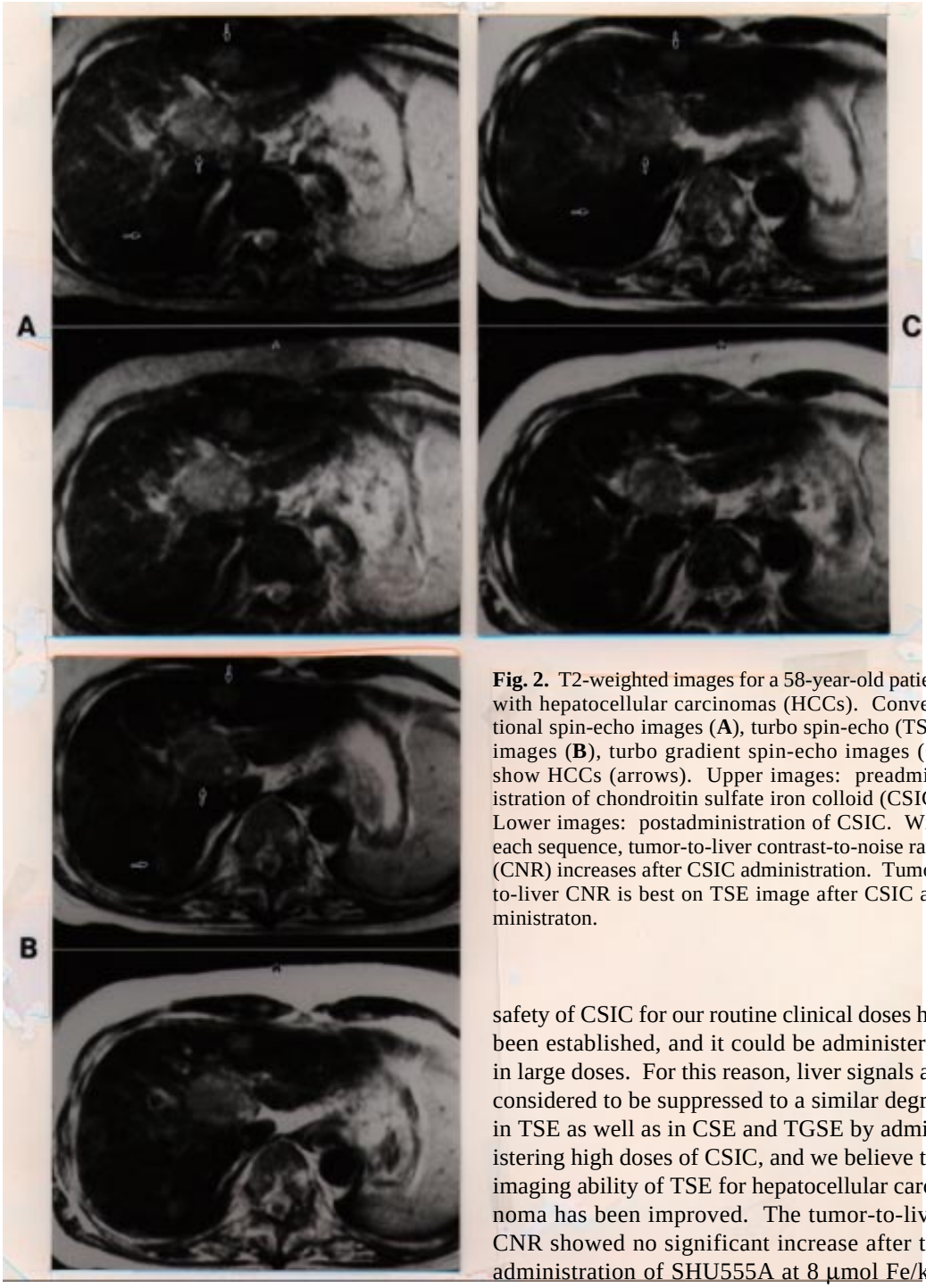

Fig. 2. T2-weighted images for a 58-year-old patient with hepatocellular carcinomas (HCCs). Conventional spin-echo images (**A**), turbo spin-echo (TSE) images (**B**), turbo gradient spin-echo images (**C**) show HCCs (arrows). Upper images: preadministration of chondroitin sulfate iron colloid (CSIC). Lower images: postadministration of CSIC. With each sequence, tumor-to-liver contrast-to-noise ratio (CNR) increases after CSIC administration. Tumor-to-liver CNR is best on TSE image after CSIC administraton.

doses has not been established. Their optimal dose is often suggested to be 8–10 μmol Fe/kg (Reimer et al.,1995; Yuasa et al., 1992). The safety of CSIC for our routine clinical doses has been established, and it could be administered in large doses. For this reason, liver signals are considered to be suppressed to a similar degree in TSE as well as in CSE and TGSE by administering high doses of CSIC, and we believe the imaging ability of TSE for hepatocellular carcinoma has been improved. The tumor-to-liver CNR showed no significant increase after the administration of SHU555A at 8 μmol Fe/kg. The contrast enhancement appears to have been slight, because SHU555A was administered at 8 μmol Fe/kg to only 2 patients (2 nodules), the SI of the tumor was reduced after the admin-

istration of the iron colloid preparation, and the tumor is considered to have been well differentiated hepatocellular carcinoma (Hirohashi et al., 1993), although no histological evidence was available.

In TGSE, the image quality was worse with truncation artifacts, which is characteristic in TGSE. Therefore, TGSE was considered to be unsuitable for diagnosis of hepatocellular carcinoma, although TGSE obtained a higher SNR in the liver and higher tumor-to-liver CNR.

From these findings, the SI of the liver is considered to be reduced by a high dose of paramagnetic CSIC similarly to a superparamagnetic preparation, although the T2-shortening effect of CSIC is weaker than those of the superparamagnetic preparation. In TSE, in which the susceptibility effect is unremarkable among fast T2-weighted sequences, the signals of the liver parenchyma appear to be reduced to a similar degree to CSE and TGSE by administering an iron colloid preparation in a high dose and increasing the density of its distribution in the normal liver parenchyma.

Conclusion

The imaging abilities of fast T2-weighted MRI using paramagnetic and superparamagnetic iron colloid preparations (CSIC and SHU555A, respectively) for hepatocellular carcinoma were compared quantitatively. In the 8 μmol Fe/kg SHU555A group at their optimal dose, a decrease in the SI of the liver was worse in TSE compared with CSE. Therefore it is considered to be unsuitable for the diagnosis of hepatocellular carcinoma in TSE. In TSE, CSIC caused a similar decrease in the SI of the liver to CSE by increasing the dose. Therefore, CSIC is considered to be a more effective MR contrast agent for the diagnosis of hepatocellular carcinoma in TSE.

References

1 Catasca JV, Mirowitz SA. T2-weighted MR imaging of the abdomen: fast spin-echo vs conventional spin-echo sequences. AJR Am J Roentogenol 1994;162:61–67.

2 Ferrucci JT, Stark DD. Iron oxide-enhanced MR imaging of the liver and spleen: review of the first 5 years. AJR Am J Roentogenol 1990; 155:943–950.

3 Feinberg DA, Oshio K. GRASE (gradient- and spin-echo) MR imaging: a new fast clinical imaging technique. Radiology 1991;181:597–602.

4 Gandon Y, Heautot JF, Brunet F. Superparamagnetic iron oxide: clinical time-responce study. Eur J Radiol 1991;12:195–200.

5 Hamm B, Staks T, Taupits M. Contrast-enhanced MR imaging of liver and spleen: first experience in humans with a new superparamagnetic iron oxide. J Magn Reson Imaging 1994;4:659–668.

6 Hennig J, Nauerth A, Friedburg H. RARE imaging: fast imaging method for clinical MR. Magn Reson Med 1986;3:823–833.

7 Hirohashi S, Uchida H, Omichi R, Kitano S, Tanaka M, Oishi . Usefulness of superparamagnetic iron oxide particles in the detection of hepatocellular carcinoma by MR imaging. Nippon Igaku Hoshasen Gakkai Zasshi 1993; 53:469–471 (in Japanese).

8 Nghiem HV, Herfkens RJ, Francis IR, Sommer FG, Jeffrey RB, Li KCP, et al. The pelvis: T2-weighted fast spin-echo MR imaging. Radiology 1992;185:213–217.

9 Majumdar S, Zoghbi SS, Gore JC. The influence of pulse sequence on the relaxation effects of superparamagnetic iron oxide contrast agents. Magn Reson Med 1989;10:289–301.

10 Muller RN, Gillis P, Moiny F, Roch A. Transverse relaxivity of particles MRI contrast media: from theories to experiments. Magn Reson Med 1991;22:178–182.

11 Okuhata Y. An experimental study on MR lymphography with various iron collid agents. Nippon Igaku Hoshasen Gakkai Zasshi 1992; 52:1148–1160 (in Japanese).

12 Outwater EK, Mitchell DG, Vinitski S. Abdominal MR imaging: evaluation of a fast spin-echo sequence. Radiology 1994;190:425–429.

13 Reimer P, Rummeny EJ, Daldrup HE, Balzer T, Tombach B, Berns T, et al. Clinical results with Resovist: a phase 2 clinical trial. Radiology 1995; 195:489–496.

14 Sugihara S, Suto Y, Kamba M, Yoshida K, Ota Y. Evaluation of chondroitin sulfate iron colloid-enhanced T2-weighted fast MR imaging of hepatocellular carcinomas: preliminary report. Nippon Jiki Kyomei Igakkai Zasshi 1996; 16:108–112 (in Japanese).

15 Siewert B, Muller MF, Foley M, Wielopolski PA, Finn JP. Fast MR imaging of the liver: quantitative comparison of techniques. Radiology

1994;193:37–42.
16 Stark DD, Weissleder R, Elizondo G, Hahn PF, Saini S, Todd LE, et al. Superparamagnetic iron oxide: clinical application as a contrast agent for MR imaging of the liver. Radiology 1988;168: 297–301.
17 Tanimoto A, Pouliquen D, Kreft BP, Stark DD. Effects of spatial distribution on proton relaxation enhancement by particulate iron oxide. J Magn Reson Imaging 1994;4:653–657.
18 Tanimoto A, Sato Y, Higuchi N. Proton T2 relaxation effect of superparamagnetic iron oxide: comparison between fast spin echo and conventional spin echo sequence. Nippon Jiki Kyomei Igakkai Zasshi 1995;15:8–12 (in Japanese).
19 Taylor PM, Hawnaur JM, Hutchinson CE. Superparamagnetic iron oxide imaging of focal liver disease. Clinical Radiology 1995;50:215–219.
20 Yuasa Y, Sakuma S, Ogawa N, Fujita N, Miyasaka K, Irie G, et al. Phase clinical trial of AMI-25 (superparamagnetic iron oxide): evaluation of its efficacy, safety and clinical usefulness in MRI of the liver tumors. Nippon Jiki Kyomei Igakkai Zasshi 1992;12:193–207 (in Japanese).

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