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MRI Findings in Radiation-Induced Hepatic Injuries

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To evaluate radiation-induced hepatic injuries (RIHI), magnetic resonance image (MRI) was conducted on 12 patients,1 to 6 months after radiotherapy on regions including the liver. T1-weighted and T2-weighted image (T1WI, T2WI), and gadopentetate dimeglumine (Gd-DTPA)-enhanced T1WI were obtained. Within 1 week, these MRI studies were repeated after chondroitin sulphate iron colloid (CSIC) administration. MRI findings and total irradiation doses were compared. Abnormalities were seen on one or more types of MRI in 7 patients. The total dose of irradiation was 40 or more Gy in these patients, and 40 or less Gy in those who showed no abnormal MR findings. Plain T2WI of the 7 cases showing MRI abnormalities demonstrated a slightly higher signal intensity (SI) in the irradiated areas in 2, an iso SI in 2, a slightly lower or lower SI in 3 cases. The irradiated and nonirradiated areas were clearly demarcated on Gd-DTPA-enhanced T1WI in 4 cases. Following CSIC administration, the irradiated areas became more marked in 3 cases. A clear demarcation between the 2 areas was obtained with double contrast MRI in the 7 cases. The present study indicates that MRI may be a useful noninvasive means of evaluating RIHI.

Key words: contrast agent; MR imaging; radiation hepatitis

Repeated partial irradiation (more than 35–40 Gy) of the liver often results in histopathological derangements although no changes are noted in blood biochemical analyses (Ingold et al., 1965; Concannon et al., 1967; Unger et., 1987; Anderson, 1990). The main changes in the acute phase of radiation-induced hepatic injuries (RIHI) are venous stasis due to injury of the sublobular hepatic veins (Reed and Cox, 1966). There is massive panlobular congestion with intramural red cell accumulation and mild proliferative changes in the sublobular (central vein) hepatic veins (Reed and Cox, 1966; Fellow et al., 1968; Tefft et al., 1970; Lewin and Millis, 1973; Jeffery et al., 1980; Garra et al., 1988; Yankelevitz et al., 1992). These histological manifestations persist for 1 to 5 months after completion of radiotherapy, and then tissues commonly return to a near-normal condition, but sometimes chronic changes develop (Reed and Cox, 1966; Tefft et al., 1970; Lewin and Millis, 1973; Jeffery et al., 1980; Garra et al., 1988; Yankelevitz et al., 1992).

So far, there have been only a few magnetic resonance imaging (MRI) studies in the acute phase of RIHI, and most of them were done using a low-magnet apparatus (Unger et al., 1987; Garra et al., 1988; Yankelevitz et al., 1992). Using a high magnetic apparatus, systematic clinical MRI studies have not been reported so far.

We have already reported that the boundary between the irradiated and nonirradiated fields became well demarcated by double-contrast MRI with combined use of chondroitin sulphate iron colloid (CSIC; Bultal, Dainippon Pharma-

Abbreviations: CSIC, chondroitin sulphate iron colloid; CT, computed tomography; FOV, field of view; Gd-DTPA, gadopentetate dimeglumine; MRI, magnetic resonance image; RIHI, radiation-induced hepatic injury; SI, signal intensity; SE, spin echo; SPIO, superparamagnetic iron oxide; TE, echo time; TR, repetition time; T1WI, T1-weighted image; T2WI, T2-weighted image

ceutical Co., Osaka, Japan) (Kato et al., 1993; Suto and Shimatani, 1995) as a negative MR contrast material for the reticuloendothelial system, and gadopentetate dimeglumine (Gd-DTPA, Magnevist, Nihon Schering, Osaka) (Weinmann et al., 1984; Niendorf et al., 1991) as a positive contrast agent (Suto et al., 1996). Nevertheless, that was a single case report.

In the present study, we carried out a retrospective investigation to evaluate RIHI by plain MRI, and CSIC- and/or Gd-DTPA-enhanced MRI. MRI findings, total irradiation dose, and the period from completion of radiotherapy until performing MRI were evaluated to investigate a possible correlation among them.

Subjects and Methods

We performed MRI in 12 patients (9 men and 3 women; 35 to 78 years old, mean: 61 years) who received radiotherapy on the thorax and abdomen, including the liver. Each patient gave written consent to participate in the MR study. Their underlying diseases were hepatocellular carcinoma (1 case), esophageal cancer (3 cases), lung cancer with metastases to the thoracic vertebrae (2 cases), metastatic adrenal cancer (3 cases), malignant lymphoma (2 cases) and colon cancer with abdominal lymphonode metastases (1 case). The irradiation was external in all cases; the irradiation dose of ^{60}Co or linear acceleration was 1.5–2 Gy/time, with a total administered dose of 30–54 Gy.

MRI was conducted 1 to 6 months after completion of radiotherapy. MR images were obtained on 2 separate days with a 1.5 Tesla superconducting system using Magnetom H15 or Vision (Siemens, Erlangen, Germany). Precontrast T1-weighted images (T1WI) (TR ms/TE ms/signal averaging = 600–700/22/3), and T2-weighted images (T2WI) (1800–2000/90/2) were obtained using the spin echo (SE) sequence. Postcontrast T1WI were also obtained 10 min after intravenous injection of 0.1 mmol/kg of Gd-DTPA. The other imaging conditions were as follows: a slice thickness of 8 mm, a gap of 2 mm, an FOV of 370 mm and an imaging matrix of 192 × 256 (T1WI) or 60 × 256 (T2WI). MRI was performed again within 1 week 1 h after intravenous injection of CSIC (23.8 μmol Fe/kg) under the same conditions. MRI findings of the irradiated area were classified into 5 patterns according to the signal intensity (SI) relative to the nonirradiated area of the liver parenchyma (higher, slightly higher, iso, slightly lower, lower). To evaluate the contrast enhancemen of CSIC and/or Gd-DTPA, the pre- and post-contrast images were compared.

Results

Abnormalities were revealed by one or more types of MRI in 7 patients who received a total dose of irradiation of 40 or more Gy. Regardless of the type of MR images, no abnormalities were observed in the remaining 5 patients who received a total dose of irradiation of 40 or less Gy (Table 1). In 3 of these 5 patients, the time elapsed from the completion of radiotherapy until MRI was 6 months.

Comparison of the irradiated with the nonirradiated regions of the liver on plain T1WI of patients with MRI abnormalities revealed a lower SI in 2, a slightly lower SI in 1 and an iso SI in 4 cases. The plain T2WI showed a slightly higher SI in 2, an iso SI in 2, a slightly lower SI in 1, and a lower SI in 2 cases.

Gd-DTPA-enhanced T1WI showed a contrast enhancement in the irradiated regions that was stronger than that in the nonirradiated regions. In 2 cases (cases 4 and 7), MRI abnormalities were not detected on the plain T1WI or T2WI, but were demonstrated on Gd-DTPA-enhanced T1WI. The irradiated and nonirradiated zones appeared clealy demarcated on Gd-DTPA-enhanced T1W in 4 of the 7 cases. However, in the other 3 cases, the irradiated regions became unclear (i.e., changed from being a lower or a slightly lower SI to an iso SI).

After intravenous injection of CSIC, the SI of the nonirradiated regions decreased, while that of the irradiated regions increased compared to the precontrast images. After CSIC administration, the irradiated areas on T1WI and T2WI became more marked in 3 cases.

Table 1. MR signal intensity of the irradiated area compared to the nonirradiated area

	MRI abnormalities							No MRI abnormalities				
	Case No.							Case No.				
	1	2	3	4	5	6	7	8	9	10	11	12
Age (year)	60	60	50	78	62	60	35	66	72	63	76	46
Sex	M	M	M	M	M	M	F	F	F	M	M	M
Underlying disease	HCC	TH	TH	Eso	Eso	Adr	Adr	ML	Eso	LN	Adr	ML
Total dose	50	40	50	40	54	50	54	40	40	40	40	30
[No. of fractions]	[25]	[20]	[25]	[20]	[27]	[25]	[27]	[20]	[20]	[20]	[20]	[20]
RT-MR (month)	6	3	3	3	2	1	1	6	6	1	6	1
T1WI												
CSIC+/Gd-DTPA+	H* ↑	H* ↑	H* ↑	H* ↑	H* ↑	H* ↑	H* ↑	I	I	I	I	I
CSIC–/Gd-DTPA+	I ↑	I ↑	SH* ↑	SH* ↑	SH* ↑	I ↑	SH* ↑	I	I	I	I	I
CSIC–/Gd-DTPA–	L ↓	L ↓	I ↓	I ↓	I ↓	SL ↓	I ↓	I	I	I	I	I
CSIC+/Gd-DTPA–	SL ↓	SL ↓	SH* ↓	SH* ↓	SH* ↓	SH ↓	I ↓	I	I	I	I	I
CSIC+/Gd-DTPA+	H*	H*	H*	H*	H*	H*	H*	I	I	I	I	I
T2WI												
CSIC–/Gd-DTPA–	SH ↓	L ↓	SH ↓	I ↓	SL ↓	L ↓	I ↓	I	I	I	I	I
CSIC+/Gd-DTPA–	H*	I	H*	SH*	I	SH	I	I	I	I	I	I

*Irradiated regions became more marked compared to the precontrast image: H, higher signal intensity; I, iso-signal intensity; L, lower signal intensity; SH, slightly higher signal intensity; SL, slightly lower signal intensity.
Adr, metastatic adrenal cancer; CSIC, chondroitin sulfate iron colloid; Eso, esophageal cancer; HCC, hepatocellular carcinoma; Gd-DTPA, gadopentetate dimeglumine; LN, abdominal lymphonode metastases; ML, malignant lymphoma; RT-MR, the period from completion of radiotherapy until performing MR; T1WI, T1 weighted image; T2WI, T2 weighted image; TH, thoracic vertebral metastases.

There was a case (case 4) of which abnormalities were not detected on the plain T1WI or T2WI, but were demonstrated on CSIC-enhanced MRI.

In all cases with identifiable abnormalities on MRI, the contrast between the irradiated and nonirradiated regions became striking on the double-contrast MRI (using CSIC and Gd-DTPA) as compared to the precontrast images (Figs. 1 and 2).

Discussion

In the present study, the irradiated fields showing MRI abnormalities coincided with the hepatic regions that received a total irradiation dose of 40 or more Gy, and thus, for the most part, our findings are in agreement with previous reports (Ingold et al., 1965; Concannon et al., 1967; Unger et al., 1987; Anderson, 1990).

The analysis of negative cases in the present study demonstrated that the total irradiation dose was 30 Gy in 1 case, i.e., less than the dose which reportedly induces hepatic radiation injuries (Ingold et al.,1965; Fellow et al., 1968). Three of the negative cases received a total dose of 40 Gy, but MRI was conducted after 6 months (cases 8, 9 and 11). On the other hand, MRI abnormalities were detected after 3 months in 2 patients (cases 2 and 4) who also received a total dose of 40 Gy. Therefore, the acute phase of RIHI might have improved by 6 months in those 3 cases. Nevertheless, no

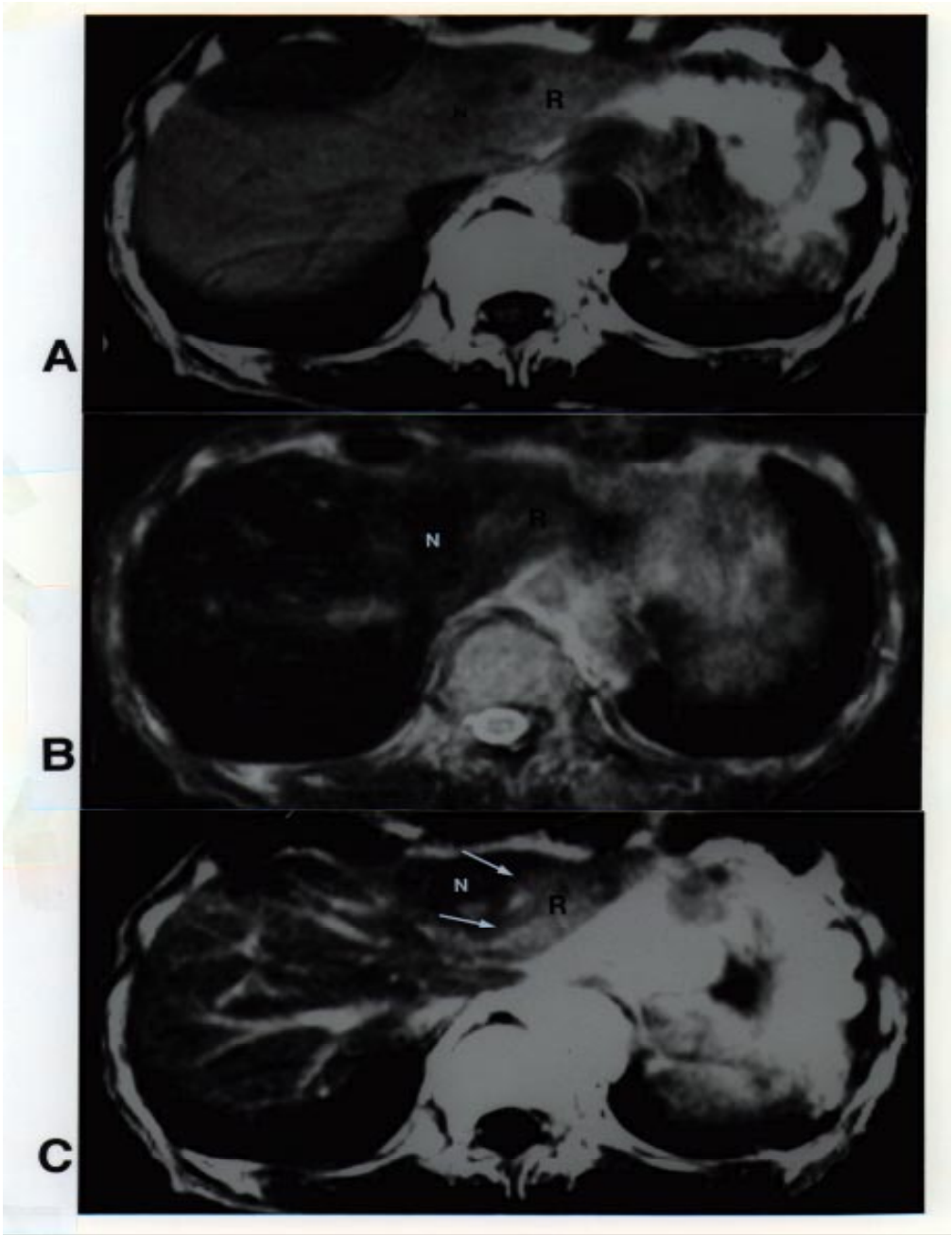


Fig. 1. A 78-year-old man with cancer of the abdominal esophagus treated by radiotherapy administered through opposed anterior and posterior portals (case 4). N, nonirradiated area; R, irradiated area. The signal intensity (SI) of the irradiated area is similar to that of the nonirradiated one on plain T1WI and T2WI. On MRI after intravenous injection of chondroitin sulfate iron colloid (CSIC), the SI in the irradiated field is slightly higher than that of the nonirradiated area on T1WI (**A**) and T2WI (**B**), but the boundary between the irradiated and nonirradiated fields is not well demarcated. By double-contrast MRI using CSIC and Gd-DTPA (**C**), the boundary between the 2 fields becomes well demarcated (arrows).

abnormalities were seen 1 month after receiving a similar total dose of 40 Gy in 1 case (case 10), and the reasons of these discrepancies are unknown. Even in previous reports, the frequency of detection of radiation hepatic injury and the detection period after receiving similar irradiation doses varied greatly (Yankelevitz et al., 1992; Clemente et al., 1992).

In the present study, the SI of the irradiated area varied widely on T2WI. Moreover, among patients showing MRI abnormalities, there was no relationship between the irradiation dose, or the period from completion of radiotherapy until conduction of MRI, and the pattern of change in SI on T2WI.

Using a low-magnet apparatus, Yankelevitz and colleagues (1992) reported that 10 patients received radiotherapy on the abdomen (36 Gy) were followed for 4 weeks. In their study, although the irradiation conditions were exactly the same, only 3 of these 10 patients showed an abnormally higher SI in some areas on T2WI, but they returned to normal within 60 days.

In our study, only 2 of 11 cases showed a slightly higher SI on T2WI. However, some irradiated areas showed a lower or slightly lower SI on T2WI. Therefore, acute radiation hepatitis was not essentially reflected by a higher or a slightly higher SI on T2WI in all cases. The reasons of such difference in findings were not obvious because of lack of specific histological findings. The differences in SI of the irradiated areas on T2WI have been suggested to result from the balance between SI reducing factors, such as the heterogenous distribution of iron due to hemorrhage, and SI elevating factors, such as edema (Suto et al., 1996). As the apparatus we used (1.5 Tesla) is different from that used in previous MR studies and is very sensitive to magnetic field inhomogeneity, a lower SI was probably detected when signal reducing factors predominated.

After the administration of CSIC, the SI of the nonirradiated hepatic parenchyma became relatively higher compared to the precontrast signal in the irradiated areas. We speculate that such change reflects the hypofunction of the reticuloendothelial system in the irradiated regions. Clemente and colleagues (1992) using an experimental animal model for RIHI and a superparamagnetic iron oxide (SPIO) for MRI, reported that regions of relatively higher (compared to the precontrast images) SI coincided with the irradiated field, reflecting hypofunction of the reticuloendothelial system. Our present findings further support their results. Furthermore, Clemente and colleagues (1992) indicated that it is possible to detect abnormalities of the reticuloendothelial system by plain MRI as early as 1 h after the completion of irradiation, when edema has not yet developed. MRI was performed minutes after completion of radiotherapy in their study, whereas in our study MRI was performed months after it. Nevertheless, in 1 case in the present study, the abnormal areas could be detected by CSIC-enhanced MRI but not by plain MRI. This has a great significance because the functional diagnosis of the reticuloendothelial system, which was not possible except by liver scintigraphy, can now be done by using MRI with iron colloid which also provides much more spatial resolution than scintigraphy.

Contrast enhancement with Gd-DTPA of the irradiated fields may be attributed to the increased capillary permeability that is associated with the hepatic disorders. Even the abnormal areas, which could not be detected with plain MRI in the present study, were enhanced, while the irradiated areas showed a slightly higher SI in some cases.

However, when using CSIC or Gd-DTPA alone, the SI of the hepatic parenchyma in some irradiated regions changed from a lower or a slightly lower SI before contrast administration to an iso SI after administration, thus becoming unclear. A thorough comparison of pre- and postcontrast images helps to understand the differences in the functions of the reticuloendothelial system as well as the histopathological changes. On the other hand, such abnormalities may be overlooked on contrast MRI using a single contrast agent alone.

By double-contrast MRI using both CSIC and Gd-DTPA, the boundary between the irradiated and nonirradiated fields, which was not obvious when only one contrast agent was used, became manifest. The superiority of double-

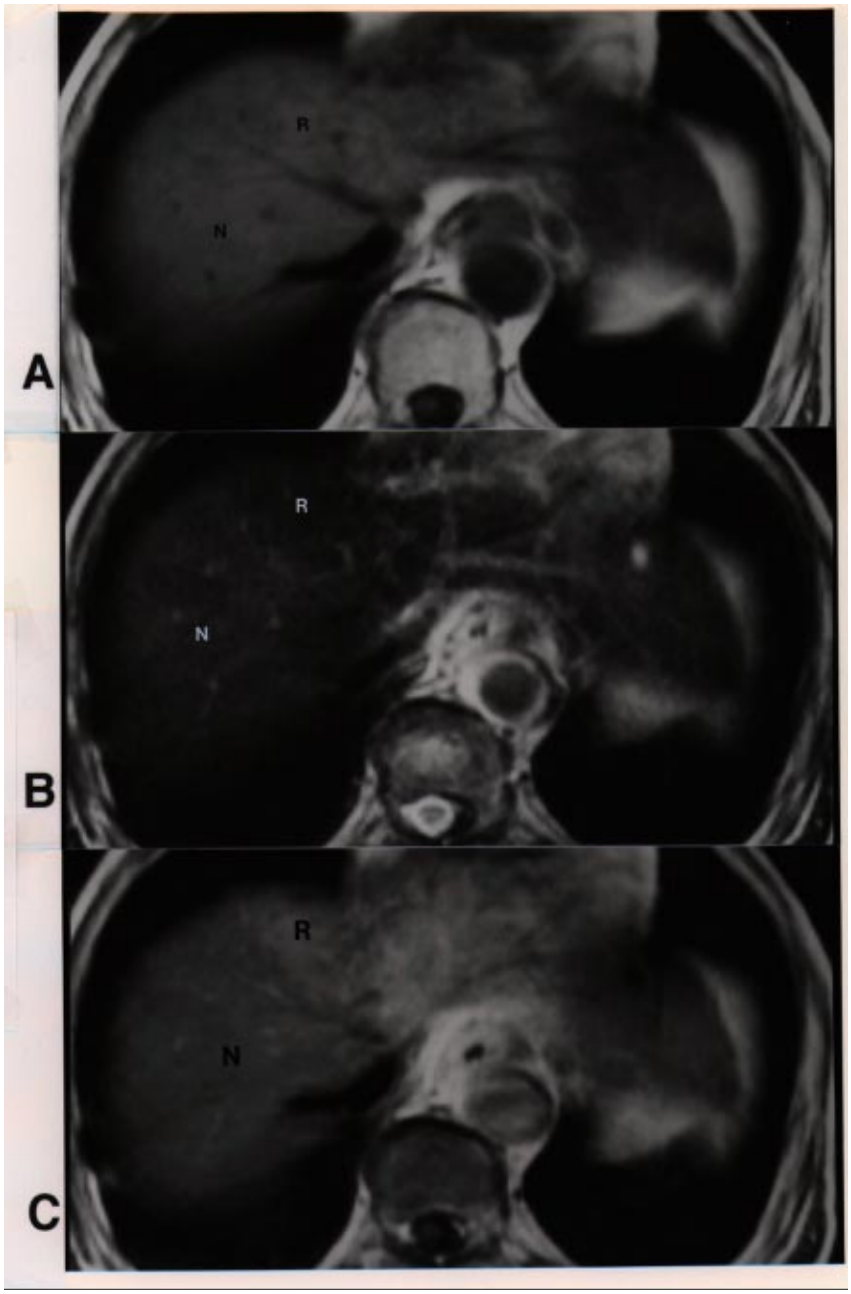
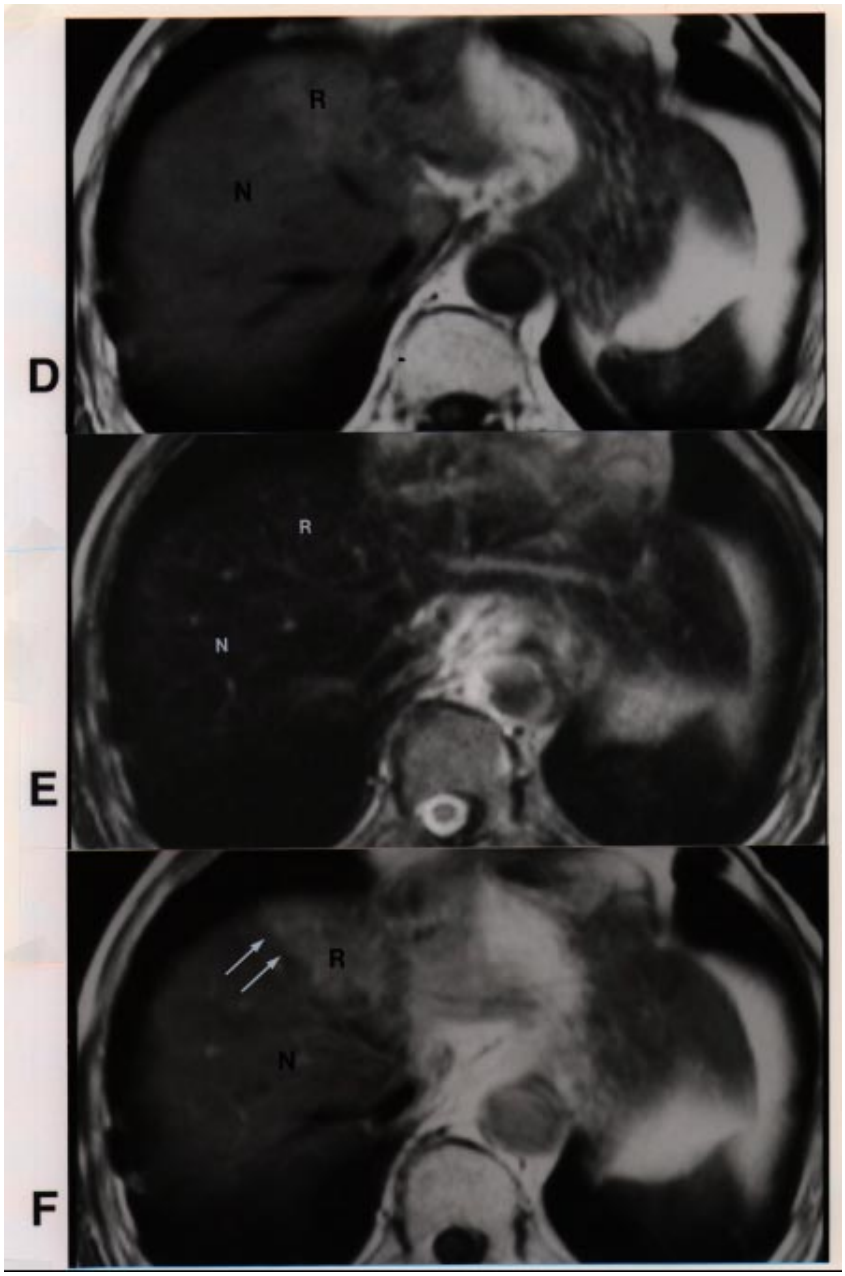


Fig. 2. A 62-year-old man with cancer of the abdominal esophagus treated by radiotherapy administered through an oblique portal (case 5). N, nonirradiated area; R, irradiated area. On plain T1WI (**A**), the SI of the irradiated area is similar to that of the nonirradiated one; but on T2WI (**B**), the SI of the irradiated area becomes lower than that of the nonirradiated one. After administration of Gd-DTPA (**C**), the SI of the irradiated area is slightly higher than that of the nonirradiated one. After intravenous injection of chondroitin sulfate iron colloid (CSIC), the SI of the irradiated field is slightly higher than that of the nonirradiated one on T1WI (**D**). On T2WI **(E**), the SI of the irradiated field is similar to that of the nonirradiated area. By double-contrast MRI using CSIC and Gd-DTPA (**F**), the boundary (arrows) between the irradiated and nonirradiated fields becomes well demarcated.



contrast MRI is thought to result from the additive combination of the positive contrast enhancement obtained with Gd-DTPA and the negative contrast enhancement obtained with CSIC (Suto and Shimatani, 1995).

In the present study, clinical follow-up and histological examination of the liver were not done, and therefore it is not clear whether the negative MRI findings obtained in some cases imply recovery from the RIHI. Therefore, further studies including histopathological examinations should be performed.

To summarize briefly, the present study indicates that MRI may be a useful noninvasive mean of evaluating RIHI.

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