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Significance of the Signal Intensity of Gadoxetic Acid-enhanced MR Imaging for Predicting the Efficacy of Hepatic Arterial Infusion Chemotherapy in Hepatocellular Carcinoma

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Purpose: We attempted to clarify the relationship between the signal intensity (SI) in the hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance (MR) imaging and the efficacy of hepatic arterial infusion chemotherapy (HAIC) in hepatocellular carcinomas (HCCs).

Methods: We enrolled 14 patients with HCCs who underwent gadoxetic acid-enhanced MR imaging prior to HAIC using cisplatin and 5-fluorouracil. In the hepatobiliary phase, we calculated the SI of the HCCs and the background liver. In cases with multiple HCCs, we calculated the SI of the largest lesion. Patients were classified into high (n = 7) and low intensity (n = 7) groups based on the median value of the SI ratio (SI of the tumor/SI of the background liver). We analyzed progression-free survival using the Kaplan-Meier method and the log-rank test. In the 5 patients with a history of HCC surgery, we compared the expression of immunohistochemical organic anion-transporting polypeptide (OATP) 8 between the high and low intensity groups by chi-square test.

Results: The SI ratios were 0.568 ± 0.093 (mean ± standard deviation) in the high intensity group and 0.251 ± 0.086 in the low intensity group. Compared to the group with low signal intensity, the group with high signal intensity demonstrated significantly lower serum levels of alpha fetoprotein (AFP) ($P = 0.0350$), significantly higher progression-free survival ($P = 0.0108$), better differentiation of tumor grade at histologic examination ($P = 0.0253$), and significantly higher OATP8 expression ($P = 0.0253$).

Conclusion: Patients with HCCs of high SI ratio in the hepatobiliary phase of gadoxetic acid-enhanced MR imaging can respond better to HAIC.

Keywords: ***EOB*, *gadoxetic acid*, *hepatic arterial infusion chemotherapy*, *hepatocellular carcinoma*, *magnetic resonance imaging***

Introduction

Gadoxetic acid is a hepatobiliary-specific contrast medium for magnetic resonance (MR) imaging,[1,2] and gadoxetic acid-enhanced MR imaging has become an important imaging modality for high accuracy diagnosis of hepatocellular carcinoma (HCC).[3,4] HCCs usually show hypointensity compared to background liver in the hepatobiliary

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phase (HBP).[2] However, some HCCs take up gadoxetic acid and are recognized as iso- or hyperintense lesions in the HBP.[5–7]

The expression in HCC of organic anion transporter 1B3 (OATP1B3, synonymous with OATP8), the uptake transporter of gadoxetic acid, is considered to determine the hyperintensity in the HBP.[5,6] The molecular correlation of the uptake of gadoxetic acid by HCCs, as well as the expression of OATP1B3, with the maintenance of mature hepatocyte function and good prognosis was recently reported.[8] Indeed, in surgically resected cases, hyperintense HCCs in the HBP showed less aggressive biological behavior or more favorable outcome than hypointense HCCs.[9–13] Hyperintense HCCs also appear to be susceptible to transcatheter arterial chemolipiodolization (TACE).[14] Findings of gadoxetic acid-enhanced MR imaging may enable prediction of the therapeutic efficacy of HCCs as well as diagnosis or detection of HCCs.

Hepatic arterial infusion chemotherapy (HAIC) is one treatment option for patients with advanced HCC whose cases are not indicated for local treatment, such as surgery, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), or TACE. An implantable drug delivery system has enabled the repeated arterial infusion of chemotherapeutic agents, and the usefulness of the administration of low dose cisplatin combined with 5-fluorouracil (low dose FP) has been reported.[15,16] However, an overall response rate to HAIC of 22 to 71% has been reported,[17] and HAIC is not effective for all patients. The median survival times reported in responders to HAIC was 18.4 to 31.6 months and in nonresponders, 5.4 to 6.7 months,[15,18] and the survival rate was significantly higher of responders than nonresponders. Thus, the prediction of patients' responses to HAIC would be very useful. To the best of our knowledge, no reports have evaluated the predictive factors for the response to HAIC.

Gadoxetic acid-enhanced MR imaging allows noninvasive evaluation of the characteristics of HCCs, including its malignancy, characteristics that may affect the response to the HAIC. The purpose of the present study was to clarify the relationship in HCC cases between the signal intensity (SI) of the tumor in the HBP of gadoxetic acid-enhanced MR imaging and the patient response to HAIC, including expression of OATP8.

Materials and Methods

Patients

Our institutional review board approved this retrospective study and waived the requirement for informed consent.

Between November 2008 and July 2013, 54 patients with HCC were treated with HAIC at our hospital. We enrolled 14 of the 54 who underwent gadoxetic acid-enhanced MR imaging prior to HAIC. HCCs were diagnosed clinically based on findings obtained by computed tomography (CT) or MR imaging and findings of elevated alpha-fetoprotein (AFP) or protein-induced vitamin K absence or antagonist-II (PIVKA-II). On CT images, HCC was diagnosed as a nodular lesion with enhancement in the arterial phase and washout in the portal venous or equilibrium phase. On gadoxetic acid-enhanced MR imaging, HCC was diagnosed as a nodular lesion with enhancement in the arterial phase and decreased uptake in the hepatobiliary phase.[19]

One of the 14 patients received HAIC as initial treatment. The other 13 had histories of surgery for their HCC ($n = 3$), nonsurgical local treatment (RFA, PEI, MCT, or TACE) ($n = 6$), or a combination of surgery and nonsurgical treatment ($n = 4$). Two patients with a history of surgery received HAIC only as postoperative adjuvant chemothera-

Table 1. Patient details and tumor profiles

Gender (male/female)	11/3
Age (years)*	61.1 ± 11.7 (37 to 82)
Etiology of liver disease	
Hepatitis B virus	5
Hepatitis C virus	8
Alcoholism	1
Background liver	
Chronic hepatitis	6
Cirrhosis	8
Child-Pugh class	
A	10
B	4
AFP (ng/mL)*	3558.1 ± 12547.4 (3.6 to 47142)
PIVKA-II (mAU/mL)*	1103.3 ± 1886.6 (7.0 to 7067)
Tumor size (cm)*,**	3.2 ± 1.5 (1.5 to 6.5)

*Data are mean ± standard deviation.
Ranges are in parentheses.
**Data are excluded of 2 patients treated with hepatic arterial infusion chemotherapy (HAIC) as postoperative chemotherapy.
AFP, alpha fetoprotein; PIVKA-II, protein-induced vitamin K absence or antagonist-II

py.[20] In 10 patients, HCCs had invaded both lobes. Two patients with history of right lobectomy demonstrated multiple nodular HCCs in the left lobe. Tumor thrombus of the main trunk of the portal vein was observed in one patient. Table 1 summarizes patient details and tumor profiles.

MR techniques

Patients underwent gadoxetic acid-enhanced MR imaging prior to HAIC (median time before HAIC, 75 days; range, 14 to 231 days) using a superconducting magnet operating at 1.5 (n = 10) or 3.0 tesla (n = 4) (Intera Achieva Nova Dual, 1.5T, or Achieva TX, 3T, Philips Healthcare, Best, The Netherlands) with a sensitivity encoding technique (SENSE) and a 16- or 32-channel phased-array coil.

For the gadoxetic acid-enhanced MR imaging, dynamic images using fat-suppressed T_1-weighted gradient-echo images with a 3-dimensional (3D) acquisition sequence (3D T_1-high resolution isotropic volume excitation [THRIVE] or enhanced THRIVE [eTHRIVE]) were obtained. Table 2 details the imaging parameters of THRIVE in the 1.5T MR system and eTHRIVE in the 3T system.

A multiphase dynamic study including arterial dominant, portal, late, and hepatobiliary phases was performed after administration of gadoxetic acid (gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid, Primovist; Bayer, Osaka, Japan). Intravenous injection of a dose of gadoxetic acid based on the patient's body weight (0.025 mmol/kg) for 5 s was followed by a 20- mL physiological saline flush administered via a power injector (Nemoto Kyorindo, Tokyo, Japan). The timing of the arterial dominant phase was determined with a test injection method using 0.5 mL of gadoxetic acid. Scanning began at the arterial dominant phase + 30 s after the injection of the contrast agent for the portal phase, + 180 s for the late phase, and + 20 min for the hepatobiliary phase.

Image analysis

In consensus, 2 radiologists specializing in hepatic MR imaging with 14 (Y.T.) and 20 (A.N.) years' experience in abdominal imaging analyzed images without information regarding clinical results. The SIs of the tumors and of the background liver parenchyma were measured in regions of interest (ROIs) in the HBP. By consensus, ROIs were placed as the maximum oval areas at the largest section of the tumor (avoiding necrosis). In cases with multiple HCCs, the SI of the largest lesion was calculated (mean ROI, $1605.6 \pm 3159.5\,mm^2$; range, 32.4 to $12033.3\,mm^2$). ROIs on the background liver parenchyma were placed by tracing the background liver to avoid the large vessels. The mean SI of the 3 areas was defined as the SI of the background liver (mean ROI, $334.2 \pm 103.0\,mm^2$; range, 218.8 to $577.8\,mm^2$).

We calculated the SI ratio in the HBP by dividing the SI of the tumor by the SI of the background liver[8,12] and divided the patients into a high intensity group and a low intensity group by their median ratios.

Table 2. Parameters of the magnetic resonance imaging systems

1.5-tesla system	
Repetition time	3.6 ms
Echo time	1.8 ms
Flip angle	18°
Matrix	240 × 168
Field of view	360 × 252 mm
Slice thickness	3 mm
Slice gap	−1.5 mm
Fat suppression	SPAIR
3.0-tesla system	
Repetition time	3.0 ms
Echo time	1.4 ms
Flip angle	10°
Matrix	252 × 200
Field of view	375 × 298 mm
Slice thickness	3 mm
Slice gap	−1.5 mm
Fat suppression	SPAIR

SPAIR, spectral attenuation with inversion recovery

Hepatic arterial infusion chemotherapy

A 5-French heparin-coated catheter (W-Spiral catheter; Piolax Medical Devices, Inc., Yokohama, Japan) was introduced through the right femoral artery with a subcutaneously implanted reservoir. A catheter with a side vent was inserted into the gastroduodenal artery, with the vent positioned in the common hepatic artery using an image-guided procedure. The right gastric artery, gastroduodenal artery, and other arteries that supplied the gastroduodenal region were embolized by metallic coils. One course of low dose FP was administered over 2 to 4 weeks and consisted of 5-fluorouracil(5-FU) (1000 to 1250 mg/body per week) and cisplatin (5 to 10 mg/body per day, 5 days per week) administered via the hepatic artery using an infusion pump. The dose of chemotherapeutic agents was decided or changed based on the patient's condition or the tox-

icity. A 2- to 4- week rest period of no treatment was allowed after each treatment course. The 14 patients enrolled in this study received one to 4 courses of low dose FP.

Progression-free survival of patients with HCC

We analyzed the progression-free survival of the 14 patients. After HAIC, patients underwent ultrasonography, dynamic CT, or MR imaging every 2 or 3 months in addition to the monthly measurement of AFP or PIVKA-II. The median follow-up period was 131 days (range, 42 to 1186 days). Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.Disease progression was defined as 20% or greater progression in tumor size or the development of new lesions, recurrence, or death. For the 2 patients who received HAIC as postoperative adjuvant chemotherapy, disease progression was defined as the development of new lesions.

Pathological diagnosis and immunohistochemical staining of OATP8

In 5 of the 7 cases with a history of surgery, we evaluated tumor differentiation grade (well, moderately and poorly differentiated) based on the classification proposed by the International Working Party.[21] Then, we classified HCCs into 3 proliferative patterns–trabecular, pseudoglandular, or solid.

Immunohistochemical staining was performed using a primary antibody to OATP8 (mouse monoclonal antibody, NB100-74482; Novus Biologicals, Littleton, CO, USA) (1:100 dilution) by the streptavidin-biotin-peroxidase method (Histofine SAB-PO Kit; Nichirei, Tokyo, Japan). Briefly, 4-μm-thick sections of tissue, including sufficient cancer tissue, were deparaffinized in xylene and rehydrated through a graded ethanol series. Endogenous peroxidase activity was blocked by incubation in methanol containing 0.3% hydrogen peroxide for 30 min. For antigen retrieval, sections were heated in an edetic acid buffer (pH 8.0) for 20 min in a microwave oven.

After nonspecific binding was blocked by a 10-min incubation with 10% rabbit serum, the slides were incubated with anti-OATP8 protein (mouse monoclonal antibody, NB100-74482; Novus Biologicals) diluted 1:100 at 4°C overnight. The antigens labeled by the primary antibody were detected with a Histofine kit (Nichirei) and visualized using 3,3′-diaminobenzidine tetrahydrochloride as a chromogen. Nuclei were counterstained with hematoxylin.

One pathologist (Y.K.) with 4 years of experience in liver pathology performed all pathological and immunohistochemical evaluations without knowledge of the clinicopathological findings. The expression of OATP8 on the tumor cell membrane was evaluated semiquantiatively. We considered the expression in hepatocytes as the positive control of OATP8.

Statistical analysis

We compared clinical factors between the high and low intensity groups using Fisher's exact test (gender, etiology of the liver disease, background liver, Child-Pugh class, history of preceding therapy) or Mann-Whitney U test (age, AFP, PIVKA-II, tumor size, courses of low dose FP). Progression-free survival was analyzed between the high and low intensity groups using the Kaplan-Meier method and the log-rank test. Tumor differentiation grade, tumor proliferative pattern, and immunohistochemical OATP8 expression were compared between the 2 groups using chi-square test. Analysis was performed using JMP 9.0.2 software (SAS Institute, Cary, NC, USA). *P*-values less than 0.05 were considered significant.

Results

Tumor SI ratio in the HBP and progression-free survival after HAIC

Visually, all lesions of the 14 patients showed hypointensity compared to the background liver in the HBP. The median SI ratio in the HBP was 0.390. We divided the patients by their median SI ratio values into high (n = 7) and low intensity (n = 7) groups. The SI ratio was 0.568 ± 0.093 (mean ± standard deviation [SD]) in the high intensity group and 0.251 ± 0.086 in the low intensity group.

Serum levels of AFP were significantly lower of the high than low intensity group ($P = 0.0350$). Other clinical findings did not differ significantly between the 2 groups (Table 3).

Figure 1 presents the progression-free survival curves of the 2 groups. The 6- and 12-month progression-free survival rates were 83.3 and 33.3% in the high intensity group and 25.7 and 0% in the low intensity group (Fig. 1a). The high intensity group showed a significantly higher progression-free survival rate than the low intensity group ($P = 0.0108$).

When we excluded the 2 patients who received HAIC as postoperative adjuvant chemotherapy, the 6- and 12-month progression-free survival rates were 80.0 and 20.0% in the high intensity group (n = 6) and 25.0 and 0% in the low intensity group (n = 6) (Fig. 1b). The high intensity group also showed a significantly higher progression-free survival rate than the low intensity group ($P = 0.0224$).

Table 3. Tumor signal intensity (SI) ratio in the hepatobiliary phase (HBP) and clinical features

	High intensity group (n = 7)	Low intensity group (n = 7)	*P* value
Gender			1
male	5	6	
female	2	1	
Age (years)*	58.1 ± 13.8 (37–80)	64 ± 9.3 (52–82)	0.3352
Etiology of liver disease			0.5921
Hepatitis B virus	2	3	
Hepatitis C virus	5	3	
Alcoholism	0	1	
Backgroud liver			0.5921
Chronic hepatitis	2	4	
Cirrhosis	5	3	
Child-Pugh class			0.5594
A	4	6	
B	3	1	
AFP (ng/mL)*	211.5 ± 318.2 (7.1 to 826.1)	6904.8 ± 17766.9 (3.6 to 47142)	0.0350
PIVKA-II (mAU/mL)*	1386.3 ± 2663.1 (7 to 7067)	820.3 ± 658.1 (82 to 1927)	0.1417
Tumor size (cm)*,**	2.6 ± 1.4 (1.5 to 5.1)	3.7 ± 1.6 (1.6 to 6.5)	0.2963
History of preceding therapy			0.1841
none	0	1	
surgery	1	2	
nonsurgical local treatment	5	1	
both	1	3	
Courses of low dose FP			0.4170
1	1	2	
2	2	4	
3	3	1	
4	1	0	

*Data are mean ± standard deviation.
Ranges are in parentheses.
**Data are excluded of 2 patients treated with hepatic arterial infusion chemotherapy (HAIC) as postoperative chemotherapy.
AFP, alpha fetoprotein; FP, cisplatin combined with 5-fluorouracil; PIVKA-II, protein-induced vitamin K absence or antagonist-II

Tumor SI ratio in the HBP and pathological features

Both HCCs in the high intensity group were moderately differentiated and showed a trabecular pattern. All 3 HCCs in the low intensity group were poorly differentiated; two showed a trabecular pattern and one, a compact pattern. The grade of tumor differentiation differed significantly between the 2 groups ($P = 0.0253$). In contrast, the tumor proliferative pattern did not differ between the 2 groups ($P = 0.3613$). Immunohistochemical analysis revealed significantly higher expression of OATP8 in the high than low intensity group ($P = 0.0253$) (Table 4).

Figures 2, 3, and 4 show 3 typical cases.

Discussion

Gadoxetic acid-enhanced MR imaging is now an important imaging modality for the high accuracy detection and diagnosis of HCC.[3,4] In addition, recent studies revealed that the SI of HCC in the HBP may be a useful biomarker to indicate the malignant potential of HCC.[9–12] Briefly, HCCS that are hyperintense in the HBP show lesser aggressive biological behavior than hypointense HCCs. The SI of HCCs in the HBP may be correlated with treatment effect or prognosis. Indeed, in surgically resected cases, a lower recurrence rate has been reported of hyperintense HCCs in the HBP compared to hypointense HCCs.[9,12] Hyperintense HCCs in

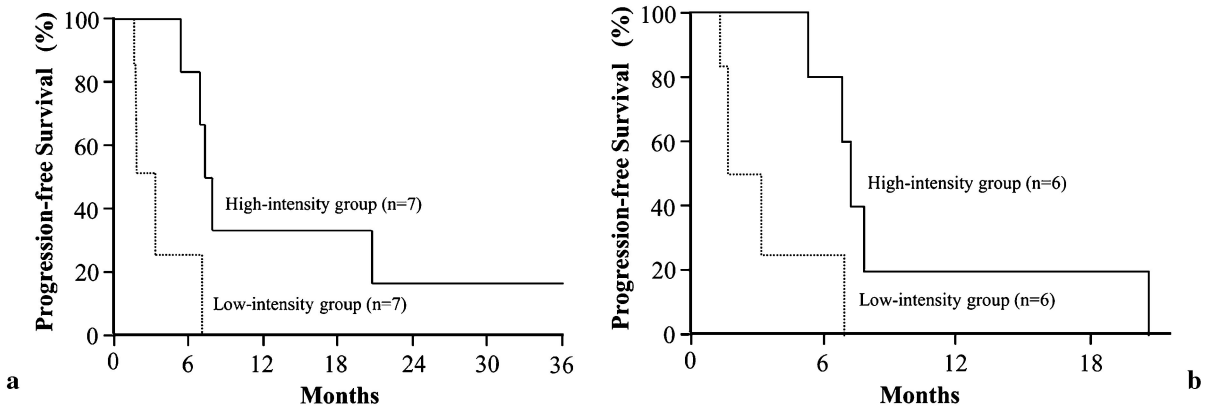

Fig. 1. The progression-free survival (PFS) curves of the patients with hepatocellular carcinoma (HCC) grouped by high and low signal intensity (SI) values. (**a**) The PFS rate was significantly higher of the high than low intensity group ($P = 0.0108$). (**b**) When we excluded the 2 patients who received hepatic arterial infusion chemotherapy (HAIC) as postoperative adjuvant chemotherapy, the PFS rate was also significantly higher of the high than low intensity group ($P = 0.0224$).

Table 4. Tumor signal intensity (SI) ratio in the hepatobiliary phase (HBP) and pathological features

	High intensity group (n = 2)	Low intensity group (n = 3)	*P* value
Differentiation			0.0253
well	0	0	
moderate	2	0	
poor	0	3	
Proliferation pattern			0.3613
trabecular	2	2	
compact	0	1	
OATP8 expression			0.0253
positive	2	0	
negative	0	3	

the HBP also appear to be susceptible to TACE.[14]

In our patients treated with HAIC, the high intensity group achieved a higher progression-free survival rate than the low intensity group. We obtained a similar result even when we excluded 2 patients who received HAIC as postoperative adjuvant chemotherapy because of the difference in treatment aim. Our results suggest that the SI in the HBP is correlated with the response to HAIC.

Yamashita and associates[8] recently reported the correlation of hyperintense HCCs in the HBP with the maintenance of hepatocyte function with the up-regulation of OATP1B3 (synonymous with OATP8) and expression of hepatocyte nuclear factor 4 alpha (HNF4α). OATP1B3 is the uptake transporter of gadoxetic acid, and its expression determines the hyperintensity in the HBP.[5,6] HNF4α is a liver-enriched nuclear orphan receptor that activates the transcription of transthyretin genes.[22] The liver-specific loss of HNF4α in adult mice results in hepatocyte proliferation.[23] The introduction of HNF4α suppresses HCC growth.[24,25]

By contrast, hypointense HCCs in the HBP were correlated with the activation of forkhead box protein M1 (FOXM1), an oncogene that regulates a myriad of biologic processes, including cell proliferation and differentiation.[26] These molecular findings may explain why HCCs that are hyperintense in the HBP show lesser aggressive biological behavior than hypointense HCCs, and they suggest a correlation between imaging findings and the treatment effect on HCCs.

Various criteria have been used to classify HCCs as hyperintense or hypointense in the HBP. Kitao and colleagues described lower SI values of hypointense HCCs than of the surrounding liver (tumor SI/background liver SI < 1.0) and equal or higher SI values of hyperintense HCCs (tumor SI/background liver SI ≥ 1.0).[8,12] According to their criteria, all HCCs in the present study would be defined as hypointense. However, Kitao's group also reported that when they excluded "hyperintense" HCCs, the SI in the HBP decreased in accordance with the decline in tumor differentiation and the decline of OATP8 expression.[27] The molecular correlation of OATP1B3 expression with the maintenance of mature hepatocyte function, low serum level of AFP, and good prognosis has been reported.[8,12] We observed different tumor differentiation grade and expression of OATP8 between our high and low intensity groups. The serum levels of AFP were significantly lower of the high than low intensity group. It can thus be suggested that the differences in the SI and the expression of OATP8 in

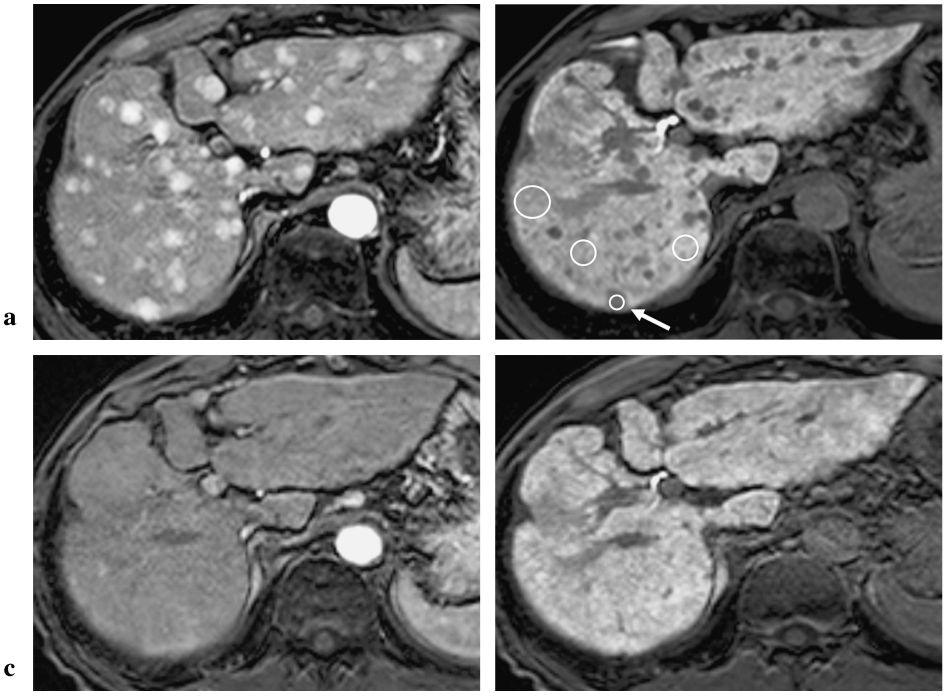

Fig. 2. An 82-year-old man with multiple hepatocellular carcinomas (HCCs) (high intensity group). Gadoxetic acid-enhanced imaging shows multiple hypervascular nodules in the arterial phase (**a**) and hypointense nodules in the hepatobiliary phase (**b**) in both lobes of the liver. Regions of interest (ROIs) were placed at the largest tumor (arrow) and the background liver (**b**); the signal intensity (SI) ratio of the largest tumor was 0.655 (i.e., high intensity group). After 2 courses of hepatic arterial infusion chemotherapy (HAIC), the lesions could not be detected in either the arterial (**c**) or hepatobiliary (**d**) phase. The progression-free days were 631 days after HAIC.

"hypointense" HCCs also reflect the malignancy of HCCs.

Our study has several limitations. First, our population of 14 patients was small, and a larger number of cases would make our findings more reliable. Second, the HAIC regimen was not unified due to variation in the patients' conditions, such as renal dysfunction. Third, because HAIC is the treatment method for patients with advanced HCC, most patients had received other treatments. We cannot deny the possibility that such other treatments prior to HAIC affected our results. However, our findings were similar to those of previous reports,[9,12,14] so we believe our evaluation method was justified. Fourth, imaging parameters varied because MR imaging was performed on 2 different scanners (1.5 and 3T). To lessen this influence, we defined the SIs of tumors as the ratio of tumor SI/background liver SI. Although we compared the SI ratio of the 1.5T group with that of the 3T group, no significant difference was obtained. Fifth, the interval between gadoxetic acid-enhanced MR imaging and HAIC was slightly long in some cases. Sixth, a lesion with maximum diameter may not always manifest the most malignant behavior. However, in our population, no lesion responded differently from others to HAIC. Seventh, liver function may affect the SI ratio of HCC in the HBP.[28] However, there was no significant difference in distribution of Child-Pugh class between our high and low intensity groups. We believe that liver function does not remarkably affect the SI ratio of HCC.

Conclusion

Patients with HCCs with a high SI ratio in the hepatobiliary phase of gadoxetic acid-enhanced MR imaging can respond better to HAIC. The SI of HCCs in the HBP on gadoxetic acid-enhanced MR imaging may be useful in predicting the effects of HAIC treatment.

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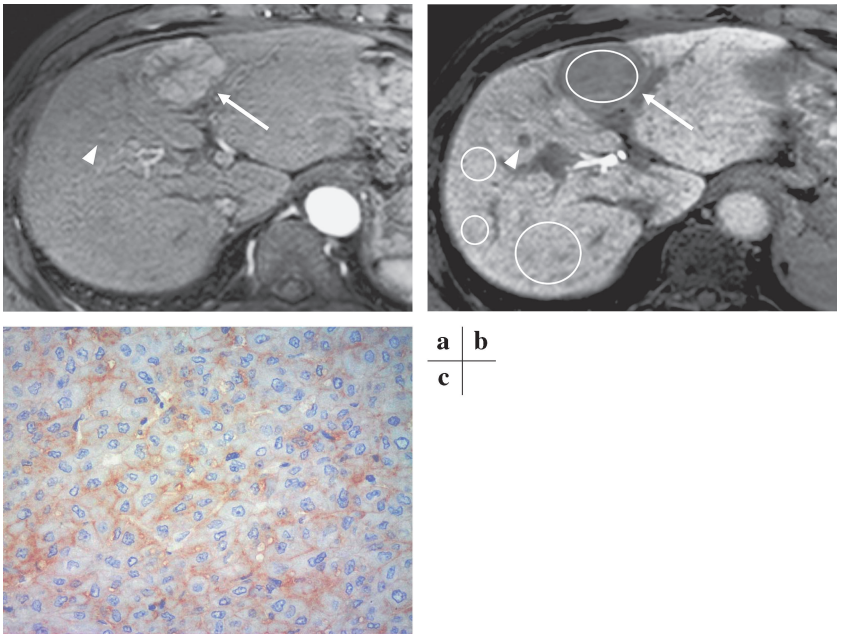

Fig. 3. A 52-year-old man with hepatocellular carcinomas (HCCs) (high intensity group). Gadoxetic acid-enhanced imaging shows a hypervascular nodule in S4 (arrow) and a slightly enhanced nodule in S8 (arrowhead) in the arterial phase (**a**). Both nodules were slightly hypointense in the hepatobiliary phase (**b**). Regions of interest (ROIs) were placed at the tumor and the background liver (**b**); the signal intensity (SI) ratio of the largest tumor was 0.680 (i.e., high intensity group). S4 segmentectomy and microwave coagulation therapy for the lesion in S8 were performed. Immunohistochemically, the tumor cells showed OATP8 expression (**c**). One course of hepatic arterial infusion chemotherapy (HAIC) was performed as postoperative adjuvant chemotherapy. The progression-free days were 494 days after HAIC.

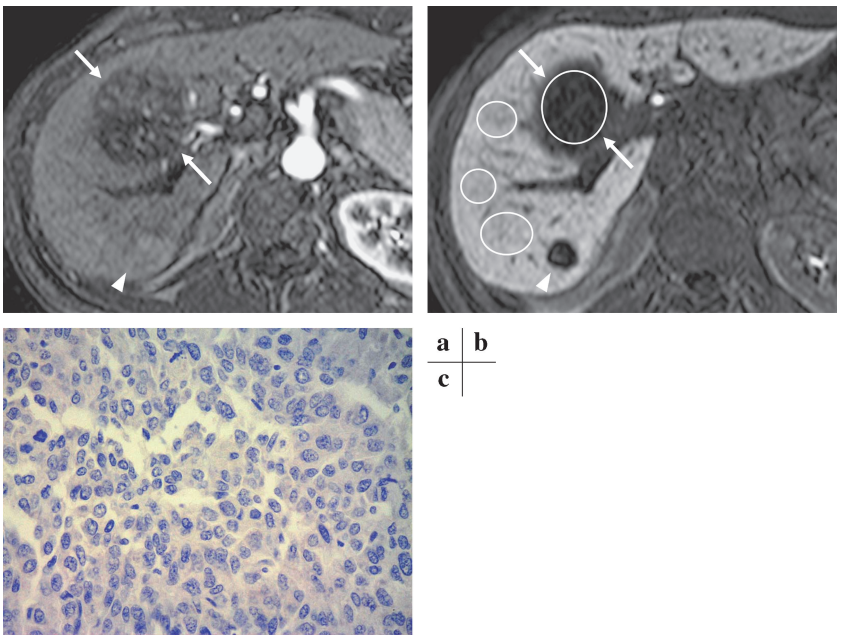

Fig. 4. A 37-year-old man with hepatocellular carcinomas (HCCs) (low intensity group). Gadoxetic acid-enhanced imaging shows a hypovascular nodule in the anterior segment of the right lobe (arrow) and a slightly enhanced nodule in the posterior segment (arrowhead) in the arterial phase (**a**). Both nodules were markedly hypointense in the hepatobiliary phase (**b**). Regions of interest (ROIs) were placed at the tumor and the background liver (**b**); the signal intensity (SI) ratio of the largest tumor was 0.120 (i.e., low intensity group). An expanded right lobectomy was performed. Immunohistochemically, the tumor cells showed no OATP8 expression (**c**). Two courses of hepatic arterial infusion chemotherapy (HAIC) were performed for the recurrent lesions after the surgery. The progression-free days were 85 days after HAIC.

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