High-signal-intensity MR Image in the Hepatobiliary Phase Predicts Long-term Survival in Patients With Hepatocellular Carcinoma

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Abstract. *Background/Aim: The aim of the study was to evaluate surgical outcomes of patients with high-signal intensity (SI) image hepatocellular carcinoma (HCC). Patients and Methods: Between 2008 and 2013, 257 HCC patients were retrospectively evaluated. A total of 21 patients were diagnosed as high-SI image HCC, 215 as low-SI image HCC, and 21 patients as mixed (high and low)-SI image HCC in the hepatobiliary (HB) phase of MRI. Five-year overall survival (OS) and recurrence-free survival (RFS) were compared among patient groups. Results: The 5-year OS and RFS rates were significantly higher in patients with high-SI image HCC (100% and 56%) than in patients with low-SI image HCC (71%; p=0.097 and 38%; p=0.0209) and in patients with mixed-SI image HCC (73%; p=0.0329 and 9%; p=0.0021). High-SI image was an independent prognostic factor for OS (relative risk 0.167, p=0.0178) and RFS (relative risk 0.471, p=0.0322) on multivariate analysis. Conclusion: Patients with high-SI image HCC showed favorable long-term survival after curative surgery.*

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Gadoxetic acid disodium (Gd-EOB-DTPA) is a newly developed liver-specific magnetic resonance imaging (MRI) contrast agent providing combined dynamic images and hepatobiliary (HB) images. This contrast agent is concentrated in the liver parenchyma in the HB phase and is reported to improve the detection of small hepatocellular carcinomas (HCCs) and metastatic liver cancers (1). Gd-EOB-DTPA-enhanced MRI is useful to predict the histological differentiation of HCC and microscopic portal vein invasion of HCC preoperatively (2-5).

This contrast agent is taken into hepatocytes *via* a transporter which is called organic anion transporting polypeptide 8 (OATP8) (6, 7). Therefore, typical HCC commonly shows a low-signal intensity (SI) on the HB images compared with the liver parenchyma because there is no OATP in cancer cells. However, high-SI HCC on HB images has been reported (6-10). The relationship between high SI on HB images and overexpression of OATP8 of HCC cells has been reported (6, 7, 9). Furthermore, the prognostic impact of high-SI HCC on 3-year survival rate has also been reported (9, 11, 12). However, long-term surgical outcomes after curative hepatectomy in patients with high-SI HCC have not been evaluated because high-SI HCC is very rare. Therefore, we attempted to clarify whether there might be a difference in long-term surgical outcomes on the basis of the HB phase images of Gd-EOB-DTPA-enhanced MRI.

Patients and Methods

Between 2008 and 2013, a total of 257 patients with Child-pugh class A and single HCC or 2 nodules HCC were retrospectively

identified from 5 medical university hospitals. Of those, 21 patients showed uncommon high-SI image in the HB phase on Gd-EOB-DTPA-enhanced MRI (Figure 1a and 1b). The patients comprised 16 men (76%) and 5 women (24%), and the median age was 71 years (range=55-82 years). All patients were given a diagnosis of HCC preoperatively because they showed typical HCC images (high density in the arterial phase and low density in the venous phase) on multidetector computed tomography (MDCT) or dynamic MRI. Of the 21 patients, 17 (81%) were given diagnoses of single HCC and 4 (19%) were given diagnoses of two nodular HCCs. The median tumor size on CT scan was 3.5 cm (range=1-10 cm). No patients showed major vascular invasion of HCC.

To determine the prognostic impact of the high-SI image HCC in the HB phase, 215 patients with typical low-SI image HCC in the HB phase were also evaluated (Figure 1c). All those 215 patients showed Child-Pugh class A, typical HCC images, single or 2 nodules, median tumor size of 3.2 cm, and no major vascular invasion of HCC. The remaining 21 patients with heterogeneous mixed (high and low)-SI image HCC were also evaluated (Figure 1d).

This study was proposed by the association for clinical research on surgery (ACRoS-1401) of 5 medical university hospitals. Information of this study was obtained by opt-out for all patients because this study was a retrospective cohort study. The local committees for medical ethics and clinical studies of each of the 5 medical universities approved this study. The ethics committee of TWMU approved this study (approval number: 3084).

Gd-EOB-DTPA-enhanced MRI. MRI was performed according to the protocol of each hospital. All patients received a dose of 0.1 ml/kg Gd-EOB-DTPA (Primovist; Bayer Schering Pharma AG, Berlin, Germany) intravenously at a rate of 1 ml/sec. Dynamic studies (arterial dominant phase, portal phase, venous phase, and equilibrium phase) and HB phase images were taken at 15-20 min after the injection (4).

Signal intensity (SI) within the tumor in the HB phase was classified into high-SI, low-SI, or mixed-SI HCC. Tumors that showed a homogenous high-SI within the tumor in the HB phase compared with that of the liver parenchyma and determined to be high-SI image HCC (Figure 1a, b). On the other hand, tumors that showed a homogenous low-SI within the tumor were determined to be low-SI image HCC (Figure 1c). Tumors that showed a heterogeneous high- and low-SI within the tumor were determined mixed-SI image HCC (Figure 1d). The relative SI within the tumor was also assessed as follows; the SI of the tumor and liver parenchyma were measured on the same image using oval regions of interest (ROI). The relative SI was calculated as follows: Relative SI=SI tumor/SI liver parenchyma (9). These findings were determined by all authors who had over 15 years of experience in liver surgery and a radiologist with 20 years of experience in radiological diagnosis.

Surgery and pathological evaluation. All patients underwent hepatectomy within 2 weeks after Gd-EOB-DTPA-enhanced MRI at each of the 5 university hospitals. Sixteen of 21 patients with high-SI HCC underwent anatomical hepatectomy, and 5 patients underwent non-anatomical partial resection. The choice of resection was made on the basis of the tumor location and liver function (ICGR15). No mortality was seen in the 21 patients with high-SI HCC. Macroscopic morphology of tumor type and pathological findings were examined according to the General Rules for the

Clinical and Pathological Study of Primary Liver Cancer of the Liver Cancer Study Group of Japan (13). The terminology of liver resection was determined based on the Terminology Committee of the International Hepato-Pancreato-Biliary Association in 2000 (14).

Follow-up and treatment of patients with recurrence. After surgery, patients were followed up every 4-12 weeks at the 5 university hospitals, and the mean follow-up period was 45±28 months (range=0.7-112 months). Ultrasonography or CT was performed once every 3-4 months. Cause-specific survival was defined as the time from hepatectomy to the date of cancer-death, liver failure-death or last contact. When a solitary HCC recurred in the liver, hepatectomy was repeated or radiofrequency ablation was performed. When multiple HCCs recurred in the liver, transarterial chemoembolization (TACE) was performed.

Statistical analysis. Categorical variables were assessed using the chi-square test or Fisher exact test, and continuous variables were assessed using the *t*-test. Continuous variables were divided into two groups according to the median value (Age, ICGR15, and tumor size) and normal cut off value (AFP and PIVKA-II). Patient overall survival (OS) and recurrence-free survival (RFS) were calculated using the Kaplan–Meier method, and comparison of survival curves was made with the log-rank test. Potential predictors of OS and RFS were evaluated in a multivariate Cox's proportional hazard model. *p*-Values less than 0.05 ($p<0.05$) were taken to indicate statistical significance. JMP software (version 13.0; SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

Twenty-one of 257 patients showed high-SI image HCC, and the rate of patients with high-SI image HCC was 8.1%. The patient clinical characteristics are shown in Table I. After comparison between patients with high-SI image HCC and low-SI image HCC, gender did not differ between groups, nor did the median age. The median tumor size did not differ between groups, nor did the number of tumors, and the number of cirrhosis cases. The median ICGR15, AFP, and PIVKA-II did not differ between groups. The number of patients with anatomical hepatectomy did not differ between groups. Eighteen of 21 patients (86%) with high-SI image HCC showed the simple nodular (SN) type and 13 of 21 patients (62%) showed the so-called green hepatoma. The SN type and so-called green hepatoma were significantly more frequent in patients with high-SI image HCC than in patients with low-SI image HCC (53%: $p=0.0035$ and 13%: $p<0.0001$). Patients with high-SI image HCC showed well (33%) or moderately (67%) differentiated HCC. No patients with high-SI image HCC had microscopic portal vein invasion or intrahepatic metastasis. Microscopic portal invasion was significantly lower in patients with high-SI image HCC than in patients with low-SI image HCC (18%: $p=0.0354$).

After comparison between patients with high-SI image HCC and those with mixed-SI image HCC, median tumor size did not differ between groups, nor did the number of

Table I. *Patient characteristics.*

		High-SI image n=21	Low-SI image n=215	Mixed-SI image n=21	*p*-Value High *vs.* Low	*p*-Value High *vs.* Mixed
Gender	Male	16 (76%)	170 (79%)	16 (76%)	0.76	0.08
Age	Median (range), year	71 (55-82)	70 (35-90)	67 (26-80)	0.49	0.85
Child-Pugh	A	21 (100%)	215 (100%)	21 (100%)	1	1
Relative signal intensity	Median (range)	1.22 (1.02-1.50)	0.65 (0.17-0.99)	0.89 (0.55-1.50)	<0.0001	<0.0001
Tumor size on CT or MRI	Median (range), cm	3.5 (1-10)	3.2 (1-12)	4.2 (1.7-17)	0.9	0.63
Number of tumors on CT or MRI	Single/2 nodules	17 (81%)/ 4 (19%)	183 (85%)/ 32 (15%)	17 (81%)/ 4 (19%)	0.61	0.68
Hepatitis C Virus	Present	7 (33%)	93 (43%)	11 (52%)	0.38	1
Cirrhosis	Present	8 (38%)	71 (33%)	9 (43%)	0.64	1
ICGR15	Median (range), %	14 (2-38)	12 (3-47)	13 (4-43)	0.24	0.88
AFP	Median (range), ng/ml	4 (1-739)	10 (1-40539)	7 (2-810)	0.33	0.76
	<10 ng/ml	15 (71%)	104 (48%)	11 (52%)	0.0437	0.12
PIVKA-II	Median (range), U/ml	27 (10-7319)	73 (10-226200)	192 (11-26170)	0.5	0.41
	<40 U/ml	14 (67%)	87 (41%)	5 (24%)	0.0238	0.21
Surgical procedure	Anatomical	16 (76%)	165 (77%)	19 (90%)	0.95	0.49
Blood loss	Median (range), ml	315 (1-2340)	491 (1-6342)	684 (159-7865)	0.39	0.54
Blood transfusion	Present	2 (10%)	27 (13%)	3 (14%)	0.68	0.58
30 days mortality	Present	0	2 (0.9%)	0	0.99	1
Macroscopic tumor type	SN/SNEG or CM	18 (86%)/ 3 (14%)	113 (53%)/ 102(47%)	11 (52%)/ 10 (48%)	0.0035	0.15
Green hepatoma	Present	13 (62%)	29 (13%)	9 (43%)	<0.0001	0.0126
Tumor differentiation	Well/Moderately/Poorly-Other	7 (33%)/ 14 (67%)/ 0 (0%)	24 (11%)/ 159 (74%)/ 32 (15%)	2 (10%)/ 17 (80%)/ 2 (10%)	0.0055	0.24
Microscopic portal invasion	Present	0 (0%)	38 (18%)	5 (24%)	0.0354	0.03
Intrahepatic metastasis	Present	0 (0%)	18 (8%)	4 (19%)	0.17	0.15

SI: Signal-intensity; Mixed: High and Low-SI; MRI: magnetic resonance imaging; ICGR15: indocyanine green retention rate at 15 min; AFP: alpha-fetoprotein; PIVKAII: protein induced by vitamin K absence and antagonist-II; SN: simple nodular type; SNEG: simple nodular with extranodular growth type; CM: confluent multinodular type.

tumors, and the number of cirrhosis cases. The median ICGR15, AFP, and PIVKA-II did not differ between groups, whereas the median relative SI was significantly different between groups (Table I). The green hepatoma was significantly more frequent in patients with high-SI image HCC than in patients with mixed-SI image HCC (43%: *p*=0.0126). Microscopic portal invasion was significantly lower in patients with high-SI image HCC than in patients with mixed-SI image HCC (24%: *p*=0.03).

No patients with high-SI image HCC died within 30 days after hepatectomy. One patient died of HCC recurrence 88 months after hepatectomy. The overall survival (OS) rate for 21 patients with high-SI image HCC was 100% at 5 years. The 5-year OS rate was significantly higher in patients with high-SI image HCC (100%) than in patients with low-SI image HCC (71%: *p*=0.0297, Figure 2a). In 7 of 21 patients with high-SI image HCC, HCC recurred in the remnant liver during follow-up. No patients showed extrahepatic recurrence. The 5-year RFS rate was significantly higher in patients with high-SI image HCC (56%) than in patients with low-SI image HCC (38%: *p*=0.0209, Figure 2b).

The 5-year OS rate and RFS rate were significantly higher in patients with high-SI image HCC (100% and 56%) than in patients with mixed-SI image HCC (73%: *p*=0.0329, Figure 2a and 9%: *p*=0.0021, Figure 2b).

The univariate analysis of prognostic factors of survival is summarized in Table II. The univariate prognostic factors were entered into a multivariate model to identify independent predictors of survival and recurrence free survival. The factors by Cox's proportional hazard model are shown in Table III. High-SI image was a significant independent prognostic factor for OS (relative risk 0.167, *p*=0.0178) and RFS (relative risk 0.471, *p*=0.0322) on multivariate analysis. However, mixed-SI image was not a significant prognostic factor for OS and RFS. Similarly, relative signal intensity was a significant independent prognositic factor for RFS, but it was not a significant prognostic factor for OS.

Discussion

Typical HCC commonly showed low-SI in the HB phase compared with the liver parenchyma. However, approximately
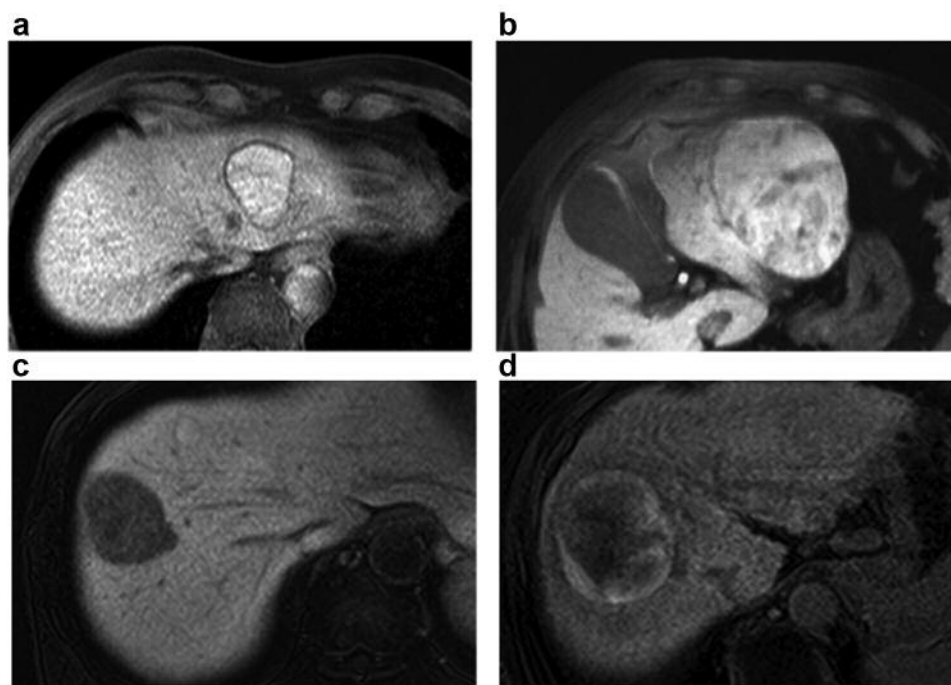
Figure 1. *A tumor showing high-signal-intensity (SI) image (a, b), a low- SI image (c), and mixed (high and low)-SI image (d) in the HB phase on Gd-EOB-DTPA-enhanced MRI.*

Table II. *The univariate analysis of prognostic factors of survival and recurrence-free survival.*

		Number	5-year overall survival (%)	*p*-Value	5-year recurrence-free survival (%)	*p*-Value
Gender	Male	203	72%	0.67	36%	0.67
	Female	54	79%		40%	
Age, year	<70	121	83%	0.0036	47%	0.0047
	≥70	136	65%		26%	
Hepatitis C Virus	Absent	147	81%	0.0026	44%	0.0018
	Present	110	64%		26%	
ICGR15, %	<15	165	83%	0.0011	43%	0.0008
	≥15	92	57%		25%	
AFP, ng/ml	<10	130	74%	0.23	38%	0.14
	≥10	127	73%		35%	
PIVKA-II, U/ml	<40	103	83%	0.0171	52%	<0.0001
	≥40	151	67%		26%	
Size, cm	<3	120	84%	0.0212	38%	0.22
	≥3	137	65%		36%	
Number	1 nodule	218	76%	0.09	38%	0.06
	2 nodules	39	63%		26%	
Hepatobiliary phase image	High-SI	21	100%	High *vs.* Low: 0.0297	56%	High *vs.* Low: 0.0209
	Low-SI	215	71%	High *vs.* Mixed: 0.0329	38%	High *vs.* Mixed: 0.0021
	Mixed-SI	21	73%		9%	
Relative signal intensity	SI>1	26	96%	0.09	47%	0.0322
	SI<1	231	71%		35%	
Surgery	Anatomical	199	77%	0.06	40%	0.15
	No anatomical	58	62%		24%	

ICGR15: Indocyanine green retention rate at 15 min; AFP: alpha-fetoprotein; PIVKAII: protein induced by vitamin K absence and antagonist-II; SI: signal-intensity.
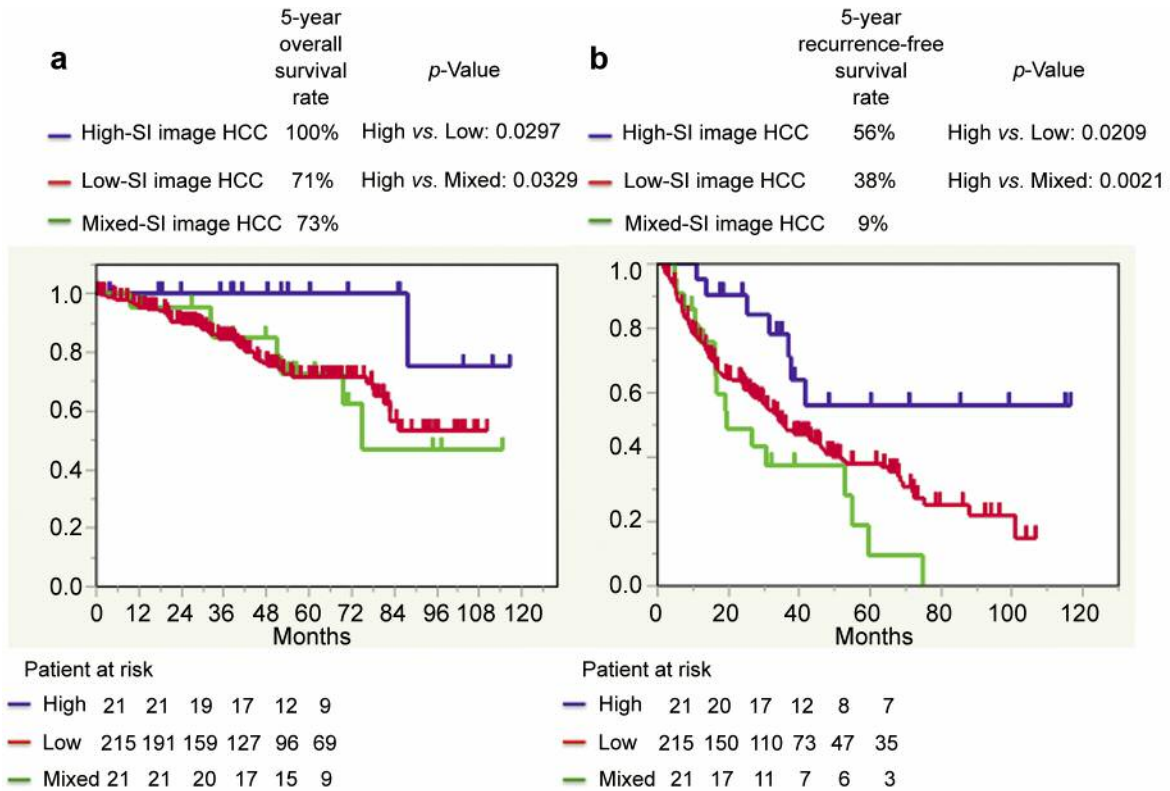
Figure 2. *The overall survival curves (a) and recurrence-free survival curves (b).*

Table III. *Multivariate analysis.*

		Overall survival			Recurrence-free survival		
		Relative risk	95%CI	*p*-Value	Relative risk	95%CI	*p*-Value
Age	<70	0.535	(0.293, 0.949)	0.0321	0.747	(0.520, 1.066)	0.11
	≥70	1			1		
Hepatitis C Virus	Absent	0.471	(0.271, 0.809)	0.0064	0.602	(0.425, 0.851)	0.0044
	Present	1			1		
ICGR15, %	<15	0.415	(0.244, 0.701)	0.0011	0.630	(0.445, 0.884)	0.0094
	≥15	1			1		
PIVKA-II, U/ml	<40	0.849	(0.443, 1.569)	0.61	0.513	(0.341, 0.733)	0.0005
	≥40	1			1		
Size, cm	<3	0.431	(0.231, 0.781)	0.0052			
	≥3	1					
Hepatobiliary phase image	High-SI	0.167	(0.009, 0.782)	0.0178	0.471	(0.198, 0.943)	0.0322
	Mixed-SI	0.751	(0.298, 1.644)	0.49	1.077	(0.597, 1.829)	0.79
	Low-SI	1			1		
Relative signal intensity	SI>1	0.431	(0.104, 1.198)	0.12	0.534	(0.261, 0.969)	0.0383
	SI<1	1			1		

ICGR15: Indocyanine green retention rate at 15 min; PIVKAII: protein induced by vitamin K absence and antagonist-II; SI: signal-intensity; CI: confidence interval.

10% of HCC has been reported to show uncommonly high-SI in the HB phase (6-10). Recently, the 3-year survival rates of patients with high-SI HCC have been reported. Kitao *et al*. have reported that 22 patients with hyperintense HCC tended to show longer survival than those with hypointense HCC, and the 3-year survival rate of 22 patients with hyperintense HCC was 100% (9). Miura *et al*. have also reported that in 14 patients with high-SI HCC the 3-year OS rate was 100% (11).

In the present study, the OS rate of patients with high-SI image HCC after curative surgery was 100% at 5 years, because no patients died due to HCC recurrence within 5 years. Moreover, multivariate analysis showed high-SI image HCC to be a significant independent prognostic factor for overall survival (relative risk=0.167, p=0.0178) and recurrence-free survival (relative risk=0.471, p=0.0322) in patients with HCC. High-SI image HCC shows uncommon MR images, but patients with high-SI image HCC showed favorable long-term survival after curative surgery.

High-SI HCC is known to show lower levels of serum AFP or PIVKA-II (7-12). Yamashita *et al*. have reported that Gd-EOB-DTPA uptake in the HB phase correlated with low serum AFP levels, maintenance of hepatocyte function with the up-regulation of OATP1B3 and HNF4A expression, and good prognosis (12). Kitao *et al*. have reported that the rate of portal vein invasion was significantly lower in patients with hyperintense HCC (13.6%) than in patients with hypointense HCCs (36.7%) (9). Kim *et al*. have also reported that the rate of microvascular invasion was significantly lower in 18 patients with hyperintense HCCs (27.8%) than in patients with hypointense HCCs (53.5%) (10). In the present study, 15 of 21 patients with high-SI image HCC showed normal AFP levels (<10 ng/ml), and no patient with microscopic portal vein invasion of HCC was observed. Moreover, the 5-year RFS rate was significantly higher in patients with high-SI image HCC (56%) than in patients with low-SI image HCC (38%; p=0.0209). Therefore, patients with high-SI image HCC had better surgical outcomes because high-SI image HCC showed less portal vein invasion, less intrahepatic metastasis, and lower recurrence of HCC.

In the present study, 21 patients showed heterogeneous high and low-SI (mixed-SI) image HCC in the HB phase. The patients with heterogeneous mixed-SI image HCC included 5 patients with relative SI >1 and 16 patients with relative SI <1. There have been no previous reports regarding surgical outcome in patients with heterogeneous mixed-SI image HCC. In our present study, 5-year OS rates and RFS rates were significantly higher in patients with high-SI image HCC (100% and 56%) than in patients with mixed-SI image HCC (73%: p=0.0329 and 9%: p=0.0021). Patients with mixed-SI image HCC showed a heterogeneous high- and low-SI within the tumor but poor surgical outcomes compared with patients with homogeneous high-SI image HCC because some patients with heterogeneous mixed-SI image HCC had microscopic portal invasion and intrahepatic metastasis.

Previous reports have shown better surgical outcomes in patients with hyperintense HCC, and they have shown 3-year OS rates and 3-year RFS rates in relation to the relative SI (between patients with SI >1 and SI <1) by univariate analysis (9, 11, 12, 15). Our results showed long-term surgical outcomes (5-year OS rate and 5-year RFS rate) after

hepatectomy in relation to the HB image, and high-SI image HCC revealed as a novel prognostic factor on univariate and multivariate analysis. Furthermore, patients with heterogeneous mixed-SI image HCC showed a high- and low-SI within the tumor but poor surgical outcomes compared with patients with high-SI image HCC. Furthermore, relative SI was not a significant prognostic factor for OS. In conclusion, high-SI image in the HB phase is a novel prognostic factor for OS and RFS in patients with HCC.

Authors' Contributions

Conflicts of Interest

Acknowledgements

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