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ORIGINAL ARTICLE

A non-smooth tumor margin in the hepatobiliary phase of gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging predicts microscopic portal vein invasion, intrahepatic metastasis, and early recurrence after hepatectomy in patients with hepatocellular carcinoma

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Abstract
Background The value of the hepatobiliary phase of gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) in patients with hepatocellular carcinoma (HCC) has not been evaluated in detail.
Methods Between 2008 and 2009, 61 patients with HCC within the Milan criteria underwent Gd-EOB-DTPA-enhanced MRI and hepatectomy. The tumor margin was determined preoperatively based on hepatobiliary phase images. Microscopic portal vein invasion (MPVI), intrahepatic metastasis (IM), and recurrence of HCC within 1 year after hepatectomy were evaluated in 24 patients with non-smooth margins at the periphery of the tumor and 37 patients with smooth margins.
Results The number of patients with MPVI and IM of HCC was significantly higher among those with non-smooth margins (42 and 38%, respectively) than among those with smooth margins (3%; $p = 0.0002$ and 5%; $p = 0.0042$, respectively). A non-smooth margin was identified as a significant predictor of MPVI (odds ratio 18.814, $p = 0.024$) and IM (odds ratio 6.498, $p = 0.036$) of HCC on multivariate analysis. Furthermore, a non-smooth margin was identified as a significant predictor of recurrence within 1 year after hepatectomy (odds ratio 4.306, $p = 0.04$) on multivariate analysis.
Conclusions A non-smooth tumor margin in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI is useful to predict MPVI, IM, and early recurrence of HCC after hepatectomy.

Keywords Hepatocellular carcinoma · Vascular invasion · MRI

Introduction

Microscopic vascular invasion (MVI) of hepatocellular carcinoma (HCC); in particular, microscopic portal vein invasion (MPVI), is known to be a prognostic factor after hepatectomy or liver transplantation even in patients with small HCC [1–7]. Tumor size, tumor grade, and tumor markers have been reported to predict MVI of HCC [8–13]. It has recently been reported that radiological findings with recent diagnostic imaging were useful for predicting MVI of HCC [14–17]. Gadoxetic acid disodium (Gd-EOB-DTPA) is a newly developed liver-specific magnetic resonance imaging (MRI) contrast agent with combined dynamic imaging and hepatocyte-selective properties. This contrast agent is concentrated in the liver parenchyma in the hepatobiliary phase and is reported to improve the detection of small HCCs and predict the histological differentiation of HCC [18–20]. However, the relationship between MVI of HCC and the hepatobiliary phase findings on Gd-EOB-DTPA-enhanced MRI has not been evaluated in detail. We therefore attempted to clarify whether there might be a difference in MVI of HCC according to the hepatobiliary phase findings on Gd-EOB-DTPA-enhanced MRI in patients with HCC within the Milan criteria [21]. Furthermore, as there

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have been no previous reports on the topic, to the best of our knowledge, we attempted to clarify whether there might be a difference in surgical outcomes based on the hepatobiliary phase findings on Gd-EOB-DTPA-enhanced MRI.

Patients, materials, and methods

Between 2008 and 2009, 135 patients were given a diagnosis of HCC based on ultrasonography and multidetector computed tomography (MDCT). Of these, 91 patients underwent Gd-EOB-DTPA-enhanced MRI, and 61 patients were enrolled in this study because they were within the Milan criteria on the imaging findings. There were 49 men (80%) and 12 women (20%), and the mean age was 67 years (range 51–83 years). The Child-Pugh class, indocyanine green retention rate at 15 min ($ICGR_{15}$), serum level of alpha-fetoprotein (AFP), and serum level of protein induced by vitamin K absence and antagonist-II (PIVKA-II) were examined preoperatively. The median and mean AFP values were 14 and 265 ng/ml, respectively, and the median and mean PIVKA-II values were 35 and 559 mAU/ml, respectively. Of the 61 patients, 53 were given diagnoses of single HCC, 5 cm or less in diameter; 4 were given diagnoses of two nodular HCCs, 3 cm or less in diameter; and 4 were given diagnoses of three nodular HCCs, 3 cm or less in diameter. In patients with multiple HCCs, only the largest lesion was analyzed. Of the 61 patients, 7 patients had a history of hepatectomy for HCC. Five of these 7 patients were given diagnoses of second primary HCC, since recurrent HCC would have been detected within 5 years after the initial hepatectomy. Two of these 7 patients were suspected to have intrahepatic recurrence of HCC, since recurrence was detected within 1 year after initial hepatectomy. However, these 2 patients were included in this study since they met the Milan criteria for MRI findings. The clinical characteristics and MRI findings of the patients are shown in Table 1. Written informed consent was obtained from all patients before hepatectomy.

All patients underwent MDCT (X vigor; Toshiba Medical System, Nasu, Japan) and Gd-EOB-DTPA -enhanced MRI at our institute. MRI was performed with a 1.5-T MRI system (INTERA ACHIEVA 1.5T; Philips Medical Systems, Best, Netherlands). Routine in-phase and opposed phase T1-weighted images (TR, 146 ms; TE, 2.3 ms and 4.6 ms, respectively; flip angle 80°, matrix, 512 × 512; field of view, 375 × 375 mm; section thickness, 7 mm; intersection gap, 1 mm) were obtained. Precontrast images were obtained in a transverse plane with a fat-suppressed two-dimensional (2D) T1-weighted gradient echo (GRE) sequence (TR, 191 ms; TE, 4.5 ms; flip angle 75°; matrix, 512 × 512; field of view, 375 × 375 mm; section thickness, 7 mm; intersection gap, 1 mm). All patients received a dose of 0.1 ml/kg Gd-EOB-DTPA (Primovist; Bayer Schering Pharma, Berlin, Germany) intravenously at a speed of 2 ml/s. The line was flushed with 20 ml of saline. Immediately after the start of the Gd-EOB-DTPA injection, dynamic studies with a fat-suppressed 2D T1-weighted GRE sequence were performed during the arterial dominant phase (20 s), portal phase (60 s), venous phase (120 s), and equilibrium phase (180 s). T2-weighted fast

Table 1 Clinical characteristics and MRI findings

	$n = 61$
Sex (men/women)	49/12
Age, years, mean ± SD (range)	67 ± 8 (51–83)
HBs antigen (positive/negative)	14/47
HCV antibody (positive/negative)	30/31
$ICGR_{15}$, % (mean ± SD)	16 ± 10
Child-Pugh (A/B)	56/5
Cirrhosis (present/absent)	26/35
AFP (ng/ml)	
Mean ± SD	265 ± 732
Median (25th percentile, 75th percentile)	14 (4, 160)
PIVKA-II (mAU/ml)	
Mean ± SD	559 ± 2137
Median (25th percentile, 75th percentile)	35 (21, 190)
Tumor size on MRI (cm) (mean ± SD)	2.9 ± 1.0
Tumor number on MRI (single/multiple)	53/8
Arterial phase findings on MRI (high/low)	51/10
Radiological tumor capsule in the dynamic studies (incomplete/complete/absent)	19/16/26
Tumor margin in the axial hepatobiliary phase (non-smooth/smooth)	24/37

MRI magnetic resonance imaging, *HBs* hepatitis B surface, *HCV* hepatitis C virus, *$ICGR_{15}$* indocyanine green retention rate at 15 min, *AFP* alpha-fetoprotein; normal level <10 ng/ml, *PIVKA-II*c protein induced by vitamin K absence and antagonist-II; normal level <40 mAU/ml

spin echo (T2W) sequences (TR, 2500; TE, 90; flip angle 90°; matrix, 512 × 512; field of view, 375 × 375 mm; section thickness, 7 mm; intersection gap, 1 mm) were taken after the dynamic images. Hepatobiliary phase images were taken at 10–15 min after the end of injection with T1W images with fat suppression. This protocol was determined and all patients were given a diagnosis of HCC by a radiologist (R.K.) and hepatic surgeons who had expertise in liver MR imaging.

The tumor capsules in the axial dynamic MRI (venous and/or equilibrium phase) and CT scans were classified as complete radiological capsules, which completely surrounded the entire circumference of the tumor; incomplete radiological capsules; which partially surrounded the tumor circumference; and absence of radiological capsules.

Tumor margins in the axial and coronal hepatobiliary phase were classified as those with a smooth margin at the periphery of the tumor and those with a non-smooth margin. If a tumor had a minute budding portion at its periphery protruding into the liver parenchyma, the tumor margin was considered to be non-smooth (Figs. 1, 2, 3). However, if a tumor had no budding portion at the periphery, the tumor margin was considered to be smooth (Fig. 4). These radiological findings were determined in each patient preoperatively by the authors, who have had over 10 years of experience in liver surgery.

Recurrence within 1 year of HCC (early recurrence) after hepatectomy was evaluated according to the tumor margin in the hepatobiliary phase.

All patients underwent hepatectomy within 2 weeks after the Gd-EOB-DTPA-enhanced MRI. Thirty of the 61 patients underwent anatomical sectionectomy or larger resection by the Glissonean pedicle transection method [22, 23], 18 patients underwent anatomical segmentectomy, and 13 patients underwent non-anatomical partial resection. The choice of resection was made on the basis of the CT findings, Gd-EOB-DTPA-enhanced MR images, and liver function ($ICGR_{15}$). In patients with an incomplete radiological capsule and/or a non-smooth margin in the hepatobiliary phase, sectionectomy or larger resection was performed considering functional liver reserve. Therefore, in patients with an incomplete radiological capsule and/or a non-smooth margin in the hepatobiliary phase and poor functional liver reserve, segmentectomy or non-anatomical partial resection was performed. However, in patients with a complete radiological capsule and a smooth margin,

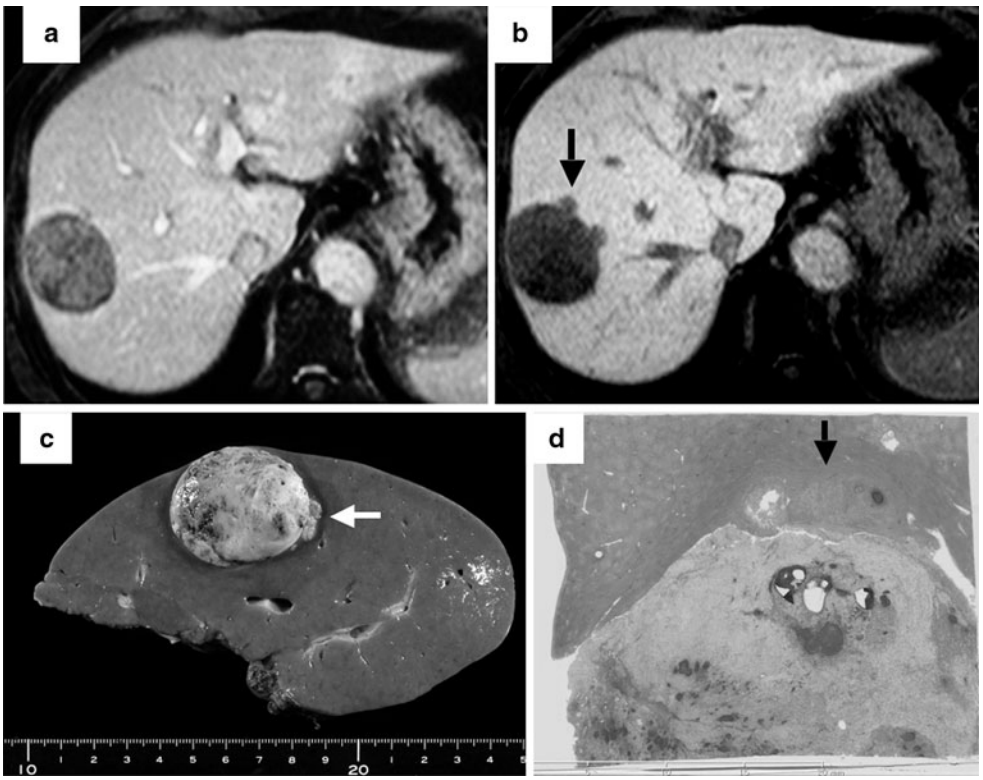

Fig. 1 A tumor shows low intensity with a thin linear-enhancing structure on a dynamic image. The tumor capsule was determined to be a complete radiological capsule (**a**). A tumor shows low intensity with a minute budding portion at its periphery protruding into the liver parenchyma in a hepatobiliary phase image on gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI). This tumor margin was considered to be non-smooth (**b** *arrow*). Macroscopically, the resected tumor was a simple nodular with extranodular growth type hepatocellular carcinoma (HCC) (**c** and **d** *arrows*)

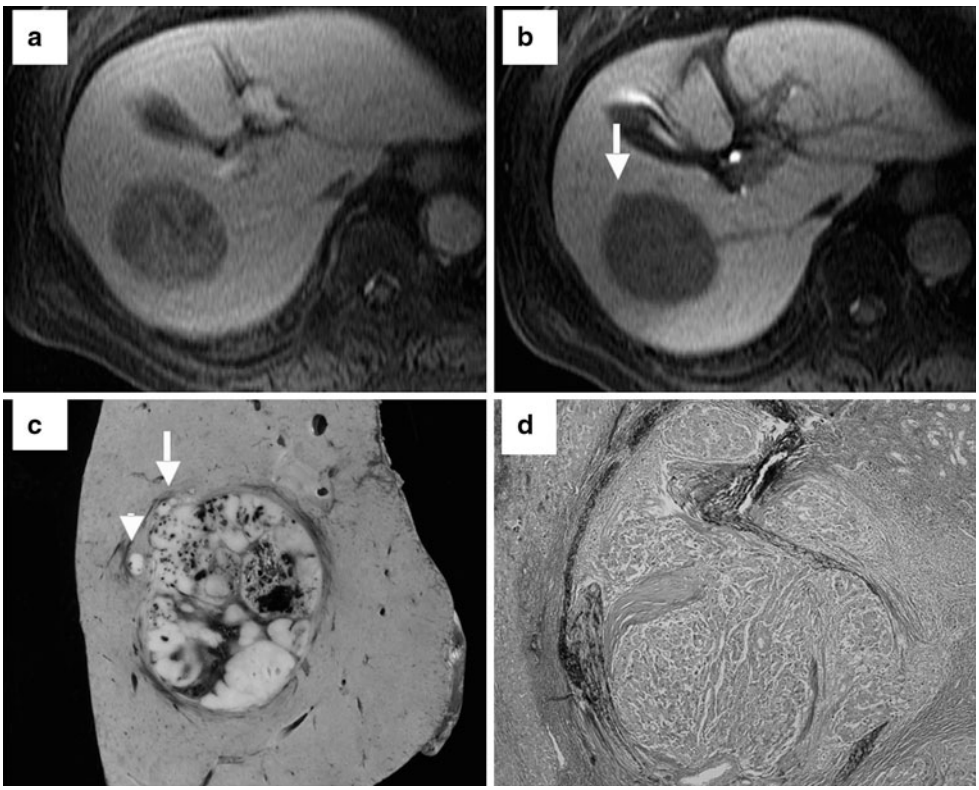

Fig. 2 A tumor shows low intensity with a thin linear-enhancing structure on a dynamic image. The tumor capsule was determined to be a complete radiological capsule (**a**). A tumor shows low intensity with a minute budding portion at its periphery protruding into the liver parenchyma in a hepatobiliary phase image on Gd-EOB-DTPA-enhanced MRI. This tumor margin was considered to be non-smooth (**b** *arrow*). Macroscopically, the resected tumor was a simple nodular with extranodular growth type HCC (**c** *arrow*) with intrahepatic metastasis (**c** *arrowhead*). Microscopically, portal vein invasion of HCC was seen. Victoria blue hematoxylin and eosin (VHE) staining, ×10 (**d**)

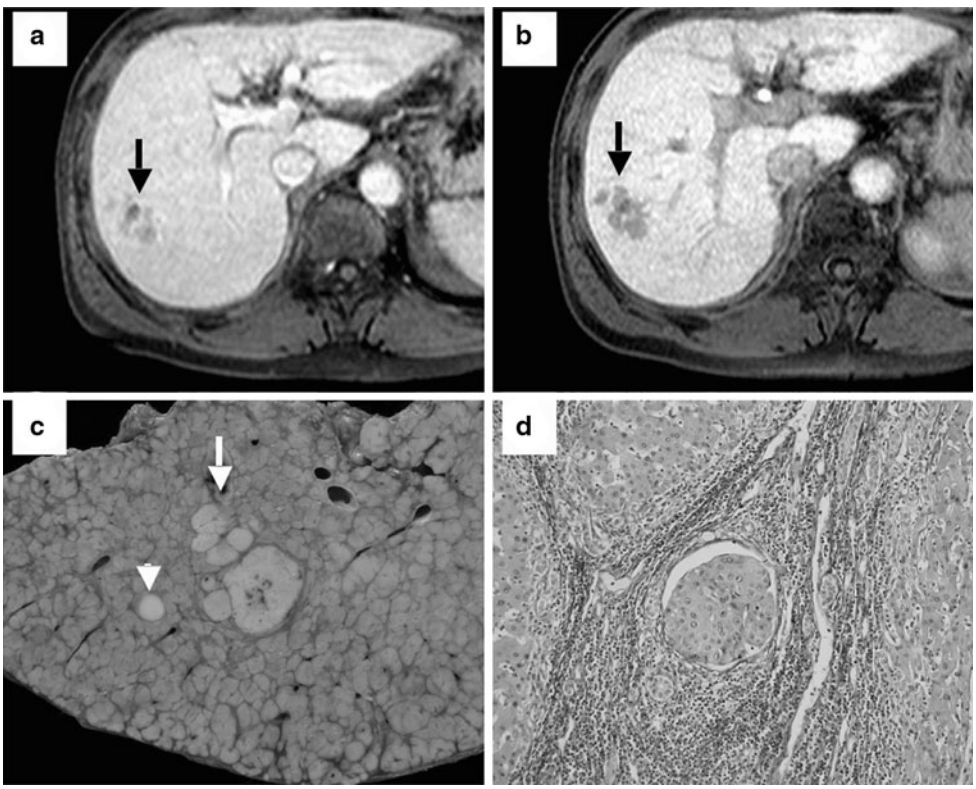

Fig. 3 A tumor shows low intensity with absence of a radiological tumor capsule on a dynamic image (**a** *arrow*). A tumor shows low intensity with a minute budding portion at its periphery protruding into the liver parenchyma in the hepatobiliary phase on Gd-EOB-DTPA-enhanced MRI. This tumor margin was considered to be non-smooth (**b** *arrow*). **b** Macroscopically, the resected tumor was confluent multinodular type HCC (**c** *arrow*) with a small intrahepatic metastasis (**c** *arrowhead*). Microscopically, portal vein invasion of HCC was seen. Victoria blue hematoxylin and eosin (VHE) staining, ×20 (**d**)

segmentectomy or non-anatomical partial resection was performed. Macroscopic tumor type, MPVI, and intrahepatic metastasis (IM) 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 [24]. The terminology of liver resection was

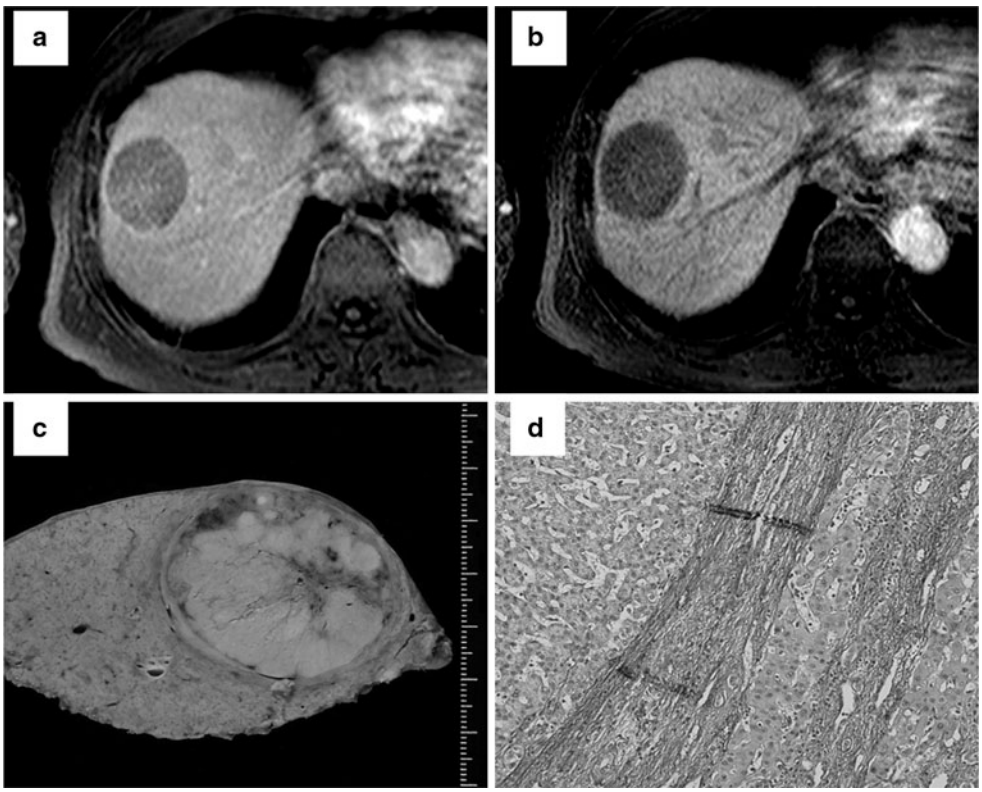

Fig. 4 A tumor shows low intensity with a thin linear-enhancing structure on a dynamic image. The tumor capsule was determined to be a complete radiological capsule (**a**). A tumor shows low intensity, with no budding portion at the periphery, in the hepatobiliary phase image; the tumor margin was considered to be smooth (**b**). Macroscopically, the resected tumor was a simple nodular type HCC with capsule (**c**). Microscopically, the tumor cells did not invade the capsule. Victoria blue hematoxylin and eosin (VHE) staining, ×20 (**d**)

determined based on the Terminology Committee of the International Hepato-Pancreato-Biliary Association in 2000 [25].

Statistical analysis

Categorical variables were assessed using the χ^2 test or Fisher's exact test, and continuous variables were assessed using the unpaired *t*-test or Mann–Whitney *U*-test. A logistic stepwise regression model was used to identify predictive factors for MPVI, IM, and early recurrence of HCC. *p* values less than 0.05 ($p < 0.05$) were taken to indicate statistical significance. We used Stat View (version 4.5; Hulinks, Tokyo, Japan) and SPSS (version 11.0J; SPSS, Tokyo, Japan) for statistical analysis.

Results

Pathological findings in relation to MRI and CT are shown in Tables 2 and 3. The number of patients with MPVI of HCC was significantly higher among those with incomplete radiological capsules in the dynamic studies (42%) than among those with complete radiological capsules (6%) and those with absence of radiological capsules (8%). The number of patients with MPVI of HCC was significantly higher in patients with a non-smooth margin in the axial hepatobiliary phase (42%) than in those with a smooth margin (3%, $p = 0.0002$). The number of patients with IM did not differ significantly in relation to the radiological capsules, whereas the number of patients with IM was significantly higher among patients with a non-smooth margin in the axial hepatobiliary phase (38%) than among patients with a smooth margin (5%, $p = 0.0043$).

The clinical and MRI findings submitted to univariate analysis to predict MPVI and IM of HCC are shown in Tables 4 and 5. There were no clinical or MRI findings that predicted MPVI, except for the radiological capsule in the dynamic studies and tumor margin in the axial hepatobiliary phase. However, the number of patients with IM of HCC was significantly higher among patients with multiple HCCs on MRI (45%) than among those with a single HCC on MRI (3%).

A logistic stepwise regression model with significant variables determined by the univariate analysis was used to identify predictive factors for MPVI and IM of HCC (Table 6). A non-smooth margin was identified as a significant predictor of both MPVI (odds ratio 18.814,

Table 2 Pathological findings in relation to MRI and CT scan

Pathological findings	Radiological capsule in the dynamic studies on MRI				Radiological capsule on CT scans			
	Incomplete ($n = 19$)	Complete ($n = 16$)	Absence ($n = 26$)	p value	Incomplete ($n = 14$)	Complete ($n = 17$)	Absence ($n = 30$)	p value
Macroscopic type								
SNIM	0	0	8 (31%)	<0.0001	0	0	8 (27%)	<0.0001
SN	2 (11%)	14 (88%)	10 (38%)		4 (29%)	11 (65%)	11 (37%)	
SNEG	14 (74%)	2 (13%)	3 (12%)		9 (64%)	6 (35%)	4 (13%)	
CM	3 (16%)	0	5 (19%)		1 (7%)	0	7 (23%)	
Capsule								
Present	14 (74%)	13 (81%)	12 (46%)	0.0402	14 (100%)	13 (76%)	12 (40%)	0.0003
Microscopic portal vein invasion								
Present	8 (42%)	1 (6%)	2 (8%)	0.0044	3 (21%)	2 (12%)	6 (20%)	0.73
Microscopic hepatic vein invasion								
Present	0	1 (6%)	0	0.24	0	1 (7%)	0	0.18
Intrahepatic metastasis								
Present	6 (32%)	1 (6%)	4 (15%)	0.14	2 (14%)	2 (12%)	7 (23%)	0.56
Histological grade								
Well-mode	15 (79%)	16 (100%)	23 (88%)	0.15	11 (79%)	17 (100%)	263 (87%)	0.16

CT computed tomography, *SNIM* small nodular type with indistinct margin, *SN* simple nodular, *SNEG* simple nodular type with extranodular growth, *CM* confluent multinodular, *well-mode* well or moderately differentiated

Table 3 Pathological findings in relation to hepatobiliary MRI

	Tumor margin				
	In the axial hepatobiliary images			In the coronal hepatobiliary images	
	Non-smooth ($n = 24$)	Smooth ($n = 37$)	p value	Non-smooth ($n = 29$)	Smooth ($n = 32$)	p value
Macroscopic type						
SNIM	3 (13%)	5 (14%)	<0.0001	2 (7%)	6 (19%)	0.0091
SN	2 (8%)	24 (65%)		8 (28%)	18 (56%)	
SNEG	13 (54%)	6 (16%)		12 (41%)	7 (22%)	
CM	6 (25%)	2 (5%)		7 (24%)	1 (3%)	
Capsule						
Present	14 (58%)	25 (68%)	0.46	18 (62%)	21 (66%)	0.77
Microscopic portal vein invasion						
Present	10 (42%)	1 (3%)	0.0002	10 (34%)	1 (3%)	0.0019
Microscopic hepatic vein invasion						
Present	0	1 (3%)	0.99	1 (3%)	0	0.48
Intrahepatic metastasis						
Present	9 (38%)	2 (5%)	0.0043	9 (31%)	2 (6%)	0.0183
Histological grade						
Well-mode	20 (83%)	34 (92%)	0.42	25 (86%)	29 (91%)	0.59

SNIM small nodular type with indistinct margin, *SN* simple nodular, *SNEG* simple nodular type with extranodular growth, *CM* confluent multinodular

$p = 0.024$) and IM (odds ratio 6.498, $p = 0.036$) of HCC on multivariate analysis.

One patient underwent non-curative hepatectomy because multiple small intrahepatic metastases were seen during surgery. One patient died within 30 days after hepatectomy. Of the remaining 59 patients, 14 had intrahepatic recurrence of HCC within 1 year after hepatectomy (early recurrence). The clinical and MRI findings submitted

Table 4 Univariate analysis to predict for microscopic portal invasion of HCC

	Microscopic portal invasion		*p* value
	Present ($n = 11$)	Absent ($n = 50$)	
Sex (men/women)	9/2	40/10	0.89
Age, years (mean ± SD)	63 ± 8	68 ± 8	0.05
HCV antibody (positive/negative)	6/5	24/26	0.69
$ICGR_{15}$, % (mean ± SD)	13 ± 8	16 ± 11	0.30
Child-Pugh (A/B)	10/1	46/4	0.99
Cirrhosis (present/absent)	5/6	21/29	0.83
AFP (ng/ml)			
Median (25th percentile, 75th percentile)	14 (5, 810)	12.5 (3.75, 140)	0.48
≤300/>300	8/3	43/7	0.37
PIVKA-II (mAU/ml)			
Median (25th percentile, 75th percentile)	95.5 (18.75, 95.5)	33 (21, 158.5)	0.43
≤600/>600	7/3	43/7	0.35
Tumor size on MRI (cm)			
Mean ± SD	3.3 ± 1.0	2.9 ± 1.0	0.28
≤3/>3	5/6	26/24	0.69
Tumor number on MRI			
Mean ± SD	1.5 ± 0.7	1.2 ± 0.5	0.11
Single/multiple	8/3	45/5	0.15
Arterial phase findings on MRI (high/low)	9/2	42/8	0.99
Radiological capsule in the dynamic studies (incomplete/complete: absent)	8/3	11/39	0.0023
Tumor margin in the axial hepatobiliary phase (non-smooth/smooth)	10/1	14/36	0.0002
Radiological capsule on CT scan (incomplete/complete: absent)	3/8	11/39	0.70
Tumor grade (well: moderately/poorly)	10/1	44/6	0.99

HCC hepatocellular carcinoma, *AFP* alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence and antagonist-II

to univariate analysis to predict early recurrence are shown in Table 7. The number of patients with early recurrence was significantly higher in the patients with a non-smooth margin in the axial hepatobiliary phase (41%) than in the patients with a smooth margin (14%, $p = 0.0168$). A non-smooth margin in the axial hepatobiliary phase was identified as a significant predictor of early recurrence of HCC (odds ratio 4.306, $p = 0.04$) on multivariate analysis (Table 8). The relationships between the tumor margin in the axial hepatobiliary phase, the surgical procedure, and early recurrence of HCC are shown in Table 9. In patients with a non-smooth margin in the axial hepatobiliary phase, 2 of 3 patients who underwent non-anatomical resection had early recurrence of HCC, whereas 7 of 19 patients who underwent anatomical resection had early recurrence of HCC.

Discussion

It has recently been reported that radiological findings with recent diagnostic imaging were useful for predicting MVI of HCC [14–17]. However, the relationship between MVI of HCC and the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI has not been evaluated in detail. In our present study, the number of patients with MPVI was significantly higher among the patients with an incomplete radiological capsule in the dynamic studies than among those without this finding. Furthermore, the number of patients with MPVI was significantly higher among those with a non-smooth margin in the hepatobiliary phase than among those without this finding. A non-smooth margin in the hepatobiliary phase was identified as a significant predictor of MPVI on multivariate analysis. Therefore, a non-smooth margin in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI is useful to predict MPVI of HCC in patients with HCC within the Milan criteria.

MPVI of HCC is thought to be difficult to detect before the treatment of HCC, since MPVI of HCC is diagnosed on the basis of histological findings. However, Miyata et al. [14] reported that distortion of coronal enhancement at the tumor periphery on CT hepatic angiography (CTHA) was the most significant variable for the risk of microscopic invasion of the portal vein. Shirabe et al. [16] reported that

Table 5 Univariate analysis to predict for intrahepatic metastasis of HCC

	Intrahepatic metastasis		*p* value
	Present ($n = 11$)	Absent ($n = 50$)	
Sex (men/women)	11/0	38/12	0.07
Age, years (mean ± SD)	64 ± 8	68 ± 9	0.21
HCV antibody (positive/negative)	7/4	23/27	0.29
$ICGR_{15}$, % (mean ± SD)	16 ± 11	15 ± 10	0.82
Child-Pugh (A/B)	10/1	46/4	0.99
Cirrhosis (present/absent)	4/7	22/29	0.74
AFP (ng/ml)			
Median (25th percentile, 75th percentile)	14 (4, 218)	12.5 (4, 140)	0.84
≤300/>300	9/2	42/8	0.99
PIVKA-II (mAU/ml)			
Median (25th percentile, 75th percentile)	142.5 (46, 1410.75)	29.5 (20.75, 158.5)	0.10
≤600/>600	7/3	43/7	0.35
Tumor size on MRI (cm)			
Mean ± SD	3.1 ± 0.8	2.9 ± 1.1	0.54
≤3/>3	5/6	26/24	0.69
Tumor number on MRI			
Mean ± SD	1.6 ± 0.8	1.1 ± 0.4	0.0040
Single/multiple	6/5	47/3	0.0033
Arterial phase findings on MRI (high/low)	9/2	42/8	0.99
Radiological capsule in the dynamic studies (incomplete/complete: absent)	6/5	13/37	0.06
Tumor margin in the axial hepatobiliary phase (non-smooth/smooth)	9/2	15/35	0.0043
Radiological capsule on CT scan (incomplete/complete: absent)	2/9	12/38	0.99
Tumor grade (well: moderately/poorly)	10/1	44/6	0.99

AFP alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence and antagonist-II

Table 6 Multivariate analysis to predict microscopic portal vein invasion and intrahepatic metastasis of HCC

	Odds ratio	95% confidence interval (CI)	*p* value
Microscopic portal vein invasion			
Radiological capsule in the dynamic images (incomplete)	1.538	0.231–10.228	0.656
Tumor margin in the axial hepatobiliary images (non-smooth)	18.814	1.467–241.343	0.024
Intrahepatic metastasis			
Tumor number (multiple)	6.360	1.061–38.111	0.043
Tumor margin in the axial hepatobiliary images (non-smooth)	6.498	1.134–37.240	0.036

the portal perfusion defect area ratio on CT arterio-portography (CTAP) was a significant independent predictor of MPVI of HCC. Nishie et al. [15] reported that the area, but not the shape of the peritumoral enhancement on CTHA and CTAP was significantly larger in HCC patients with minute portal invasion than in those without minute portal invasion. Thus, useful radiological findings on CTHA and CTAP for predicting MVI of HCC have recently been reported. However, CTHA and CTAP cannot be routinely applied worldwide, and they are more invasive than other examinations because angiography is required.

Kim et al. [17] recently reported that irregular circumferential peritumoral enhancement on contrast-enhanced multi-arterial phase dynamic MRI showed a high probability of microvessel invasion of HCC. Their protocol is thought to be quite complicated because 4 arterial phases have to be taken within 30 s. However, Kim et al. [17] also reported that a non-smooth tumor margin in the hepatobiliary images was a significant risk factor for microvessel invasion on univariate analysis, but not on multivariate analysis. Their radiological findings in the hepatobiliary phase images and our findings in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI are thought to be similar. Therefore, a non-smooth margin at

Table 7 Univariate analysis to predict for early recurrence of HCC (within 1 year) after hepatectomy

	Early recurrence		*p* value
	Present ($n = 14$)	Absent ($n = 45$)	
Sex (men/women)	12/2	35/10	0.71
Age, years (mean ± SD)	66 ± 8	67 ± 9	0.63
HCV antibody (positive/negative)	7/7	21/24	0.83
$ICGR_{15}$, % (mean ± SD)	17 ± 10	15 ± 11	0.63
Child-Pugh (A/B)	13/1	42/3	0.99
Cirrhosis (present/absent)	4/10	21/24	0.35
AFP (ng/ml)			
Median (25th percentile, 75th percentile)	35.5 (4,75, 334)	11 (4, 145)	0.44
≤300/>300	11/3	38/7	0.69
PIVKA-II (mAU/ml)			
Median (25th percentile, 75th percentile)	103.5 (33.25, 791.5)	29 (18.5, 175.5)	0.06
≤600/>600	10/4	38/6	0.23
Tumor size on MRI (cm)			
Mean ± SD	3.5 ± 1.2	2.8 ± 1.0	0.0361
≤3/>3	6/8	24/21	0.49
Tumor number on MRI			
Mean ± SD	1.3 ± 0.6	1.1 ± 0.4	0.24
Single/multiple	11/3	42/3	0.14
Arterial phase findings on MRI (high/low)	13/1	36/9	0.42
Radiological capsule in the dynamic studies (incomplete/complete: absent)	7/7	11/34	0.07
Tumor margin in the axial hepatobiliary phase (non-smooth/smooth)	9/5	13/32	0.0168
Radiological capsule on CT scan (incomplete/complete: absent)	4/10	10/35	0.63
Surgical procedure (anatomical/non-anatomical)	9/5	38/7	0.10
Pathological portal invasion (present/absent)	5/9	6/39	0.06
Pathological intrahepatic metastasis (present/absent)	4/10	6/39	0.18
Tumor grade (well: moderately/poorly)	13/1	39/6	0.99

AFP alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence and antagonist-II

Table 8 Multivariate analysis to predict for early recurrence of HCC (within 1 year) after hepatectomy

	Early recurrence		
	Odds ratio	95% CI	*p* value
Tumor size on MRI (cm)	1.840	0.922-3.672	0.084
Tumor margin in the axial hepatobiliary images (non-smooth vs. smooth)	4.306	1.070-17.331	0.040

the periphery of the tumor in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI is useful to predict MPVI of HCC in patients with HCC within the Milan criteria.

Previously, high serum levels of AFP or PIVKA-II were reported to predict MVI of small HCC [11–13]. Tumor size and tumor grade have also been reported to predict MVI of small HCC [8–10]. Furthermore, Poon et al. [26] reported that high serum levels of vascular endothelial growth factor (VEGF) were shown to predict not only MVI but also IM of HCC. In our present study, the number of patients with IM was significantly higher among those with non-smooth margins in the hepatobiliary phase (38%) than among those with smooth margins (5%, $p = 0.0043$). A non-smooth margin in the hepatobiliary phase was identified as a significant predictor of IM of HCC on our multivariate analysis. Therefore, a non-smooth margin in the hepatobiliary phase image on Gd-EOB-DTPA-enhanced MRI is useful to predict not only MPVI of HCC but also IM of HCC in patients with HCC.

The simple nodular with extranodular growth (SNEG) type and confluent multinodular (CM) type of HCC in resected specimens have been reported to pose a greater risk of MPVI or IM of HCC than the SN type of HCC

Table 9 Relationships between tumor margin in the hepatobiliary phase, surgical procedure, and early recurrence of HCC

	Early recurrence of HCC		*p* value
	Present	Absent	
Tumor margin in the axial hepatobiliary images (non-smooth)			
Anatomical surgical procedure ($n = 19$)	7 (37%)	12 (63%)	0.54
Non-anatomical surgical procedure ($n = 3$)	2 (67%)	1 (33%)	
Tumor margin in the axial hepatobiliary images (smooth)			
Anatomical surgical procedure ($n = 28$)	2 (7%)	26 (93%)	0.08
Non-anatomical surgical procedure ($n = 9$)	3 (33%)	6 (67%)	

[27–32]. We therefore attempted to evaluate the macroscopic tumor type in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. In our present study, the numbers of patients with SNEG type and CM type in resected specimens were higher among those with non-smooth margins in the hepatobiliary phase than among those without this finding. However, the accuracy of determination of each macroscopic tumor type was not adequate, probably due to the small sample size. Therefore, further studies of larger numbers are required to accurately evaluate the macroscopic tumor type.

MPVI of HCC has been reported to be one of the important prognostic factors not only for survival but also for early recurrence after hepatectomy in patients with HCC [33–35]. There have been no previous reports of the relation between surgical outcome and the hepatobiliary phase of new Gd-EOB-DTPA-enhanced MRI. In our present study, a non-smooth margin in the hepatobiliary phase was a significant predictor not only for MPVI of HCC but also for early recurrence of HCC. In conclusion, a non-smooth margin in the hepatobiliary phase of new Gd-EOB-DTPA-enhanced MRI could be a useful preoperative predictive marker for MPVI and IM of HCC and early recurrence after hepatectomy in patients with HCC within the Milan criteria.

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