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Peritumoral decreased uptake area of gadoxetic acid enhanced magnetic resonance imaging and tumor recurrence after surgical resection in hepatocellular carcinoma

A STROBE-compliant article

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Abstract

Recently, it has been suggested that peritumoral decreased uptake area (PDUA) in the hepatobiliary phase (HBP) of gadoxetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) was associated with vascular invasion in hepatocellular carcinoma (HCC). We aimed to investigate correlations between microvascular invasion and PDUA, and elucidate the predictability of PDUA for tumor recurrence after resection.

We retrospectively analyzed clinicopathological and radiological data from 126 consecutive patients with single HCC ≤5 cm without macrovascular invasion who underwent preoperative Gd-EOB-DTPA-enhanced MRI and surgical resection. The presence of a faint and hypointense area around the tumor in the HBP was defined as PDUA.

Among 126 patients with HCCs, microvascular invasion was observed in 29 (23.0%) patients and PDUA was observed in 15 (11.9%) patients. PDUA [odds ratio (OR) 20.06, confidence interval (CI) 4.74–84.96, $P < .001$] was an independent risk factor for microvascular invasion. In multivariate survival analysis using Cox regression, PDUA [hazard ratio (HR) 4.51, CI 2.17–9.38, $P < .001$], pathologically confirmed satellite nodules (HR 5.18, CI 1.50–17.88, $P = .009$), and AFP (≥100 ng/mL, HR 2.28, CI 1.04–5.01, $P = .040$) were independent risk factors for recurrence after resection. Recurrence-free survival in the group with PDUA was significantly lower than that in the group without PDUA according to analysis using the Kaplan–Meier method with the log-rank test ($P < .001$).

PDUA in the HBP of Gd-EOB-DTPA-enhanced MRI could be a useful preoperative predictor of microvascular invasion and independent prognostic factor after surgical resection in patients with single HCC ≤5 cm without macrovascular invasion.

Abbreviations: AFP = alpha-fetoprotein, CT = computed tomography, DWI = diffusion-weighted imaging, Gd-EOB-DTPA = gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid, HBP = hepatobiliary phase, HCC =hepatocellular carcinoma, HR = hazard ratio, ICG R15 = indocyanine green retention rate at 15 minutes, MRI = magnetic resonance imaging, OATP = organic anionic transporting polypeptides, OR = odds ratio, PDUA = peritumoral decreased uptake area, PIVKA-II = protein induced by vitamin K absence or antagonist-II, TE = echo time, TR = repetition time.

Keywords: hepatocellular carcinoma, microvascular invasion, peritumoral decreased uptake area, tumor recurrence

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and the third most common cause of cancer-related death.[1,2] The incidence of HCC is increasing globally. Although several treatment modalities are available according to the disease extent and the severity of underlying liver disease, liver transplantation is the best option for curative treatment in patients with HCC and cirrhosis. However, liver transplantation is associated with considerable problems, including perioperative risks, postoperative complications, and the requirement for donors.[3] Surgical resection in patients with good liver function, normal bilirubin, and hepatic venous pressure gradient <10 mm Hg constitutes a suitable treatment for patients with a single HCC.[4] However, although significant improvements in survival after resection of HCC have been achieved, long-term prognosis remains poor, and the 5-year overall survival rate ranges between 33% and 44% with a 5-year cumulative recurrence rate of 80% to 100%.[5,6] If recurrence can be predicted before surgery, patients may receive more effective treatment.

The presence of microvascular invasion has been reported to be one of the most important risk factor related to tumor recurrence after surgery.[7–9] However, despite the significance of microvascular invasion in HCC, preoperative diagnosis of microvascular invasion is quite difficult.

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Gadoxetic acid (Gd-EOB-DTPA, Primovist; Bayer Schering Pharma AG, Berlin, Germany) is a relatively new, safe, and well-tolerated liver-specific contrast agent for magnetic resonance imaging (MRI) of the liver that allows for the acquisition of both dynamic and hepatobiliary phase images.

Recently, it has been suggested that the peritumoral decreased uptake area (PDUA) in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI could be observed in cases of impaired hepatocyte function induced by decreased portal flow.[10] PDUA was defined as the presence of a faint and hypointense area around the tumor in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI. The 3 suggested types of PDUA in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI are the following: wedge-shaped, irregular belt-shaped, and linear PDUA. Previous reports have suggested that PDUA in the hepatobiliary phase of MRI may be associated with vascular invasion in HCC.[10,11] However, whether PDUA in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI has a clinically significant effect on the incidence of tumor recurrence following resection remains unclear.

The present study was conducted to investigate correlations between microvascular invasion and PDUA in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI, and to elucidate the predictability of PDUA for tumor recurrence after resection in patients with a single HCC ≤ 5 cm in diameter without macrovascular invasion.

2. Methods

2.1. Patients

We conducted a retrospective study including 137 consecutive patients with radiological single HCC ≤ 5 cm in diameter without macrovascular invasion who underwent preoperative Gd-EOB-DTPA enhanced MRI and surgical resection between January 2008 and December 2015. Inclusion criteria for survival analysis after resection were as follows: patients with a single tumor up to 5 cm in diameter; patients without radiological evidence of macroscopic portal and hepatic vein tumor invasion; patients without extrahepatic metastasis; and patients who underwent curative hepatic resection defined as the removal of all macroscopic and microscopic residual tumors. The 3 patients who died within 1 month, and the 2 patients who were lost to follow-up within 6 months after resection, were excluded. The causes of death in the 3 patients were hepatorenal syndrome, hepatic failure, and sudden cardiac arrest after the surgical resection. Among the patients with HCC, 126 patients met the inclusion criteria, and were retrospectively included for analysis of correlations between microvascular invasion and PDUA in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI, and analysis of the predictability of PDUA for tumor recurrence after resection (Fig. 1). The surgical methods performed included anatomical resection (n = 66, segmentectomy; n = 31, sectionectomy; n = 18, hemihepatectomy) or nonanatomical resection (n = 11). Anatomical resection was defined as the complete removal of at least 1 Couinaud segment containing the tumor, including segmentectomy, sectionectomy, and hemihepatectomy. Nonanatomical resection was defined as the removal of the tumor and the rim of the nontumoral liver parenchyma without regard to segmental, sectional, or lobar anatomy as described previously.[12] The indocyanine green retention rate at 15 minutes (ICG R15) test was performed in all patients to evaluate residual hepatic function before surgical resection. The Child–Turcotte–Pugh (CTP) score is used to assess the hepatic function before surgical resection in patients with cirrhosis.

Following surgery, patients were followed with dynamic computed tomography (CT) scans or MRI and alpha-fetoprotein levels.[13] All patients in this survival analysis underwent CT or MRI every 3 months. Clinical and laboratory parameters, MRI findings, and final pathologic diagnoses were analyzed. The study protocol was approved by the Institutional Review Board of Gachon University Gil Medical Center (IRB No. GAIRB 2016-335).

2.2. Histology of liver nodules

Pathologic specimens were reviewed for tumor characteristics: number and size of tumors, tumor grade, capsular invasion, satellite nodules, vascular invasion, and microscopic margins. If the distance between the cancer and the margin was greater than 1 mm, it was considered to be a negative margin. Postoperative

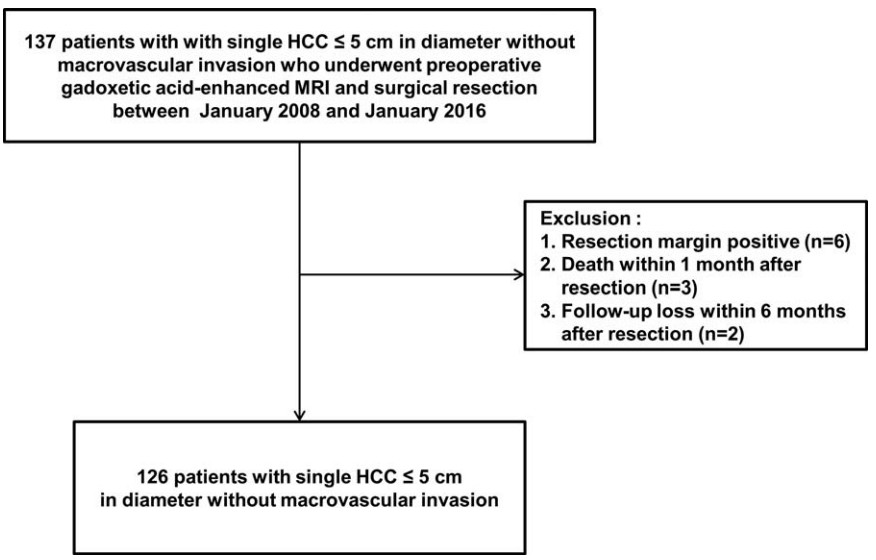

Figure 1. Flow chart of patients. HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging.

pathologic vascular invasion was defined as histologic involvement of lobar or segmental branches of portal or hepatic veins or gross invasion of the right or left main branches of the portal or hepatic veins. Tumor grades were determined by histology using the modified Edmondson–Steiner grading system.[14] In order to eliminate interobserver variation affecting the pathologic diagnosis of liver nodules, all histology slides were reviewed by a single experienced hepatopathologist. When a tumor had more than 2 histologic grades, the major grade was recorded for the analysis.

2.3. Magnetic resonance imaging

MR images were obtained using a 3T unit (Verio; Siemens Medical Solutions, Inc., Erlangen, Germany). The MRI sequence consisted of a breath-hold fat-saturated T2-weighted fast spin-echo or turbo spin-echo sequence, a breath-hold T1-weighted dual-echo (in-phase and opposed-phase) sequence, dynamic 3-dimensional fat-saturated T1-weighted sequences, and free-breathing diffusion-weighted imaging (DWI), using a single-shot echo-planar imaging sequence. MR images were obtained using a T2-weighted single-shot fast spin-echo or a half-Fourier acquisition single-shot turbo spin-echo sequence [repetition time (TR)/echo time (TE), 700–980/90–100; flip angle, 90°–150°; echo-train length, 1; matrix size, 320–380 × 256–305; slice thickness, 3.5–5 mm], a breath-hold T1-weighted gradient-recalled echo in-phase sequence (TR/TE 5–170/2.5–5.0; flip angle, 9°–70°; echo-train length, 1; matrix size, 256–320 × 170–280; slice thickness, 3.5–5 mm), and an out-of-phase sequence (TR/TE 5–170/1.5–2.5; flip angle, 10°–70°; matrix size, 256–320 × 170–280; slice thickness, 3.5–5 mm). Arterial phase images were acquired 7 seconds after arrival of the contrast medium at the thoracic aorta, and portal venous, delayed, and hepatobiliary phase images were subsequently acquired 60 seconds, 180 seconds, and 20 minutes, respectively, after commencing the bolus injection of Gd-EOB-DTPA (Primovist, Eovist; Bayer Schering Pharma AG) at 0.025 mmol/kg of body weight. DWI with simultaneous respiratory triggering was performed during the period before the 20-minute delayed imaging. For each patient, the TR was matched to the length of the respiratory cycle; every patient had b-values of 0, 400, and 1000 s/mm^2.

An area of relative hypointensity compared with the surrounding liver parenchyma but less hypointense than the tumor in the hepatobiliary phase was defined as PDUA. PDUA was assessed in the axial plane. PDUA was classified into 3 types: wedge-shaped, irregular belt-shaped, and linear type, as previously reported.[10] The MR images were retrospectively analyzed by 2 radiologists who were unaware of the pathologic results. The κ value representing interobserver agreement in the presence of PDUA was 0.84.

2.4. Statistical analysis

Interobserver agreement for the presence of PDUA was evaluated using κ statistics, with a κ value of 0 to 0.20 indicating slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.80 to 1.00 almost perfect agreement.[15] Statistically significant differences were analyzed using the χ^2 test for categorical variables and Student *t* test for continuous variables. All significant predictors of recurrence in the univariate analysis were analyzed in a logistic regression model to show an independent value in the multivariate analysis. Factors independently related to recurrence were tested using a Cox proportional hazards regression analysis adjusted for variables. Recurrence-free survival was calculated by the Kaplan–Meier method, and differences in survival between the groups were compared using the log-rank test. The statistical analysis was performed using SPSS 12 Windows (SPSS Inc., Chicago, IL). A value of $P < .05$ was considered significant.

3. Results

3.1. Baseline characteristics of the patients

The mean age of the 126 patients with single HCC ≤5 cm in diameter without macrovascular invasion was 57.0 ± 9.9 years, and 96 patients (76.2%) were men. Liver cirrhosis was present in 96 (76.2%) patients. During a median follow-up period of 24 months (range, 1–83 months) after resection, 36 (28.6%) of the 126 patients with a single HCC ≤5 cm in diameter without macrovascular invasion experienced tumor recurrence. The 1-, 2-, 3-, and 5-year cumulative recurrence-free survivals of these 126 patients were 87.7%, 78.2%, 71.7%, and 50.8%, respectively, after surgical resection. Among 126 patients, microvascular invasion was observed in 29 (23.0%) patients and PDUA (10 wedge, 3 irregular belt, 2 linear-type) in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI was observed in 15 (11.9%) patients. Of the tumors showing PDUA, 86.7% (13/15) of PDUAs were observed in tumors larger than 2 cm. Of the tumors with microvascular invasion, 82.8% (24/29) of microvascular invasions were observed in tumors larger than 2 cm. Microvascular invasion (44.4% vs 14.4%, $P = .001$) and PDUA (33.3% vs. 3.3%, $P < .001$) were more frequently observed in patients with recurrence. On the contrary, the mean CTP score, ICG R15, tumor size, and tumor grade did not significantly differ between patients with and without tumor recurrence (Table 1).

3.2. Tumor recurrence-free survival after resection in patients with HCC with microvasular invasion

The 1-, 2-, and 3-year cumulative recurrence-free survivals of these patients with HCC without microvascular invasion were 91.1%, 83.1%, and 70.8%, respectively, after surgical resection. The 1-, 2-, and 3-year cumulative recurrence-free survivals of these patients with HCC with microvascular invasion were 68.0%, 35.0%, and 17.6%, respectively, after surgical resection. Recurrence-free survival in the group with microvascular invasion was significantly lower than that in the group without microvascular invasion according to analysis using the Kaplan–Meier method with the log-rank test ($P < .001$) (Fig. 2).

3.3. Correlations between microvascular invasion and PDUA

Among 29 patients with single HCC ≤5 cm in diameter with microvascular invasion, PDUA was observed in 12 (41.4%) patients. In univariate analysis, PDUA [odds ratio (OR) 22.12, confidence interval (CI) 5.64–86.74, $P < .001$], Edmonson tumor grade (OR 2.91, CI 1.20–7.04, $P = .018$), and tumor size (>2 cm, OR 3.99 CI 1.40–11.31, $P = .009$) were associated with microvascular invasion. In multivariate analysis, PDUA (OR 20.06, CI 4.74–84.96, $P < .001$) and Edmonson tumor grade (OR 2.98, CI 1.05–8.52, $P = .041$) were associated with microvascular invasion (Table 2).

Table 1

Baseline characteristics of the patients with or without tumor recurrence after resection in patients with single hepatocellular carcinoma ≤5 cm in diameter without macrovascular invasion (n = 126).

Characteristics	Tumor recurrence (n = 36)	No recurrence (n = 90)	*P*
Age, y	56.0 ± 9.8	57.4 ± 10.0	.478
Male sex, n (%)	27 (75.0)	69 (71.9)	.999
Liver cirrhosis, n (%)	31 (86.1)	65 (72.2)	.111
Etiology of liver disease, n (%)	32 (88.9)	79 (87.8)	.218
HBV			
HCV	2 (5.6)	1 (1.1)	
Alcohol	2 (5.6)	10 (11.1)	
Duration of follow-up after resection, mo	14.5 (1–67)	24.5 (6–83)	.006
CTP score	5.19 ± 0.40	5.12 ± 0.33	.366
ICG R15	13.25 ± 6.82	12.49 ± 7.47	.600
Nonanatomical resection, n (%)	4 (11.1)	7 (7.8)	.728
Tumor size, cm	2.8 ± 1.1	2.5 ± 1.1	.178
AFP, ng/mL	453.7 ± 1421.7	161.2 ± 438.2	.087
PIVKA-II, AU/mL	909.1 ± 2285.1	237.2 ± 603.4	.051
Edmonson grade, n (%)			.695
I/II	17 (47.2)	47 (52.2)	
III/IV	19 (52.8)	43 (47.8)	
Microvascular invasion, n (%)	16 (44.4)	13 (14.4)	.001
Capsule invasion, n (%)	1 (2.8)	4 (4.4)	.999
Satellite nodule, n (%)	3 (8.3)	1 (1.1)	.070
Infiltrative type, n (%)	1 (2.8)	1 (1.1)	.999
PDUA, n (%)	12 (33.3)	3 (3.3)	<.001

Data are expressed as mean ± standard deviation, median (range), or number (%). AFP = alpha-fetoprotein, CTP = Child–Turcotte–Pugh, HBV = hepatitis B virus, HCV = hepatitis C virus, ICG R15 = indocyanine green retention rate at 15 min, PDUA = peritumoral decreased uptake area, PIVKA-II = protein induced by vitamin K absence or antagonist-II.

3.4. Risk factors for tumor recurrence after resection in patients with HCC

In univariate survival analysis using Cox regression, PDUA [hazard ratio (HR) 4.37, CI 2.8 −8.76, $P < .001$], pathologically confirmed satellite nodules (HR 4.10, CI 1.24–13.55, $P = .021$), and AFP (≥100 ng/mL, HR 2.25, CI 1.04–4.89, $P = .040$) were risk factors for recurrence after resection. However, microvascular invasion without PDUA (HR 2.47, CI 0.98–6.21, $P = .055$) was not a significant risk factor for recurrence after resection. In multivariate survival analysis using Cox regression, PDUA (HR 4.51, CI 2.17–9.38, $P < .001$), pathologically confirmed satellite nodules (HR 5.18, CI 1.50–17.88, $P = .009$), and AFP (≥100 ng/mL, HR 2.28, CI 1.04–5.01, $P = .040$) were independent risk factors for recurrence after resection (Table 3).

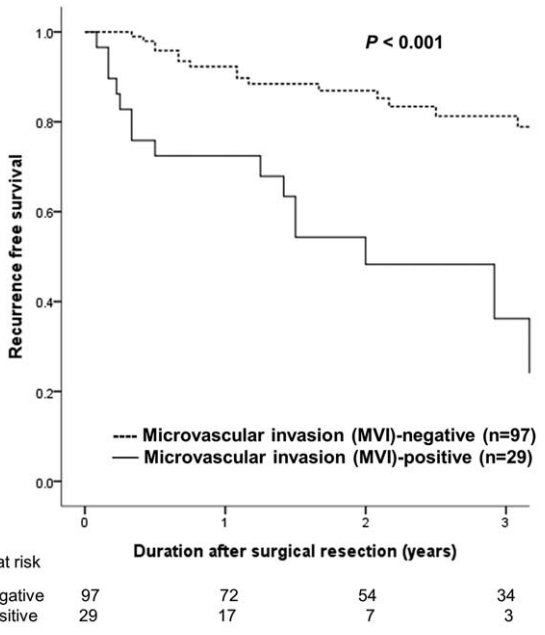

Figure 2. Comparison of tumor recurrence-free survival after resection between microvascular invasion positive and microvascular invasion negative tumors in patients with single HCC ≤5 cm in diameter without macrovascular invasion by Kaplan–Meier survival analysis. MVI = microvascular invasion.

3.5. Tumor recurrence-free survival after resection in patients with HCC with PDUA

The 1-, 2-, and 3-year cumulative recurrence-free survivals of these patients with HCC not showing PDUA were 88.8%, 76.1%, and 63.5%, respectively, after surgical resection. The 1-, 2-, and 3-year cumulative recurrence-free survivals of these patients with HCC showing PDUA were 66.7%, 42.9%, and 30.8%, respectively, after surgical resection. Recurrence-free survival in the group with PDUA was significantly lower than that in the group without PDUA according to analysis using the Kaplan–Meier method with the log-rank test ($P < .001$) (Fig. 3).

4. Discussion

Vascular invasion, histological differentiation grade, tumor size, and satellite nodules have been suggested as the predictors of HCC recurrence following surgical resection.[16,17] Vascular invasion has been shown to be significantly more common in patients with tumor diameter greater than 5 cm than those with smaller tumors.[18] Although tumor size is not a clear limiting factor for performing surgical resection, a consensus exists on recommending resection of single HCCs ≤5 cm because of the increased risk of vascular invasion and dissemination in larger

Table 2

Univariate and multivariate analysis of predictive factors for microvascular invasion in patients with single hepatocellular varcinoma ≤5 cm in diameter without macrovascular invasion (n = 126).

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*P*	Odds ratio	95% confidence interval	*P*
Age, y						
<60						
≥60	0.95	0.40–2.23	.949			
Sex						
Female						
Male	0.61	0.24–1.55	.614			
Liver cirrhosis						
No						
Yes	2.29	0.73–7.21	.157			
Tumor size, cm						
<2						
2–5	3.99	1.40–11.31	.009	2.71	0.85–8.61	.091
Edmonson tumor grade						
I/II						
III/IV	2.91	1.20–7.04	.018	2.98	1.05–8.52	.041
PDUA						
No						
Yes	22.12	5.64–86.74	<.001	20.06	4.74–84.96	<.001
Capsule invasion						
No						
Yes	0.83	0.09–7.74	.870			
Pathologically confirmed satellite nodule						
No						
Yes	3.52	0.47–26.16	.219			
Infiltrative type						
No						
Yes	7.11	0.62–81.43	.115			
AFP, ng/mL						
<100						
≥100	2.54	0.93–6.96	.070			
PIVKA-II, mAu/mL						
<200						
≥200	3.03	0.92–9.93	.067			

AFP = alpha-fetoprotein, PDUA = peritumoral decreased uptake area, PIVKA-II = protein induced by vitamin K absence or antagonist-II.

tumors.[16,19] However, Yuki et al[20] reported that vascular invasion can be found in small tumors on the basis of an autopsy study, in which portal vein thrombi were found in 40% of individuals with tumors less than 5 cm in diameter. In the present study, microvascular invasion was observed in 23.0% of patients with a single HCC ≤5 cm in diameter without macrovascular invasion. Because the patients with HCCs showing macrovascular invasion were excluded in our study, microvascular invasion appears to be less than other studies.

Microvascular invasion was more frequently observed in patients with recurrence. Recurrence-free survival in the group with microvascular invasion was significantly lower than that in the group without microvascular invasion in our study.

Macrovascular invasion is defined as invasion of tumor into a major vessel that can be identified during macroscopic examination or radiological imaging, and microvascular invasion as the presence of tumor emboli within the central hepatic vein, the portal vein, or the large capsular vessels.[21] Although macrovascular invasion can be preoperatively detected by conventional imaging modalities such as CT, MRI, and ultrasound, the preoperative imaging determination of microvascular invasion is difficult because microvascular invasion is a microscopic parameter and it is unclear which radiologic characteristics can be specific predictive factors for microvascular invasion.

In functioning hepatocytes, organic anionic transporting polypeptide (OATP)-8 is responsible for uptake of 2 gadolinium-based contrast agents: Gd-EOB-DTPA and gadobenate dimeglumine. Nodules with low or no OATP expression do not take up the hepatobiliary agents, and appear as hypointense areas during the hepatobiliary phase.[22] If microvascular invasion is present in a tumor, impaired hepatocyte function resulting from decreased portal flow could also result in decreased OATP expression and PDUA could be observed in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI.

Recently, some reports have suggested that PDUA was associated with microvascular invasion in patients with HCC.[10,11] A previous report confirmed whether the location of pathologic vascular invasion accorded with PDUA by means of joint evaluation by radiologist and pathologist.[10] Kim et al[11] reported that PDUA was observed in 26 (25.0%) of 104 HCCs, and 23 (88.5%) of these showed microvascular invasion. PDUA was a significant factor in predicting microvascular invasion of HCC in the study. Nishie et al[10] showed that PDUA was observed in 25 (41.0%) of 61 HCCs, and 18 (72.0%) of these showed microvascular invasion. PDUA was significantly correlated with tumor size and vascular invasion. The results of the present study also demonstrated that PDUA was associated with microvascular invasion in patients with a single HCC ≤5 cm in

Table 3

Univariate and multivariate analysis of risk factors for tumor recurrence after resection in patients with single hepatocellular carcinoma ≤5 cm in diameter without macrovascular invasion (n = 126).

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	*P*	Hazard ratio	95% confidence interval	*P*
Age, y						
<60						
≥60	1.23	0.63–2.39	.542			
Sex						
Female						
Male	1.18	0.55–2.52	.679			
Liver cirrhosis						
No						
Yes	1.95	0.76–5.02	.167			
Tumor size, cm						
≤2						
2–5	1.81	0.85–3.86	.124			
Edmonson tumor grade						
I/II						
III/IV	1.24	0.64–2.38	.529			
PDUA						
No						
Yes	4.37	2.18–8.76	<.001	4.51	2.17–9.38	<.001
Microvascular invasion without PDUA						
No						
Yes	2.47	0.98–6.21	.055			
Capsule invasion						
No						
Yes	0.87	0.12–6.41	.894			
Pathologically confirmed satellite nodule						
No						
Yes	4.10	1.24–13.55	.021	5.18	1.50–17.88	.009
Infiltrative type						
No						
Yes	2.09	0.28–15.44	.471			
AFP, ng/mL						
<100						
≥100	2.25	1.04–4.89	.040	2.28	1.04–5.01	.040
PIVKA-II, mAu/mL						
<200						
≥200	2.21	0.88–5.59	.093			

AFP = alpha-fetoprotein, PDUA = peritumoral decreased uptake area, PIVKA-II = protein induced by vitamin K absence or antagonist-II.

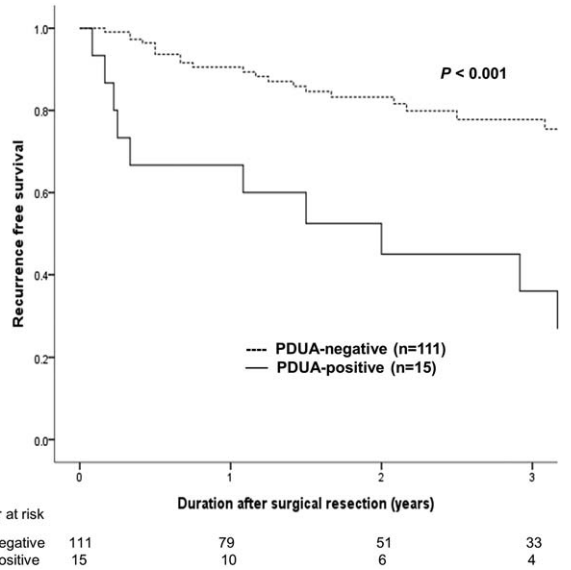

Figure 3. Comparison of tumor recurrence-free survival after resection between PDUA-positive and PDUA-negative tumors in patients with single HCC ≤5 cm in diameter without macrovascular invasion by Kaplan–Meier survival analysis. PDUA = peritumoral decreased uptake area.

diameter without macrovascular invasion. However, PDUA was less frequently observed in our study (11.9%) than in previous reports (25.0%–41.0%).[10,11] Our study only included patients with a single HCC ≤5 cm in diameter without macrovascular invasion. In addition, among the 3 types of PDUA in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI, the linear type was almost indistinguishable from pseudo-lesions such as artifact in our study. Most of these indistinguishable lesions were excluded in our study, and this could be one reason for the less frequent observation of PDUA.

In our study, PDUA, pathologically confirmed satellite nodules, and increased AFP were independent risk factors for recurrence after resection. On the contrary, microvascular invasion without PDUA, tumor size, and tumor grade were not significant risk factors for recurrence after resection. Recurrence-free survival after resection in the group with PDUA was significantly lower than that in the group without PDUA. These results suggest that conventional surgical resection may be insufficient for patients with HCC showing PUDA in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI even in the case of a single HCC ≤5 cm in diameter without macrovascular invasion. Other treatment methods such as extended surgical resection, transarterial radioembolization, or adjuvant therapies following resection could be required in patients with HCCs demonstrating PDUA.

The present study has several limitations. First, we did not evaluate the relationship between the location of vascular invasion and PDUA on hepatobiliary phase of Gd-EOB-DTPA enhanced MRI according to the joint evaluation of radiologists and pathologists. Second, our study was conducted on a relatively small number of patients with PDUA. However, this study is the first to date to elucidate the predictability of PDUA for tumor recurrence after resection in HCC. Third, we did not compare the disease-related mortality or overall survival because of the limitation of the retrospective study.

In conclusion, PDUA in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI could be a useful preoperative predictor of microvascular invasion, and an independent prognostic factor after surgical resection in patients with a single HCC ≤ 5 cm in diameter without macrovascular invasion. If PDUA on hepatobiliary phase of Gd-EOB-DTPA enhanced MRI is found, more extensive treatment might be selected considering the possibility of microvascular invasion, and large-scale prospective studies are needed.

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