Contents lists available at ScienceDirect

Surgery

Is disease progression a contraindication for the strategy of portal vein embolization followed by hepatectomy for hepatocellular carcinoma?

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ARTICLE INFO

ABSTRACT

Background: Portal vein embolization has been used worldwide to induce hypertrophy of the future liver remnant and to reduce the risk of hepatic insufficiency and death after major hepatectomy. However, whether disease progression after portal vein embolization can affect long-term oncologic outcomes in patients with hepatocellular carcinoma is uncertain.

Methods: From a total of 107 patients who underwent portal vein embolization and subsequent hepatectomy between 2000 and 2016, 57 patients with hepatocellular carcinoma were enrolled. We evaluated their long-term oncologic outcomes and investigated whether the disease progression between portal vein embolization and subsequent hepatectomy affected survival.

Results: The 5-year overall survival and disease-free survival after hepatectomy were 74.5% and 31.7%, respectively. Multivariate analyses revealed that tumor number before hepatectomy ≥ 3 (hazard ratio 3.59, $P = .019$), des-γ-carboxy prothrombin >200 mAU/mL (hazard ratio 3.36, $P = .045$), and red blood cell transfusion (hazard ratio 11.03, $P = .0008$) were independent prognostic factors for overall survival. Male sex (hazard ratio 3.74, $P = .029$), bilobar tumor distribution (hazard ratio 3.65, $P = .004$), and red blood cell transfusion (hazard ratio 6.22, $P = .0026$) were independent prognostic factors for disease-free survival. Disease progressions after portal vein embolization, including increases in tumor size, tumor number, α-fetoprotein, lens culinaris agglutinin-reactive fraction of α-fetoprotein, and des-γ-carboxy prothrombin, were observed in 22.8%, 14.0%, 29.8%, 19.3%, and 47.4% of patients, respectively. Only an increase of tumor number significantly decreased the disease-free survival rate after hepatectomy in a univariate analysis, and none of the variables affected overall survival.

Conclusion: Disease progression after portal vein embolization did not affect long-term survival in patients with hepatocellular carcinoma if the planned subsequent hepatectomy could be completed.

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Introduction

Primary liver cancer is the sixth most common cancer and the second leading cause of cancer-related death worldwide.[1] Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is responsible for 70%–90% of cases.[2,3] Curative intent treatment options for HCC include liver transplantation, hepatectomy, and local ablation therapy. Liver transplantation has been proposed as an effective treatment modality for HCC, especially in patients with cirrhosis, but its feasibility is restricted by organ donor shortage and high cost.[4] Although hepatectomy is considered to be a surgical option for a broad range of patients with various stages of disease, it is suitable for only a small number of patients because of the impaired liver function caused by underlying chronic liver disease.[5,6] Major hepatectomy for these patients can lead to postoperative morbidity and mortality.

Currently, to overcome this problem, portal vein embolization (PVE) has been widely used throughout the world. Preoperative PVE was first described by Makuuchi et al.[7] in 1980s, and was rapidly adopted by many centers worldwide. This strategy induces atrophy of the embolized liver lobe with compensatory hypertrophy of the nonembolized contralateral liver lobe, and thereby can reduce the risk of hepatic insufficiency and death after major

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hepatectomy in patients with an insufficient future liver remnant (FLR).[8–10]

In survival analysis, it is reported that PVE has no adverse effect on survival in patients who underwent major hepatectomy for colorectal liver metastases (CRLM)[11–15] and HCC.[16–19]

However, previous studies have reported that stimulation of liver hypertrophy could also accelerate tumor progression after PVE.[15,20–23] Although it is a matter of concern that enhanced tumor growth subsequent to PVE might influence resectability and survival, this issue has been addressed only with CRLM, not HCC. The aims of the present study were to evaluate long-term oncologic outcome in patients with HCC who underwent PVE followed by hepatectomy and to investigate whether disease progression between PVE and subsequent hepatectomy could affect their survival.

Patients and Methods

Study cohort

From a total cohort of 145 patients who were scheduled for PVE followed by hepatectomy between June 2000 and February 2016, 90 patients had HCC. Among these, 29 patients could not undergo hepatectomy after PVE because of insufficient FLR ($n = 11$), disease progression ($n = 10$), poor liver function ($n = 6$), or poor general condition ($n = 2$), and were excluded from this study. A total of 4 patients died of postoperative complications within 90 days because of liver failure ($n = 3$) or acute respiratory distress syndrome ($n = 1$) and were also excluded. The remaining 57 HCC patients were enrolled in this study. The patients were identified retrospectively from a prospectively maintained database, and any additional data were obtained by reviewing each patient's medical record. Written informed consent was obtained from all patients before treatment. This study was approved by the institutional review board of Kumamoto University, Japan.

Treatment strategy

Before treatment, all patients underwent routine laboratory tests and imaging modalities, including ultrasonography (US), enhanced computed tomography (CT), and magnetic resonance imaging (MRI). Liver function tests, including indocyanine green retention rate at 15 minutes (ICG-R15) and ^{99m}Tc-galactosyl human serum albumin (GSA) scintigraphy, were also performed. The type of hepatectomy was selected based on tumor location, extent of tumor invasion, parenchymal liver function, and patients' general condition, as described elsewhere.[24,25] Generally, anatomic resection was employed if liver function allowed. In the case of anatomic resection, CT scan volumetric measurements were performed before PVE and hepatectomy.

The decision to perform PVE was made after careful evaluation of the CT scan volumetry and patients' liver function reserve. The criteria for PVE before hepatectomy in our department were described earlier in this report. In brief, preoperative PVE was indicated for patients with a value of ICG-R15 less than 10%, 20%, 30%, or 40%, and with a percentage of future liver remnant volume (%FLRV) smaller than 35%, 60%, 80%, or 90%, respectively.[19,26–28] The ratio of the liver-to-heart plus liver radioactivity at 15 minutes (LHL15) determined by ^{99m}Tc-galactosyl human serum albumin was also taken into account for the assessment of liver functional reserve before hepatectomy.[28]

After PVE, if the %FLRV was considered to be sufficient for safe hepatectomy, we performed resection of the deportalized liver lobe. If there were incidental tumors in the FLR, we treated them by partial hepatectomy or radiofrequency ablation (RFA), in combination with main hepatectomy. RFA is indicated for small tumors (<2 cm) that are deeply located in the FLR. Two-stage hepatectomy is not indicated for HCC disease in our institution.

CT volumetry

CT scans of the liver were used to measure the volume of the tumor, the total liver volume, and FLRV. Each slice of the liver was traced with a cursor and the corresponding area was calculated with a computer program, as described elsewhere.[19,27] The %FLRV was estimated using the following formula: %FLRV = 100 × FLRV (mL) / [total liver volume (mL) – tumor volume (mL)]. More recently, %FLRV was calculated with a high-speed 3-dimensional (3D) image analysis system (SYNAPSE VINCENT, Fujifilm, Tokyo, Japan) using CT imaging. All patients underwent CT before and 3–4 weeks after PVE. When %FLRV was considered to be insufficient for safe hepatectomy, surgery was postponed and %FLRV was re-evaluated after 4 weeks.

Postoperative workup

All postoperative complications were graded according to the Dindo-Clavien classification,[29] and major complication was defined as any complication of grade III or higher. After treatment, all patients underwent regular follow-up examinations of their α-fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and des-γ-carboxy prothrombin (DCP) levels, and imaging studies, including US, CT, or MRI, to detect any intrahepatic recurrence or distant metastasis, as described elsewhere.[24,25] When tumor recurrence was confined, various treatment modalities were selected, including repeat hepatectomy, RFA, transcatheter arterial chemoembolization, sorafenib, or a combination of these methods.

Statistical analysis

Continuous variables were expressed as median (range). Continuous and categorical variables were compared using the Mann-Whitney U test and χ^2 test, respectively. Survival analyses were performed using the Kaplan-Meier method, with comparisons by means of the log-rank test. Overall survival (OS) was calculated from the date of hepatectomy until death or last follow-up. Disease-free survival (DFS) was defined as the time between hepatectomy and first recurrence or death. Variables in which the P value for the univariate analysis was $< .05$ were subjected to subsequent Cox regression analysis by stepwise backward elimination procedures. All statistical analyses were performed using JMP software (SAS Institute, Cary, NC, USA).

Results

The demographic and clinical characteristics of the 57 patients who underwent PVE followed by hepatectomy for HCC are summarized in Table 1. There were 49 men and 8 women, with a median age of 65 years (range, 31–83 years). The majority of patients had chronic viral infection with hepatitis C (43.9%) or B (33.3%). A total of 29 patients (50.9%) received hepatectomy as an initial treatment for HCC, and 12 patients (21.1%) had bilobar tumor distribution. Tumor number and size before PVE and hepatectomy were 2 (range, 1–6) and 2 (range, 1–8) and 51 mm (range, 17–130) and 60 mm (range, 20–160), respectively. AFP and DCP before PVE and hepatectomy were 18.1 ng/mL (range, 1.1–190,185), 20.2 ng/mL (range, 0–194,887), and 291 mAU/mL (16–62,989), 223 (range, 15–95,120), respectively. Most of the patients (96.5%) had well-reserved liver function (Child-Pugh classification A); whereas 2 patients (3.5%) had Child-Pugh classification B functional status. ICG-R15 values before PVE and hepatectomy were 11.2% (range,

Table 1
Demographic and clinical characteristics of study patients.

	Number of patients (n = 57)
Age (years)	65 (31–3)
Sex (male/female)	49/8
HBs-Ag positive	19 (33.3%)
HCV-Ab positive	25 (43.9%)
Initial treatment	29 (50.9%)
Tumor size before PVE (mm)	51 (17–130)
Tumor size before hepatectomy (mm)	60 (20–160)
Tumor number before PVE	2 (1–6)
Tumor number before hepatectomy	2 (1–8)
Tumor distribution (unilobar/bilobar)	45/12
AFP before PVE (ng/mL)	18.1 (1.1–190,185)
AFP before hepatectomy (ng/mL)	20.2 (0–194,887)
AFP-L3 > 10 before PVE (%)	24 (42.1%)
AFP-L3 > 10 before hepatectomy (%)	27 (47.4%)
DCP before PVE (mAU/mL)	291 (16–62,989)
DCP before hepatectomy (mAU/mL)	223 (15–95,120)
Child-Pugh classification (A/B)	55/2
Platelet count before PVE (/mL)	17.2 (5.5-34.2)
Platelet count before hepatectomy (/mL)	15.4 (5.0-36.0)
Total bilirubin before PVE (mg/dL)	0.8 (0.4-2.6)
Total bilirubin before hepatectomy (mg/dL)	0.8 (0.3-2.2)
Albumin before PVE (g/dL)	4.1 (2.0-4.9)
Albumin before hepatectomy (g/dL)	3.9 (2.7-4.9)
Prothrombin activity before PVE (%)	96 (72-150)
Prothrombin activity before hepatectomy (%)	95 (63-131)
ICG-R15 before PVE (%)	11.2 (2.3-31.8)
ICG-R15 before hepatectomy (%)	12.8 (6.3–39.8)
^{99m}Tc-GSA LHL15 before PVE	0.92 (0.80–0.96)
^{99m}Tc-GSA LHL15 before hepatectomy	0.92 (0.79–0.97)
Resection rate before PVE (%)	58.4 (24.2–79.0)
Resection rate before hepatectomy (%)	38.3 (16.0–67.8)
Duration between PVE and hepatectomy (months)	1.4 (0.6–14.8)
Interval TACE	8 (14.0%)
Type of hepatectomy	
Right trisectionectomy	3
Right or extended right hepatectomy	40
Left or extended left hepatectomy	5
Sectionectomy	6
Segmentectomy	3
Concomitant use of RFA	7 (12.3%)
Operating time (min)	414 (248–711)
Blood loss (g)	495 (23–11,992)
Red blood cell transfusion	6 (10.5%)
Major complication (Clavien >III)	15 (26.3%)

HBs-Ag, hepatitis B surface antigen; *HCV-Ab*, antihepatitis C antibody; *^{99m}Tc-GSA*, ^{99m}Tc-galactosyl human serum albumin; *LHL15*, ratio of the liver-to-heart plus liver radioactivity at 15 minutes.

2.3–31.8) and 12.8% (6.3–39.8). Resection rates before PVE and hepatectomy were 58.4% (range, 24.2–79.0) and 38.3% (16.0–67.8%). Duration between PVE and hepatectomy was 1.4 months (range, 0.6–14.8), and major complication after hepatectomy was observed in 15 patients (26.3%). Disease progression after PVE, including tumor size increase (>20%), tumor number increase, AFP increase (>20%), AFP-L3 increase (>20%), and DCP increase (>20%), was observed in 13 (22.8), 8 (14.0), 17 (29.8%), 11 (19.3%), and 27 patients (47.4%), respectively. Among the 8 patients whose tumor number increased, new lesions were detected in the FLR in 4 patients and in the deportalized liver in 4 patients.

Survival

The median (range) length of follow-up was 71.6 (3.6–201.5) months after PVE and 70.1 (2.6–200.7) months after hepatectomy. Cumulative 5-year OS and DFS rates after hepatectomy were 74.5% and 31.7%, respectively (Fig. 1). According to univariate analyses, 5 variables, including bilobar tumor distribution (*P* = .0028), tumor number before hepatectomy ≥3 (*P* = .0096), DCP before hepatectomy >200 mAU/mL (*P* = 0.021), albumin before hepatectomy ≤3.5
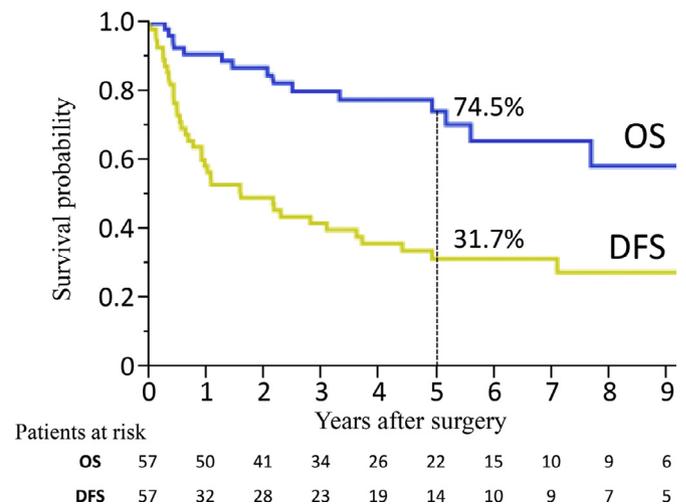

Fig. 1. Overall survival (OS) and disease-free survival (DFS) in patients who underwent portal vein embolization (PVE) followed by hepatectomy.

g/dL (*P* = .013), and red blood cell transfusion (*P* < .0001) were related to OS after hepatectomy, and 6 variables, including male sex (*P* = .028), bilobar tumor distribution (*P* < .0001), tumor number before hepatectomy ≥3 (*P* = .027), increase of tumor number after PVE (*P* = .0022), albumin before hepatectomy ≤3.5 g/dL (*P* = .024), and red blood cell transfusion (*P* < .0001) were related to DFS after hepatectomy (Table 2). Multivariate Cox regression analyses revealed that tumor number before hepatectomy ≥3 (hazard ratio [HR] 3.59, *P* = .019), DCP before hepatectomy >200 mAU/mL (HR 3.36, *P* = 0.045), and red blood cell transfusion (HR 11.03, *P* = .0008) were independent prognostic factors for OS. Male sex (HR 3.74, *P* = .029), bilobar tumor distribution (HR 3.65, P = .004), and red blood cell transfusion (HR 6.22, *P* = .0026) were independent prognostic factors for DFS (Table 3). Among the factors related to tumor progression after PVE, including increase of tumor size, number, AFP, AFP-L3, and DCP, none were associated with OS after hepatectomy (Fig. 2), and only increase of tumor number after PVE was associated with DFS after hepatectomy (Fig. 3).

Among the 57 patients who underwent PVE and subsequent hepatectomy, 38 developed recurrence after hepatectomy during the study period. The sites of first recurrence and treatment details are summarized in Table 4. Intrahepatic recurrence was observed in 34 patients (89.5%), and the other recurrence sites were lung in 2 patients, and lung plus lymph node and adrenal gland in 1 patient each. For intrahepatic recurrence, potentially radical treatment was performed in 16 patients (47.1%), including repeat hepatectomy (*n* = 6), RFA (*n* = 9), and hepatectomy plus RFA (*n* = 1). Among the remaining 18 patients, 15 received transarterial chemoembolization (TACE) and 3 received best supportive care.

Discussion

Patients with HCC often have impaired liver function because of underlying chronic liver disease and thus sometimes require PVE before major hepatectomy to increase the FLR. One of the concerns of PVE is the disease progression after PVE and subsequent failure to perform planned hepatectomy. For colorectal liver metastases, it has been reported that at times PVE induces tumor progression and leads to reduced long-term survival.[15,20–23] In contrast, in the case of HCC, earlier studies reported that long-term outcomes were comparable between patients with and without PVE before hepatectomy for HCC.[16–18] Another multi-institutional study has demonstrated that patients who underwent PVE followed by right-side hemihepatectomy had similar long-term outcomes (OS and DFS) to

Table 2
Univariate analyses of factors related to overall and disease-free survival after hepatectomy.

Variables		n	5-year OS (%)	P	5-year DFS (%)	P
Age (years)	>65	26	66.5	.11	19.7	.26
	≤65	31	81.2		41.0	
Sex	Male	49	25.4	.090	25.3	.028
	Female	8	71.4		71.4	
HBs-Ag	Positive	19	94.7	.063	36.1	.99
	Negative	38	64.6		28.8	
HCV-Ab	Positive	25	65.3	.10	37.6	.43
	Negative	32	81.9		27.8	
Initial treatment	Initial	29	70.4	.50	40.5	.084
	Not initial	28	76.1		22.9	
Tumor distribution	Unilobar	45	79.3	.0028	39.6	< .0001
	Bilobar	12	43.6		0	
Tumor size before PVE (mm)	>50	29	65.3	.094	36.2	.94
	≤50	28	85.0		28.0	
Tumor size before hepatectomy (mm)	>50	34	69.4	.34	37.7	.67
	≤50	23	81.8		23.9	
Change of tumor size after PVE	Increase	13	70.5	.87	23.1	.71
	Stable	44	75.6		35.3	
Tumor number before PVE	≥3	16	79.6	.27	22.5	.38
	<3	41	72.4		35.5	
Tumor number before hepatectomy	≥3	20	66.7	.0096	18.0	.027
	<3	37	78.8		39.5	
Change of tumor number after PVE	Increase	8	50.0	.21	12.5	.0022
	Stable	49	77.6		34.8	
AFP before PVE (ng/mL)	>20	25	79.0	.24	47.7	.070
	≤20	31	71.2		16.8	
AFP before hepatectomy (ng/mL)	>20	29	77.5	.77	2.9	.16
	≤20	28	68.3		17.9	
AFP increase after PVE	Increase	17	88.2	.88	30.8	.82
	Stable	39	72.0		32.8	
AFP-L3 before PVE (%)	>10	24	87.1	.067	36.7	.66
	≤10	33	65.7		27.7	
AFP-L3 before hepatectomy (%)	>10	27	80.9	.30	32.6	.89
	≤10	30	69.4		30.0	
AFP-L3 increase after PVE	Increase	11	72.7	.50	24.2	.48
	Stable	46	75.9		33.2	
DCP before PVE (mAU/mL)	>200	29	73.2	.37	35.8	.94
	≤200	27	78.4		27.6	
DCP before hepatectomy (mAU/ml)	>200	31	61.1	.021	37.5	.71
	≤200	26	90.8		26.4	
DCP increase after PVE	Increase	27	68.7	.68	25.9	.43
	Stable	29	81.3		37.9	
Platelet count before PVE (/mL)	>10	51	71.5	.57	35.9	.13
	≤10	6	100		-	
Platelet count before hepatectomy (/mL)	>10	49	70.7	.47	35.4	.28
	≤10	8	100		-	
Total bilirubin before PVE (mg/dL)	>1.0	13	92.3	.18	30.8	.85
	≤1.0	44	69.7		32.8	
Total bilirubin before hepatectomy (mg/dL)	>1.0	11	100	.068	27.3	.70
	≤1.0	46	69.1		33.0	
Albumin before PVE (g/dL)	>3.5	52	76.8	.32	34.9	.14
	≤3.5	5	53.3		0	
Albumin before hepatectomy (g/dL)	>3.5	43	82.5	.013	39.3	.024
	≤3.5	14	47.5		7.7	
Prothrombin activity before PVE (%)	>80	47	71.2	.70	37.0	.32
	≤80	10	90.0		10.0	
Prothrombin activity before hepatectomy (%)	>80	45	80.5	.076	36.8	.094
	≤80	12	55.6		11.1	
ICG-R15 before PVE (%)	>10	34	67.7	.54	27.2	.59
	≤10	20	80.6		39.4	
ICG-R15 before hepatectomy (%)	>10	42	70.6	.58	26.5	.35
	≤10	13	83.1		46.2	
99mTc-GSA LHL15 before PVE	>0.90	42	8.7	.53	37.3	.56
	≤0.90	14	57.5		17.4	
99mTc-GSA LHL15 before hepatectomy	>0.90	43	79.0	.38	36.1	.48
	≤0.90	14	62.9		17.3	
Resection rate before PVE (%)	>60	24	77.2	.48	47.4	.11
	≤60	28	75.8		17.0	
Resection rate before hepatectomy (%)	>40	24	85.9	.074	46.8	.075
	≤40	28	71.1		20.4	
Duration between PVE and hepatectomy (months)	>1.3	30	67.7	.24	21.6	.19
	≤1.3	27	84.1		43.9	
Interval TACE	Yes	8	70.0	.93	25.0	.31
	No	49	75.1		32.6	

Table 2 (*continued*)

Variables		n	5-year OS (%)	P	5-year DFS (%)	P
Operating time (min)	>414	28	66.5	.19	27.6	.46
	≤414	29	83.1		36.5	
Blood loss (g)	>495	28	76.0	.94	23.8	.32
	≤495	29	74.0		40.3	
Red blood cell transfusion	Yes	6	0	< .0001	0	< .0001
	No	51	82.7		35.5	
Major complication (Clavien >III)	Presence	15	56.0	.12	37.0	.97
	Absence	42	80.7		29.7	

HBs-Ag, hepatitis B surface antigen; *HCV-Ab*, anti-hepatitis C antibody; ^{99m}Tc-*GSA*, ^{99m}Tc-galactosyl human serum albumin; *LHL15*, ratio of the liver-to-heart plus liver radioactivity at 15 minutes; *TACE*, transarterial chemoembolization; *OS*, overall survival; *DFS*, disease-free survival.

Table 3
Multivariate Cox regression analyses of factors related to overall and disease-free survival after hepatectomy.

Variables	Hazard ratio	95% CI	P
Overall survival			
Bilobar tumor distribution	NS		
Tumor number before hepatectomy ≥3	3.59	1.23–11.30	.019
DCP before hepatectomy >200 (mAU/mL)	3.36	1.02–15.11	.045
Albumin before hepatectomy ≤ 3.5 (g/dL)	NS		
Red blood cell transfusion	11.03	2.90–42.85	.0008
Disease-free survival			
Male gender	3.74	1.12–23.16	.029
Bilobar tumor distribution	3.65	1.54–8.18	.004
Tumor number before hepatectomy ≥3	NS		
Increase of tumor number after PVE	NS		
Albumin before hepatectomy ≤ 3.5 (g/dL)	NS		
Red blood cell transfusion	6.22	1.99–18.01	.0026

DCP, des-γ-carboxy prothrombin, *CI*, confidence interval; *NS*, not significant.
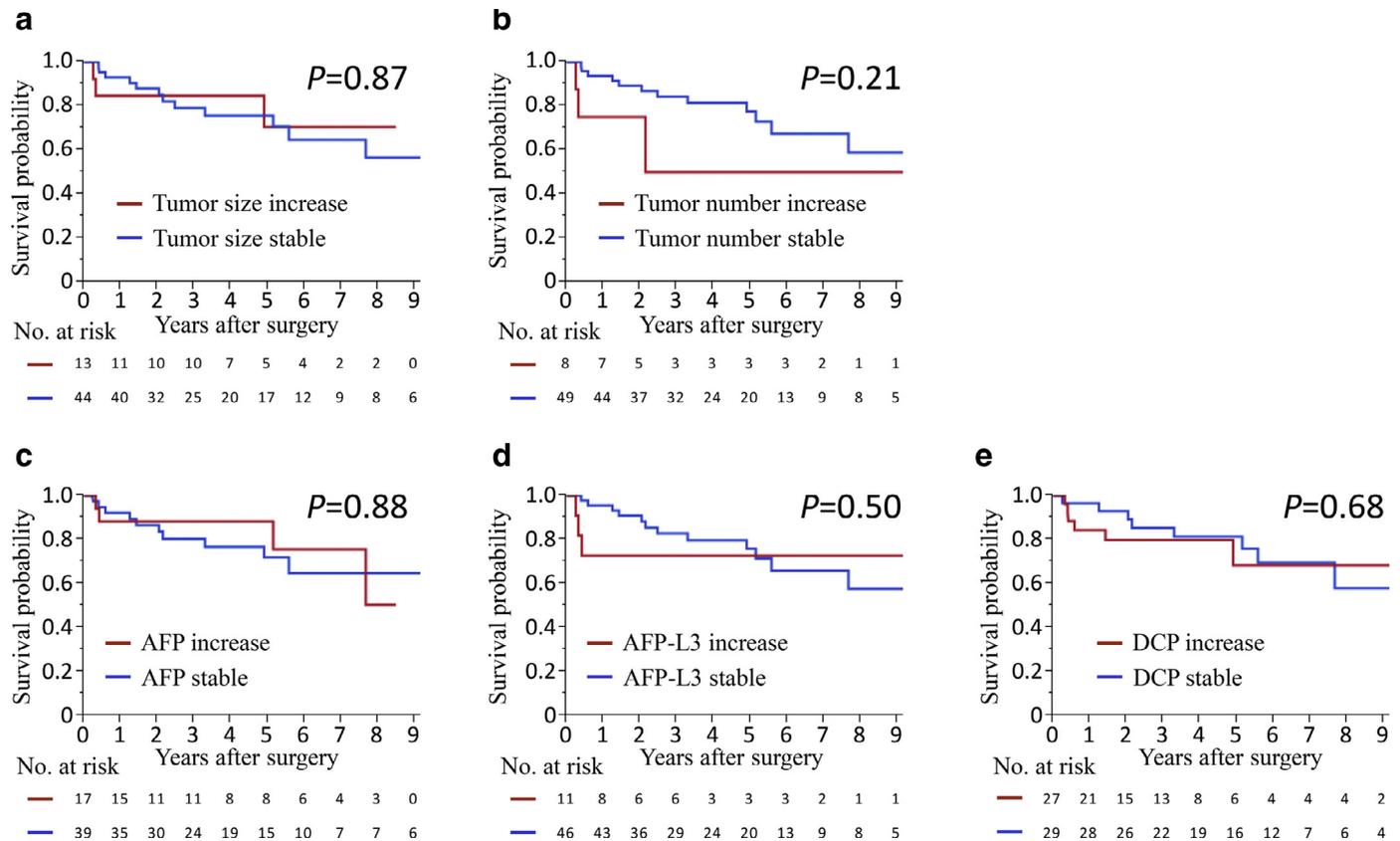

Fig. 2. Overall survival in patients who underwent portal vein embolization (PVE) followed by hepatectomy according to changes before and after PVE. (*A*) Tumor size, (*B*) tumor number, (*C*) AFP, (*D*) AFP-L3, (*E*) DCP. *AFP*, α-fetoprotein; *AFP-L3*, lens culinaris agglutinin-reactive fraction of α-fetoprotein; *DCP*, des-γ-carboxy prothrombin.
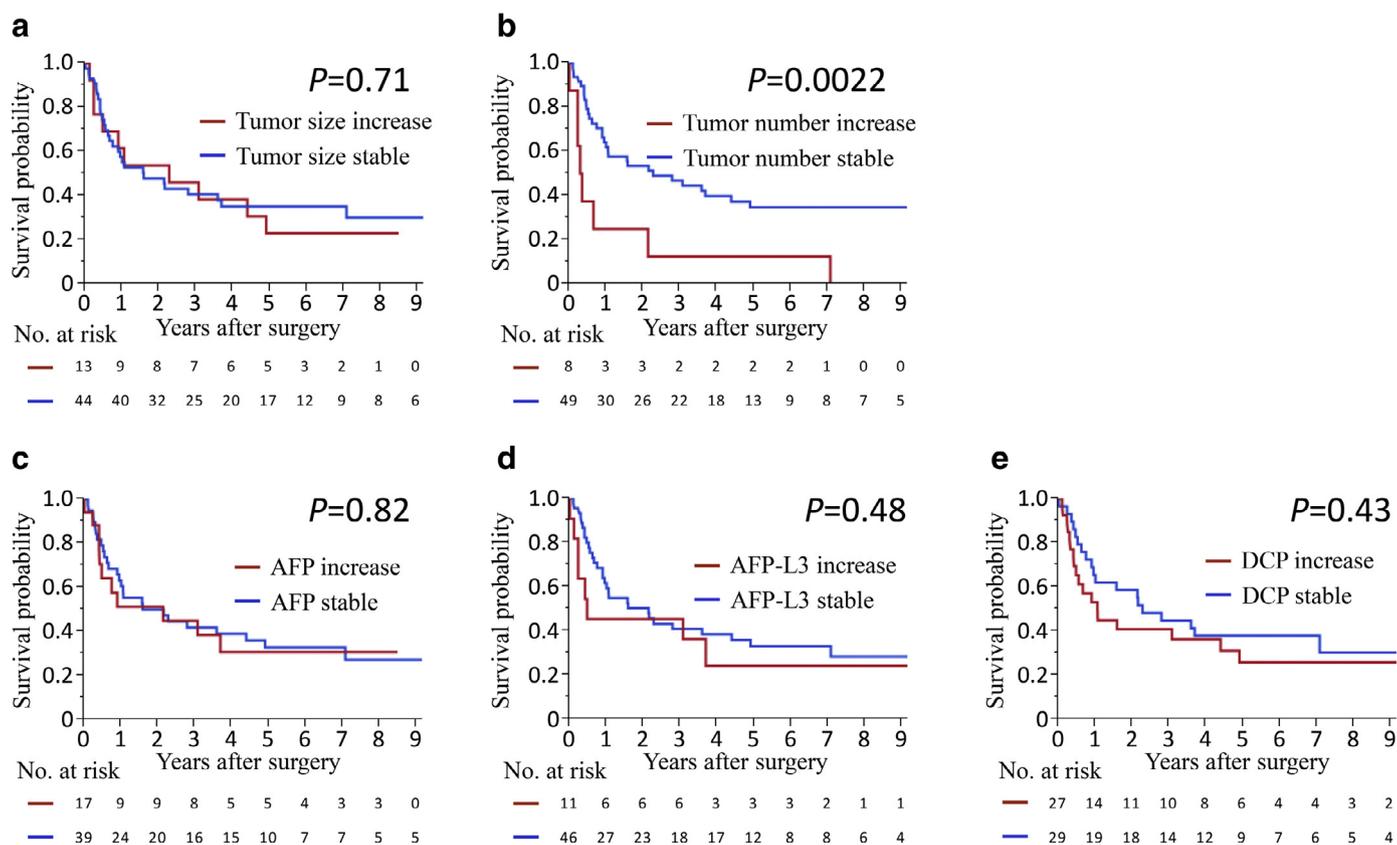
Fig. 3. Disease-free survival in patients who underwent portal vein embolization (PVE) followed by hepatectomy, according to changes before and after PVE. (*A*) Tumor size, (*B*) tumor number, (*C*) AFP, (*D*) AFP-L3, (*E*) DCP.
AFP, α-fetoprotein; *AFP-L3*, lens culinaris agglutinin-reactive fraction of α-fetoprotein; *DCP*, des-γ-carboxy prothrombin.

Table 4
First recurrence site and treatment for recurrence.

Recurrence site	
Liver	33
Lung	2
Adrenal gland	1
Liver + bone	1
Lung + lymph node	1
Treatment for recurrence	
Intrahepatic recurrence (*n* = 34)	
Hepatectomy	6
RFA	9
Hepatectomy + RFA	1
TACE	15
Best supportive care	3
extrahepatic recurrence (*n* = 5)	
Resection of adrenal gland	1
Sorafenib	2
Best supportive care	1

TACE, transarterial chemoembolization; *RFA*, radiofrequency ablation.

those who underwent upfront hepatectomy, even though they had a significantly larger resected liver volume on admission.[18] In the current study, the cumulative 5-year OS and DFS rates after hepatectomy were 74.5% and 31.7%, respectively, which are comparable to other studies that have reported 5-year OS and DFS rates (5-year OS: 50%–72%; 5-year DFS: 33%–54%).[16–18,30–32] However, there are few studies reporting tumor progression after PVE and oncologic outcomes after planned hepatectomy for HCC.

PVE is designed to increase the FLR and allow subsequent major liver resection to be performed safely, but not to suppress tumor progression, raising the concern that stimulation of liver hypertrophy could accelerate tumor progression. In the current study, disease progressions between PVE and hepatectomy, including tumor size increase, tumor number increase, AFP increase, AFP-L3 increase, and DCP increase, were observed in 22.8%, 14.0%, 29.8%, 19.3%, and 47.4% of patients, respectively. An increase of tumor number was the only variable that decreased the DFS rate after hepatectomy only in the univariate analysis, and none of them affected OS (Fig. 2). These findings suggest that if a planned hepatectomy can be carried out, disease progression after PVE does not affect survival after hepatectomy in patients with HCC. HCC tumors usually invade the portal system at a relatively early stage and disseminate through the liver via the portal circulation.[33] PVE may prevent portal dissemination of tumor cells, and this may be one reason why disease progression between PVE and hepatectomy did not affect the observed survival in the present study.

An important question is whether the new lesions that appeared between PVE and hepatectomy were present in the FLR. In the current study, eight patients showed an increased tumor number after PVE: 4 patients developed new lesions in the FLR and 4 patients developed lesions in the deportalized liver. Because the number of patients who displayed an increased tumor number was very small in the current study, it is difficult to elucidate the significance of the observed pattern of tumor number increase for long-term outcomes. However, this issue is highly relevant to the treatment strategy of PVE followed by hepatectomy, and larger multicentric studies should be undertaken.

Disease progression after PVE may lead to failure to achieve planned hepatectomy. Yamashita et al.[30] reported that, among 70 patients with HCC who underwent PVE, 6 patients (8.6%) could not achieve radical resection. Compared with patients with bile tract cancer (*n* = 133) and CRLM (*n* = 59), patients with HCC had

a significantly lower dropout rate. The reasons for dropout in HCC patients were less frequently associated with disease progression compared with bile tract cancer and CRLM. However, patients who could not achieve planned hepatectomy after PVE had significantly worse survival than those who could complete the planned strategy.[30] A potential way to prevent disease progression after PVE is to combine TACE and PVE. Earlier studies have reported better antitumor effects of a combination of TACE and PVE.[34,35] In the present study, we performed interval TACE between PVE and hepatectomy in 8 patients (14.0%) to suppress tumor growth. Because of the small sample size and retrospective nature, however, its efficacy for oncologic outcome is uncertain, and further prospective study is desirable.

The present study has several limitations. First, it is a retrospective data analysis from a single institution. Second, the number of cases is relatively small. Finally, the study period of more than 17 years may have led to some historical bias because significant developments occurred during that period in surgical techniques, perioperative management, and patient selection. However, the policy applied by this study's unique surgical team changed little throughout that time. Any historical bias in the present study is therefore assumed to have had negligible impact on the results. Our study included only patients who completed the planned strategy. Thus, the overall significance of disease progression after PVE has not yet been determined. However, the present study represents the first investigation that addresses the significance of disease progression after PVE in HCC. A multicenter large cohort study will be needed to validate these results.

In conclusion, disease progression after PVE did not affect long-term survival in patients with HCC if the planned subsequent hepatectomy could be completed. On the other hand, an increase of tumor number after PVE may be associated with tumor relapse after subsequent hepatectomy.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359–E386.
2. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: An emphasis on demographic and regional variability. *Clin Liver Dis*. 2015;19:223–238.
3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87–108.
4. Befeler AS, Hayashi PH, Di Bisceglie AM. Liver transplantation for hepatocellular carcinoma. *Gastroenterology*. 2005;128:1752–1764.
5. Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. *Hepatol Res*. 2007;37:676–691.
6. Borie F, Bouvier AM, Herrero A, Faivre J, Launoy G, Delafosse P, et al. Treatment and prognosis of hepatocellular carcinoma: A population based study in France. *J Surg Oncol*. 2008;98:505–509.
7. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery*. 1990;107:521–527.
8. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med*. 2007;356:1545–1559.
9. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, et al. Preoperative portal vein embolization for major liver resection: A meta-analysis. *Ann Surg*. 2008;247:49–57.
10. Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. *Arch Surg*. 2002;137:675–680 discussion 80–1.
11. Giglio MC, Giakoustidis A, Draz A, Jawad ZAR, Pai M, Habib NA, et al. Oncological outcomes of major liver resection following portal vein embolization: A systematic review and meta-analysis. *Ann Surg Oncol*. 2016;23:3709–3717.
12. Huiskens J, Olthof PB, van der Stok EP, Bais T, van Lienden KP, Moelker A, et al. Does portal vein embolization prior to liver resection influence the oncological outcomes—A propensity score matched comparison. *Eur J Surg Oncol*. 2018;44:108–114.
13. Wicherts DA, de Haas RJ, Andreani P, Sotirov D, Salloum C, Castaing D, et al. Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases. *Br J Surg*. 2010;97:240–250.
14. Ardito F, Vellone M, Barbaro B, Grande G, Clemente G, Giovannini I, et al. Right and extended-right hepatectomies for unilobar colorectal metastases: Impact of portal vein embolization on long-term outcome and liver recurrence. *Surgery*. 2013;153:801–810.
15. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, et al. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. *Hepatology*. 2001;34:267–272.
16. Palavecino M, Chun YS, Madoff DC, Zorzi D, Kishi Y, Kaseb AO, et al. Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: Perioperative outcome and survival. *Surgery*. 2009;145:399–405.
17. Siriwardana RC, Lo CM, Chan SC, Fan ST. Role of portal vein embolization in hepatocellular carcinoma management and its effect on recurrence: A case-control study. *World J Surg*. 2012;36:1640–1646.
18. Beppu T, Okabe H, Okuda K, Eguchi S, Kitahara K, Taniai N, et al. Portal vein embolization followed by right-side hemihepatectomy for hepatocellular carcinoma patients: A Japanese multi-institutional study. *J Am Coll Surg*. 2016;222 1138–48.e2.
19. Okabe H, Beppu T, Ishiko T, Masuda T, Hayashi H, Otao R, et al. Preoperative portal vein embolization (PVE) for patients with hepatocellular carcinoma can improve resectability and may improve disease-free survival. *J Surg Oncol*. 2011;104:641–646.
20. Hoekstra LT, van Lienden KP, Doets A, Busch OR, Gouma DJ, van Gulik TM. Tumor progression after preoperative portal vein embolization. *Ann Surg*. 2012;256:812–817 discussion 7–8.
21. Elias D, De Baere T, Roche A, Mducreux LeclereJ, Lasser P. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. *Br J Surg*. 1999;86:784–788.
22. Simoneau E, Hassanain M, Shaheen M, Aljiffry M, Molla N, Chaudhury P, et al. Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases. *Br J Surg*. 2015;102:1240–1249.
23. de Graaf W, van den Esschert JW, van Lienden KP, van Gulik TM. Induction of tumor growth after preoperative portal vein embolization: Is it a real problem? *Ann Surg Oncol*. 2009;16:423–430.
24. Imai K, Beppu T, Chikamoto A, Doi K, Okabe H, Hayashi H, et al. Comparison between hepatic resection and radiofrequency ablation as first-line treatment for solitary small-sized hepatocellular carcinoma of 3 cm or less. *Hepatol Res*. 2013;43:853–864.
25. Imai K, Beppu T, Yamao T, Okabe H, Hayashi H, Nitta H, et al. Clinicopathological and prognostic significance of preoperative serum zinc status in patients with hepatocellular carcinoma after initial hepatectomy. *Ann Surg Oncol*. 2014;21:3817–3826.
26. Beppu T, Hayashi H, Okabe H, Masuda T, Mima K, Otao R, et al. Liver functional volumetry for portal vein embolization using a newly developed 99mTc-galactosyl human serum albumin scintigraphy SPECT-computed tomography fusion system. *J Gastroenterol*. 2011;46:938–3.
27. Beppu T, Iwatsuki M, Okabe H, Okabe K, Masuda T, Hayashi H, et al. A new approach to percutaneous transhepatic portal embolization using ethanolamine oleate iopamidol. *J Gastroenterol*. 2010;45:211–217.
28. Hayashi H, Beppu T, Okabe H, Kuroki H, Nakagawa S, Imai K, et al. Functional assessment versus conventional volumetric assessment in the prediction of operative outcomes after major hepatectomy. *Surgery*. 2015;157:20–26.
29. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
30. Yamashita S, Sakamoto Y, Yamamoto S, Takemura N, Omichi K, Shinkawa H, et al. Efficacy of preoperative portal vein embolization among patients with hepatocellular carcinoma, biliary tract cancer, and colorectal liver metastases: A comparative study based on single-center experience of 319 cases. *Ann Surg Oncol*. 2017;24:1557–1568.
31. Seo DD, Lee HC, Jang MK, Min HJ, Kim KM, Lim YS, et al. Preoperative portal vein embolization and surgical resection in patients with hepatocellular carcinoma and small future liver remnant volume: Comparison with transarterial chemoembolization. *Ann Surg Oncol*. 2007;14:3501–3509.
32. Tanaka H, Hirohashi K, Kubo S, Shuto T, Higaki I, Kinoshita H. Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function. *Br J Surg*. 2000;87:879–882.
33. Azoulay D, Castaing D, Krissat J, Smail A, Hargreaves GM, Lemoine A, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. *Ann Surg*. 2000;232:665–672.
34. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. *Br J Surg*. 2006;93:1091–1098.
35. Aoki T, Imamura H, Hasegawa K, Matsukura A, Sano K, Sugawara Y, et al. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. *Arch Surg*. 2004;139:766–774.