Portal Vein Embolization Followed by Right-Side Hemihepatectomy for Hepatocellular Carcinoma Patients: A Japanese Multi-Institutional Study

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BACKGROUND: Portal vein embolization (PVE) is useful to expand the indications of major hepatectomy; however, its oncologic effects are not fully understood. This study aimed to confirm the efficacy of preoperative PVE for hepatocellular carcinoma patients.

STUDY DESIGN: Between 2000 and 2012, five hundred and ten patients with hepatocellular carcinoma undergoing right-side hemihepatectomy were enrolled (PVE group, n = 162 and non-PVE group, n = 348). To equalize background factors, one-to-one propensity case-matched analysis and multivariate analysis were performed. Short- and long-term outcomes were evaluated.

RESULTS: Propensity score-matched patients, 148 in each group, were selected. The percentage of resected liver volume on admission was significantly greater in the PVE group (60.5% vs 48.3%; $p < 0.001$), but decreased considerably after PVE, from 60.5% to 50.3% ($p < 0.001$). The 5-year cumulative recurrence-free survival (36.4% vs 35.3%) and overall survival (58.6% vs 52.8%) rates were comparable. Extrahepatic recurrences were less common in the PVE group (18.1% vs 38.8%; $p = 0.004$). Independent prognostic factors for recurrence-free survival were morbidity (hazard ratio [HR] = 1.56), multiple tumors (HR = 1.97), red cell concentrate administration (HR = 1.57), older age (HR = 2.09), and massive portal invasion (HR = 2.33); and those for overall survival were morbidity (HR = 2.37), multiple tumors (HR = 1.71), and massive hepatic venous invasion (HR = 3.49).

CONCLUSIONS: Even though hepatocellular carcinoma patients who underwent preoperative PVE and right-side hemihepatectomy had a significantly larger resected liver volume on admission, they have a comparable long-term prognosis as patients with up front hepatectomy. In addition, PVE might decrease extrahepatic recurrences. (J Am Coll Surg 2016;222:1138–1148. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

AFP = α-fetoprotein
AFP-L3 = lens culinaris agglutinin-reactive fraction of α-fetoprotein
DFS = disease-free survival
HCC = hepatocellular carcinoma
HR = hazard ratio
ICG R15 = 15-minute indocyanine retention rate
OS = overall survival
PSM = propensity score-matched
PVE = portal vein embolization
%RLV = percentage of resected liver volume
RCC = red cell concentrate
RFS = recurrence-free survival

Portal vein embolization (PVE) has been widely considered to provide larger future functional remnant liver volume for patients undergoing major hepatectomy.[1,2] Consequently, PVE can expand the indications of major hepatic resection requiring the removal of a large functional liver parenchyma and can reduce the risks of postoperative morbidity and mortality.[3-6]

Although the short-term benefits of PVE on liver function have been demonstrated in patients with or without injured liver, the oncologic effects of PVE are not fully understood. Most articles have confirmed the presence of identical disease-free survival (DFS) and overall survival (OS) curves in hepatocellular carcinoma (HCC) patients who underwent hepatectomy with or without PVE.[7-9] One article reported better OS in HCC patients treated with PVE and hepatectomy than those treated with hepatectomy alone, but this was limited to patients with a 15-minute indocyanine retention rate (ICG R15) >13%.[10] In addition, our previous single-institution study demonstrated that preoperative PVE can improve DFS for HCC patients requiring right hepatectomy.[11] We used ethanolamine oleate as an embolic material for PVE because it rarely caused recanalization, therefore, DFS can increase.[12] To minimize selection bias, we conducted a multi-institutional study in Kyushu, a region with a high risk for HCC in Japan.[13] We first conducted propensity score-matched (PSM) analysis to decrease selection bias in retrospective studies and allow comparison among different therapies.[14-16] After this, we applied multivariate analysis using the multivariate Cox proportional hazards model.

The current multicenter study aimed to assess the impact of preoperative PVE on the recurrence and long-term prognosis of HCC patients and to determine the prognostic factors in HCC patients treated with PVE and right-side hemihepatectomy.

METHODS

Patients

This clinical study was performed by the "Project Committee of the Multi-institutional Study by the Kyushu Study Group of Liver Surgery." From January 2000 to December 2012, five hundred and ten consecutive HCC patients undergoing right or extended right hemihepatectomy were enrolled from 13 institutions. Patients receiving PVE without the intention of performing hepatic resection were excluded.[17] Using a shared database, we retrospectively collected the clinicopathologic and prognostic data of the patients. Written informed consent and IRB approval (approval number, 705; Kumamoto University) were obtained for this study.

We recorded the following preoperative items: sex, age, hepatitis B surface antigen, hepatitis C virus antibody, ICG R15, liver damage grade, Child-Pugh score, tumor number, maximal tumor size, existence of distant metastasis, clinical stage, existence of microscopic vessel invasion, α-fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and protein induced by vitamin K absence or antagonists II, percentage of the resected liver volume (%RLV) on admission and before hepatic resection, initial therapy (yes, no), extent of hepatectomy (right or extended right), and procedures for hepatectomy (conventional or anterior approach). Liver damage grade and clinical stage were decided according to the Criteria of the Liver Cancer Study Group of Japan.[18] Right-side hemihepatectomy without other earlier therapies for HCC, except for PVE, was considered "initial therapy."

Indications for portal vein embolization

Portal vein embolization was performed depending on the indication for PVE in individual institutions. In Japan, PVE is basically selected before right-side hemihepatectomy for HCC if non-tumor resection rates were >60% and 40% for patients with normal ICG R15 and 10%<ICG R15≤20%, respectively.[12,19] If the criteria for hepatectomy were fulfilled after PVE, a right-side hemihepatectomy was actually performed.

Portal vein embolization procedure and operative method

Procedures for PVE and hepatectomy were based on individual institutional strategies. For right-side hemihepatectomy, the operative procedure of the conventional approach or anterior approach was recorded. "Conventional approach" referred to hepatic resection after mobilization of the entire right liver, and "anterior approach" referred to earlier dissection of inflow vessels and

transection of hepatic parenchyma followed by the removal of the right liver.[19] Hanging maneuver was used according to the surgeons' preference.[20]

Volumetric measurements

Resection rates were calculated from enhanced CT volumetry.[21] The %RLV was calculated as follows: (resection liver volume − tumor volume) / (total liver volume − tumor volume) × 100.

In the PVE group, %RLV was systematically assessed before PVE and again before surgery. In the non-PVE group, the assessment was performed once on admission. The final decision of whether to perform hepatectomy after PVE or to perform upfront hepatectomy was made after careful evaluation of CT volumetry and liver function.

Perioperative parameters

Operative time, estimated intraoperative blood loss, and frequency of red cell concentrate (RCC) transfusion were recorded. Morbidity was graded according to the Clavien-Dindo classification,[22] and complications with grade IIIA or higher were defined as morbidity. The following complications were individually noted: postoperative intra-abdominal bleeding, hepatic failure, bile leakage, intra-abdominal abscess, surgical site infection, pleural effusion/ascites, ARDS, and apoplexy. Surgical site infections were superficial and deep incisional surgical site infections. Other morbidities were recorded separately. In addition, 1- and 3-month mortality were evaluated.

Pathologic findings of the resected specimen

Pathologic examination included tumor differentiation (well, moderate, or poor); vessel invasion (hepatic artery, portal vein, hepatic vein, and bile duct) according to the Criteria of the Liver Cancer Study Group of Japan[18]; and staging for fibrosis and grading for activity in the background liver by Inuyama classification.[23]

Propensity score analysis

Propensity score analysis was used to create a matched cohort of patients for comparison of clinical variables, long-term recurrence, and survival between the PVE group and non-PVE groups.[14-16] We included the following 18 clinical variables for propensity score generation: sex, age, hepatitis B surface antigen, hepatitis C virus antibody, ICG R15, liver damage grade, number and maximal size of the tumor, existence of extrahepatic metastasis or microscopic vessel invasion, clinical stage, tumor markers (AFP, AFP-L3, and protein induced by vitamin K absence or antagonists II), %RLV before hepatic resection, initial therapy rate, extent of hepatectomy, and procedures for hepatectomy. Logistic regression was applied to create a continuous propensity score ranging from 0 to 1. Matched PVE and non-PVE groups (each containing 148 subjects) were generated by one-to-one greedy data matching by Mahalanobis distance without replacement on the logit of the propensity score using calipers of width equal to 0.2 times the SD of the logit of the propensity score.

Statistical analyses

For the overall cohort, clinical parameters were compared using Mann-Whitney U test for ordinal data and Fisher's exact test for categorical data. For the PSM cohort, exact McNemar test was used for 2 × 2 categorical data, stratified conditional logistic regression analysis for m × 2 categorical data, and Wilcoxon signed rank test for continuous data. The 95% CIs for medians were estimated using the bootstrap method. The Kaplan-Meier method was used to calculate recurrence-free survival (RFS) and OS rates. The starting point of survival was the day of initial hepatectomy. All p values were calculated using the log-rank test for the overall cohort and using 5 stratified Cox proportional hazard models for the PSM cohort. Univariate Cox proportional hazards models of all 24 potential perioperative predictors were built to compute hazard ratio (HR) and 95% CIs. Multivariate regression analysis was performed using the Cox proportional hazards model, and all factors were entered into the final model. Even for stage IVb HCC patients, the duration to recurrence was defined as the period between the date of first recurrence and the date of initial hepatic resection in patients who experienced any recurrence. A p value <0.05 was considered statistically significant. Statistical analyses were performed using STATA statistical software (release 13.1, 2013, StataCorp) and NCSS 10 statistical software (2015, NCSS).

RESULTS

In total, 510 HCC patients were divided into the PVE group (n = 162) and the non-PVE group (n = 348). Characteristics of patients in the overall cohort and the PSM cohort are found in Table 1. In the 2 groups, the following 5 of 18 factors were found to be positively related in univariate analysis ($p < 0.05$): hepatitis C virus antibody, maximal tumor size, microscopic vessel invasion, clinical stage, and levels of protein induced by vitamin K absence or antagonists II and AFP-L3. However, clinical stage and AFP-L3 were excluded for further PSM analysis because clinical stage was a confounding factor and the missing rate of AFP-L3 was 39%, which was >25%.[24]

Table 1. Perioperative Clinical Characteristics of Hepatocellular Carcinoma Patients Who Did and Did Not Undergo Portal Vein Embolization: Overall Cohort and Propensity Score-Matched Cohort

	Overall cohort (n = 510)			Propensity score-matched cohort (n = 296)		
Characteristic	**PVE (n = 162)**	**Non-PVE (n = 348)**	**p Value**	**PVE (n = 148)**	**Non-PVE (n = 148)**	**p Value**
Categorical data, n						
Sex			0.904			0.511
Female	32	66		29	24	
Male	130	282		119	124	
Age			0.635			0.586
67 y or younger	82	168		74	68	
Older than 67 y	80	180		74	80	
Hepatitis B surface antigen			0.838			0.053
Negative	109	239		100	115	
Positive	52	109		48	33	
Hepatitis C virus antibody			0.011*			>0.999
Negative	86	228		80	80	
Positive	75	120		68	68	
ICG R15			0.436			0.539
≤12.8%	74	165		70	72	
>12.8%	83	157		74	64	
Liver damage grade			0.850			0.632
A	140	301		128	131	
B	22	44		20	17	
C	0	1		0	0	
Child-Pugh score			0.816			>0.999
A	156	333		142	141	
B	6	15		6	7	
No. of tumors			>0.999			>0.999
≤1	99	220		92	91	
>1	56	127		54	56	
Maximum tumor size			0.007*			>0.999
≤69 mm	90	154		85	86	
>69 mm	66	192		63	62	
Distant metastasis			0.484			>0.999
Negative	152	131		143	143	
Positive	5	17		5	5	
Clinical stage			<0.001*			0.096
I	4	3		4	2	
II	61	96		57	51	
III	65	123		61	57	
IVa	21	109		21	35	
IVb	5	16		5	3	
Microscopic vessel invasion			0.001*			>0.999
No	77	109		65	65	
Yes	85	238		83	83	
AFP-L3			0.049*			>0.999
≤5.9%	71	85		69	45	
>5.9%	53	103		51	37	
PIVKA-II			<0.001*			>0.999
≤850 mAU/mL	103	142		98	98	

(Continued)

Table 1. Continued

Characteristic	Overall cohort (n = 510)			Propensity score-matched cohort (n = 296)		
	PVE (n = 162)	Non-PVE (n = 348)	p Value	PVE (n = 148)	Non-PVE (n = 148)	p Value
>850 mAU/mL	50	195		50	50	
Initial therapy			0.911			>0.999
Yes	122	262		111	108	
No	37	82		35	37	
Operative method			0.912			>0.999
Right-side hemihepatectomy	123	262		115	115	
Extended right-side hemihepatectomy	39	86		33	33	
Approach			0.109			0.148
Conventional	87	225		82	95	
Anterior	66	122		63	52	
Continuous data, median (range)						
Age, y	67 (31–84)	68 (17–87)	0.878	67.5 (31–84)	69 (17–86)	0.595
ICG R15, %	13 (1.9–49.5)	12.4 (1–73.9)	0.292	13.0 (1.9–49.5)	12.2 (1–37)	0.118
No. of tumors	1 (1–8)	1 (1–38)	0.595	1 (1–8)	1 (1–12)	0.672
Tumor size, mm	60 (5–180)	75 (2.5–200)	0.001*	60 (5–180)	55 (2.5–200)	0.646
AFP, ng/mL	28 (0–240,000)	76.3 (0.8–1,057,400)	0.021*	28.0 (1.5–240,000)	29.5 (1.2–1,057,400)	0.985
AFP-L3, %	1.9 (0–88.6)	9.4 (0–87.3)	0.027*	1.6 (0–88.6)	1.5 (0–86.6)	0.695
PIVKA-II	331 (0–123,200)	1,910 (2.4–672,900)	<0.001*	343 (0–123,200)	290 (2.4–75,000)	0.730
Initial %RLV	61 (27.4–85)	49.9 (0–82.5)	<0.001*	60.5 (27.4–85)	48.3 (0–73.6)	<0.001*
Prehepatectomy %RLV	50.3 (25–73.9)	49.9 (0–82.5)	0.624	50.3 (25–73.9)	48.3 (0–73.6)	0.308

Clinical parameters were compared with Wilcoxon rank sum (Mann-Whitney) test for ordinal, and Fisher's exact test for categorical data for overall cohort, exact McNemar test for 2 × 2 categorical data, stratified conditional logistic regression analysis for m × 2 categorical data, and Wilcoxon signed rank test for continuous data for propensity score-matched cohort.

*Significant.

AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonists II; PVE, portal vein embolization; %RLV, percentage of resected liver volume.

After one-to-one case propensity score matching, 148 PVE patients and 148 non-PVE patients were subjected to additional analysis. All baseline characteristics of the PSM cohort were identical between the 2 groups. Standardized differences before and after PSM were demonstrated (Supplementary Figure 1; available online). The imbalance was defined as an absolute value >10%; however, all values were well balanced. Receiver operating characteristic curves were used to estimate the accuracy of PSM. The area under the curve of the propensity score was 0.67.

The PSM cohort included 8 stage IVb HCC patients: 5 in the PVE group and 3 in the non-PVE group. The sites of distant metastasis included direct invasion to mediastinum, pericardium, and adrenal gland; 2 lung metastases; bone metastasis; peritoneal dissemination; and supradiaphragmatic lymph node metastasis. Simultaneous resection was performed for 5 patients with 3 cases of direct invasion, peritoneal dissemination, and supradiaphragmatic lymph node metastasis. Bone metastasis was treated with radiotherapy and defined as complete remission. Two patients with lung metastasis were still in the tumor-bearing state, therefore, they were excluded from the calculation of the interval to recurrence.

Impact of portal vein embolization on remnant liver volume and liver function before operation

In the PSM cohort, the median interval between PVE and the operation was 21 days (range 8 to 456 days). Before PVE, the mean %RLV of the PVE group was significantly larger than that of the non-PVE group (60.5% vs 48.3%; $p < 0.001$). However, %RLV significantly decreased from 60.5% to 50.3% by PVE ($p < 0.001$), and % RLV of the PVE group prehepatectomy and %RLV of the non-PVE group became comparable (50.3% vs 48.3%; Table 1).

Intraoperative and postoperative course after right-side hemihepatectomy

In the PSM cohort, the median intraoperative blood loss and frequency of blood transfusion were comparable between the 2 groups (Table 2). Median operation time was significantly longer in the PVE group than in the non-PVE group (417 vs 393 minutes; $p = 0.026$). The morbidity was identical (30.3% in the PVE group and 26.0% in the non-PVE group; $p = 0.512$). No specific postoperative complications were encountered. In the PVE group and non-PVE group, 30-day mortality was 2.0% vs 1.4% ($p > 0.999$) and 90-day mortality was 2.0% vs. 2.7% ($p > 0.999$).

Pathologic findings of the resected specimen

Resected specimen showed 110 (21.6%) with poor tumor differentiation and positive vessel invasion; 23 (4.5%) for hepatic artery, 244 (47.8%) for portal vein, 140 (27.5%) for hepatic vein, and 37 (7.3%) for bile duct. Fibrosis stage (F4 in 9 [1.8%], F3 in 9 [1.8%], F1+F2 in 162 [31.8%]) and activity grade (A2+A3 in 17 [3.3%]) were investigated.

Patient recurrence and prognosis

In the overall cohort, RFS and OS rates for the PVE group were significantly greater than those for the non-PVE group (RFS for 1, 3, and 5 years: 75.2%, 49.3%, and 38.9%, respectively, vs 54.6%, 38.0%, and 32.1%, respectively; $p = 0.005$ and OS for 1, 3, and 5 years: 88.7%, 65.8%, and 59.7%, respectively, vs 79.9%, 56.8%, and 47.0%, respectively; $p = 0.037$; Fig. 1A, B). In the PSM cohort, the median observation periods in the PVE and non-PVE groups were 21.7 months (range 16.4 to 28.6 months) vs 12.4 months (range 8.2 to 16.2 months) for RFS and 35.1 months (range 30.9 to 39.5 months) vs 27.8 months (range 24.4 to 39.1 months) for OS. Recurrence-free survival and OS in the PVE group were not significantly better than those of the non-PVE group (RFS for 1, 3, and 5 years: 74.0%, 46.8%, and 36.4%, respectively, vs 60.6%, 42.3%, and 35.3%, respectively; $p = 0.281$ and OS for 1, 3, and 5 years: 89.0%, 65.5%, and 58.6%, respectively, vs 87.2%, 63.3%, and 52.8%, respectively; $p = 0.519$; Fig. 1C, D). We additionally performed 10 random trials for PSM assessment (Supplementary Table 1; available online). Median values were 0.153 (range 0.048 to 0.334) for RFS and 0.209 (range 0.019 to 0.519) for OS. Minimum p values were significant for both RFS and OS.

The pattern of recurrence was thoroughly investigated (Table 3). The incidences of overall and within 2-year recurrence were similar between the 2 groups (58.9% vs 56.9% and 38.3% vs 46.8%, respectively). Duration to the first recurrence was not significantly different in the PVE group and in the non-PVE group (median 15.3 months; range 1.3 to 89.4 months vs median 8.0 months; range 0.2 to 123 months; $p = 0.992$). Initial recurrence sites were significantly different between the 2 groups; in particular, extrahepatic recurrences were encountered more frequently in the non-PVE group than in the PVE group (18.1% vs 38.8%; $p = 0.004$). Additionally, we evaluated the interval to the first recurrence and recurrence pattern limited to the patients without stage IVb. Results are almost similar in all patients with recurrence (Supplementary Table 2; available online).

Prognostic factors for recurrence-free survival and overall survival

In the overall cohort, all 24 perioperative and pathologic factors were tested using multivariate analysis (Table 4).

Table 2. Perioperative Data in Hepatocellular Carcinoma Patients Who Did and Did Not Undergo Portal Vein Embolization: Overall Cohort and Propensity Score-Matched Cohort

	Overall patients (n = 510)			Propensity score-matched patients (n = 296)		
Variable	**PVE (n = 162)**	**Non-PVE (n = 348)**	**p Value**	**PVE (n = 148)**	**Non-PVE (n = 148)**	**p Value**
Operation time, min, median (range)	415 (220–995)	402 (190–1,120)	0.426	417 (220–995)	393 (190–922)	0.026*
Blood loss, g, median (range)	815 (23–5,470)	950 (50–13,000)	0.048*	815 (23–5,470)	830 (50–9,940)	0.650
Red cell concentrate administration, n (%)	46 (31.3)	136 (39.9)	0.083	45 (32.1)	53 (36.8)	0.704
Morbidity, n (%)	45 (28.9)	94 (27.3)	0.747	44 (30.3)	38 (26.0)	0.512
Mortality, n (%)						
Within 1 mo	3 (1.9)	6 (1.7)	>0.999	3 (2.0)	2 (1.4)	>0.999
Within 3 mo	3 (1.9)	20 (5.8)	0.065	3 (2.0)	4 (2.7)	>0.999

Clinical parameters were compared with Wilcoxon rank sum (Mann-Whitney) test for ordinal, and Fisher's exact test for categorical data for overall cohort, exact McNemar test for categorical data, and Wilcoxon signed rank test for continuous data for propensity score-matched cohort.
*Significant.
PVE, portal vein embolization.

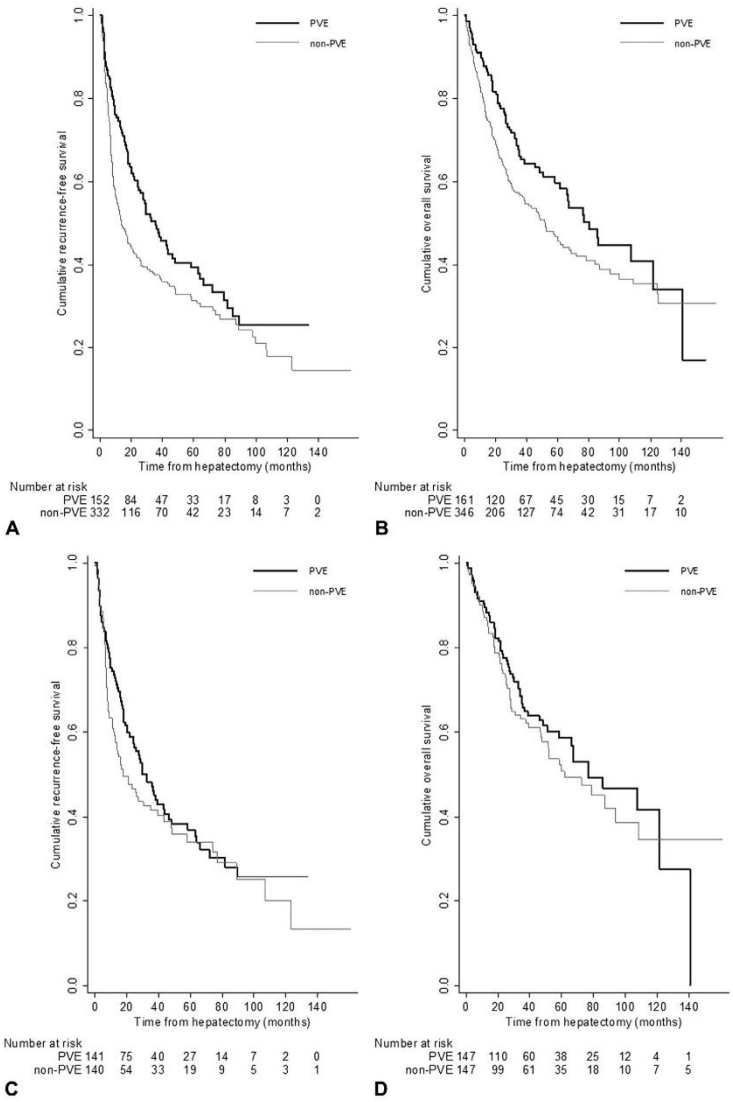

Figure 1. Cumulative survival curves in the portal vein embolization (PVE) group and non-PVE group. (A) Recurrence-free survival (RFS). (B) Overall survival (OS) in overall cohort. (C) Recurrence-free survival in propensity score-matched cohort. (D) Overall survival in propensity score-matched cohort. In overall cohort, RFS and OS in the PVE group were significantly greater than those of the non-PVE group ($p = 0.005$ for RFS and $p = 0.037$ for OS). In the propensity score-matched cohort, RFS and OS were not significantly different in the 2 groups ($p = 0.281$ for RFS and $p = 0.519$ for OS).

Table 3. Details of Initial Recurrence in Propensity Score-Matched Cohort

Variable	PVE (n = 148)	Non-PVE (n = 148)	p Value
Recurrence, yes/no, n (%)	86/60 (58.9)	82/62 (56.9)	0.736
Recurrence within 2-y, yes/no, n (%)	54/87 (38.3)	66/75 (46.8)	0.182
Interval to initial recurrence, mo, median (range)	15.3 (1.3–89.4)	8 (0.2–123)	0.922
Initial recurrence site			0.012*
Intrahepatic only	68	49	
Intrahepatic and extrahepatic	2	9	
Extrahepatic only	13	22	
Initial recurrence site			0.004*
Intrahepatic only	68	49	
Including extrahepatic	15	31	

*Significant.
PVE, portal vein embolization.

Independent prognostic factors for RFS were morbidity (HR = 1.56; 95% CI, 1.00–2.42; p = 0.049), multiple tumors (HR = 1.97; 95% CI, 1.29–3.01; p = 0.002), RCC administration (HR = 1.57; 95% CI, 1.01–2.44; p = 0.046), older age (HR = 2.09; 95% CI, 1.27–3.45; p = 0.004), and massive portal invasion: vp3/vp4 (HR = 2.33; 95% CI, 1.17–4.66; p = 0.016). Independent prognostic factors for OS were morbidity (HR = 2.37; 95% CI, 1.47–3.83; p < 0.001), multiple tumors (HR = 1.71; 95% CI, 1.06–2.77; p = 0.029), and massive hepatic venous invasion: vv3/vv4 (HR = 3.49; 95% CI, 1.06–14.7; p = 0.041).

DISCUSSION

To our best knowledge, this multi-institutional study includes the largest number of patients with HCC (n = 162) undergoing PVE followed by hemihepatectomy.[7-12,25] We enrolled only patients undergoing right-side hemihepatectomy to obtain similar %RLV immediately before hepatic resection. In fact, preoperative %RLV was equivalent in the groups with or without PVE. To equalize the background factors, one-to-one PSM analysis using 4 significant factors was performed; therefore, all variables were well balanced (Supplementary Figure 1; available online). Finally, 148 patients in the PVE group and 148 in the non-PVE group were further analyzed.

The current study was conducted mainly to prove the previous results that PVE can provide better DFS or OS for patients with HCC after right-side hemihepatectomy.[10,11] A crucial problem remained in validating this hypothesis. A randomized controlled trial was not feasible to compare HCC patients with or without PVE because %RLV on admission in the 2 groups was always significantly different. Unfortunately, after PSM, the application of PVE was not a significant prognostic factor for RFS (p = 0.281) and OS (p = 0.519). However, based on our results of 10 random PSM analyses (Supplementary Table 2; available online), median p values were 0.153 (range 0.048 to 0.334) and 0.209 (range 0.019 to 0.519) for RFS and OS, respectively, and the smallest p values were significant for both. Portal vein embolism might lead to better RFS and OS.

Interestingly, the incidence of recurrence was similar between the 2 groups; however, extrahepatic recurrences were more frequent in the non-PVE group. There are some hypotheses about why PVE followed by right-side hemihepatectomy can decrease extrahepatic recurrences or can withdraw better outcomes. First, the selection of suitable patients was done after preoperative PVE and some patients were excluded because of early recurrence, deterioration of liver function, or insufficient liver regeneration. We have reported that in approximately 21% of HCC patients, subsequent hepatectomy was canceled after PVE.[11] Second, in patients undergoing PVE followed by right-side hemihepatectomy, liver volume regeneration was accomplished in a 2-step manner.[26] Inflammatory cytokines, growth factors, and serum bile acid accelerated after liver resection[27,28]; however, the peak levels may be lower than those after hepatectomy without PVE. Portal vein is usually dissected early in the liver resection; however , hepatic vein is dissected immediately before the end of liver transection. Therefore, extrahepatic recurrences can be accelerated. Most recently, we reported that branched-chain amino acid supplementation can modify functional liver regeneration in patients undergoing PVE followed by major hepatic resection.[29] Third, portal pressure had elevated at the time of earlier PVE and did not increase simultaneously during hepatectomy.

In the current study, PVE was not an independent prognostic factor for RFS and OS. Multivariate analyses showed 5 significant prognostic factors for RFS and 3 factors for OS. Multiple tumors and "morbidity related to hepatectomy" were significant factors for RFS and OS.

Table 4. Multivariate Analyses for Recurrence-Free Survival and Overall Survival in Hepatocellular Carcinoma Patients Undergoing Portal Vein Embolization Followed by Right-Side Hepatectomy

	Recurrence-free survival			Overall survival		
Factor	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Portal vein embolization, yes vs no	0.90	0.59–1.39	0.644	0.97	0.59–1.61	0.918
Sex, male vs female	1.67	0.99–2.83	0.054	1.36	0.73–2.55	0.334
Hepatitis B surface antigen, yes vs no	1.16	0.67–2.01	0.601	0.90	0.49–1.65	0.737
Hepatitis C virus antibody, yes vs no	1.19	0.73–1.94	0.497	0.87	0.50–1.52	0.628
Liver damage, grade B vs grade A	1.02	0.53–1.98	0.947	0.63	0.27–1.48	0.292
Distant metastases, yes vs no	1.22	0.38–3.97	0.737	2.56	0.78–8.39	0.121
Initial therapy, yes vs no	0.70	0.43–1.15	0.159	0.85	0.46–1.57	0.606
Operative method, extended right hepatectomy vs right hepatectomy	1.32	0.86–2.02	0.200	0.82	0.47–1.43	0.477
Red cell concentrate, yes vs no	1.57	1.01–2.44	0.046*	1.33	0.79–2.22	0.279
Morbidity, yes vs no	1.56	1.00–2.42	0.049*	2.37	1.47–3.83	<0.001*
Differentiation, poor vs well-moderate	0.87	0.52–1.47	0.614	0.74	0.40–1.37	0.336
Fibrosis stage, F3–F4 vs F0–F2	1.40	0.87–2.24	0.166	1.45	0.82–2.55	0.205
Activity grade, A2–A3 vs A0–A1	0.98	0.63–1.52	0.914	0.98	0.58–1.69	0.954
Va, va1–va2 vs va0	0.95	0.34–2.72	0.931	1.06	0.35–3.21	0.912
vp–vp0		Reference			Reference	
vp1–vp2	0.99	0.62–1.58	0.962	0.69	0.40–1.19	0.183
vp3	2.33	1.17–4.66	0.016*	1.42	0.63–3.19	0.399
vv–vv0		Reference			Reference	
vv1–vv2	0.96	0.57–1.62	0.882	1.71	0.98–3.00	0.059
vv3	3.20	0.90–11.4	0.071	3.94	1.06–14.7	0.041*
b–b0		Reference			Reference	
b1–b2	1.94	0.86–4.33	0.108	0.68	0.25–1.89	0.461
b3–b4	1.81	0.50–6.56	0.368	1.00	0.20–5.09	0.995
Age, older than 70 y vs 70 y or younger	2.09	1.27–3.45	0.004*	1.67	0.93–2.97	0.083
15-min indocyanine retention rate, >10% vs ≤10%	0.66	0.43–1.02	0.062	0.92	0.56–1.51	0.737
No. of tumors, >1 vs 1	1.97	1.29–3.01	0.002*	1.71	1.06–2.77	0.029*
Maximum tumor size, >5 cm vs ≤5 cm	1.21	0.76–1.95	0.420	1.11	0.63–1.96	0.725
α-Fetoprotein, >400 ng/mL vs ≤400 ng/mL	1.41	0.87–2.28	0.161	1.30	0.74–2.30	0.365
AFP-L3, >10% vs ≤10%	1.04	0.65–1.67	0.878	1.68	0.94–2.99	0.077
PIVKA-II, >400AU/mL vs ≤400 AU/mL	1.21	0.77–1.92	0.409	1.11	0.64–1.94	0.711

Fibrosis stage and activity grade were assessed with Inuyama criteria,[23] and vessel invasion were evaluated using Liver Cancer Study Group of Japan criteria.[18]
*Significant.
AFP-L3, lens culinaris agglutinin-reactive fraction of α-fetoprotein; HR, hazard ratio; PIVKA-II, protein induced by vitamin K absence or antagonists II.

In addition, RCC administration, older age (older than 70 years), and massive portal invasion were significant for RFS, and massive hepatic venous invasion was significant for OS. Interestingly, perioperative factors such as "morbidity related to hepatectomy" and RCC administration were selected as significant prognostic factors. Blood transfusion showed a negative impact on recurrence and prognosis of HCC after hepatic resection.[30] We have reported that postoperative complication is one of the high risk factors for recurrence in HCC patients undergoing hepatectomy.[31] Preoperative PVE followed by surgical resection for HCC can improve patient survival when compared with chemoembolization alone for patients with matched background factors.[32]

Portal vein embolization can expand the indications of major hepatectomy in HCC patients without increasing morbidity and mortality.[7-11] Portal vein embolization is a unique treatment for HCC because PVE itself has no direct therapeutic effect on HCC and can lead to tumor progression during a waiting time for regeneration of the future remnant liver.[33] Using a rat model of liver cirrhosis, portal vein occlusion can accelerate tumor growth in occluded lobes but not in contralateral lobes.[34] Based on this theory, if there were subclinical tumors in

the remnant liver, the oncologic disadvantage of PVE before hepatectomy might not be serious.

There are some limitations in this study. This is a multi-institutional study based on limited data from a shared database. There included various procedures for PVE (eg, percutaneous or trans-ileocolic, ipsilateral or contralateral, balloon-occluded or not) and different operative procedures for right-side hemihepatectomy. The patients who received PVE had significantly higher %RLV on admission than those who underwent up front hepatectomy, therefore, propensity score matching might be strictly impossible.

CONCLUSIONS

Portal vein embolization can assure liver regeneration and extend the indications of right-side hemihepatectomy for HCC patients without perioperative disadvantage, with the exception of prolonging the operation time. In addition, RFS and OS were quite comparable in patients with or without PVE, and extrahepatic recurrences can be decreased by PVE. It would be advisable to design a randomized controlled trial to compare the recurrence and prognosis for initially resectable HCC patients with or without PVE.

Author Contributions

Study conception and design: Beppu, Okabe
Acquisition of data: Okuda, Eguchi, Kitahara, Taniai, Ueno, Shirabe, Ohta, Kondo, Nanashima, Noritomi, Okamoto, Fujioka
Analysis and interpretation of data: Beppu, Okabe, Kikuchi
Drafting of manuscript: Beppu, Okabe
Critical revision: Okuda, Eguchi, Kitahara, Taniai, Ueno, Shirabe, Ohta, Kondo, Nanashima, Noritomi, Okamoto, Baba, Fujioka

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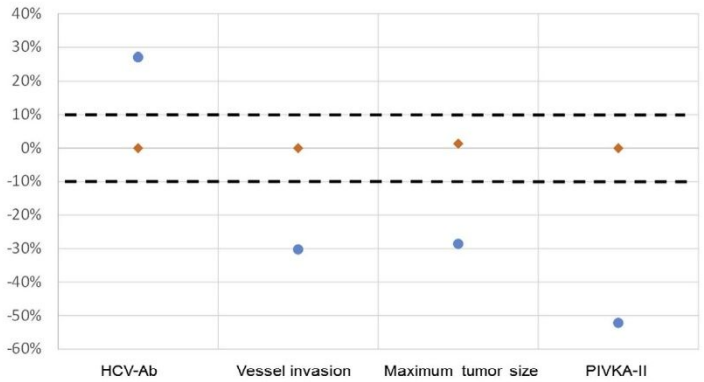

Supplementary Figure 1. Standardized differences before and after propensity score matching (PSM). Closed circle, blue, before PSM; closed diamond, orange, after PSM. HCV-Ab, hepatitis C virus antibody; PIVKA-II, protein induced by vitamin K absence or antagonists-II.

Supplementary Table 1. Details of Initial Recurrence in Propensity Score-Matched Cohort Excluding Stage IVb Patients

	PVE (n = 143)	Non-PVE (n = 145)	p Value
Recurrence, yes/no, n (%)	82/60 (57.8)	80/62 (56.3)	0.822
Recurrence within 2 y, yes/no, n (%)	50/87 (36.5)	64/75 (46.0)	0.142
Interval to initial recurrence, mo, median (range)	16.2 (0.3–89.4)	8.0 (0.2–123)	0.980
Initial recurrence site			0.002*
Intrahepatic only	66	47	
Including extrahepatic	13	31	

*Significant.
PVE, portal vein embolization.

Supplementary Table 2. Random 10 Trials for Propensity Matching

Trial	p Value for recurrence-free survival	p Value for overall survival
1	0.281	0.519
2	0.160	0.076
3	0.260	0.235
4	0.048	0.053
5	0.052	0.019
6	0.179	0.183
7	0.146	0.240
8	0.065	0.291
9	0.081	0.063
10	0.334	0.293