Original Article

Clinical impact of anatomical resection on long-term outcomes after hepatectomy for primary solitary hepatocellular carcinoma with or without preoperative positron emission tomography positivity

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Background: There is little evidence indicating that anatomical resection (AR) is associated with improved survival in patients with solitary hepatocellular carcinoma (HCC) who were preoperatively evaluated by positron emission tomography (PET). The aim of our study was to compare the oncologic outcomes of AR in PET-positive versus PET-negative patients with HCC.

Methods: From January 2007 to September 2015, 259 patients with preoperative PET underwent hepatectomy as the primary treatment for solitary HCC. Patients were divided into four groups according to PET uptake and hepatectomy type [AR or non-anatomical resection (NAR)]: Group 1 (PET-negative and AR, n=62); Group 2 (PET-negative and NAR, n= 46); Group 3 (PET-positive and AR, n=100); Group 4 (PET-positive and NAR, n=51).

Results: PET positivity was associated with higher protein induced by vitamin K antagonist-II (P=0.025), lager tumor size (P=0.05), microvascular invasion (MVI) (P=0.012), and portal vein invasion (P=0.031). In Kaplan-Meier analysis for RFS, Group 1 showed remarkable difference from Group 3 and Group 4 (P=0.045, P=0.023, respectively). In the PET-positive subgroup with HCC under 3 cm, AR was associated with better RFS than NAR (P=0.016).

Conclusions: A combination of AR and PET negativity showed good prognosis in long-term outcomes. Finally, AR can decrease the risk of tumor recurrence in patients with a solitary PET-positive HCC less than 3 cm.

Keywords: Hepatocellular carcinoma (HCC); anatomical resection (AR); positron emission tomography (PET)

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Introduction

Liver resection is a curative treatment option for patients with solitary hepatocellular carcinoma (HCC) and preserved liver function (1,2). Anatomical resection (AR) including the area covered by the tumor-feeding portal vein was preferred over non-anatomical resection (NAR) as a surgical technique to prevent potential micrometastasis surrounding the tumor because HCC tends to invade

intrahepatic vascular structures and is often close to the portal vein (3,4). Despite establishment of improved surgical techniques, tumor recurrence is still a major concern for the long-term survival of patients who undergo liver resection. The recurrence rate of HCC after curative hepatectomy reaches up to 70% within 5 years (5,6). Tumor size, serum alpha-fetoprotein (AFP), protein induced by vitamin K antagonist-II (PIVKA-II), c-reactive protein, alkaline phosphatase, neutrophil to lymphocyte ratio (NLR), and neutrophil to monocyte ratio (NMR) were reported as risk factors of tumor recurrence that can be preoperatively evaluated (7-10). Microvascular invasion (MVI) is also considered an independent prognostic factor predicting HCC recurrence or poor survival in HCC after curative resection, but it is difficult to assess prior to operation. Recently, increasing evidence demonstrates that preoperative 18F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) can predict MVI and early recurrence after liver resection (11-14).

In this study, we assessed whether combined AR with preoperative PET negativity was associated with positive prognostic factors. We also investigated whether AR achieves better oncologic outcomes than NAR regarding preemptive control of MVI among patients with primary solitary HCC and positive PET findings. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-1583).

Methods

Study design and population

This study was conducted on patients who underwent liver resection for solitary HCC diagnosed by radiologic imaging at Yeungnam University Medical Center and Samsung Medical Center in Korea between January 2007 and September 2015. HCC patients meeting the following criteria were excluded: history of previous treatments for HCC such as liver resection, transarterial chemoembolization, percutaneous ethanol injection, radiofrequency ablation (RFA), and radiation therapy; concurrent intraoperative RFA; combined HCC and cholangiocarcinoma on pathology; loss to follow-up after liver resection; no PET/CT performed for preoperative assessment; and multiple HCCs on pathology. As a result, this study included 259 treatment-naïve HCC patients who underwent preoperative PET/CT and subsequent curative liver resection as a primary treatment at two institutions. Baseline demographic, laboratory, pathologic, and surgical data were retrospectively collected and analyzed from the electronic medical record. Patients were divided into four groups according to preoperative PET uptake and liver resection type (AR or NAR): Group 1 (PET-negative and AR); Group 2 (PET-negative and NAR); Group 3 (PET-positive and AR); Group 4 (PET-positive and NAR). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional review boards of Samsung Medical Center (number 2016-08-161) and Yeungnam University Medical Center (number 2019-02-041) approved this study. Individual informed consent was waived because of the retrospective nature of the study.

Study criteria

The main purpose of our study was to compare recurrence-free survival (RFS) and overall survival (OS) among four groups and to identify the combined impact of AR and preoperative PET positivity on long-term oncologic outcomes in patients with primary solitary HCC. Liver-related mortality was defined as death from HCC recurrence after hepatectomy, as well as death caused by hepatectomy-related complications including hepatic failure, sepsis due to bile leakage, and postoperative bleeding. AR was defined as complete resection of an anatomic region demarcated by preceding ischemia, along with division of the Glisson associated with tumor location. With solitary HCC located peripherally or presenting with exophytic growth, NAR was performed when patients required limited resection due to insufficient liver function or remnant liver volume. By comparing pre- and postoperative CT of each patient, the resection type was evaluated to conform to the definition of AR identifying the location of the tumor, the extent of the resected liver parenchyme, and the ligated portal pedicle. Major hepatectomy was defined as removal of 3 or more liver segments (15). The histologic grade of HCC was evaluated according to Edmonson-Steiner grade (E-S grade) as 'well differentiated' (grade I), 'moderately differentiated' (grade II), or 'poorly differentiated' (grade III, IV) (16).

^{18}F-FDG PET/CT

All ^{18}F-FDG PET/CT imaging was performed using Discovery VCT scanners and Discovery STe scanners (GE

Medical Systems, Milwaukee, WI, USA) at Yeungnam University Medical Center and Samsung Medical Center, respectively. PET/CT scans were acquired after a single FDG injection. Patients fasted for 6 hours before the ^{18}F-FDG injection (serum glucose level <140 mg/dL). FDG dose was corrected for body mass index, and approximately 5.5 MBq/kg of FDG was administered intravenously. Uptake of ^{18}F-FDG on PET/CT was visually interpreted as positive or negative by comparing the foci of increased metabolic activity between normal surrounding tissues and tumor tissue (12).

Statistical analysis

Continuous data were presented as mean [± standard deviation (SD)]. Categorical data were described in numbers and percentages. Statistical analysis was conducted using an independent-sample *t*-test or a Mann-Whitney test for continuous values and a Chi-square test or Fisher's exact test for categorical values, especially when expected cell frequencies were below five. RFS and liver-related OS rates were analyzed via the Kaplan-Meier method. The log-rank test was used to compare survival curves produced from two groups. Univariate and multivariate analyses for risk factors affecting HCC recurrence or liver-related mortality following hepatectomy were conducted using a Cox proportional hazard model. P values below 0.05 were considered statistically significant. Data handling and analysis were performed using the Statistical Package for Social Science for Windows™ 22.0 release (SPSS Inc., Chicago, IL).

Results

Baseline demographic, laboratory, pathologic, and surgical factors

Table 1 shows the baseline characteristics of HCC patients with PET-positive and PET-negative findings. The main (92.6% *vs.* 97.3%) etiology in both groups was hepatitis B virus (HBV). PIVKA-II (P=0.025), tumor size (P=0.05), MVI (P=0.012), and portal vein invasion (P=0.031) were significantly higher in the PET-positive group than in the PET-negative group. There were no significant differences in demographic factors such as age, sex, Child-Turcotte-Pugh (CTP) class; laboratory factors such as white blood cells, NLR, NMR, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, prothrombin time international normalized ratio (PT INR), albumin, AFP, and indocyanine green retention rate at 15 minutes (ICG R15); pathologic factors such as Edmonson-Steiner grade, Glisson capsule invasion, bile duct invasion, intrahepatic metastasis, multicentric occurrence, tumor-free margin, and cirrhosis; or surgical factors such as laparoscopic approach, AR, and major hepatectomy.

Impact of ^{18}F-FDG PET/CT positivity on long-term oncologic outcomes

The mean follow-up duration of the entire cohort was 42.2±22.2 months. The 1-, 3-, and 5-year RFS rates were 68.0%, 59.6%, and 51.5% in the PET-positive group, respectively, and 85.0%, 68.2%, and 59.8% in the PET-negative group. The RFS rate in the PET-negative group was higher than in the PET-positive group, although this trend was not statistically significant (P=0.055; *Figure 1A*). The 1-, 3-, and 5-year liver-related OS rates were 94.0%, 89.0%, and 84.8%, respectively, in the PET-positive group and 100%, 93.1%, and 85.7% in the PET-negative group. However, these tendencies of liver-related OS were not significantly different between the groups (P=0.337; *Figure 1B*).

Risk factors for disease-free survival and liver-related mortality

Univariate and multivariate analyses for risk factors affecting HCC recurrence and liver-related mortality are presented in *Tables 2* and *3*, respectively. Multivariate analysis revealed that higher E-S grade, MVI, intrahepatic metastasis, and multicentric occurrences were significantly associated with HCC recurrence (P=0.001, P=0.037, P=0.004, and P=0.001, respectively; *Table 2*). Independent risk factors affecting liver-related mortality were determined to be higher E-S grade, Glisson capsule invasion, MVI, and multicentric occurrence (P=0.013, P=0.001, P=0.002, and P<0.001, respectively; *Table 3*). Neither preoperative PET positivity nor AR was an independent factor of HCC recurrence and liver-related mortality.

Impacts of ^{18}Preoperative PET uptake and AR on long-term oncologic outcomes

Four groups divided according to preoperative PET uptake

Table 1 Demographic, laboratory, pathologic, and surgical factors of preoperative PET-negative and PET-positive patients who underwent liver resection as primary treatment for hepatocellular carcinoma

Characteristics	PET-negative (n=108)	PET-positive (n=151)	P value
Demographic factors			
Mean age, years (± SD)	54.2 (±9.8)	55.3 (±9.4)	0.346
Male	81 (75.0%)	119 (78.8%)	0.548
Etiology			0.139*
HBV	100 (92.6%)	147 (97.3%)	
HCV	1 (0.9%)	1 (0.7%)	
Others	7 (6.5%)	3 (2.0%)	
CTP class			0.173*
A	106 (98.1%)	151 (100%)	
B	2 (1.9%)	0 (0%)	
Laboratory factors, mean (± SD)			
White blood cells (K/μL)	5.776 (±1.817)	5.711 (±1.947)	0.786
Neutrophil to leukocyte ratio	2.29 (±2.47)	1.91 (±1.28)	0.110
Neutrophil to monocyte ratio	8.70 (±4.83)	9.01 (±6.51)	0.679
Platelet count ($\times 10^3$/μL)	167 (±62)	167 (±57)	0.995
AST (IU/L)	36 (±23)	37 (±24)	0.855
ALT (IU/L)	35 (±24)	35 (±28)	0.973
Total bilirubin (mg/dL)	0.7 (±0.5)	0.7 (±0.4)	0.713
PT INR	1.05 (±0.08)	1.04 (±0.08)	0.436
Albumin (g/dL)	4.3 (±0.4)	4.3 (±0.4)	0.141
AFP (ng/mL)	1,073.6 (±5,413.5)	4,579.1 (±23,722.2)	0.079
PIVKA-II (mAU/mL)	603.3 (±4,013.9)	2,463.2 (±8,944.8)	0.025
Mean ICG R15 (%)	11.5 (±5.3)	10.5 (±4.8)	0.131
Pathologic factors			
Mean tumor size, cm (± SD)	3.7 (±3.1)	4.5 (±3.1)	0.050
Edmondson-Steiner grade			0.539*
I	8 (7.4%)	10 (6.6%)	
II	89 (82.4%)	117 (77.5%)	
III	10 (9.3%)	23 (15.2%)	
IV	1 (0.9%)	1 (0.7%)	
Microvascular invasion	44 (40.7%)	86 (57.0%)	0.012
Glisson capsule invasion	6 (5.6%)	11 (7.3%)	0.622
Portal vein invasion	5 (4.6%)	19 (12.6%)	0.031
Bile duct invasion	6 (5.6%)	2 (1.3%)	0.071*

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	PET-negative (n=108)	PET-positive (n=151)	P value
Intrahepatic metastasis	9 (8.3%)	20 (13.2%)	0.237
Multicentric occurrence	6 (5.6%)	9 (6.0%)	1.000
Tumor-free margin, mm (± SD)	13.9 (±13.8)	14.3 (±12.6)	0.821
Cirrhosis	55 (50.9%)	67 (44.4%)	0.315
Surgical factors			
Laparoscopic approach	24 (22.2%)	30 (19.9%)	0.757
Anatomical resection	62 (52.4%)	100 (66.2%)	0.155
Major hepatectomy	37 (34.3%)	62 (41.1%)	0.300

*, Fisher exact test. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh; HBV, hepatitis B; HCV, hepatitis C; ICG R15, indocyanine green retention rate at 15 minutes; INR, international normalized ratio; PET, positron emission tomography; PIVKA-II, proteins induced by vitamin K antagonist-II; PT, prothrombin time; SD, standard deviation.

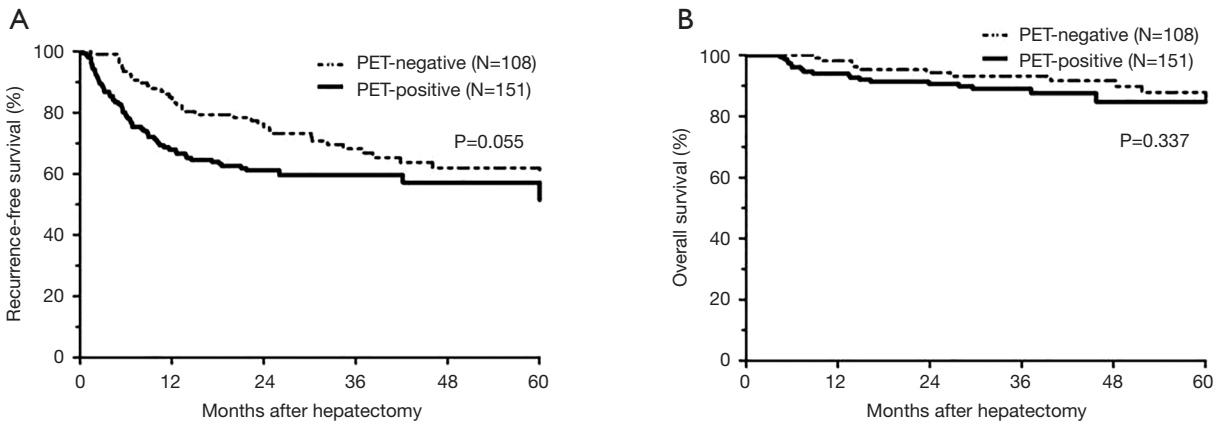

Figure 1 Recurrence-free survival (A) and overall survival (B) of PET-positive and PET-negative groups. PET, positron emission tomography.

and AR did not show statistically significant differences in pathologic factors including E-S grade, Glisson capsule invasion, MVI, intrahepatic metastasis, and multicentric occurrence (P=0.387, P=0.614, P=0.057, P=0.480, and P=0.659, respectively; *Table 4*). Kaplan-Meier analysis revealed that the RFS and OS of AR were not significantly different from those of NAR among PET-negative groups (P=0.100, *Figure 2A* and P=0.142, *Figure 2B*, respectively) and among PET-positive groups (P=0.743, *Figure 2C* and P=0.630, *Figure 2D*, respectively). In Kaplan-Meier analysis among four groups, Group 1 (PET-negative and AR) showed remarkably better RFS than Group 3 (PET-positive and AR) and Group 4 (PET-positive and NAR) (P=0.045, P=0.023, respectively; *Figure 3*). In subgroup analysis based on tumor size, Group 1 patients with HCC over 3 cm showed significantly better RFS than Group 2 (P=0.047, *Figure 4*), and Group 3 patients with HCC under 3 cm had remarkably better RFS than Group 4 (P=0.016, *Figure 4*). There was no significant difference among subgroups in Kaplan-Meier analysis for OS (*Figure 5*).

Discussion

MVI is an independent predictor of HCC recurrence and is related to poor outcome and low survival rates after liver resection (17,18). Therefore, detection of MVI is important to predict the prognosis of patients with HCC at the beginning of treatment. In previous conventional

Table 2 Univariate and multivariate analyses of risk factors for HCC recurrence

Risk factors	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	0.985	0.964–1.006	0.158			
Male	0.834	0.512–1.357	0.464			
White blood cells	1.037	0.936–1.148	0.489			
NLR	0.951	0.841–1.076	0.427			
NMR	0.972	0.929–1.016	0.207			
Total bilirubin	1.251	0.822–1.905	0.295			
Platelet	1.002	0.998–1.005	0.357			
AST	1.009	1.004–1.015	0.001	1.001	0.993–1.010	0.730
ALT	1.006	0.999–1.012	0.083			
Albumin	0.632	0.410–0.974	0.038	0.655	0.408–1.053	0.080
PT INR	0.616	0.053–7.178	0.699			
ICGR15	0.992	0.954–1.033	0.702			
AFP >200	1.178	0.601–1.328	0.447			
PIVKA-II >40	1.634	1.083–2.466	0.019	1.279	0.789–2.073	0.319
PET-positive	1.521	1.006–2.299	0.047	1.487	0.973–2.273	0.067
Tumor size	1.806	1.030–1.144	0.002	0.970	0.893–1.052	0.457
E-S grades 3 and 4	3.036	1.894–4.868	<0.001	2.331	1.426–3.809	0.001
Tumor-free margin	0.989	0.973–1.006	0.195			
Glisson capsule invasion	2.759	1.506–5.055	0.001	1.273	0.608–2.666	0.522
Microvascular invasion	2.274	1.508–3.430	<0.001	1.626	1.030–2.568	0.037
Portal vein invasion	3.558	2.127–5.951	<0.001	1.537	0.766–3.082	0.226
Bile duct invasion	0.823	0.258–2.617	0.741			
Intrahepatic metastasis	3.250	1.979–5.337	<0.001	2.201	1.280–3.786	0.004
Multicentric occurrence	3.383	1.844–6.207	<0.001	2.972	1.591–5.551	0.001
Cirrhosis	1.130	0.761–1.680	0.544			
Laparoscopic approach	0.784	0.470–1.307	0.350			
Non-anatomical resection	1.251	0.839–1.863	0.272			
Major hepatectomy	0.901	0.597–1.361	0.620			

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; E-S grade, Edmonson-Steiner grade; HR, hazard ratio; INR, international normalized ratio; ICG, indocyanine green; NLR, neutrophil to leukocyte ratio; NMR, neutrophil to monocyte ratio; PET, positron emission tomography; PIVKA-II, proteins induced by vitamin K antagonist-II; PT, prothrombin time.

imaging studies, MVI is indirectly predicted based on capsule disruption, irregular tumor margin, and peritumoral enhancement (17). In a recent study, Kim *et al.* reported that the presence of peritumoral hypointensity on hepatobiliary phase of Gadoxetic acid-enhanced magnetic resonance imaging (MRI) showed high specificity (93.2%) and a positive predictive value of 88.5%. Kim *et al.* concluded that peritumoral hypointensity on hepatobiliary phase of

Table 3 Univariate and multivariate analyses of risk factors for liver-related mortality

Risk factors	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	0.977	0.940–1.015	0.229			
Male	1.277	0.565–2.886	0.556			
White blood cells	1.075	0.897–1.288	0.436			
NLR	1.027	0.888–1.188	0.718			
NMR	1.013	0.972–1.057	0.534			
Total bilirubin	1.898	1.130–3.188	0.015	1.741	0.898–3.377	0.101
Platelet	1.004	0.998–1.010	0.169			
AST	1.011	1.001–1.020	0.025	0.996	0.982–1.011	0.591
ALT	1.002	0.991–1.014	0.701			
Albumin	0.727	0.322–1.644	0.444			
PT INR	0.032	0.000–4.679	0.176			
ICGR15	1.019	0.950–1.093	0.601			
AFP >200	2.215	0.879–3.944	0.024	1.133	0.508–2.528	0.761
PIVKA-II >40	1.401	0.661–2.967	0.379			
PET-positive	1.486	0.687–3.217	0.314			
Tumor size	1.144	1.050–1.246	0.002	1.046	0.927–1.181	0.465
E-S grade 3 and 4	5.641	2.615–12.171	<0.001	2.724	1.234–6.012	0.013
Tumor-free margin	0.978	0.944–1.014	0.978			
Glisson capsule invasion	8.486	3.856–18.674	<0.001	3.768	1.666–8.523	0.001
Microvascular invasion	5.301	2.021–13.908	0.001	4.676	1.729–12.645	0.002
Portal vein invasion	4.794	2.111–10.886	<0.001	1.249	0.385–4.051	0.711
Bile duct invasion	2.960	0.880–9.953	0.079			
Intrahepatic metastasis	4.804	2.231–10.341	<0.001	1.513	0.582–3.933	0.396
Multicentric occurrence	7.739	3.417–17.529	<0.001	5.121	2.152–12.187	<0.001
Cirrhosis	1.523	0.727–3.190	0.265			
Laparoscopic approach	0.604	0.210–1.738	0.350			
Non-anatomical resection	1.528	0.737–3.167	0.255			
Major hepatectomy	0.863	0.401–1.856	0.706			

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; E-S grade, Edmonson-Steiner grade; HR, hazard ratio; INR, international normalized ratio; ICG, indocyanine green; NLR, neutrophil to leukocyte ratio; NMR, neutrophil to monocyte ratio; PET, positron emission tomography; PIVKA-II, proteins induced by vitamin K antagonist-II; PT, prothrombin time.

gadoxetic acid-enhanced MRI can be useful preoperative predictor of MVI in HCC patients (19). Tumor markers including AFP and PIVKA-II are also adopted to evaluate the biological aggressiveness of HCC prior to surgical resection. PIVKA-II is more sensitive and specific than AFP because it is associated with tumor growth rate, increased cellular proliferation, infiltrative pattern, and vascular invasion. However, these time-dependent laboratory tests

Table 4 Pathologic factors of groups divided according to preoperative PET uptake and anatomical resection

Characteristics	Group 1 (n=62), PET(–)/AR	Group 2 (n=46), PET(–)/NAR	Group 3 (n=100), PET(+)/AR	Group 4 (n=51), PET(+)/NAR	P value
Mean tumor size, cm (± SD)	4.1 (±3.4)	3.3 (±2.5)	4.6 (±3.0)	4.3 (±3.2)	0.308
E-S grade 3 and 4	7 (11.3%)	4 (8.7%)	18 (18%)	6 (11.8%)	0.387
Tumor-free margin, mm (± SD)	17.0 (±16.4)	9.7 (±7.8)	16.9 (±13.9)	9.2 (±7.5)	0.863
Glisson capsule invasion	2 (3.2%)	4 (8.7%)	8 (8%)	3 (5.9%)	0.614*
Microvascular invasion	23 (37.1%)	21 (45.7%)	58 (58%)	28 (54.9%)	0.057
Portal vein invasion	3 (4.8%)	2 (4.3%)	12 (12%)	7 (13.7%)	0.190*
Bile duct invasion	5 (8.1%)	1 (2.2%)	2 (2%)	0 (0%)	0.077
Intrahepatic metastasis	4 (6.5%)	5 (10.9%)	12 (12%)	8 (15.7%)	0.480
Multicentric occurrence	5 (8.1%)	1 (2.2%)	6 (6%)	3 (5.9%)	0.659*

*, Fisher exact test. AR, anatomical resection; E-S grade, Edmonson-Steiner grade; PET, positron emission tomography; NAR, non-anatomical resection; SD, standard deviation.

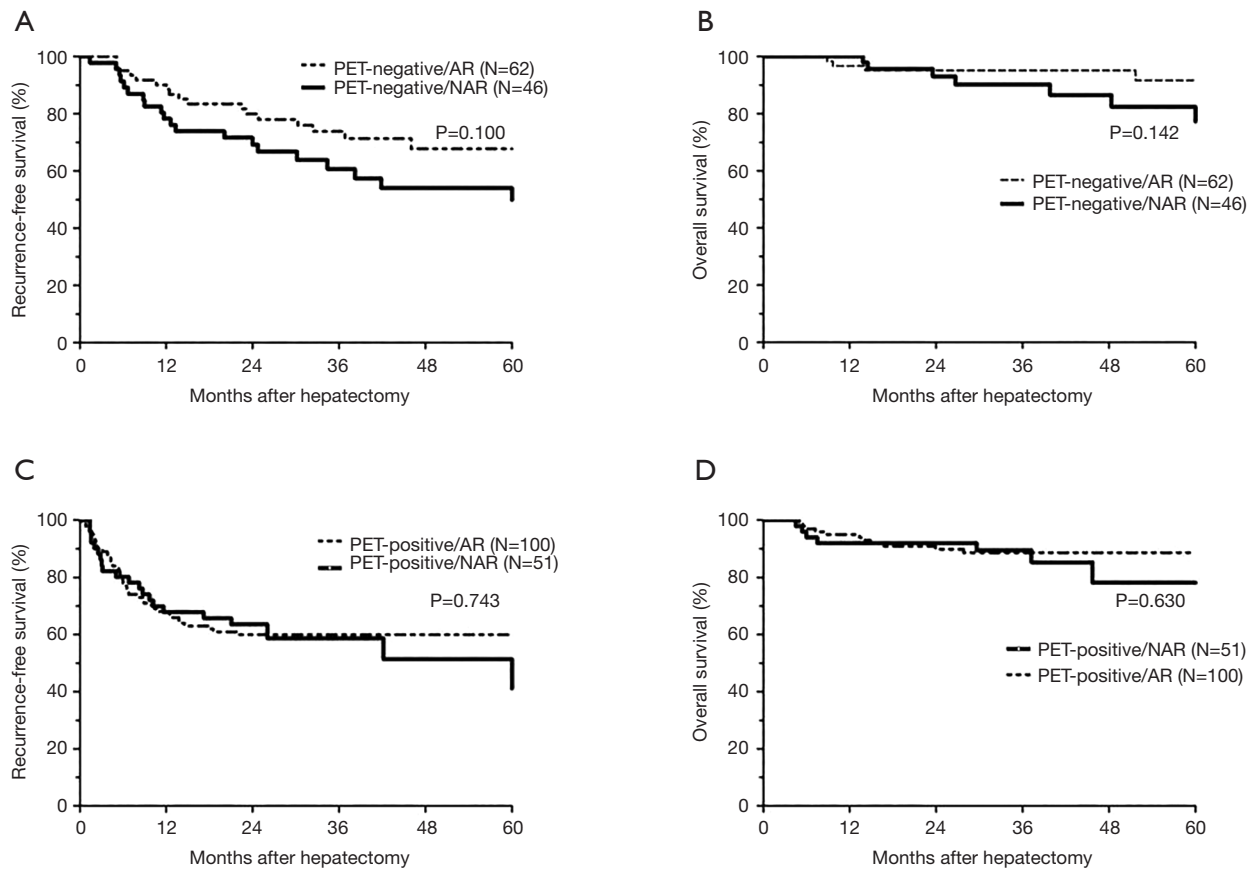

Figure 2 Recurrence-free survival (A) and overall survival (B) of Group 1 and Group 2. Recurrence-free survival (C) and overall survival (D) of Group 3 and Group 4.

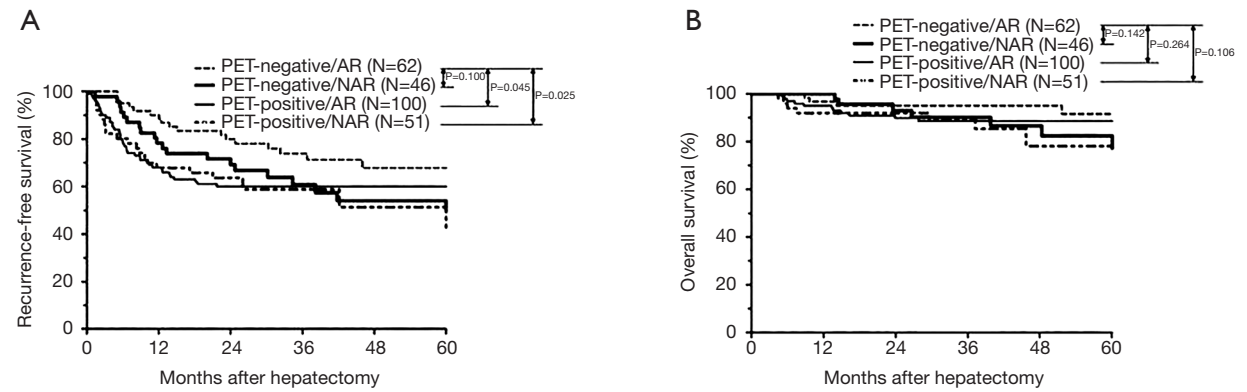

Figure 3 Recurrence-free survival (A) and overall survival (B) of four groups.

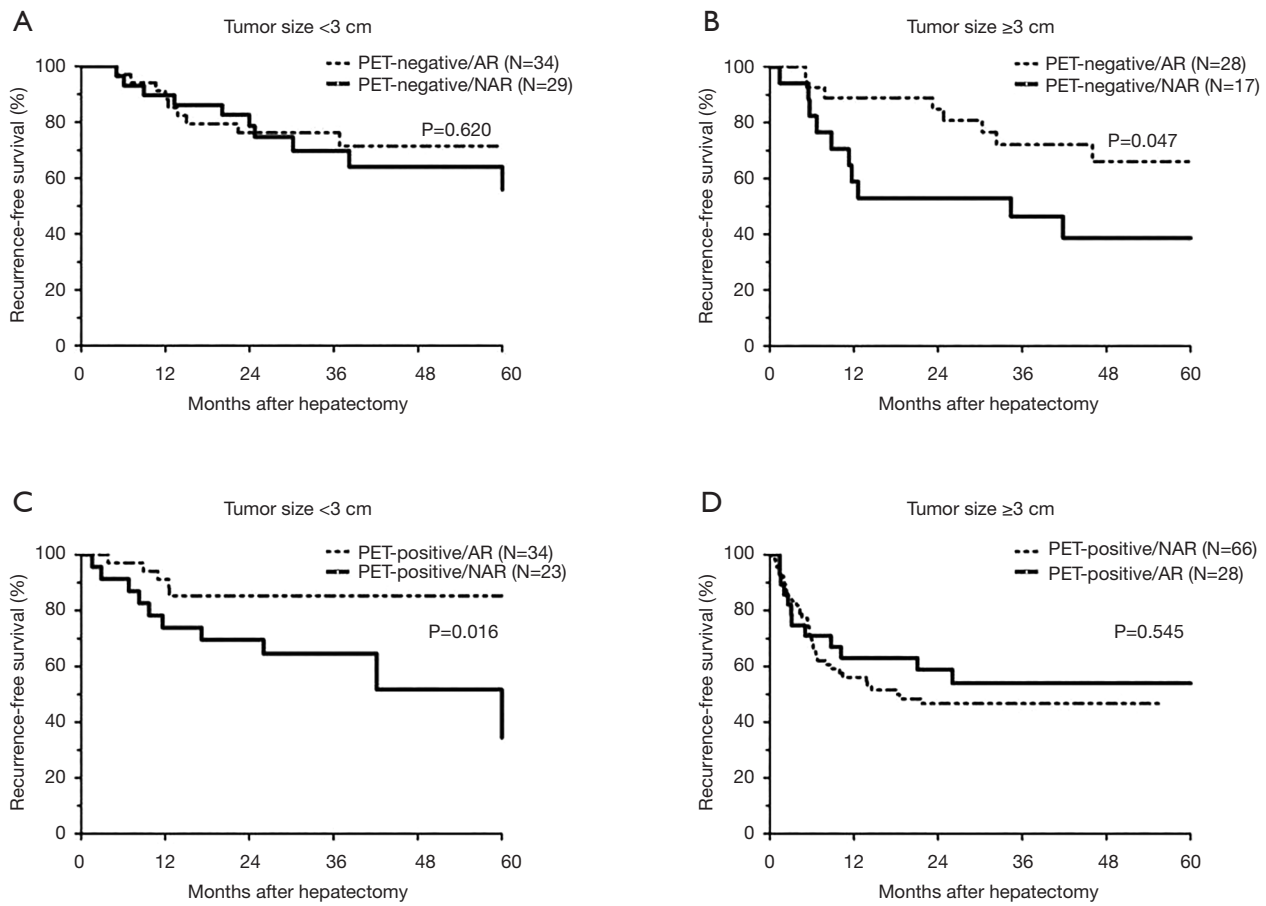

Figure 4 Recurrence-free survival of Group 1 and Group 2 based on tumors less than 3 cm (A) and more than 3 cm (B). Recurrence-free survival of Group 3 and Group 4 based on tumors less than 3 cm (C) and more than 3 cm (D).

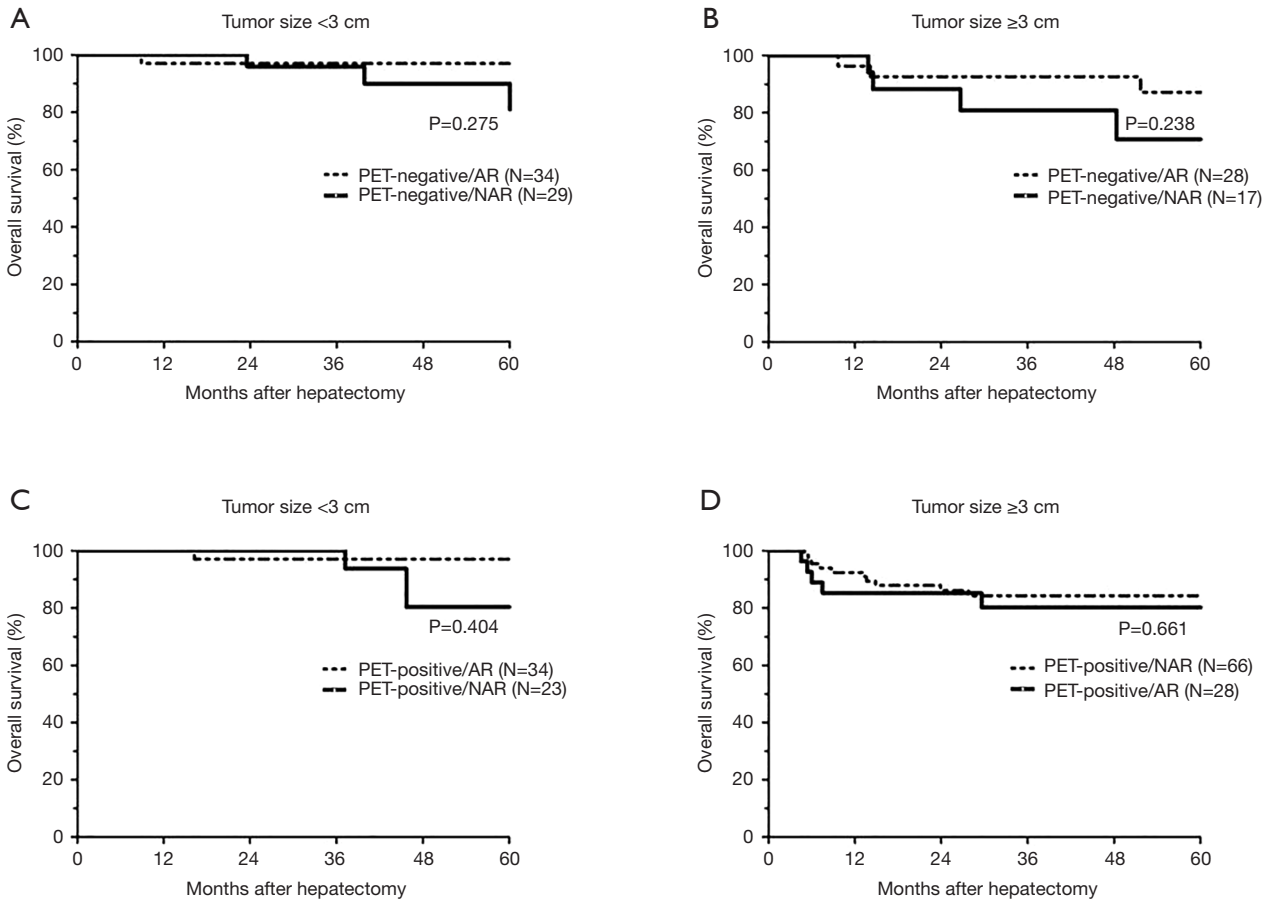

Figure 5 Overall survival of Group 1 and Group 2 based on tumors less than 3 cm (A) and more than 3 cm (B). Overall survival of Group 3 and Group 4 based on tumors less than 3 cm (C) and more than 3 cm (D).

cannot determine whether or not MVI has occurred, and they only assess the effects of treatment or whether the disease is stationary or progressing.

Since ^{18}F-FDG PET/CT shows relatively high physiologic liver uptake and variable uptake in HCC resulting from increased glucose-6-phosphatase activity in normal liver tissues, it has limited use for primary diagnosis of HCC (20). Previous studies have already shown that high standard uptake value (SUV) on PET was significantly associated with high-grade tumor differentiation and was a poor prognostic factor following liver resection for HCC. Lin *et al.* concluded that the ratio of maximal tumor SUV to mean normal liver SUV of ^{18}F-FDG PET/CT was an independent predictor of MVI (21). Thus, increasing evidence has accumulated demonstrating that positive PET findings can predict MVI (11,17,22) based on the close correlation between MVI and poor tumor grade (23-25).

In the present study, patients with PET-positive HCC tended to have significantly higher PIVKA-II (P=0.025), portal vein invasion (P=0.031), and MVI (P=0.012) than patients with PET negative HCC (*Table 1*). This implies that positive PET findings reflect more aggressive HCC biology. However, in multivariate analysis, our study failed to prove that PET positivity was an independent prognostic factor for HCC recurrence and liver-related mortality. Kaplan-Meier analysis for RFS identified a tendency for higher relapse in the PET-positive group (P=0.055, *Figure 1A*).

AR is preferred for HCC that tends to invade into tumor-feeding vascular structures and theoretically can achieve better oncologic outcomes than NAR. However, there is little clinical evidence that AR is superior to NAR in the long-term survival of HCC patients with preserved liver function (26,27). A recent multicenter-based collaboration

study using propensity score matching concluded that AR decreases HCC recurrence and improves OS in patients with a primary solitary HCC <5.0 cm in diameter (28). In real clinical situations, AR is not applicable to all patients with HCC because of poor liver function, unfavorable tumor location, or insufficient remnant liver volume. Therefore, it is important to make surgical plans according to preoperative assessment for vascular invasion by tumor.

We analyzed long-term oncologic outcomes of AR versus NAR in patients with solitary HCC who were preoperatively evaluated by PET/CT uptake as a surrogate marker of vascular invasion. As shown in *Figure 2*, AR and NAR in the PET-negative group did not show any significant differences in RFS (P=0.100) and OS (P=0.142). However, the RFS of PET-negative HCC patients who underwent AR was significantly higher than that of PET-positive HCC patients who underwent AR (P=0.045) and NAR (P=0.023). This result supports that AR for PET-negative HCC might be associated with positive prognosis to prevent recurrence after hepatectomy for solitary HCC. Both MVI and tumor size are known to reflect oncologic properties. MVI is confirmed by invasion on pathologic study, but our study proved that PET positivity can predict the presence of MVI without tissue confirmation. When tumor size and PET positivity were subdivided, AR had better RFS than NAR. For example, AR had better RFS than NAR in the subgroup with HCC over 3 cm and PET negativity (*Figure 4B*) than in the subgroup with HCC under 3 cm and PET positivity (*Figure 4C*). In other words, in HCC patients whose tumors are too aggressive or too mild, AR may not be superior to NAR. Therefore, although there is selection bias due to the nature of the retrospective study, it can be said that this study has clinical implications to help the surgeon choose the resection type (AR *vs.* NAR) by assessing the biological characteristics of the tumor shown in preoperative tests including PET.

A major limitation of our study is the inability to determine PET positivity according to the cut-off value using SUV. Instead of measuring SUV, we visually interpreted the presence of FDG uptake to compare the difference in metabolic activity between tumor and normal liver tissue. In addition, our study had a retrospective design with a relatively short follow-up period. There could be potential selection bias due to inclusion of patients with solitary HCC who underwent ^{18}F-FDG PET/CT prior to hepatectomy. Further prospective studies with long-term follow-up in a larger cohort are necessary to confirm our results.

In conclusion, we identified that ^{18}F-FDG uptake of HCC on preoperative PET predicts MVI in hepatectomy patients. In addition, preoperative PET/CT can provide useful clinical information about prognosis after liver resection for HCC, reflecting aggressiveness and tumor differentiation. Although AR and PET negativity were not independent factors affecting HCC recurrence, a combination of AR and PET negativity might indicate good prognosis in long-term outcomes. Finally, AR decreases the risk of tumor recurrence in patients with a solitary PET-positive HCC less than 3 cm.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the institutional review boards of Samsung Medical Center (number 2016-08-161) and Yeungnam University Medical Center (number 2019-02-041). Individual informed consent was waived because of the retrospective nature of the study.

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