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^{18}F-FDG-PET/CT predicts early tumor recurrence in living donor liver transplantation for hepatocellular carcinoma

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Summary

The prognosis including ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) for the early recurrence for hepatocellular carcinoma (HCC) after living donor liver transplantation (LDLT) was not well established. Consecutive patients who underwent ^{18}F-FDG-PET/CT and subsequent LDLT for HCC from March 2005 to June 2011 were enrolled. The 191 patients with a median follow-up of 26.1 months were evaluated. There were 20 patients (10.5%) with early recurrence (≤6 months), 18 patients (9.4%) with late recurrence (>6 months), and 153 patients (80.1%) with no recurrence. Fifty-five patients (28.8%) displayed increased PET/CT tumor uptake. Three-year overall and disease-free survival for PET/CT-positive patients were 65.5% and 57.1%, respectively, while PET/CT-negative patients showed respective values of 89.8% and 86.8% ($P = 0.001$ vs. $P < 0.001$). Tumor variables associated with PET/CT-positive finding were preoperative AFP level, Milan, UCSF criteria, maximum tumor size, total tumor size, differentiation, vascular invasion, and serosal invasion. PET/CT-positive status was identified as an independent prognostic factor for disease-free survival influencing early recurrence in multivariable analysis (HR 3.945, 95% CI 1.196–13.016, $P = 0.024$). ^{18}F-FDG-PET/CT is an independent and significant predictor of early tumor recurrence in LDLT for HCC.

Introduction

Hepatocellular carcinoma (HCC) in liver cirrhosis is a major indication for liver transplantation (LT) [1]. Unfortunately, HCC recurs up to 60% based on pretransplant stage. However, selective patients with HCC showed low recurrence after LT [2,3]. Since the introduction of the Milan criteria (a solitary tumor no more than 5 cm in diameter, or two or three tumors no more than 3 cm in diameter) [2], the survival outcome has improved. Recently, based on the consideration that the Milan criteria may be too restrictive, expanded criteria like the University of California at San Francisco (UCSF) criteria (a solitary tumor no more than 6.5 cm in diameter, or patients with two or three tumors of which the largest diameter is no more than 4.5 cm and the sum of the diameters is no more than 8 cm) showed good clinical results [4].

The critical shortage of deceased organs has led to the development of living donor LT (LDLT). Advances in LDLT that have eliminated any restriction by organ allocation system have produced survival benefits over deceased donor LT that include decreased waiting time and dropout [5,6]. In LDLT, expanded criteria based on biologic activity as well as tumor morphology have been proposed [7,8]. However, expansion of the criteria carries a risk of increased recurrence after transplantation. Especially, early post-transplant recurrence is dependent on tumor stage and tumor biologic features like microvascular invasion and is related to a very poor prognosis [3]. Predicting early recurrence has been an issue for LDLT.

Preoperative studies evaluating tumor size and number as an approach to predict recurrence have been limited because they might differ from pathologic reports of explant liver. Moreover, evaluation of size and number of tumors has become more complicated because of the increase in preoperative local therapy and transarterial chemoembolization for tumor control [9]. A recent studies with positron emission tomography/computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) reported a potential role of this approach in the prediction of tumor recurrence or microvascular invasion in LT [10,11]. Preoperative ^{18}F-FDG-PET has been established as a useful diagnostic tool for evaluating metastatic lesions and a prognostic marker in various cancers [12].

In this study, we tried to find the prognostic factors including PET/CT for early HCC recurrence in LT and investigated the associated tumor variables with PET/CT findings.

Patients and methods

Patients

Patients who underwent PET/CT and subsequent LDLT for HCC between May 2005 and June 2011 were retrieved from a prospective database at the National Cancer Centre, Republic of Korea. All patients were confirmed with HCC in postoperative pathologic results. The medical records of the patients were reviewed for clinicopathologic information, including sex, age, viral marker, serum α-fetoprotein (AFP) level, Model for End-Stage Liver Disease score, PET/CT finding, preoperative treatment, and pathologic reports. Tumors were graded from I to IV according to the criteria of the Edmondson and Steiner grading [13]. Preoperative diagnosis of HCC was based on two abdominal imaging studies, including ultrasound and multi-detector CT or magnetic resonance imaging (MRI) without protocol tumor biopsy. The level of AFP was used to support suspected HCC diagnosis. The detailed surgical technique of the recipient, donor, and bench operation was described previously [14]. The mean follow-up period was 28.2 months (range 1.2–79.0 months).

In our institute, on the basis of imaging studies like CT, MRI, or PET/CT, patients who met the Milan criteria were selected for transplantation. If patients did not meet the Milan criteria, but had neither major vascular invasion nor extrahepatic metastasis and strongly desired LDLT, we performed transplantation. LDLT was usually performed within 1 month after the pretransplant workup. No one received any treatment for downstaging of HCC before transplantation. Immunosuppressive therapy after LDLT consisted of tacrolimus and mycophenolate mofetil with combination with corticosteroid. Corticosteroid was tapered to discontinuation by 6 months after LDLT. The prophylaxis for hepatitis B virus recurrence after LDLT consisted of entecavir and hepatitis B immunoglobulin. Patients had follow-up examinations for recurrence approximately every 3 months for the first 2 years, and every 6 months for the next 3 years. During the routine follow-up, imaging studies including abdomen CT, chest CT, and bone scan were performed every 3 or 6 months, and AFP level was also checked. If the recurrence was suspected based on the imaging tests, additional PET/CT was performed for the examination of distant metastasis. In this study, the patients recurred at less than 6 months showed very dismal prognosis, then early recurrence was defined as detecting the recurrence on imaging studies or biopsy at less than 6 months, postoperatively. For HCC recurrence after LT, we performed the resection in patients who had one or two resectable tumors in liver, lung, bone, or brain without other metastases. If the patients had unresectable or multiple hepatic metastases, we treated the tumors with transarterial chemoembolization, radiofrequency ablation, or radiation therapy. In patients with multiple extrahepatic metastases, chemotherapy or sorafenib treatment was performed by hepatologists. In patients with both intrahepatic and extrahepatic metastases, we treated them with multimodality therapy. The study protocol was approved by the institutional review board of the National Cancer Centre, Republic of Korea.

^{18}F-FDG-PET/CT

^{18}F-FDG-PET/CT was performed using a PET/CT scanner (Biograph LSO; Siemens Medical Systems and Discovery LS; GE Healthcare, New Jersey, USA). The mean period between LT and performance of the PET/CT scan was 16.7 days. After patients had fasted for at least 6 h, they were injected with FDG (dose: 448.8 ± 95.6 MBq) and the images were acquired 60 min later. For the Biograph LSO scanner, we used a scout view of 30 mA and 130 kVp, followed by a spiral CT scan of the patient with the following settings: effective 50 mA, 130 kVp, 5-mm section width, 4-mm collimation, 12-mm table feed per rotation, 0.8 s per ration, and arms raised. For the Discovery LS scanner, we used a scout view with 30 mA and 120 kVp, followed by a spiral CT of the patient under the following conditions: 80 mA, 140 kVp, 5-mm section thickness, 4.25-mm interval in high speed mode, 0.8-s ration time, and arms at the sides of the torso. PET images were acquired after the CT scans at a 3 min/bed position of 11.2 cm in the three-dimensional acquisition mode (Biograph LSO) or a 4 min/bed position of 14.2 cm in the two-dimensional acquisition mode (Discovery LS). CT images were then reconstructed onto a 512 × 512 matrix and converted into 511-keV-

equivalent attenuation factors for attenuation correction. PET images were reconstructed onto a 128 × 128 matrix using ordered-subsets expectation maximization with attenuation correction. PET images were smoothed using 6-mm full width at half maximum Gaussian filters to reduce the effects of noises and image resolutions. All of the ^{18}F-FDG-PET images were interpreted by experienced nuclear medicine physicians. SUV (standardized uptake value) was calculated as (decay-corrected activity kBq/ml of tissue volume)/(injected FDG activity kBq/body mass g). SUVs of the lesions were obtained by manually placing a circular region of interest at the site of the maximum FDG uptake in the smoothed PET images. The region of interest was drawn to encircle the highest activity of each tumor, with guidance from the CT scans that were acquired from PET/CT or from MRI scans or additional diagnostic images. All tumors and normal-liver regions were defined by careful correlation with diagnostic CT or MRI scans. PET positivity was assessed by nuclear medicine physician whether the ^{18}F-FDG uptake in tumor was PET-positive status or not significantly higher than in the surrounding noncancerous hepatic tissue. Maximum SUV (SUV_{max}) within a region of interest was used in this study (Fig. 1).

Statistical analysis

Categorical variables were compared with the chi-squared test or Fisher's exact test. Continuous variables were expressed as means and standard deviations and compared with the Student's *t*-test. Overall survival curves were analyzed using the Kaplan–Meier method and compared by means of the log rank test. Cox proportional hazard models were used to determine prognostic factors. Variables found to be significant on univariate analysis ($P < 0.050$) were considered in a multivariable model. $P < 0.050$ was considered statistically significant. All analyses were performed using SAS® version 9.1.3 for Windows® (SAS institute, Cary, NC, USA).

Results

Clinicopathologic characteristics and overall survival

Of the total 191 patients, 20 (10.5%) patients had early recurrence at less than 6 months post-transplantation, and 18 (9.4%) patients had late recurrence more than 6 months after transplantation. Clinicopathologic data are shown in Table 1 in comparison with early recurrence group versus late recurrence group, and early recurrence group versus no recurrence group. Preoperative AFP level (>400 ng/ml), PET/CT positivity, total tumor size (>10 cm), differentiation (grade III–IV), microvascular invasion, major vessel invasion, and serosal invasion were observed significantly more in the early recurrence group than in the late recurrence group. Median SUVmax of PET/CT-positive tumors in the early, late, and no recurrence group was 5.2, 3.7, and 3.2, respectively. In overall survival rate according to these groups (early versus late versus no recurrence), the early recurrence group showed significantly worse overall survival [mean survival 20.2 months, 95% confidence interval (CI) 14.5–25.9 months], with no survivors beyond 3 years (Fig. 2). Furthermore, the late recurrence group showed significantly worse overall survival than those of no recurrence (late recurrence: mean survival 46.8 months, 95% CI 37.2–56.4 months; no recurrence: mean 77.4 months, 95% CI 74.3–80.4 months, $P < 0.001$). The recurrence

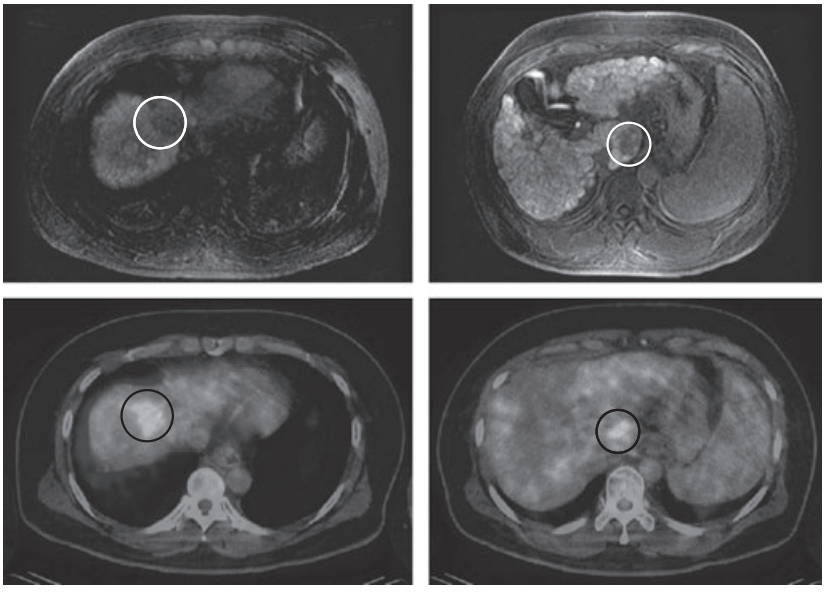


Figure 1 ^{18}F-FDG-PET/CT and MRI images of the patient with HCC before liver transplantation. TACE was performed three times, but the patient still had two regions of increased ^{18}F-FDG tumor uptake (SUVmax 5.0 and 4.7). Four months following liver transplantation, the tumor recurred inside the transplanted liver.

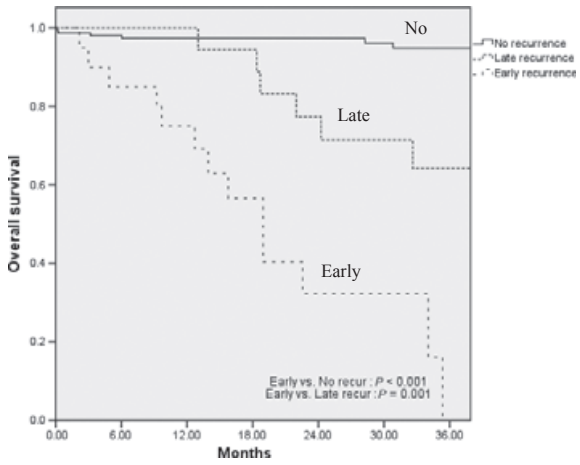
Table 1. Clinicopathologic characteristics of patients according to the time of recurrence. [Correction added on 24 December 2012, after online and print publication: missed standard deviation of MELD score for Late recurrence and the P-value of major vessel invasion were inlcuded]

Variables	Early recurrence (*n* = 20)	Late recurrence (*n* = 18)	No recurrence (*n* = 153)	*P*-value	
				Early vs. late	Early vs. no
Sex, *n* (%)					
Male	18 (90.0)	16 (88.9)	127 (83.0)	1.000*	0.537*
Female	2 (10.0)	2 (11.1)	26 (17.0)		
Age (year), mean (SD)	55.00 (7.68)	53.40 (7.70)	54.08 (7.02)	0.537	0.588
MELD† score, mean (SD)	12.20 (7.40)	11.83 (7.40)	14.84 (7.33)	0.880	0.132
AFP‡, *n* (%)					
≤400 ng/mL	12 (60.0)	17 (94.4)	136 (88.9)	0.021*	0.001
>400 ng/mL	8 (40.0)	1 (5.6)	17 (11.1)		
PET/CT					
Negative	5 (25.0)	11 (61.1)	120 (78.4)	0.024	<0.001
Positive	15 (75.0)	7 (38.9)	33 (21.6)		
Preoperative therapy, *n* (%)					
No therapy	5 (25.0)	3 (16.7)	32 (20.9)	0.637	0.954
Surgery only	0 (0.0)	1 (5.6)	1 (0.7)		
TACE§ only	8 (40.0)	7 (38.9)	74 (48.4)		
RFA¶ only	1 (5.0)	0 (0.0)	7 (4.6)		
Combination	6 (30.0)	7 (38.9)	39 (25.5)		
Milan criteria, *n* (%)					
Within	6 (30.0)	4 (22.2)	122 (79.7)	0.719*	<0.001
Beyond	14 (70.0)	14 (77.8)	31 (20.3)		
UCSF criteria, *n* (%)					
Within	5 (25.0)	6 (33.3)	97 (63.4)	0.572	0.001
Beyond	15 (75.0)	12 (66.7)	56 (36.6)		
Tumor number, *n* (%)					
≤3	11 (55.0)	10 (55.6)	108 (70.6)	0.973	0.157
>3	9 (45.0)	8 (44.4)	45 (29.4)		
Maximum tumor size					
≤5 cm	11 (55.0)	14 (77.8)	138 (90.2)	0.182*	<0.001
>5 cm	9 (45.0)	4 (22.2)	15 (9.8)		
Total tumor size					
≤10 cm	8 (40.0)	14 (77.8)	135 (88.2)	0.025*	<0.001
>10 cm	12 (60.0)	4 (22.2)	18 (11.8)		
Differentiation**, *n* (%)					
I–II	1 (5.0)	6 (33.3)	64 (45.4)	0.038*	<0.001*
III–IV	19 (95.0)	12 (66.7)	77 (54.6)		
Microvascular invasion, *n* (%)					
Absent	2 (10.0)	8 (44.4)	92 (65.2)	0.027*	<0.001*
Present	18 (90.0)	10 (55.6)	49 (34.8)		
Capsule formation, *n* (%)					
Absent	9 (45.0)	6 (33.3)	37 (26.2)	0.463	0.082
Present	11 (55.0)	12 (66.7)	104 (73.8)		
Major vessel invasion, *n* (%)					
Absent	13 (65.0)	18 (100.0)	136 (96.5)	0.009*	<0.001
Present	7 (35.0)	0 (0.0)	5 (3.5)		
Ductal invasion, *n* (%)					
Absent	18 (90.0)	18 (100.0)	138 (97.9)	0.488*	0.117*
Present	2 (10.0)	0 (0.0)	3 (2.1)		
Serosal invasion, *n* (%)					
Absent	8 (40.0)	15 (83.3)	124 (87.9)	0.009*	<0.001
Present	12 (60.0)	3 (16.7)	17 (12.1)		
Intrahepatic metastasis, *n* (%)					
Absent	3 (15.0)	8 (44.4)	102 (72.3)	0.074*	<0.001*
Present	17 (85.0)	10 (55.6)	39 (27.7)		

Table 1. continued

Variables	Early recurrence (n = 20)	Late recurrence (n = 18)	No recurrence (n = 153)	*P*-value	
				Early vs. late	Early vs. no
Cirrhosis, *n* (%)					
Absent	1 (5.0)	1 (5.6)	9 (5.9)	1.000*	1.000*
Present	19 (95.0)	17 (94.4)	144 (94.1)		
Dysplastic nodule, *n* (%)					
Absent	15 (75.0)	16 (88.9)	98 (66.2)	0.410*	0.432
Present	5 (25.0)	2 (11.1)	50 (33.8)		
Viral hepatitis					
HBV	18 (90.0)	15 (83.3)	132 (86.3)	0.365	0.635
HCV	1 (5.0)	1 (5.6)	12 (7.8)		
NBNC	0 (0.0)	2 (11.1)	3 (2.0)		
HBV + HCV	1 (5.0)	0 (0.0)	6 (3.9)		

HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, nonhepatitis B and nonhepatitis C virus; B+C, hepatitis B and C virus.
*Fisher's exact test.
†Model for end-stage liver disease.
‡α-Fetoprotein.
§Transarterial chemoembolization.
¶Radiofrequency ablation.
**Edmondson–Steiner grade.



OS/No. at risk	0 year	1 year	2 year	3 year
No recurrence	100%/153	97.4%/126	97.4%/98	94.9%/58
Late recurrence	100%/18	100%/18	77.4%/13	64.3%/8
Early recurrence	100%/20	75.0%/13	32.4%/4	0.0%/0

Figure 2 Overall survival rate of HCC patients after LDLT according to the time of recurrence.

sites between early and late recurrence group were not significantly different (Table 2.).

Association between PET/CT finding and tumor variables

Tumor characteristics according to PET finding are summarized in Table 3. Fifty-five patients (28.8%) showed PET/CT positivity in this study, while 136 patients (71.2%) had no increased ^{18}F-FDG uptake. PET/CT-positive status was significantly associated with preoperative AFP level, Milan criteria, UCSF criteria, maximum tumor size, total tumor size, differentiation, microvascular invasion, major vessel invasion, and serosal invasion.

Table 2. Recurrence patterns between early and late recurrence.

Site of recurrence	Early recurrence (n = 20)	Late recurrence (n = 18)	*P*-Value
Intrahepatic	3 (15.0%)	1 (5.6%)	0.248
Extrahepatic	6 (30.0%)	10 (55.6%)	
Both	11 (55.0%)	7 (38.9%)	

Prognostic significance of ^{18}F-FDG-PET/CT

Overall survival and disease-free 1- and 3-year survival rates were 95.2% and 82.4%, respectively, and 84.3% and 77.8%, respectively. The mean recurrence time in overall population was 61.8 months (95% CI 56.7–66.9 months). PET/CT-positive status showed a significantly worse overall survival and disease-free survival rate than PET/CT-negative status (overall survival: mean 57.0 vs. 69.7 months, $P = 0.001$; disease-free survival: mean 48.5 vs. 66.5 months, $P < 0.001$; Fig. 3). In combination with preoperative AFP level and PET/CT findings, 13 patients had elevated AFP (>400 ng/ml) and PET/CT-positive status. These patients showed significantly worse overall survival and disease-free survival rate than the other patients

Table 3. Association between PET-CT findings and tumor variables.

Variables	PET/CT negative (n = 136)	PET/CT positive (n = 55)	P-value
AFP*, *n* (%)			
≤400 ng/mL	123 (90.4)	42 (76.4)	0.010
>400 ng/mL	13 (9.6)	13 (23.6)	
Milan criteria, *n* (%)			
Within	105 (77.2)	27 (49.1)	<0.001
Beyond	31 (22.8)	28 (50.9)	
UCSF criteria, *n* (%)			
Within	85 (62.5)	23 (41.8)	0.009
Beyond	51 (37.5)	32 (58.2)	
Tumor number, *n* (%)			
≤3	95 (69.9)	34 (61.8)	0.283
>3	41 (30.1)	21 (38.2)	
Maximum tumor size			
≤5 cm	125 (91.9)	38 (69.1)	<0.001
>5 cm	11 (8.1)	17 (30.9)	
Total tumor size			
≤10 cm	120 (88.2)	37 (67.3)	0.001
>10 cm	16 (11.8)	18 (32.7)	
Differentiation†			
I–II	58 (46.0)	13 (24.5)	0.007
III–IV	68 (54.0)	40 (75.5)	
Microvascular invasion, *n* (%)			
Absent	94 (66.7)	18 (34.0)	<0.001
Present	42 (33.3)	35 (66.0)	
Capsule formation, *n* (%)			
Absent	39 (31.0)	13 (24.5)	0.387
Present	87 (69.0)	40 (75.5)	
Major vessel invasion, *n* (%)			
Absent	123 (97.6)	44 (83.0)	0.001‡
Present	3 (2.4)	9 (17.0)	
Ductal invasion, *n* (%)			
Absent	124 (98.4)	50 (94.3)	0.155‡
Present	2 (1.6)	3 (5.7)	
Serosal invasion, *n* (%)			
Absent	112 (88.9)	35 (66.0)	<0.001
Present	14 (11.1)	18 (34.0)	
Intrahepatic metastasis, *n* (%)			
Absent	84 (66.7)	29 (54.7)	0.130
Present	42 (33.3)	24 (45.3)	

*α-Fetoprotein.
†Edmondson–Steiner grade.
‡Fisher's exact test.

($P < 0.001$ for both rates; Fig. 4). The median overall and disease-free survival rates of these patients were only 18.4 and 6.0 months, respectively.

^{18}F-FDG-PET/CT and early recurrence

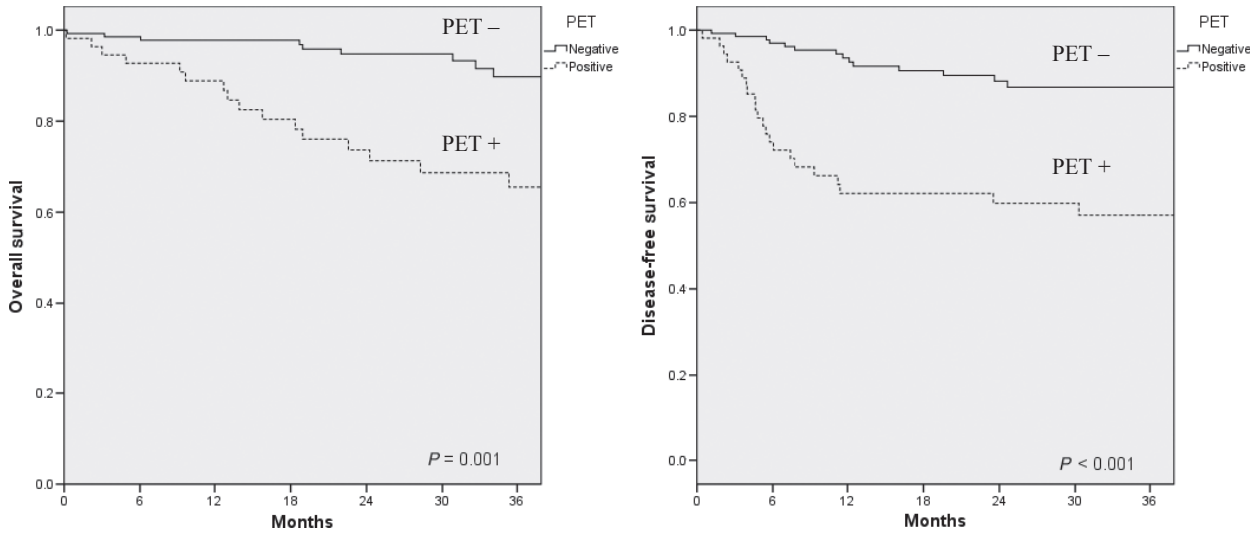
Prognostic factors for early recurrence are summarized in Table 4. In univariate analysis, preoperative AFP level, PET/CT finding, Milan criteria, UCSF criteria, maximum tumor size, total tumor size, differentiation, microvascular invasion, major vessel invasion, serosal invasion, and intrahepatic metastasis were significantly correlated with an increased risk of post-transplant early HCC recurrence. In multivariable analysis, only PET/CT finding was a significant prognostic factor (hazard ratio: 3.945, 95% CI 1.196–13.016, $P = 0.024$).

Discussion

The results of this study indicate that preoperative ^{18}F-FDG-PET/CT finding in LT for HCC is a useful predictive parameter for the evaluation of early tumor recurrence. In this study, early tumor recurrence less than 6 months after LT was associated with a dismal overall survival rate. Preoperative ^{18}F-FDG-PET/CT was an independent and significant prognostic factor for early tumor recurrence. PET/CT positivity was correlated with several tumor variables, which indicated bad tumor biology.

LDLT has become an established HCC treatment option in dealing with the reality of a shortage of decreased donor organs [5]. As LDLT is not restricted by waiting time and organ allocation from a deceased donor, it provides a substantial advantage for patients with early stage HCC who would otherwise have waited several months or years for deceased donor LT (DDLT). Several studies have supported the theoretical advantage of LDLT over DDLT based on the latter's long waiting time and dropout rate [15,16]. However, a higher recurrence rate has been reported in LDLT [6]. This finding may have related to selection bias, as LDLT eliminates the waiting period for grafts. In DDLT, the waiting period provides time for a natural selection process in which patients with biologically more aggressive tumors drop out because of tumor progression [17]. Therefore, selection of candidates for LDLT should carefully be considered with cost, donor safety, and especially survival benefit. Consistent with the results of the aforementioned study [17], presently patients with early recurrence after LDLT had a very dismal overall survival rate (Fig. 1). Although the mortality and morbidity of LDLT is decreasing and donor safety is secured, early recurrent patients are typically advised to avoid transplantation by physicians. The prediction of early recurrence for LDLT of HCC has not been adequately studied.

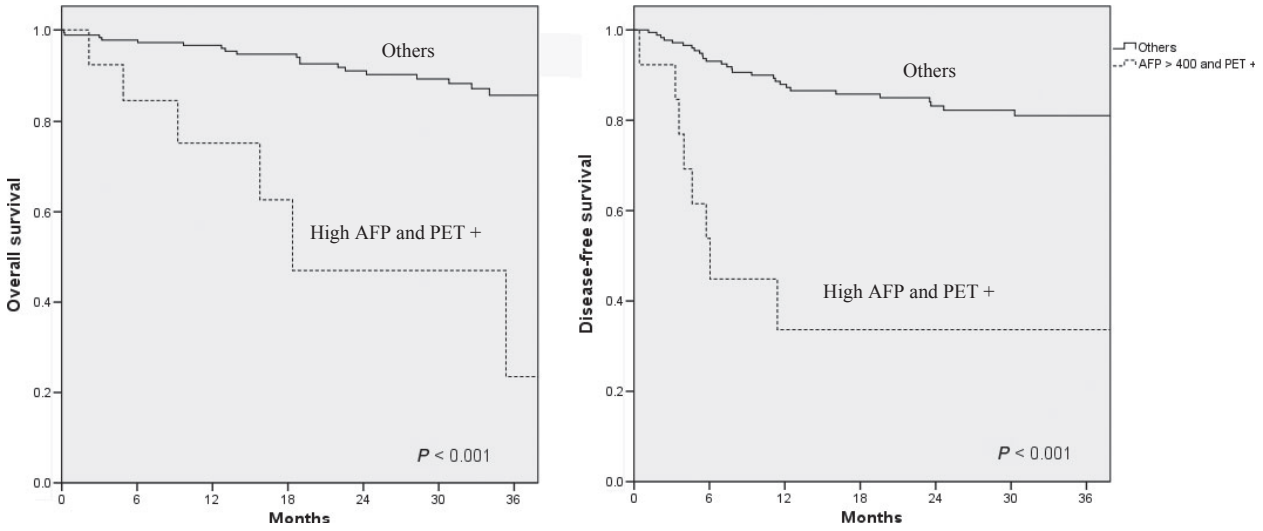
Several prognostic factors to predict recurrence of tumor have been investigated and suggested [2,6,18,19]. Among them, the Milan criteria using size and number of tumors have been adopted in commonly used selection criteria. The Milan criteria reported the excellent recurrence-free survival of 92% at 3 years and a 4-year survival rate equivalent to patients transplanted without HCC [2]. However, it is not so easy to correctly diagnose the size and number of tumors in patients with cirrhotic HCC,



OS/No. at risk	0 year	1 year	2 year	3 year
Negative	100%/136	97.8%/115	94.8%/84	89.8%/46
Positive	100%/55	88.9%/42	73.7%/31	65.5%/20

DFS/No. at risk	0 year	1 year	2 year	3 year
Negative	100%/136	93.5%/99	88.2%/64	86.8%/37
Positive	100%/55	62.1%/29	59.8%/25	57.1%/15

Figure 3 Overall survival rate and disease-free survival rate of patients with HCC after LDLT according to the positivity of PET-CT.



OS/No. at risk	0 year	1 year	2 year	3 year
Others	100%/178	96.6%/151	90.9%/113	85.8%/65
AFP > 400 IU/ml and PET +	100%/13	75.2%/6	47.0%/2	23.5%/1

DFS/No. at risk	0 year	1 year	2 year	3 year
Others	100%/178	87.9%/126	83.2%/88	81.0%/51
AFP > 400 IU/ml and PET +	100%/13	33.7%/2	33.7%/1	33.7%/1

Figure 4 Overall survival rate and disease-free survival rate of patients with HCC after LDLT according to the positivity of PET-CT and AFP.

although preoperative evaluation was advanced using conventional radiologic imaging such as CT, MRI, and ultrasonography [20]. Sotiropoulos *et al.* reported that the agreement ratio was as low as 41% between preoperative radiologic and postoperative pathologic assessments of tumor size and number [21]. Recently, the criteria

Table 4. Prognostic factors of disease-free survival influencing early recurrence.

	Univariate analysis			Multivariable analysis		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Sex						
Male	Referent		0.472			
Female	0.585	0.136–2.521				
Age (years)						
≤60	Referent		0.566			
>60	1.345	0.489–3.701				
AFP*						
≤400 ng/mL	Referent		0.001			0.889
>400 ng/mL	4.811	1.965–11.779		0.920	0.286–2.962	
MELD†						
≤20	Referent		0.243			
>20	0.302	0.040–2.254				
PET/CT						
Negative	Referent		<0.001			0.024
Positive	8.472	3.077–23.325		3.945	1.196–13.016	
Milan criteria						
Within	Referent		<0.001			0.503
Beyond	5.521	2.121–14.371		0.577	0.116–2.883	
UCSF criteria						
Within	Referent		0.008			0.436
Beyond	3.968	1.442–10.920		0.529	0.107–2.623	
Tumor number						
≤3	Referent		0.248			
>3	1.681	0.696–4.056				
Maximum tumor size						
≤5 cm	Referent		<0.001			0.540
>5 cm	5.159	2.136–12.461		0.625	0.139–2.808	
Total tumor size						
≤10 cm	Referent		<0.001			0.196
>10 cm	7.837	3.200–19.192		2.701	0.600–12.169	
Differentiation‡						
I–II	Referent		0.011			0.183
III–IV	13.464	1.802–100.592		4.523	0.490–41.747	
Microvascular invasion						
Absent	Referent		0.001			0.703
Present	12.763	2.961–55.015		1.432	0.226–9.077	
Capsule formation						
Absent	Referent		0.092			
Present	0.469	0.194–1.132				
Major vessel invasion						
Absent	Referent		<0.001			0.178
Present	10.172	4.037–25.635		2.563	0.652–10.077	
Ductal invasion						
Absent	Referent		0.065			
Present	3.962	0.918–17.089				
Serosal invasion						
Absent	Referent		<0.001			0.256
Present	8.099	3.308–19.829		2.040	0.596–6.989	
Intrahepatic metastasis						
Absent	Referent		<0.001			0.057
Present	10.388	3.043–35.457		5.111	0.952–27.428	
Cirrhosis						
Absent	Referent		0.879			
Present	1.169	0.156–8.730				

Table 4. continued

	Univariate analysis			Multivariable analysis		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Dysplastic nodule						
Absent	Referent		0.599			
Present	0.762	0.277–2.097				

*α-Fetoprotein.
†Model for end-stage liver disease.
‡Edmondson–Steiner grade.

including preoperative markers of biologic behavior as well as tumor size and number were reported to minimize the risk of HCC recurrence [7,10,22,23]. Use of some criteria including preoperative serum des-γ-carboxy prothrombin or serum AFP level has yielded low recurrence rate on retrospective analysis [22]. Furthermore, ^{18}F-FDG tumor uptake on preoperative PET scan has been reported as a strong predictive factor for recurrence in LT [9,10].

In this study, ^{18}F-FDG-PET/CT tumor uptake was a poor independent prognostic factor for early recurrence, as well as all recurrence (Table 3 and Fig. 3) PET/CT is a noninvasive and useful tool for evaluating metastasis and tumor biology. PET/CT is widely used to assess extrahepatic metastasis before LT [24,25]. Furthermore, glucose metabolism assessed on ^{18}F-FDG-PET/CT is a factor related to tumor progression or aggressiveness [26–28]. Positive uptake of PET/CT has been observed in poorly differentiated HCC and a correlation between tumor growth rate and PET/CT uptake has been reported [27]. These findings reveal that the biologic activity of viable cancer cells in primary lesion is represented by PET/CT uptake and is deemed to be closely correlated with the tumor aggressiveness and the probability of metastasis. In this study, PET/CT findings were significantly correlated with tumor variables showing poorly differentiation and progressed stage, such as high AFP level, beyond Milan and UCSF criteria, large tumor size, microvascular invasion, major vessel invasion, and serosal invasion (Table 2). Especially, microvascular invasion has been demonstrated to be a very strong predictor of tumor recurrence and poor survival after LT and liver resection of HCC [29,30]. Kornberg *et al.* reported that increased ^{18}F-FDG uptake on PET was predictive for microvascular invasion and tumor recurrence after LT [11]. In contrast to gross vascular invasion, which can be frequently diagnosed prior to LT by conventional imaging techniques, microvascular invasion is a histopathologic diagnosis that cannot be made before LT. Therefore, PET/CT for correlation with microvascular invasion is useful method to predict tumor biology prior to LT.

Moreover, a positive PET/CT finding together with preoperative high AFP level was presently significantly associated with poor survival (Fig. 4). AFP level is a well-known diagnostic and prognostic factor for HCC [31]. Although in this study, a preoperative high AFP level was a significant prognostic factor only in univariate analysis of early recurrence, a combined index with PET/CT-positive status showed significantly poor survival compared with other combinations. This result supports the view that PET/CT findings with AFP level can be easily used to predict the poor prognosis in patients with HCC before LDLT in the clinical setting.

There are some limitations in this study. First, we analyzed only LDLT cases without deceased donor LT. Unfortunately, the comparison between LDLT and deceased donor LT using PET/CT finding was not performed. Second, this study was limited by its retrospective nature, and selection bias may have influenced survival data. However, only five patients without PET/CT evaluation before LT were excluded during the study period. Our exclusion criteria of LDLT for HCC were patients without extrahepatic metastasis or gross vessel invasion in preoperative imaging studies, such as CT, MRI, and PET/CT. Therefore, there were a bit more early recurrence cases after LDLT. On the basis of this study, our selection criteria should be changed using PET/CT finding and preoperative AFP level.

In conclusion, ^{18}F-FDG-PET/CT appears to be an independent and significant predictor of early tumor recurrence in LDLT for HCC. Considering this finding with preoperative AFP level, poor survivors were predicted and selected for exclusion. Preoperative PET/CT can provide effective information for the selection of adequate candidates for LDLT.

Authorship

SDL: collected and analyzed data, and wrote the paper. SHK: designed and performed the study. Y-KK: performed study and collected data. CK: performed the study and collected data. S-KK: performed the study and

collected data. S-SH: performed the study and contributed important reagents. S-JP: performed the study and contributed important reagents.

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