^{18}F-FDG PET/CT Can Predict Survival of Advanced Hepatocellular Carcinoma Patients: A Multicenter Retrospective Cohort Study

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Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) consists of a heterogeneous group of patients with a wide range of survival times, requiring further prognostic stratification to facilitate treatment allocation. We evaluated the prognostic value of ^{18}F-FDG uptake on PET/CT at the time of presentation in patients with BCLC stage C HCC. **Methods:** A total of 291 patients with BCLC stage C HCC who underwent ^{18}F-FDG PET/CT between 2009 and 2010 for staging were retrospectively enrolled from 7 university hospitals. The patients were further divided into 2 groups according to the extent of disease, as intrahepatic or extrahepatic. Tumor-to-liver SUV ratio (TLR) of the primary tumor was measured on ^{18}F-FDG PET/CT. Prognostic values of TLR and other clinical variables were analyzed to predict overall survival (OS) in univariate and multivariate analyses. Differences in the OS stratified by TLR were examined by the Kaplan–Meier method. **Results:** Higher TLR was associated with extrahepatic disease ($P = 0.018$). On multivariate analysis, Child–Pugh classification and TLR were independent prognostic factors in the intrahepatic disease group (all $P < 0.05$), whereas TLR was the only independent prognostic factor in the extrahepatic disease group ($P < 0.05$). Patients with high TLR showed a significantly worse OS than those with low TLR ($P < 0.05$) in both groups. **Conclusion:** In patients with BCLC stage C HCC, ^{18}F-FDG uptake in the primary tumor was significantly higher in patients with extrahepatic disease than in those with intrahepatic disease. In addition, ^{18}F-FDG uptake on pretreatment PET/CT had an incremental prognostic value for OS in both intrahepatic and extrahepatic disease groups.

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Liver cancer is the second most common cause of cancer-related deaths in men and the sixth in women worldwide (*1*). The Barcelona Clinic Liver Cancer (BCLC) staging system is the most commonly used for predicting survival by international guidelines of hepatocellular carcinoma (HCC) management (*2*). Performance status, Child–Pugh score, tumor size, multiple tumors, vascular invasion, nodal spread, and extrahepatic metastasis can classify patients into 4 stages—early, intermediated, advanced, and end-stage (*3*). The BCLC staging system includes a wide spectrum of diseases with different prognoses, especially in intermediate to advanced stages (*4,5*).

BCLC stage C includes patients with portal vein invasion, lymph node or distant metastasis, Eastern Cooperative Group performance status 1 or 2, and Child–Pugh A or B. Sorafenib, the multitargeted tyrosine kinase inhibitor, remains the only standard of care that can be offered for this stage, although clinically various local and systemic therapies are given for palliative purposes (*6–8*). In some BCLC C patients with portal vein tumor thrombosis, long-term survival can be achieved by surgical resection followed by postoperative transarterial chemoembolization (*9*). Studies have proposed a need for new prognostic systems for better prediction of patient survival and facilitation of treatment allocation (*2,10,11*).

Despite the poor sensitivity for well-differentiated HCC, ^{18}F-FDG PET/CT or PET has been helpful for the detection of moderately to poorly differentiated or advanced HCC (*12–18*) and, particularly, for the prediction of prognosis of patients (*19*). To date, most studies regarding the prognostic role of ^{18}F-FDG PET have focused on patients with early stage HCC (*20–23*). There are only a few studies

that enrolled patients with advanced stage, and most of them included small populations (*24,25*). In this study, we evaluated the prognostic value of ^{18}F-FDG uptake on pretreatment PET/CT scans in a larger number of patients with BCLC stage C HCC from a multicenter retrospective cohort.

MATERIALS AND METHODS

Study Population

The institutional review boards of the 7 participating university hospitals (Dongsan Medical Center, Incheon St. Mary's Hospital, Kyung Hee University Hospital, Samsung Medical Center, Seoul St. Mary's Hospital, Uijeongbu St. Mary's Hospital, and Yonsei University Health System) approved this retrospective multicenter study, and the requirement to obtain informed consent was waived. We retrospectively reviewed the medical records of 847 consecutive patients with HCC who underwent pretreatment staging with ^{18}F-FDG PET/CT between January 2009 and December 2010, and the images were sent for review at a single institution. All patients were assessed at presentation using the BCLC staging classification, laboratory findings, and several imaging modalities (CT, MRI, and PET/CT).

Of a total 847 HCC patients, 291 were enrolled in the study and met the following eligibility criteria: diagnosed as HCC with BLCL stage C, PET/CT performed before the start of initial treatment, and no previous history of other malignancy. The patients were further divided into 2 groups according to the extent of disease as intrahepatic (n = 153) or extrahepatic (n = 138). Intrahepatic disease was defined as HCC confined to the liver parenchyma with portal vein invasion, whereas extrahepatic disease included tumor

TABLE 1
Patient Characteristics in Relation to ^{18}F-FDG Uptake in Primary Tumors (n = 291)

Characteristic	Value	TLR (mean ± SD)	*P*
Age (y)	57.1 ± 10.5 (range, 29–84)		0.72
	<57 vs. ≥57	4.0 ± 1.9 vs. 3.9 ± 2.3	
Sex (*n*)			0.14
Male	251 (86.3)	3.8 ± 2.1	
Female	40 (13.7)	4.4 ± 2.2	
Etiology of hepatitis (*n*)			0.52
HBV	225 (77.3)	4.0 ± 2.0	
HCV	20 (6.9)	3.5 ± 1.9	
Alcoholic	20 (6.9)	3.7 ± 2.9	
Unknown	26 (8.9)	3.8 ± 2.1	
Child–Pugh classification (*n*)			0.69
A	233 (80.0)	3.9 ± 2.1	
B	58 (20.0)	3.8 ± 1.9	
Tumor size on CT or MRI (cm)	10.3 ± 4.1 (range, 3.1–21.1)		0.09
	<10.3 vs. ≥10.3	3.7 ± 2.2 vs. 4.1 ± 2.0	
Tumor number (*n*)			0.64
<4	123 (42.4)	3.8 ± 2.0	
≥4	161 (57.6)	4.0 ± 2.1	
AFP (ng/mL)	Median, 1,466 (range, 1.0–3,500,000)		0.54
	<1,466 vs. ≥1,466	3.9 ± 2.3 vs. 4.0 ± 1.8	
PIVKA-II (mAU/mL)	Median, 1,200 (range, 6–20,000)		0.78
	<1,200 vs. ≥1,200	4.0 ± 2.3 vs 3.9 ± 2.0	
Disease extent (*n*)			0.018
Intrahepatic	153 (52.6)	3.6 ± 2.0	
Extrahepatic	138 (47.4)	4.2 ± 2.2	
Portal vein invasion			0.84
Absence	55 (18.9)	3.9 ± 1.9	
Presence	236 (81.1)	3.9 ± 2.1	
Treatment (*n*)			0.61
Local therapy	232 (79.7)	3.9 ± 2.2	
Systemic therapy	59 (20.3)	4.0 ± 1.7	

HBV = hepatitis B virus; HCV = hepatitis C virus.
Data are mean ± SD or *n,* and data in parentheses are percentages unless otherwise marked.

involvement in the lymph node or distant sites. All clinical data of the enrolled patients were collected and managed using the Internet-based Clinical Research and Trial Management System of the Korean National Institute of Health.

^{18}F-FDG PET/CT

All ^{18}F-FDG PET/CT scans were obtained on dedicated PET/CT scanners (Discovery Ste [GE Healthcare] for Dongsan Medical Center, Incheon St. Mary's Hospital, Samsung Medical Center, and Yonsei University Health System; Gemini TF16 [Philips Healthcare] for Kyung Hee University Hospital; Biograph TruePoint [Siemens Healthcare] for Seoul St. Mary's Hospital, Uijeongbu St. Mary's Hospital, and Yonsei University Health System; Biography Duo [Siemens Healthcare] for Seoul St. Mary's Hospital). All patients fasted for at least 6 h, and blood glucose levels were less than 140 mg/dL before intravenous administration of ^{18}F-FDG. ^{18}F-FDG at doses of approximately 5.5 MBq/kg, 6.0 MBq/kg, and 333 MBq for the Discovery Ste, Biograph TruePoint and Biograph Duo, and Gemini TF16, respectively, was intravenously administered. In all institutions, PET images were acquired from the cerebellum to the proximal thighs in 3-dimensional mode 60 min after injection of ^{18}F-FDG immediately after the acquisition of a precontrast CT scan. PET images were reconstructed by an iterative reconstruction algorithm using the CT images for attenuation correction.

Image Analysis

All ^{18}F-FDG PET/CT and contrast-enhanced CT or MR images of 847 HCC patients were transferred to the image archive server (National Cancer Center, Korea) using the DICOM format. The ^{18}F-FDG PET/CT and contrast-enhanced CT or MR images of patients were centrally reviewed by *2* board-certified nuclear medicine physicians using a fusion module by the imaging software (MIM 6.4; MIM Software Inc.). Discrepancies between the interpreters were resolved by consensus. Tumor size and number were measured on contrast-enhanced MRI or CT scans.

For semiquantitative analysis, a spheric-shaped volume of interest was drawn for each HCC lesion and the SUV_{max} of the lesion was calculated as follows: (decay-corrected activity [kBq]/tissue volume [mL])/(injected ^{18}F-FDG activity [kBq]/body mass [g]). To measure normal liver activity, 3 spheric 1-cm-sized volumes of interest were drawn in the liver, 2 in the right lobe and 1 in the left lobe, where HCC was not detected on contrast-enhanced CT or MRI. SUV_{mean} of the normal liver was defined as the mean value of SUV_{mean} of 3 spheric-shaped volumes of interest. The uptake ratio of SUV_{max} of HCC to SUV_{mean} of the normal liver (TLR) was calculated.

Statistical Analysis

The primary endpoint of this study was the duration of overall survival (OS). It was measured from the start date of treatment to the date of death from any cause, with surviving patients censored at the time of last follow-up.

ANOVA and independent-sample *t* test were used to compare TLR according to patient clinical characteristics. For univariate analysis, log-rank tests were performed using the following factors: age, sex, treatment, Child–Pugh classification, etiology of hepatitis, disease extent, tumor markers, and TLR from ^{18}F-FDG PET/CT. All continuous variables were dichotomized according to median cutoff values. For TLR, the optimal cutoff values were determined using receiver-operating-characteristic curve analysis. Cox proportional hazards regression tests in multivariate analysis were performed with variables that were significant in the univariate analyses. Survival curves were estimated using the Kaplan–Meier method, and differences between subgroups were compared with the log-rank test. Cumulative OS stratified by the TLR cutoff value was compared between the patients with intrahepatic and extrahepatic disease. All statistical analysis was performed using the statistical software SPSS (version 19; SPSS Inc.), in which a P value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics in Relation to ^{18}F-FDG Uptake in Primary Tumors

The characteristics of 291 patients are shown in Table 1. The mean age ± SD of the enrolled patients was 57.1 ± 10.5 y (range, 29–84 y). The mean interval between PET/CT scan and start of treatment was 5.8 d (range, 0–45 d). The treatments were as follows: in the intrahepatic disease group, 141 received local therapy and 12 systemic, compared with 91 and 47 in the extrahepatic, respectively. The median duration of follow-up was 6.3 mo (range, 0.5–67.4 mo). The mean TLR was 3.9 ± 2.1. The primary tumor showed a significantly higher ^{18}F-FDG uptake in patients with extrahepatic disease (n = 138) than intrahepatic disease (n = 153) (4.2 ± 2.2 vs. 3.6 ± 2.0, P = 0.018). Otherwise, there was no difference in TLR based on Child–Pugh classification, tumor size, tumor number, level of serum a-fetoprotein (AFP) and prothrombin induced by vitamin K absence-II (PIVKA-II), presence of portal vein invasion, or treatment modality (local vs. systemic).

Prognostic Factor Analyses for OS

During follow-up, 250 of the 291 patients died. The Kaplan–Meier estimate of 5-y OS was 6.9%, with a median OS duration of 7.1 mo. There was a significant difference in OS only according to the extent of disease, whether intrahepatic or extrahepatic (Fig. 1; $P < 0.001$). Accordingly, the prognostic values of the variables were analyzed in 2 separate groups. Age, sex, etiology, Child–Pugh classification, serum AFP and PIVKA-II level, tumor size and number, and TLR were included in OS analysis (Tables 2 and 3). The optimal cutoff values for TLR in the intrahepatic

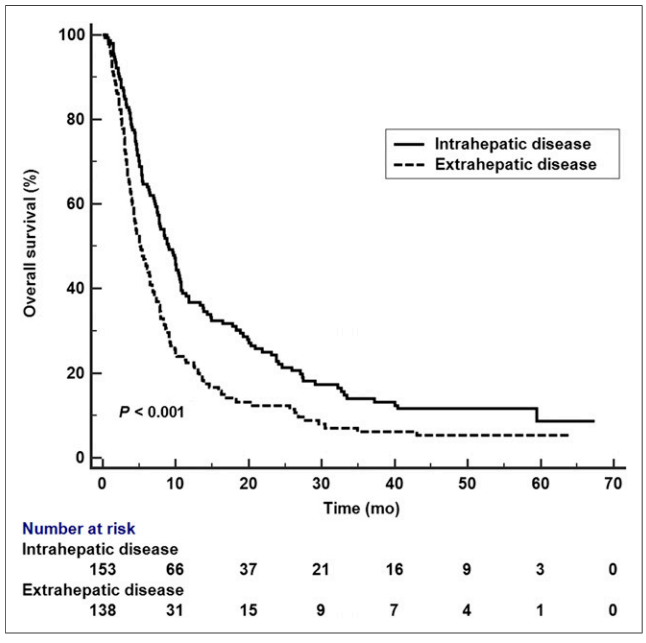

FIGURE 1. Cumulative OS curves according to disease extent of BCLC stage C HCC.

and extrahepatic disease for OS were 3.0 and 3.2, respectively. The median cutoff values for age, serum AFP level, PIVKA-II level, tumor size, and tumor number were 57 y, 1,466 ng/dL, 1,200 mAU/mL, 10.3 cm, and 4, respectively.

In patients with intrahepatic disease, Child–Pugh classification, PIVKA-II level, and TLR were significant for OS in univariate analysis (Table 2; all $P < 0.05$). In multivariate analysis, Child–Pugh classification and TLR were independent prognostic factors for OS (both $P < 0.05$). High TLR was the most significant prognostic factor, with a 1.89-fold increase in the risk of death (hazard ratio, 1.89; 95% confidence interval, 1.3–2.73; $P < 0.001$, Table 2).

In patients with extrahepatic disease, Child–Pugh classification, tumor size, tumor number, portal vein invasion, and TLR were significant in univariate analysis (Table 3; all $P < 0.05$). Of these variables, TLR was the only independent prognostic factor for OS in multivariate analysis ($P < 0.05$). In patients with a TLR $\geq$ 3.2, there was a 1.69-fold increase in the risk of death (hazard ratio, 1.69; 95% confidence interval, 1.13–2.51; $P = 0.01$, Table 3, Fig. 2).

Kaplan–Meier Survival Analyses According to Tumor ^{18}F-FDG Uptake

In patients with intrahepatic BCLC stage C, the median OS was different according to TLR: 14.9 mo with a TLR < 3.0 versus 6.4 mo with a TLR ≥ 3.0 ($P = 0.001$, Table 4). In addition, prognostic stratification by TLR was also significantly different in patients with extrahepatic disease. The median OS was 7.7 mo with a TLR < 3.2 versus 4.3 mo with a TLR ≥ 3.2 ($P = 0.003$). Patients with intrahepatic disease and a TLR < 3.0 in the primary tumor showed a more than 3 times longer median OS than those with extrahepatic disease and a TLR ≥ 3.2 (14.9 vs. 4.3 mo). There was no significant difference in median OS between patients

TABLE 2
Univariate and Multivariate Analysis of Prognostic Factors for OS in Intrahepatic BCLC Stage C HCC Patients ($n = 153$)

		Univariate		Multivariate	
Variable	*n*	HR	*P*	HR	*P*
Age (y)		1.09 (0.77–1.54)	0.64		
<57	74				
≥57	79				
Sex		0.81 (0.48–1.37)	0.48		
Male	134				
Female	19				
Etiology		0.90 (0.75–1.08)	0.27		
HBV	117				
HCV	10				
Alcohol	13				
Unknown	13				
Child–Pugh classification		1.76 (1.17–2.66)	0.007	1.74 (1.14–2.67)	0.011
A	122				
B	31				
AFP (ng/mL)		1.09 (0.77–1.55)	0.64		
<1,466	77				
≥1,466	73				
PIVKA-II (mAU/mL)		1.53 (1.05–2.24)	0.03	1.45 (0.99–2.12)	0.053
<1,200	52				
≥1,200	92				
Tumor size		1.01 (0.71–1.44)	0.96		
<10.3	87				
≥10.3	66				
Tumor number		1.12 (0.79–1.59)	0.51		
<4	77				
≥4	76				
TLR		1.85 (1.30–2.65)	0.001	1.89 (1.30–2.73)	0.001
<3.0	69				
≥3.0	84				

HR = hazard ratio; HBV = hepatitis B virus; HCV = hepatitis C virus.
Data in parentheses are 95% confidence intervals.

TABLE 3
Univariate and Multivariate Analysis of Prognostic Factors for OS in Extrahepatic BCLC Stage C HCC Patients (n = 138)

Variable	n	Univariate		Multivariate	
		HR	P	HR	P
Age (y)		0.75 (0.52–1.08)	0.12		
<57	77				
≥57	61				
Sex		1.02 (0.62–1.69)	0.94		
Male	117				
Female	21				
Etiology		0.90 (0.74–1.09)	0.27		
HBV	108				
HCV	10				
Alcohol	7				
Unknown	13				
Child–Pugh classification		1.97 (1.26–3.08)	0.003	1.48 (0.93–2.36)	0.1
A	111				
B	27				
AFP (ng/mL)		1.35 (0.95–1.93)	0.1		
<1,466	66				
≥1,466	72				
PIVKA-II (mAU/mL)		1.30 (0.89–1.89)	0.18		
<1,200	57				
≥1,200	74				
Tumor size		1.71 (1.19–2.45)	0.005	1.46 (0.99–2.14)	0.06
<10.3	67				
≥10.3	71				
Tumor number		1.54 (1.04–2.27)	0.03	1.42 (0.94–2.13)	0.09
<4	46				
≥4	92				
Portal vein invasion		1.59 (1.09–2.31)	0.02	1.18 (0.79–1.77)	0.41
Absence	55				
Presence	83				
TLR		1.78 (1.21–2.61)	0.003	1.69 (1.13–2.51)	0.01
<3.2	49				
≥3.2	89				

HR = hazard ratio; HBV = hepatitis B virus; HCV = hepatitis C virus.
Data in parentheses are 95% confidence intervals.

with intrahepatic disease but a high TLR ≥ 3.0 and patients with extrahepatic disease but a low TLR < 3.2 (P = 0.39, Fig. 3).

DISCUSSION

Studies have shown the potential prognostic value of ^{18}F-FDG uptake in patients with various stages of HCC. Primary tumors with positive ^{18}F-FDG uptake on preoperative PET or PET/CT showed early recurrence after liver transplantation (*20–22*). In a large, multicenter retrospective cohort of BCLC 0 and A patients undergoing curative treatment, those with a high TLR ≥ 2 had significantly worse OS than patients with a lower TLR < 2 (5-y OS, 61% vs. 79.4%) (*23*). TLR was an independent prognostic factor for progression-free survival and OS in patients with intermediate to advanced stage HCC confined to the liver (*5*). For advanced stage HCCs, 1 previous study showed the prognostic value of SUV_{max} for progression-free survival and OS in 25 patients with extrahepatic metastasis (*25*).

In the present study, we evaluated the prognostic value of clinical factors and TLR, tumor ^{18}F-FDG uptake normalized to the liver on pretreatment ^{18}F-FDG PET/CT in 291 patients with solely BCLC stage C in a multicenter cohort. With a median OS of 7.1 mo in all patients, we found a significant difference in OS according to the extent of disease. The median OS of the intrahepatic disease group was significantly longer than that of the extrahepatic

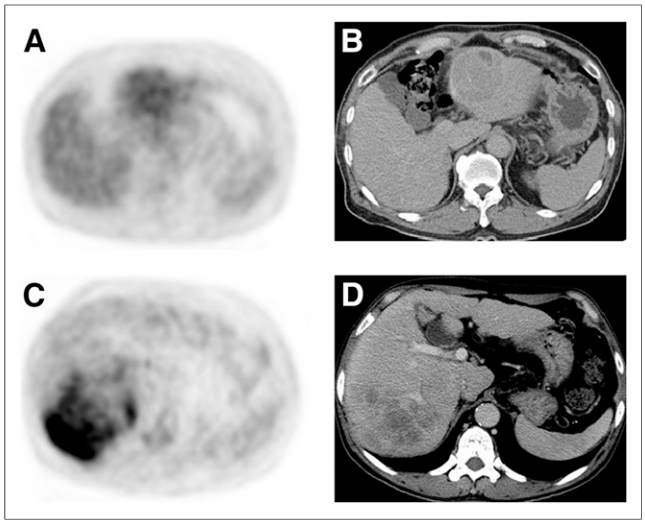

FIGURE 2. (A and B) HCC in left hepatic lobe shows low ^{18}F-FDG uptake (TLR, 1.5). This patient survived for 20 mo. (C and D) Heterogeneous high ^{18}F-FDG uptake (TLR, 4.3) is seen in right hepatic lobe, and this patient died after 2 mo. Both patients had bone metastasis.

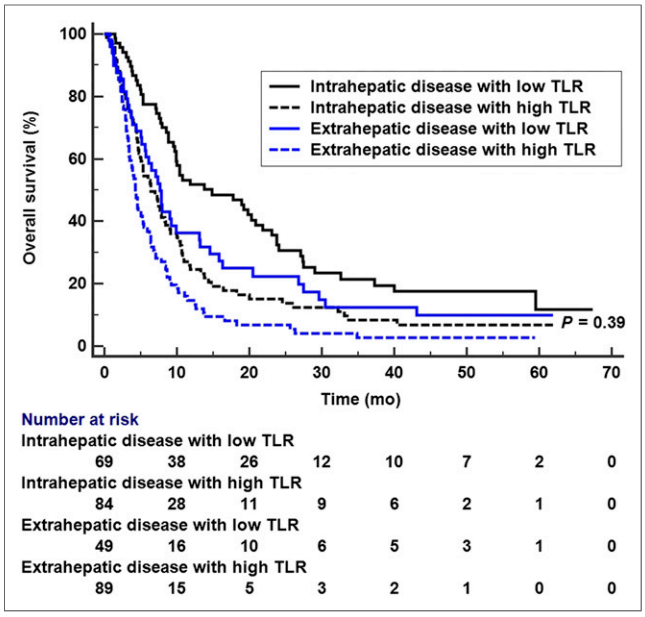

FIGURE 3. Cumulative OS curves according to disease extent and TLR. There was no significant difference in median OS between patients with intrahepatic disease but high TLR ≥ 3.0 and patients with extrahepatic disease but low TLR < 3.2 (P = 0.39).

disease group (9 vs. 5.1 mo). Within the same BCLC stage C, the prognosis of HCC was poor in the presence of extrahepatic metastasis similar to other solid tumors.

In the intrahepatic disease group, Child–Pugh classification and TLR were independent prognostic factors for OS in multivariate analysis. Liver function variables such as Child–Pugh classification, but not TLR, are well-known factors in predicting prognosis (*26*). In this study, we added TLR as a new metabolic prognostic variable for OS. Because TLR is reflective of tumor aggressiveness and rapid tumor proliferation (*27,28*), intrahepatic tumor progression with high-TLR HCCs seems attributable to poor OS. Further studies are warranted to investigate whether therapeutic approaches to control intrahepatic tumors with high TLR can improve patient survival in intrahepatic BCLC stage C.

In the extrahepatic disease group, TLR was the only independent prognostic factor for OS in multivariate analysis. The mean TLR of patients with extrahepatic metastasis was significantly higher than that of patients without extrahepatic metastasis (4.2 vs. 3.6). This finding seemed consistent with the biologic aggressiveness of primary tumors with a high TLR. With a TLR cutoff of ≥ 3.2, there was a 1.69-fold increase in the risk of death. Patients with extrahepatic metastasis can die from intrahepatic tumor progression, liver failure, or extrahepatic disease (*29,30*). Because TLR is associated with tumor aggressiveness as well as extrahepatic metastasis, the poorer prognosis of higher TLR in the extrahepatic group was well expected. Unlike in the intrahepatic disease group, however, Child–Pugh classification did not demonstrate such prognostic value. There was a significant difference in OS between patients with intrahepatic and extrahepatic disease (9 vs. 5.1 mo). It is likely that Child–Pugh classification may not have any remarkable prognostic significance in those with shorter survival.

TABLE 4
OS According to ^{18}F-FDG Uptake

Group	Median OS (mo)		95% CI	*P*
Intrahepatic disease (n = 153)	TLR < 3.0, 14.9	TLR ≥ 3.0, 6.4	1.3–2.65	0.001
Extrahepatic disease (n = 138)	TLR < 3.2, 7.7	TLR ≥ 3.2, 4.3	1.21–2.61	0.003

CI = confidence interval.

One of the main findings of this study was the risk stratification using the extent of disease and TLR in primary HCC. In the intrahepatic disease group, the median OS was longer with a TLR < 3.0 than with a TLR ≥ 3.0 (14.9 vs. 6.4 mo). In the extrahepatic disease group, the median OS was again longer with a TLR < 3.2 than with a TLR ≥ 3.2 (7.7 vs. 4.3 mo). No significant difference in median OS was found between patients with intrahepatic disease and a TLR ≥ 3.0 and patients with extrahepatic disease and a TLR < 3.2. In our previous report, BCLC B or C patients treated with concurrent chemoradiotherapy (CCRT) showed a significantly better prognosis than those treated with transarterial chemoembolization (TACE) when the TLR was > 2. In contrast, there was no difference in prognosis between patients treated with TACE or CCRT when the TLR was ≤ 2.0 (*31*). It has been suggested that ^{18}F-FDG uptake on PET/CT could be used for choice of treatment. On the basis of our results, the incremental prognostic value of ^{18}F-FDG PET/CT may provide indispensable information for treatment allocation among conventional therapies and for selecting those BCLC C patients who would benefit from new drugs. Further studies will be presented in the future.

There are several limitations of the current study. Although we selected patients in a large, multicenter, retrospective cohort, there might have been an inherent risk of selection bias adherent to the

retrospective design. Second, different PET scanners were used from multiple medical centers. Although we did not perform PET/CT scanner calibration by phantom or qualification by any criteria, we centralized PET images from each center, verified image quality, and measured parameters using the same software. Moreover, we used TLR normalized to the internal reference organ of the liver instead of SUV_{max} to reduce problems related to different scanners.

CONCLUSION

In patients with BCLC stage C HCC, ^{18}F-FDG uptake in the primary tumor was significantly higher in patients with extrahepatic disease than intrahepatic disease. In addition, ^{18}F-FDG uptake on pretreatment PET/CT has an incremental prognostic value for OS in both intrahepatic and extrahepatic disease groups.

DISCLOSURE

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