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^{18}F-FDG PET/CT can predict survival of advanced hepatocellular carcinoma patients: A multicenter retrospective cohort study

Short running title: ^{18}F-FDG PET in hepatocellular carcinoma

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ABSTRACT

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 treament allocation. We evaluated the prognostic value of ^{18}F-flurodeoxyglucose (^{18}F-FDG) uptake on positron emission tomography/computed tomography (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 two groups according to the extent of disease, as intrahepatic or extrahepatic. Tumor-to-liver standardized uptake value 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 (all $P < 0.05$). 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 those with intrahepatic disease. In addition, ^{18}F-FDG uptake on pretreatment PET/CT has an incremental prognostic value for overall survival in both intrahepatic and extrahepatic disease groups.

Key Words: Hepatocellular carcinoma; ^{18}F-FDG; PET/CT; survival; prognosis

INTRODUCTION

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 be classify patients into four stages – early (A), intermediated (B), advanced (C), and end-stage (D)(*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 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, the majority of 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 seven 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 pre-treatment 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, magnetic resonance imaging [MRI] and PET/CT).

Out 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 two 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 while extrahepatic disease included tumor involvement in the portal vein, 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 performed on a dedicated PET/CT scanner (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 hours and blood glucose levels were less than 140 mg/dL before intravenous administration of ^{18}F-FDG. A dose of approximately 5.5 MBq/Kg of ^{18}F-FDG was intravenously administered for Discovery STe and approximately 6.0 MBq/Kg for Biograph TruePoint and Biograph Duo, and 333 MBq for Gemini TF16. In all institutions, PET images were acquired from the cerebellum to the proximal thighs in 3-D mode 60 minutes after injection of ^{18}F-FDG immediately after acquiring a pre-contrast 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 Digital

Imaging and Communications in Medicine format. The ^{18}F-FDG PET/CT and contrast enhanced CT or MR images of patients were centrally reviewed by two board-certified nuclear medicine physicians (JKO, SJN) using a fusion module by the imaging software (MIM 6.4, MIM software Inc., Cleveland, OH, USA). Discrepancies between the readers were resolved by consensus. Tumor size and number were measured on contrast enhanced MRI or CT scans.

For semi-quantitative analysis, a spherical-shaped volume of interest was drawn for each HCC lesion and the maximum standardized uptake value (SUVmax) 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, three spherical 1 cm-sized volumes of interest were drawn in the liver, two in the right lobe and one in the left lobe, where HCC was not detected on contrast-enhanced CT or MRI. SUVmean of the normal liver was defined as the mean value of SUVmean of 3 spheric-shaped volumes of interest. The uptake ratio of SUVmax of HCC to mean SUV of the normal liver (TLR) was calculated.

Statistical Analysis

The primary end-point of this study was the duration of overall survival. 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, gender, 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 cut-off values. For TLR, the optimal cut-off 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 overall survival (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 19 version (SPSS Inc., Chicago, IL, United States), in which $P < 0.05$ 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 days (range, 0-45 days). The treatments were as follows: in the intrahepatic disease group, 141 received local therapy and 12 systemic, compared to 91 and 47 in the extrahepatic, respectively. The median duration of follow-up was 6.3 months (range, 0.5-67.4 months). The mean TLR was 3.9 ± 2.1. The primary tumor showed significantly higher ^{18}F-FDG uptake in patients with extrahepatic disease (n = 138) compared to those with 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 Overall Survival

During follow-up, 250 of the 291 patients expired. The Kaplan-Meier estimate of 5-year OS was 6.9% with a median OS duration of 7.1 months. There was a significant difference in OS only according to the extent of disease, whether intrahepatic or extrahepatic (Figure 1; $P < 0.001$). Accordingly, the prognostic values of the variables were analyzed in two separate groups. Age, gender, etiology, Child-Pugh classification, serum AFP and PIVKA-II level, tumor size and number, TLR and treatment modality were included in OS analysis (Table 2 and 3). The optimal cut-off values for TLR in the intrahepatic and extrahepatic disease for OS were 3.0 and 3.2, respectively. The median cut-off values for age, serum AFP level, PIVKA-II level, tumor size, and tumor number were 57 year, 1466 ng/dL, 1200 mAU/mL, 10.3cm, 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 (HR [hazard ratio] = 1.89; 95% confidence interval [CI], 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 factors for OS in multivariate analysis (both $P < 0.05$). In patients with TLR ≥ 3.2, there was a 1.69-fold increase in the risk of death (HR=1.69; 95% CI, 1.13-2.51; $P = 0.01$, Table 3, Figure 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 months with TLR < 3.0 vs 6.4 months with 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 months with TLR < 3.2 versus 4.3 months with TLR ≥ 3.2 (P = 0.003). Patients with intrahepatic disease and TLR < 3.0 in the primary tumor showed more than 3 times longer median OS than those with extrahepatic disease and TLR ≥ 3.2 (14.9 vs. 4.3 months). 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, Figure 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-year OS, 61% vs. 79.4%) (*23*). TLR was an independent prognostic factor for progression free survival (PFS) and OS in patients with intermediate to advanced stage HCC confined to the liver (*5*). For advanced stage HCCs, one previous study showed the prognostic value of SUVmax for PFS and OS in 25 patients with

extrahepatic metastasis (*25*).

In the present study, we evaluated the prognostic value of clinical factors and TLR, tumor 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 overall survival of 7.1 months in all patients, we found a significant difference in OS according to the extent of disease. Median OS of the intrahepatic disease group was significantly longer than that of the extrahepatic (9 vs. 5.1 months). 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. Since 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 prognostics factors 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 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*). Since

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 demonstrated such prognostic value. There was a significant difference in OS between patients with intrahepatic and extrahepatic disease (9 months vs 5.1 months). It is likely that Child-Pugh classification may not have any remarkable prognostic significance in those with shorter survival.

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 months). 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 months). 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 CCRT showed significantly better prognosis than those treated with 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. Based on 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 who would benefit from new drugs in BCLC C patients. Further studies will be persented in the near 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 SUVmax 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 those with intrahepatic disease. In addition, ^{18}F-FDG uptake on pretreatment PET/CT has an incremental prognostic value for overall survival in both intrahepatic and extrahepatic disease groups.

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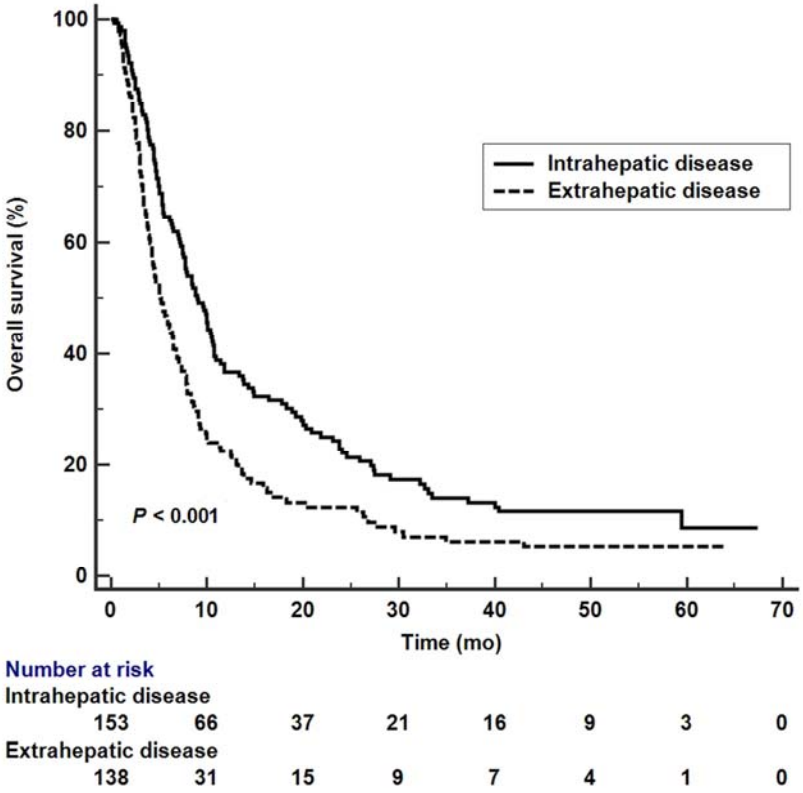

FIGURE 1. Cumulative overall survival curves according to disease extent of BCLC stage C HCC.

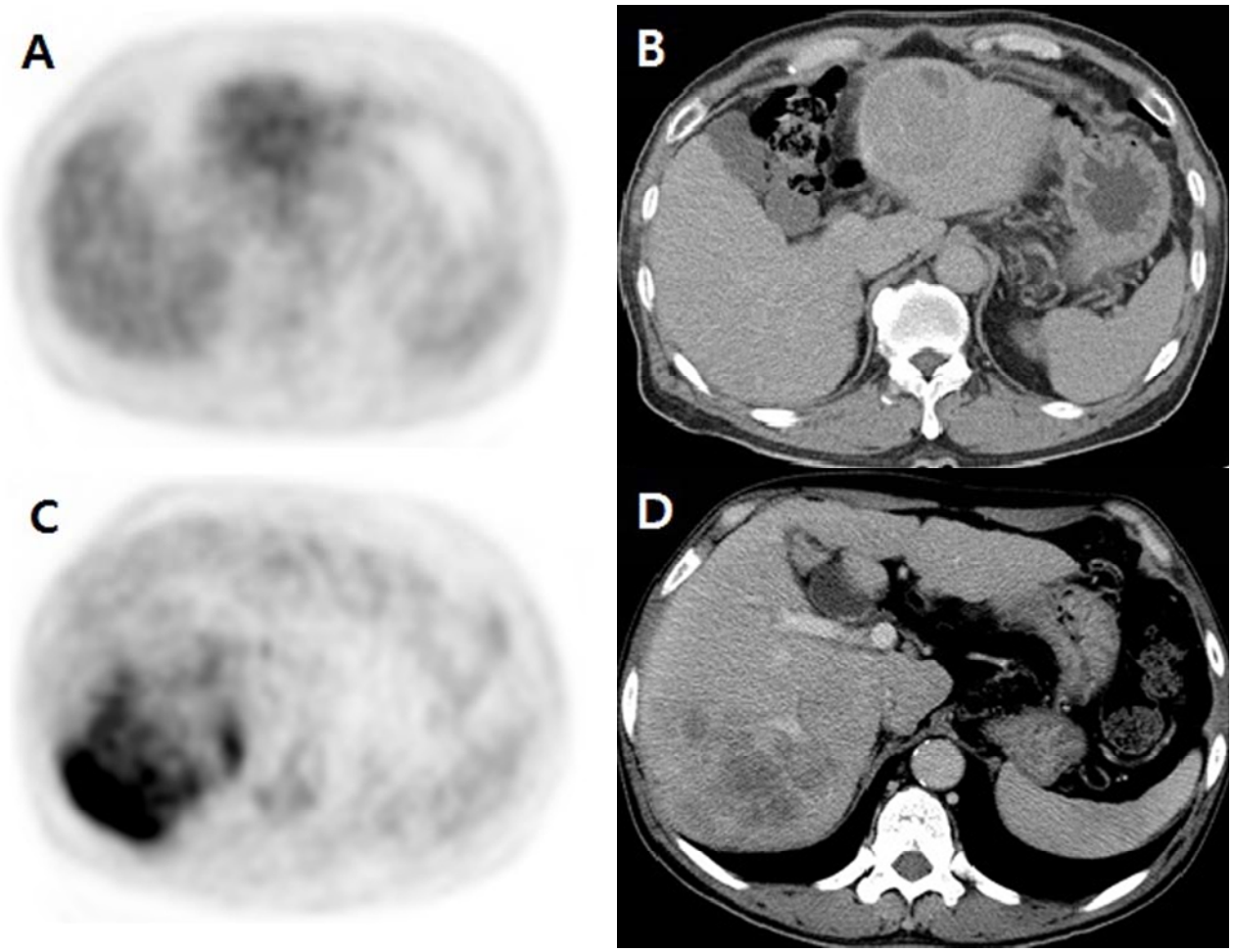

FIGURE 2. Hepatocellar carcinoma in the left hepatic lobe shows low ^{18}F-FDG uptake (TLR 1.5). This patient survived for 20 months (A, B). Heterogeneous high ^{18}F-FDG uptake (TLR 4.3) is seen in the right hepatic lobe and this patient died after 2 months (C, D). Both patients had bone metastasis.

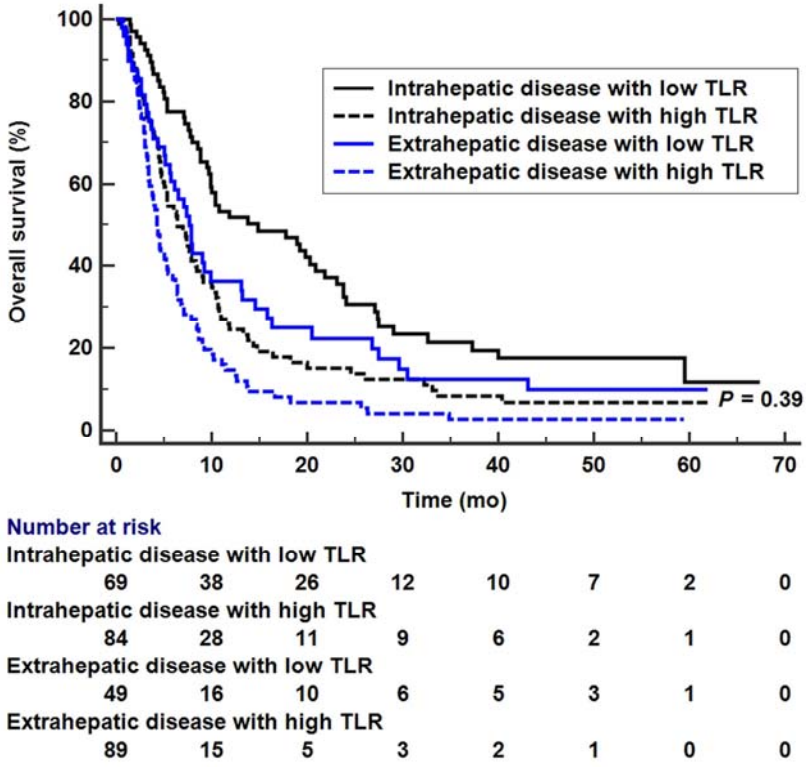

FIGURE 3. Cumulative overall survival curves according to disease extent and TLR. TLR, tumor to liver ratio. There was no significant difference in median OS between patients with intrahepatic disease but high TLR ≥ 3.0 and patients with extrahepatic disease but low TLR < 3.2 ($P = 0.39$).

TABLE 1. Patient characteristics in relation to FDG uptake in primary tumors (n=291)

Characteristics		Value	TLR (mean±SD)	*P*
Age (y)	Mean±SD (range)	57 ± 10.5 (29-84)		
		< 57 vs. ≥ 57	4.0 ± 1.9 vs. 3.9 ± 2.3	0.72
Gender, n (%)	Male	251 (86.3)	3.8 ± 2.1	0.14
	Female	40 (13.7)	4.4 ± 2.2	
Etiology of hepatitis, n (%)	HBV	225 (77.3)	4.0 ± 2.0	0.52
	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 (%)	A	233 (80.0)	3.9 ± 2.1	0.69
	B	58 (20.0)	3.8 ± 1.9	
Tumor size on CT or MRI (cm)	Mean±SD (range)	10.3 ± 4.1 (3.1-21.1)		
		< 10.3 vs. ≥ 10.3	3.7 ± 2.2 vs. 4.1 ± 2.0	0.09
Tumor number, n (%)	<4	123 (42.4)	3.8 ± 2.0	0.64
	≥4	161 (57.6)	4.0 ± 2.1	
AFP (ng/mL)	Median (range)	1466 (1.0-3500000)		
		< 1466 vs. ≥ 1466	3.9 ± 2.3 vs. 4.0 ± 1.8	0.54
PIVKA-II (mAU/mL)	Median (range)	1200 (6-20000)		
		< 1200 vs. ≥ 1200	4.0 ± 2.3 vs 3.9 ± 2.0	0.78
Disease extent, n (%)	Intrahepatic	153 (52.6)	3.6 ± 2.0	0.01
	Extrahepatic	138 (47.4)	4.2 ± 2.2	
Portal vein invasion	Absence	55 (18.9)	3.9 ± 1.9	0.84
	presence	236 (81.1)	3.9 ± 2.1	
Treatment, n (%)	Local therapy	232 (79.7)	3.9 ± 2.2	0.61
	Systemic therapy	59 (20.3)	4.0 ± 1.7	

HBV = Hepatitis B virus; HCV = Hepatitis C virus.

TABLE 2. Univariate and multivariate analysis of prognostic factors for overall survival in intrahepatic BCLC stage C HCC patients (n=153)

Variables		n	Univariate		Multivariate	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Age (y)	< 57	74				
	≥ 57	79	1.09 (0.77-1.54)	0.64		
Gender	Male	134				
	Female	19	0.81 (0.48-1.37)	0.48		
Etiology	HBV	117				
	HCV	10				
	Alcohol	13				
	Unknown	13	0.90 (0.75-1.08)	0.27		
Child-Pugh classification	A	122				
	B	31	1.76 (1.17-2.66)	0.007	1.74 (1.14-2.67)	0.011
AFP (ng/mL)	< 1466	77				
	≥ 1466	73	1.09 (0.77-1.55)	0.64		
PIVKA-II (mAU/mL)	< 1200	52				
	≥ 1200	92	1.53 (1.05-2.24)	0.03	1.45 (0.99-2.12)	0.053
Tumor size	< 10.3	87				
	≥ 10.3	66	1.01 (0.71-1.44)	0.96		
Tumor number	< 4	77				
	≥ 4	76	1.12 (0.79-1.59)	0.51		
TLR	< 3.0	69				
	≥ 3.0	84	1.85 (1.30-2.65)	0.001	1.89 (1.30-2.73)	0.001

HBV = Hepatitis B virus; HCV = Hepatitis C virus

TABLE 3. Univariable and multivariable analysis of prognostic factors for overall survival in extrahepatic BCLC stage C HCC patients (n=138)

Variables		n	Univariate		Multivariate	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Age (y)	< 57	77				
	≥ 57	61	0.75 (0.52-1.08)	0.12		
Gender	Male	117				
	Female	21	1.02 (0.62-1.69)	0.94		
Etiology	HBV	108				
	HCV	10				
	Alcohol	7				
	Unknown	13	0.90 (0.74-1.09)	0.27		
Child-Pugh classification	A	111				
	B	27	1.97 (1.26-3.08)	0.003	1.48 (0.93-2.36)	0.1
AFP (ng/mL)	< 1466	66				
	≥ 1466	72	1.35 (0.95-1.93)	0.1		
PIVKA-II (mAU/mL)	< 1200	57				
	≥ 1200	74	1.30 (0.89-1.89)	0.18		
Tumor size	< 10.3	67				
	≥ 10.3	71	1.71 (1.19-2.45)	0.005	1.46 (0.99-2.14)	0.06
Tumor number	< 4	46				
	≥ 4	92	1.54 (1.04-2.27)	0.03	1.42 (0.94-2.13)	0.09
Portal vein invasion	Absence	55				
	Presence	83	1.59 (1.09-2.31)	0.02	1.18 (0.79-1.77)	0.41
TLR	< 3.2	49				
	≥ 3.2	89	1.78 (1.21-2.61)	0.003	1.69 (1.13-2.51)	0.01

HBV = Hepatitis B virus; HCV = Hepatitis C virus

TABLE 4. The overall survival for BCLC stage C HCC patients according to ^{18}F-FDG uptake

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