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Refining prognosis in patients with hepatocellular carcinoma through incorporation of metabolic imaging biomarkers

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Abstract

Purpose—^{18}F-fluorodeoxyglucose positron emission tomopraphy/computed tomography (FDGPET/CT) has been proven to be useful for imaging many types of cancer; however, its role is not well defined in hepatocellular carcinoma (HCC). We assessed the prognostic value of metabolic imaging biomarkers as established by baseline pretreatment FDG PET/CT in patients with HCC.

Methods—We retrospectively analyzed the records of patients with HCC who underwent FDG PET/CT before initial treatment from May 2013 through May 2014. Four PET/CT parameters were measured: maximum standardized uptake value (SUV_{max}), total lesion glycolysis (TLG), metabolic tumor volume (MTV), and tumor-to-normal-liver SUV ratio (TNR). Optimal cut-off values for the PET/CT parameters to stratify patients in terms of overall survival (OS) were

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Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of our institution and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was approved by the local institutional review board and the requirement for written informed consent was waived. This article does not describe any studies with animals performed by any of the authors.

determined. Multivariate analysis was performed to determine whether the PET/CT parameters could add to the prognostic value of the Cancer of the Liver Italian Program (CLIP) scoring system and the Barcelona-Clinic Liver Cancer (BCLC) staging system.

Results—The analysis included 56 patients. Univariate analysis of the association between OS and continuous variables, including the PET/CT parameters SUV_{max}, TLG, tumor size, total bilirubin level, and alkaline phosphatase level were significant predictors of OS. $SUV_{max} \geq 11.7$, TLG ≥ 1,341, MTV ≥ 230 mL, and TNR ≥ 4.8 were identified as cut-off values. Multivariate analysis revealed that $SUV_{max} \geq 11.7$ and TNR ≥ 4.8 were independent factors predicting a poor prognosis in both the CLIP scoring system and the BCLC staging system, as was TLG in the BCLC staging system.

Conclusion—Pretreatment FDG PET/CT in patients with HCC can add to the prognostic value of standard clinical measures. Incorporation of imaging biomarkers derived from FDG PET/CT into HCC staging systems should be considered.

Keywords

FDG PET/CT; Hepatocellular carcinoma; CLIP scoring system; BCLC staging system

Introduction

Liver cancer is the second leading cause of cancer-related death in the world [1]. The most common form of liver cancer is hepatocellular carcinoma (HCC). The occurrence of liver cancer is closely associated with chronic liver damage, such as that caused by chronic hepatitis due to hepatitis virus infection, liver cirrhosis, or fatty liver disease [2]. Other metabolic diseases (such as obesity and diabetes mellitus) and alcohol intake are also well known risk factors for liver cancer [3, 4].

In patients with cancer, prognostic modeling can facilitate decision making regarding treatment; however, in patients with HCC, evaluating prognosis is difficult and complicated because cirrhosis is often present [5]. Both tumor features and functional hepatic reserve must be taken into account. At present, several different staging systems for HCC are available, and there is no universally accepted staging system [6]. The Cancer of the Liver Italian Program (CLIP) scoring system for HCC takes into account both liver function and tumor characteristics relevant to prognosis [7]. The Barcelona Clinic Liver Cancer (BCLC) staging system was constructed on the basis of the results of several cohort studies and randomized controlled trials conducted by the Barcelona group [8]. Other staging systems are also available for HCC, including the American Joint Committee on Cancer staging system, the Japanese Integrated Staging system, the Okuda staging system, Groupe d'Etude et de Traitement du Carcinoma Hépatocellulaire (GRETCH), and the Chinese University Prognostic Index (CUPI) [5, 9–11]. Some of these staging systems have been shown to be applicable for all stages of HCC and are widely accepted; however, none is predictive in every situation, so there is room for improvement. Although both the CLIP scoring system and the BCLC staging system have been validated in different cohorts of patients, a more reliable prognostic classification for HCC is still needed.

In patients with cancer, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) has been used for surveillance after treatment and for evaluation of response to therapy. During the past decade, combined FDG PET and computed tomography (FDG PET/CT) has also been used for imaging various malignancies [12]. However, the use of FDG PET/CT in HCC is limited because, whereas FDG uptake in cholangiocarcinoma, hepatocholangiocarcinoma, and liver metastases is higher than in normal liver tissue [13–15], FDG uptake in well-differentiated HCC is similar to uptake in normal liver tissue because of a high rate of gluconeogenesis in well-differentiated HCC [16]. In patients with many types of cancer, not only the highest metabolic activity within the tumor (maximum standard uptake value; SUV_{max}) in a two-dimensional region of interest, but also total lesion glycolysis (TLG) and metabolic tumor volume (MTV) in a three-dimensional region of interest are considered to provide valuable prognostic information. However, the prognostic value of findings on baseline pretreatment FDG PET/CT in patients with HCC remains to be elucidated.

The aim of this study was to determine the associations between overall survival (OS) and established prognostic factors and FDG PET/CT parameters and to determine whether baseline pretreatment FDG PET/CT parameters add to the prognostic value of the CLIP score or BCLC staging system in patients with HCC.

Materials and methods

Patients

This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center, which waived the requirement for informed consent, and was performed in compliance with the Health Insurance Portability and Accountability Act. We retrospectively reviewed the database of MD Anderson's Tumor Registry and identified 98 consecutive patients with liver tumors who were referred to our institution for treatment during the period from May 2013 through May 2014. Of these patients, 30 were excluded because they did not undergo FDG PET/CT before initial treatment. An additional 12 patients were excluded because OS data were unavailable (five patients), the patient had another type of liver cancer (cholangiocarcinoma, gallbladder carcinoma, hepatic adenoma, or adenomatosis; four patients), the patient had already had surgery at the time of referral to MD Anderson Cancer Center (two patients), or FDG PET/CT was false-negative for HCC (one patient). The remaining 56 patients were included in the analysis. In all patients, the diagnosis of HCC was confirmed at MD Anderson as part of the institution's standard practice based on pathological or radiological HCC characteristics.

Patient information was obtained by direct chart review. Information extracted from charts included demographics, HCC risk factors, clinical characteristics, Eastern Cooperative Oncology Group (ECOG) performance status, and pathological differentiation. Furthermore, patients' radiological images were reviewed to retrieve different tumor parameters mandatory for stage calculation including number of tumor nodules, tumor size, endovascular invasion, lymph node, and distant metastasis. Accordingly, TNM stage (seventh edition), CLIP score and BCLC staging system were calculated using information in the patients' charts. The CLIP score is calculated by assigning a score (0, 1, or 2) to each

of four clinical factors: (1) Child-Turcotte-Pugh score (CTP), (2) number of tumor nodules and whether the tumor occupies ≤50 % or >50 % of the liver on radiological images obtained on first presentation, (3) alfa-fetoprotein level, and (4) portal vein thrombosis. These scores are summed to calculate the CLIP score that ranges from 0 to 6 [7]. The BCLC staging system classifies disease into four categories based on several independent prognostic factors identified in several studies: (1) early stage, (2) intermediate stage, (3) advanced stage, and (4) end stage. These factors are variables related to tumor stage including number of tumor nodules, tumor size, distant metastasis, lymph node involvement, and vascular invasion. The BCLC staging system also includes parameters to assess underlying liver functional status in terms of CTP score, the patient's ECOG performance status, and cancer-related symptoms [17].

FDG PET/CT imaging

FDG PET/CT scans were performed using a standard clinical protocol. Briefly, patients fasted for 6 h before ^{18}F-FDG administration. All patients were confirmed to have a serum blood glucose level of ≤200 mg/dL before injection of the radiopharmaceutical. ^{18}F-FDG (typically 259 – 444 MBq/7 – 12 mCi) was administered intravenously. Approximately 60 min later, imaging data were acquired using an integrated PET/CT system (Discovery ST, STe, or RX; GE Healthcare). CT was performed concomitantly with each PET acquisition for anatomical localization and attenuation correction with the following parameters: axial slice thickness 3.75 mm, 140 kV, and 120 mA, table speed 13.5 mm. PET was performed in three-dimensional mode at 3 to 5 min per bed position based on body mass index. PET, CT, and fusion images were displayed in slices of 3.75 mm. Datasets with and without attenuation correction were reconstructed. All FDG PET/CT scans were obtained during the 30 days before initiation of treatment.

Image review and tumor analysis

Imaging data were reviewed by experienced nuclear medicine physicians and radiologists at MD Anderson. Four PET/CT parameters, SUV_{max}, TLG, MTV, and tumor-to-normal-liver SUV ratio (TNR), were measured using a MIM workstation (MIM Software, Cleveland, OH). Volumetric parameters were defined using MIM contouring software as described previously [18]. SUV was defined as measured activity concentration (becquerels per gram) multiplied by body weight (grams) divided by injected activity (becquerels). TLG was defined as average metabolic activity within the tumor multiplied by tumor volume. MTV (mL) was defined using an automated contouring program based on the SUV.

Statistical analysis

Statistical analyses were performed with S-Plus software, version 8.2 (TIBCO, Palo Alto, CA), and SAS software, version 9.3 (SAS Institute Inc., Cary, NC). OS was defined as the time from the date of initial treatment to death from any cause or last follow-up. A univariate Cox model was used to determine the association between OS and continuous variables, including PET/CT parameters. The log-rank test was used to compare OS stratified by various potential prognostic factors. Martingale residual plots and recursive partitioning and regression trees analysis were used to determine cut-off values for PET/CT parameters to stratify patients in terms of OS. A Cox proportional hazards regression model was used for

multivariate analysis to evaluate significant PET/CT parameters for both the CLIP score and the BCLC staging system. Fisher's exact test was used to assess the association between variables. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Of the 56 patients, 39 (70 %) had stage III or IV disease. The median time from initial treatment to last follow-up was 5.3 months (range 0.1 – 26.9 months), and 24 patients (43 %) died during follow-up. The estimated median OS was 17.0 months (95 % confidence interval 5.1 months – not assessable). In 26 patients (46 %) the HCC was well or moderately differentiated. Hepatitis B or C virus infection was seen in 27 patients (48 %). Multifocality and capsular nodularity were seen in 29 patients (52 %) and 37 patients (66 %), respectively, and 31 patients (55 %) had a history of alcohol consumption. Moderate or slight ascites was seen in 23 patients (41 %), and portal vein thrombosis was seen in 23 patients (41 %). The median alfafetoprotein value was 60.7 ng/mL (range 1.3 – 76,717.2 ng/mL). The median tumor size was 8.2 cm (range 1.1 – 18.2 cm), and 20 patients (36 %) had a tumor volume more than 50 % of the liver volume.

Associations between OS, established prognostic factors, and FDG PET/CT parameters

The median values of FDG PET/CT parameters for the primary lesion were as follows: SUV_{max} 6.0 (range 2.2 – 20.0), TLG 541.0 (range 4.6 – 5,631.7), MTV 151.9 mL (range 8.3 – 2,003.8), and TNR 2.0 (range 0.8 – 12.9). Table 2 shows the results of the univariate analysis of the associations between OS and continuous variables, including PET/CT parameters. SUV_{max}, TLG, tumor size, total bilirubin level, and alkaline phosphatase level were significant predictors of OS. MTV and TNR were not significant predictors of OS. Table 3 shows the results of the log-rank test to compare OS between patient subgroups. If there are no data for the 2-year OS rate, the patient died or was censored within 1 year so that no follow-up data were available beyond 1 year. ECOG performance status 0 or 1, no endovascular invasion, CTP score A, tumor volume ≤50 % of liver volume, TNM stage I/II, and CLIP score 0 were significant good predictors of OS.

Additional prognostic value of PET/CT parameters

Martingale residual plots and recursive partitioning and regression trees analysis revealed the following optimal cut-off points for PET/CT parameters to stratify patients in terms of OS: SUV_{max} 11.7, TLG 1,341, MTV 230 mL, and TNR 4.8. Figure 1 shows Kaplan-Meier curves for OS in relation to the determined cut-off values of PET/CT parameters. OS was significantly worse in patients with SUV ≥ 11.7 (Fig. 1a), TLG ≥ 1,341 (Fig. 1b), MTV ≥ 230 (Fig. 1c), and TNR ≥ 4.8 (Fig. 1d). The results of the multivariate analysis to determine whether PET/CT parameters provide additional prognostic value beyond that provided by the CLIP score and the BCLC staging system in predicting OS are shown in Tables 4 and 5, respectively. Each table includes four different sets of data. These correspond to four different models, one for each of the PET/CT parameters. For the CLIP scoring system, both SUV_{max} ≥ 11.7 and TNR ≥ 4.8 were independent poor prognostic factors (Table 4). For the

BCLC staging system, both SUV ≥ 11.7 and TNR ≥ 4.8 were independent poor prognostic factors, as was TLG ≥ 1,341 (Table 5).

Discussion

This study confirmed associations between established prognostic factors and OS, and also showed statistically significant associations between OS and metabolic imaging biomarkers. In this study in 56 consecutive patients with HCC who underwent FDG PET/CT before initial treatment, FDG PET/CT-derived parameters were significant predictors of OS, and the optimal cut-off values for these parameters were determined. Patients with values higher than the cut-off values had significantly worse survival. PET/CT parameters, especially SUV_{max} and TNR, added to the prognostic value of the CLIP score and BCLC staging system, and TLG added to the value of BCLC staging system. To our knowledge, this is the first analysis showing that initial pretreatment PET/CT parameters can add to the prognostic value of prognostic scoring systems in patients with untreated HCC.

Previous studies on the role of FDG PET/CT in the evaluation of patients with HCC have indicated that the value of FDG PET/CT may depend on the degree of differentiation or tumor size. In well-differentiated HCC, FDG PET/CT may not be an appropriate modality because a high rate of gluconeogenesis comparable with that in normal liver tissue results in similar uptake of FDG [16]. Trojan et al. found high FDG uptake in patients with moderately or poorly differentiated HCC, with tumors >5 cm, or with elevated alfa-fetoprotein levels [19]. Hayakawa et al. found that less well differentiated HCC express more hexokinase, resulting in higher FDG uptake [20]. In our study, many patients already had large tumors before initiation of treatment (the median tumor size at the time of pretreatment FDG PET/CT was 8.2 cm). Thus, PET/CT can be considered to have been of value in our patient cohort. Information with regard to tumor differentiation was not available in all our patients. Our findings are partly consistent with those of Ahn et al., who found that preoperative FDG PET/CT can predict early recurrence after curative resection of HCC [21]. They found that both TNR ≥2 and SUV_{max} ≥4 were significant predictors in a univariate analysis. However, the factors they examined were not significant independent predictors in a multivariate analysis.

To our knowledge, this is the first report indicating that PET/CT parameters may add to the prognostic value of staging systems. In a multivariate analysis that SUV_{max} and TNR added to the prognostic value of the CLIP score and BCLC staging system, and TLG added to the value of BCLC staging system. Our results suggest that both SUV_{max} and TNR clearly add to the prognostic value of the CLIP score and BCLC staging system, and TLG might also be prognostic; in contrast, TLG was not an independent poor prognostic factor in a multivariate analysis. Tumor volume is not taken into account in the calculation of either SUV_{max} or TNR. These results contrast with previous findings indicating that volume-based PET/CT parameters aid in predicting prognosis in many types of malignancy, including non-small-cell lung cancer, head and neck cancer, ovarian cancer, and soft tissue sarcoma [22–25]. However, which PET/CT parameter is the most reliable predictor of outcome in patients with HCC is still unknown. Further prospective study is necessary to clarify this issue.

Although we focused on FDG PET/CT, tracers other than ^{18}F-FDG might also be promising for predicting prognosis in patients with HCC. PET tracers that visualize lipid metabolism may be superior to ^{18}F-FDG for the detection of HCC. The sensitivity of ^{11}C-acetate has been reported to be better for the detection of well-differentiated HCC [26, 27]. In a prospective study, Talbot et al. found that ^{18}F-fluorocholine PET/CT shows significantly greater sensitivity than FDG PET/CT in the detection of well-differentiated HCC, similar sensitivity in the detection of less differentiated HCC, and lower sensitivity in the detection of poorly differentiated HCC [28]. The prognostic value of ^{11}C-acetate and ^{18}F-fluorocholine PET/CT in patients with HCC has not yet been examined.

Our study had several potential limitations. This was a single-center retrospective study, with a relatively small number of patients. Cut-off values found in the present study should be validated in a larger patient group. Additionally, we were not able to categorize patients according to type of systemic therapy, which could be a factor in patient outcome. For example, the number of patients treated with a multikinase inhibitor such as sorafenib was unknown. It has been suggested that molecularly targeted therapy might prolong survival in patients with advanced HCC [29]. Additionally, information about tumor differentiation was not available in all patients. ^{18} F-FDG uptake varies between well-differentiated and poorly differentiated HCC [26]. Despite these limitations, this study is noteworthy in demonstrating that pretreatment FDG PET/CT not only was important in terms of OS but also added to the prognostic value of the CLIP score and BCLC staging system.

Conclusion

This study demonstrated that metabolic imaging parameters derived from FDG PET/CT are prognostic factors for OS in patients with newly diagnosed untreated HCC. Furthermore, FDG PET/CT imaging parameters add to the prognostic value of and complement the CLIP score and BCLC staging system in patients with untreated HCC. SUV_{max} and TNR seem to be the most prognostically valuable of the FDG PET/CT parameters, but TLG may also be an important prognostic factor. We believe that incorporation of metabolic imaging parameters into HCC staging systems should be considered, with future studies aimed at further defining the use of these biomarkers.

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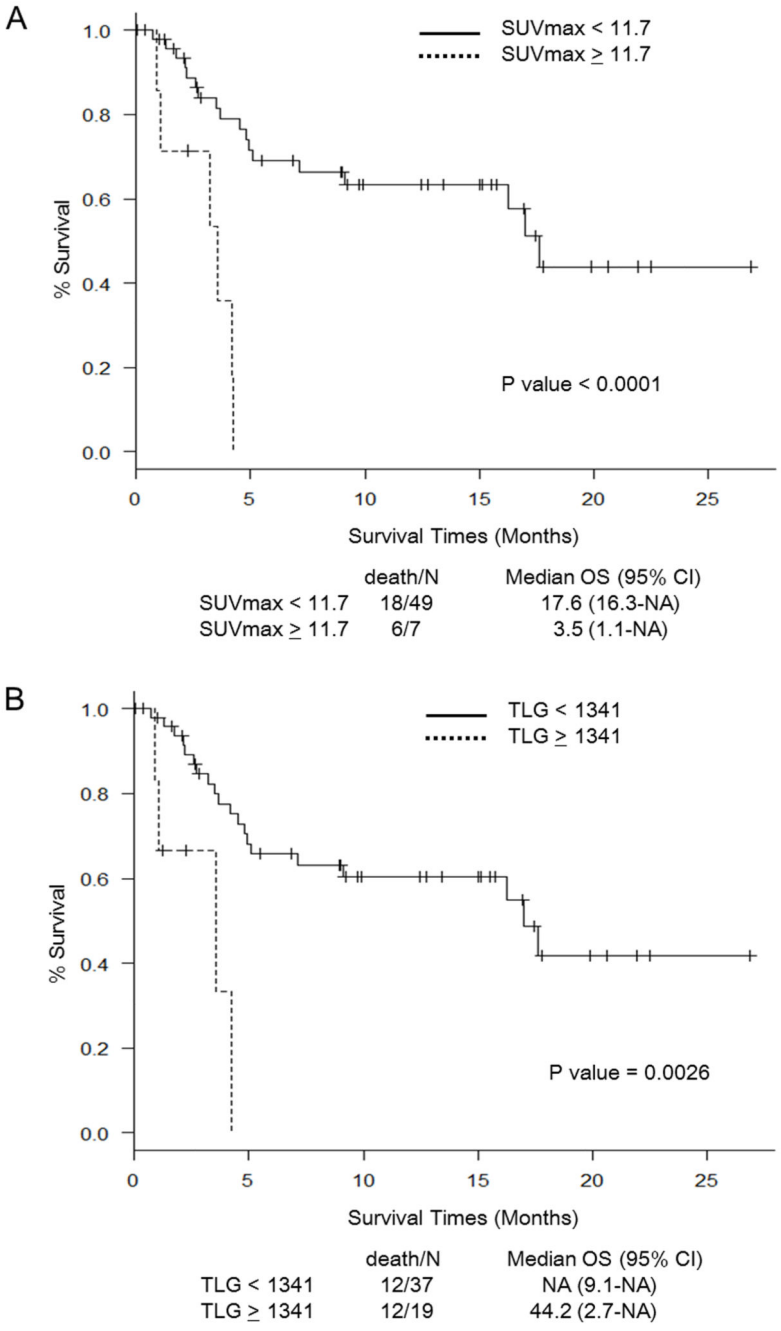

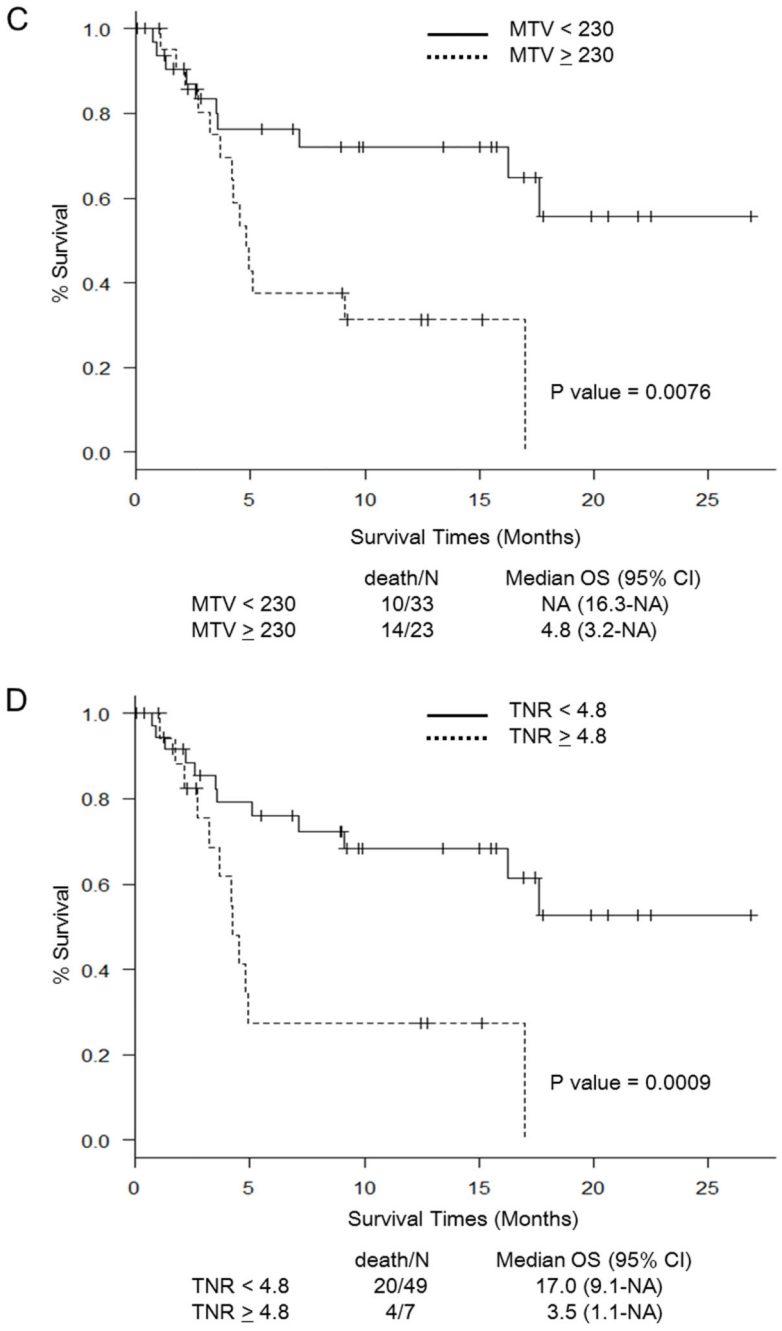

Fig. 1.

Survival curves for patients in relation to cut-off values for PET/CT parameters. **a** Maximum standardized uptake value (SUV_{max}). **b** Total lesion glycolysis (TLG). **c** Metabolic tumor volume (MTV). **d** Tumor-to-normal-liver SUV ratio (TNR). *NA* not assessable, *OS* overall survival, *CI* confidence interval

Table 1

Patient demographics and clinical characteristics

Characteristic	No. of patient (%) (n=56)
Age, median (range)	65 years (21-91 years)
Sex	
Male	49 (88)
Female	7 (12)
Race/ethnicity	
Caucasian	36 (64)
Latino	10 (18)
African American	7 (13)
Asian	3 (5)
ECOG performance status	
0-1	45 (80)
2-3	9 (16)
Unknown	2 (4)
Tumor differentiation	
Well	8 (14)
Moderately	18 (32)
Poorly	6 (11)
Unknown	24 (43)
Hepatitis infection	
HBV	6 (11)
HCV	20 (36)
HBV and HCV	1 (1)
None	29 (52)
Cirrhosis	
Yes	33 (59)
No	23 (41)
Varices	
Yes	15 (27)
No	41 (73)
Endovascular invasion	
Yes	30 (54)
No	26 (46)
Child-Pugh score	
A	37 (66)
B	17 (30)
C	1 (2)
Unknown	1 (2)
TNM stage	

Characteristic	No. of patient (%) (n=56)
I	6 (11)
II	8 (14)
III	18 (32)
IV	24 (43)
CLIP score	
0	8 (14)
1	8 (14)
2	12 (21)
3	14 (25)
4	4 (8)
5	3 (5)
Unknown	7 (13)
BCLC stage	
0	1 (2)
A	4 (7)
B	6 (11)
C	42 (75)
D	3 (5)

BCLC, Barcelona-Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2

Univariate analysis of the association between OS and continuous variables

Variable	HR	95% CI	*P* value
SUV_{max}	1.11	1.0026-1.23	0.045*
TLG	1.00020	1.0000-1.00050	0.024*
MTV	1.00050	0.99-1.0010	0.099
TNR	1.17	0.97-1.42	0.11
Age	1.00030	0.97-1.032	0.98
Creatinine level	1.74	0.74-4.11	0.20
Albumin level	0.72	0.38-1.36	0.31
Tumor size	1.11	1.015-1.21	0.022*
PT	1.084	0.81-1.46	0.59
PT-INR	8.58	0.50-147.25	0.14
Total bilirubin level	1.20	1.011-1.41	0.037*
ALK	1.0033	1.00050-1.0061	0.020*

OS, overall survival; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; MTV, maximum tumor volume; TNR, tumor-to-normal liver ratios of SUV; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; ALK, alkaline phosphatase; HR, hazard ratio; CI, confidence interval.glycolysis; TNR, tumor-to-normal liver ratios of SUV.

*$P < 0.05$

Table 3

Log-rank test to compare OS among patient subgroups

Variable	No. of patients	No. of events	Median OS (95% CI), mo	1-year OS rate (95% CI)	2-year OS rate (95% CI)	*P* value
Age, years						
≤ 60	22	10	4.9 (3.67-NA)	0.40 (0.22-0.73)		0.16
> 60	34	14	17.0 (9.13-NA)	0.64 (0.49-0.84)	0.41 (0.23-0.73)	
Sex						
Female	7	2	NA (7.1-NA)	0.64 (0.34-1.00)		0.66
Male	49	22	16.3 (4.8-NA)	0.55 (0.41-0.72)	0.38 (0.23-0.63)	
Race/ethnicity						
Other	20	8	17.0 (3.7-NA)	0.55 (0.35-0.87)	0.28 (0.060-1.00)	0.87
Caucasian	36	16	16.3(4.9-NA)	0.56 (0.41-0.76)		
ECOG PS						
0-1	45	20	17.0 (5.1-NA)	0.57 (0.43-0.75)	0.4 (0.24-0.66)	0.02*
2-3	9	4	2.9 (1.3-NA)	0.25 (0.05-1.00)		
Hepatitis infection						
HBV/HCV	27	13	4.9 (3.7-NA)	0.49 (0.32-0.76)	0.26 (0.10-0.72)	0.21
None	29	11	17.0 (7.1-NA)	0.61 (0.44-0.84)		
Cirrhosis						
No	23	10	17.0 (5.1-NA)	0.61 (0.43-0.87)	0.38 (0.18-0.81)	0.47
Yes	33	14	17.6 (4.2-NA)	0.51 (0.34-0.75)		
Varices						
No	41	18	17.0 (4.5-NA)	0.53 (0.39-0.72)	0.42 (0.25-0.72)	0.69
Yes	15	6	17.6 (7.1-NA)	0.65 (0.42-1.00)		
Endovascular invasion						
No	26	8	NA (16.3-NA)	0.74 (0.57-0.94)	0.55 (0.33-0.89)	0.0025*
Yes	30	16	4.5 (3.2-NA)	0.37 (0.21-0.63)		
Focality						
Multifocal	29	14	5.1 (3.5-NA)	0.47 (0.30-0.74)		0.058
Unifocal	27	10	NA (9.1-NA)	0.64 (0.47-0.86)	0.56 (0.37-0.83)	
AFP level, ng/mL						
< 400	34	12	NA (9.1-NA)	0.63 (0.47-0.83)	0.55 (0.37-0.81)	0.16
≥ 400	20	10	7.1 (4.2-NA)	0.5 (0.3-0.82)		
Child-Pugh score						
A	37	14	17.6 (7.1-NA)	0.63 (0.48-0.82)	0.47 (0.28-0.77)	0.0016*
B	17	8	5.1 (2.6-NA)	0.47 (0.26-0.84)		
C	1	1	1.3 (NA-NA)			
Tumor volume as a percentage of liver volume						

Variable	No. of patients	No. of events	Median OS (95% CI), mo	1-year OS rate (95% CI)	2-year OS rate (95% CI)	*P* value
≤ 50%	32	10	NA (16.3-NA)	0.71 (0.56-0.91)	0.55 (0.36-0.85)	0.019
> 50%	20	11	4.8 (3.7-NA)	0.38 (0.21-0.72)		
TNM stage						
III/IV	42	22	5.1 (4.2-NA)	0.43 (0.29-0.64)		0.0059
I/II	14	2	NA (NA-NA)	0.92 (0.77-1.00)	0.76 (0.51-1.00)	
Ascites						
Moderate	8	4	2.1 (1.1-NA)	0.34 (0.11-1.00)		0.059
None	33	14	17.6 (7.1-NA)	0.61 (0.46-0.81)	0.43 (0.24-0.77)	
Slight	15	6	16.97 (3.5 , NA)	0.51 (0.28 , 0.94)		
CLIP score						
0	8	1	NA (16.3-NA)	1.00 (1.00-1.00)	0.75 (0.43-1.00)	0.018 *
1	8	4	7.1 (4.9-NA)	0.47 (0.21-1.00)		
2	12	3	17.6 (17.6-NA)	0.82 (0.63-1.00)		
3	14	7	4.8 (3.7-NA)	0.37 (0.17-0.80)		
4	4	2	3.1 (1.7-NA)			
5	3	2	17.0 (2.6-NA)	0.67 (0.30-1.00)		
BCLC stage						
0	1	0	NA (NA-NA)			0.18
A	4	1	17.0 (16.3-NA)	1.00 (1.00-1.00)		
B	6	2	NA (17.6-NA)	0.83 (0.58-1.00)	0.56 (0.23-1.00)	
C	42	20	9.1 (4.5-NA)	0.47 (0.33-0.67)		
D	3	1	1.8 (1.3-NA)			

OS, overall survival; AFP, alfa-fetoprotein; CI, confidence interval; CLIP, Cancer of the Liver Italian Program; BCLC, Barcelona-Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, not available.

* $P < 0.05$

Table 4

Multivariate Cox regression analysis using PET/CT parameters and Cancer of the Liver Italian Program (CLIP) score

Variable	Coefficient	*P* value	HR (95% CI)
CLIP 1 (vs. 0)	1.52	0.181	4.59 (0.49-42.97)
CLIP 2 (vs. 0)	1.16	0.318	3.18 (0.33-30.78)
CLIP 3 (vs. 0)	1.92	0.100	6.82 (0.69-67.01)
CLIP 4 (vs. 0)	3.78	0.004*	43.96 (3.36-574.48)
CLIP 5 (vs. 0)	2.15	0.084	8.60 (0.75-99.12)
SUV_{max} ≥ 11.7 (vs. < 11.7)	2.08	0.004*	8.00 (1.96-32.76)
CLIP 1 (vs. 0)	1.67	0.140	5.31 (0.58-48.84)
CLIP 2 (vs. 0)	1.11	0.340	3.03 (0.31-29.49)
CLIP 3 (vs. 0)	2.25	0.054	9.44 (0.96-93.04)
CLIP 4 (vs. 0)	3.14	0.025*	23.04 (1.50-354.97)
CLIP 5 (vs. 0)	1.88	0.149	6.57 (0.51-84.38)
TLG ≥ 1341 (vs. < 1341)	0.38	0.509	1.46 (0.47-4.55)
CLIP 1 (vs. 0)	1.71	0.129	5.54 (0.61-50.46)
CLIP 2 (vs. 0)	1.12	0.336	3.06 (0.31-29.70)
CLIP 3 (vs. 0)	2.28	0.050*	9.76 (1.00-94.79)
CLIP 4 (vs. 0)	3.22	0.018*	25.13 (1.72-367.09)
CLIP 5 (vs. 0)	1.95	0.128	7.04 (0.57-86.91)
MTV ≥ 230 mL (vs. < 230 mL)	0.33	0.571	1.39 (0.45-4.30)
CLIP 1 (vs. 0)	1.74	0.122	5.69 (0.63-51.72)
CLIP 2 (vs. 0)	1.14	0.327	3.11 (0.32-30.15)
CLIP 3 (vs. 0)	2.09	0.070	8.11 (0.84-78.33)
CLIP 4 (vs. 0)	3.60	0.005*	36.57 (2.91-459.45)
CLIP 5 (vs. 0)	2.13	0.088	8.38 (0.73-95.94)
TNR ≥ 4.8 (vs. < 4.8)	1.58	0.047*	4.85 (1.02-22.92)

CI, confidence interval; HR, hazard ratio; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis; MTV, maximum tumor volume; TNR, tumor-to-normal liver ratios of SUV.

*$P < 0.05$

Table 5

Multivariate Cox regression analysis using PET/CT parameters and Barcelona-Clinic Liver Cancer (BCLC) stage

Variable	Coefficient	*P* value	HR (95% CI)
BCLC B (vs. A/0)	0.20	0.870	1.22 (0.11-13.64)
BCLC C (vs. A/0)	1.07	0.300	2.92 (0.38-22.23)
BCLC D (vs. A/0)	1.63	0.284	5.09 (0.26-100.01)
SUV_{max} ≥ 11.7 (vs. < 11.7)	1.65	0.003*	5.19 (1.73-15.56)
BCLC B (vs. A/0)	0.20	0.869	1.22 (0.11-13.65)
BCLC C (vs. A/0)	0.87	0.411	2.38 (0.30-18.84)
BCLC D (vs. A/0)	2.11	0.160	8.29 (0.44-157.75)
TLG ≥ 1341 (vs. < 1341)	0.97	0.033*	2.64 (1.08-6.45)
BCLC B (vs. A/0)	0.05	0.968	1.05 (0.09-11.80)
BCLC C (vs. A/0)	0.83	0.436	2.29 (0.28-18.41)
BCLC D (vs. A/0)	2.17	0.150	8.73 (0.46-166.13)
MTV ≥ 230 mL (vs. < 230 mL)	0.89	0.053	2.44 (0.99-6.02)
BCLC B (vs. A/0)	0.22	0.861	1.24 (0.11-13.82)
BCLC C (vs. A/0)	1.16	0.260	3.19 (0.42-24.08)
BCLC D (vs. A/0)	1.69	0.273	5.43 (0.26-112.19)
TNR ≥ 4.8 (vs. < 4.8)	1.48	0.021*	4.37 (1.24-15.38)

CI, confidence interval; HR, hazard ratio; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis; MTV, maximum tumor volume; TNR, tumor-to-normal liver ratios of SUV.

*$P < 0.05$