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^{18}F-FDG PET CT as a prognostic factor in hepatocellular carcinoma

LIVER

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Original Article

ABSTRACT

Background/Aims: To elucidate the role of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) imaging as an independent prognostic factor in hepatocellular carcinoma (HCC).

Materials and Methods: A total of 104 patients with newly diagnosed HCC who underwent ^{18}F-FDG-PET/CT imaging from 2009 to 2014 were reviewed retrospectively. The ratio of the maximal tumor standardized uptake value (SUV) to the mean mediastinum SUV (TSUVmax/MSUVmean) was evaluated as the predictive factor.

Results: A high TSUVmax/MSUVmean ratio (≥3.1) was significantly associated with tumor burden indices, including α-fetoprotein (p<0.001), amino transaminase (AST) (p=0.007), tumor size (p=0.043), Tumor, Node, and Metastasis (TNM) stage (p<0.001), and Barcelona Clinic Liver Cancer (BCLC) staging (p<0.001). The mortality rate was higher (48.1% vs. 23.1%, p<0.001) in patients with a high TSUVmax/MSUVmean ratio (≥3.1). Among the 47 patients who underwent transarterial chemoembolization (TACE), patients with a high TSUVmax/MSUVmean ratio (≥3.1) were more likely to have recurrence following TACE (18/19 vs. 18/28, p=0.016).

Conclusion: A high TSUVmax/MSUVmean ratio on 18F-FDG-PET/CT imaging can serve as an independent prognostic factor in HCC and may predict tumor recurrence after TACE.

Keywords: Positron emission tomography, hepatocellular carcinoma, patient outcome assessment, disease-free survival

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common cancer worldwide and the third most common cause of cancer-related death (1). In South Korea, the age-standardized incidence rate of HCC is 46.5 per 100,000 individuals, although the incidence of HCC is increasing progressively with advancing age in all populations (2,3). The prognosis of patients with HCC is generally poor, and life expectancy is difficult to predict because of variable factors such as portal vein thrombosis, tumor stage, alpha-fetoprotein (AFP), Child–Pugh class, and high recurrence of the tumor (4). Therefore, accurate staging of HCC is important. The widely accepted imaging modalities for staging HCC are dynamic computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) (5). However, CT and MRI have a limited ability to identify distant metastases (6). Previous studies have reported the role of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) in detecting distant metastasis in a variety of malignancies (7).

^{18}F-FDG-PET is an imaging modality that can gauge the glucose metabolism of tumors, which has been established as a useful diagnostic tool for evaluating extrahepatic metastasis (8). However, ^{18}F-FDG-PET has limitations in its ability to detect primary HCC because of the variable ^{18}F-FDG uptakes observed in HCC (9). Recently, some studies have reported that ^{18}F-FDG-PET is useful for tumor characterization, prognosis prediction, and assessment of therapeutic response (10,11). However, there are few data regarding the appropriate cutoff value for ^{18}F-FDG uptake, correlation with HCC prognosis, or the variables associated with high ^{18}F-FDG uptake.

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Thus, the purpose of this study was to evaluate the correlation of ^{18}F-FDG uptake with the characteristics of HCC and to determine the prognostic ability of ^{18}F-FDG-PET/CT in the assessment of HCC.

MATERIALS AND METHODS

Subjects

A total of 104 patients with newly diagnosed HCC who underwent ^{18}F-FDG-PET/CT before treatment from January 2009 to March 2014 at the Chonnam National University Hospital, South Korea were selected and analyzed retrospectively. Patients who were diagnosed and received treatments at other centers before referral to our institution were excluded. The patients were followed up until July 2014. Medical records included patient demographics, laboratory results, tumor characteristics and stage, treatment modalities, recurrence, tumor progression-free survival, and overall survival. All data, including the Child–Pugh score, the Tumor, Node, and Metastasis (TNM) stage maintained by the American Joint Committee on Cancer staging system classification (12), and the Barcelona Clinic Liver Cancer (BCLC) staging were determined at the time of HCC diagnosis (13). The study was approved by the Ethics Review Board of our university and was performed in compliance with the Declaration of Helsinki.

Diagnosis and treatment of HCC

The diagnosis of HCC was based on dynamic imaging techniques such as abdominal CT using multi-detector CT scanners (Somatom Definition Flasth, Siemens Medical Systems, Erlangen, Germany; Light-Speen QX/I, GE Medical systems, Milwaukee, WI, USA) and/or liver MRI using a 3.0-T whole-body MR system (Magnetom Tim Trio, Siemens AG, Munich, Germany) showing arterial uptake of the lesion followed by washout of contrast in the venous-delayed phases according to the American Association for the Study of Liver Disease Criteria (14). Treatments were performed based on the Korean Association for the Study of the Liver (15) and the National Cancer center and the BCLC staging system (13). Consent was obtained from all patients.

^{18}F-FDG-PET/CT study and image analysis

PET studies were performed prior to treatment for all patients using a dedicated PET scanner (DST PET/CT; Discovery ST PET-CT, General Electric Medical Systems, Milwaukee, WI, USA). PET scans were checked within 4 weeks (median 11 days) after diagnosis of HCC with abdominal CT/MRI. The patients had fasted for at least 6 h, except for water and medications, and were normoglycemic before the PET studies. Approximately 375 MBq of ^{18}F-FDG was injected intravenously, and PET scans (3 min/bed, 6–8 beds) were checked 60 min after FDG injection. The images were reconstructed by ordered subset expectation maximization (OSEM) after attenuation correction (128×128 matrix, 3.27 mm slice thickness). Two experienced nuclear physicians interpreted the ^{18}F-FDG-PET images in conjunction with CT. To evaluate ^{18}F-FDG uptake, the region of interest (ROI) was drawn around each tumor, the normal liver, and the mediastinum, and standardized uptake value (SUV) in each ROI was measured. Maximal SUV of the tumor (TSUVmax) and mean SUV of the mediastinum (MSUVmean) were obtained.

Statistical analysis

The ratio of the maximal tumor SUV to the mean mediastinum SUV (TSUVmax/MSUVmean) was evaluated as the predictive factor. Continuous variables were compared using the Mann–Whitney U test or the Student's *t*-test and expressed as mean±standard deviation. The Pearson's $\chi 2$-test and Fisher's exact test were used to compare categorical variables. Survival probabilities were estimated using the Kaplan–Meier method. Multivariate logistic regression analysis was used to determine the independent predictors of outcome. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) statistics (version 21.0, IBM Corp., Armonk, NY, USA).

RESULTS

Patient demographics

The patients included 86 men and 18 women. The mean age of the enrolled patients was 60±11.7 years (range, 25–97 years), and the mean duration of follow-up was 8 months (range, 1–59 months). Sixty-two (59.6%) patients had hepatitis B virus (HBV) infection, six (5.8%) patients had hepatitis C (HCV) infection, and 28 (26.9%) patients had alcoholic liver disease. The Child–Pugh classification was A in 71 (68.3%) patients, B in 27 (26.0%) patients, and C in 6 (5.8%) patients. The Eastern Cooperative Oncology Group (ECOG) Performance Status score was 0 in 43 (41.3%) patients, 1 in 31 (29.8%) patients, 2 in 16 (15.4%) patients, 3 in 13 (12.5%) patients, and 4 in 1 (1.0 %) patient. According to the TNM staging system for HCC, 31 (29.8%) patients had stage I disease, 14 (13.5%) had stage II disease, 18 (17.3%) had stage III disease, and 41 (39.4%) had stage IV disease. BCLC stage was also evaluated; 24 (23.1%) patients had stage A disease, 21 (20.2%) had stage B disease, 47 (45.2%) had stage C disease, and 12 (11.5%) had stage D disease. Sixty-eight patients (65.4%) had necrotic tumor masses. Eleven (10.6%) patients underwent surgical resection, five (4.8%) patients underwent radiofrequency ablation (RFA), 47 (45.2%) patients underwent transarterial chemoembolization (TACE), 14 (13.5%) patients received sorafenib, and 27 (26.0%) patients were treated with supportive care only.

Tumor characteristics according to the TSUVmax/MSUVmean ratio

The median value of the TSUVmax/MSUVmean ratio was 3.13, and 3.1 was used as the cutoff level for the prediction of HCC prognosis. The ROC curve analysis revealed an area under the curve (AUC) of 0.744 (p<0.001) for TSUVmax/MSUVmean ratio for mortality. The tumor characteristics in relation to the cutoff value of TSUVmax/MSUVmean ratio are summarized in Table 1. Fifty-two patients had a TSUVmax/MSUVmean ratio <3.1, and the other 52 patients had a TSUVmax/MSUVmean ratio ≥3.1. A high TSUVmax/MSUVmean ratio (≥3.1) was significantly related to high tumor burden indices, including AFP (p<0.001), AST (p=0.007), and tumor size (p=0.043). When correlating the TSUVmax/MSUVmean ratio with the TNM stage, advanced stage disease (IIIB)

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Table 1. Baseline characteristics of patients with hepatocellular carcinoma according to the TSUVmax/MSUVmean ratio

	TSUVmax/MSUVmean < 3.1 (n=52)	TSUVmax/MSUVmean ≥3.1 (n=52)	p value
Age (years)	62.56±10.91	58.94±12.45	0.990
Gender (male), n (%)	44 (84.6%)	42 (80.8%)	0.604
Etiology, n (%)			0.332
HBV	28 (53.8%)	34 (65.4%)	
HCV	3 (5.8%)	3 (5.8%)	
Alcohol	17 (32.7%)	11 (21.2%)	
Others	4 (7.7%)	4 (7.7%)	
Child–Pugh class, n (%)			0.528
A	38 (73.1%)	33 (63.5%)	
B	11 (21.2%)	16 (30.8%)	
C	3 (5.8%)	3 (5.8%)	
MELD score	8.81±2.93	10.08±4.26	0.358
AFP (IU/mL)	2523.90±6626.39	14484.00±20279.54	<0.001
>400 (IU/mL), n (%)	13 (25.0%)	30 (57.7%)	0.001
AST (U/L)	64.10±58.62	109.13±100.31	0.007
ECOG PS score, n (%)			0.210
0	26 (50.0%)	17 (32.7%)	
1	13 (25.0%)	18 (34.6%)	
2	9 (17.3%)	7 (13.5%)	
3	4 (7.7%)	9 (17.3%)	
4	0 (0%)	1 (2.0%)	
TNM stage, n (%)			<0.001
I	22 (42.3%)	9 (17.3%)	
II	11 (21.2%)	3 (5.8%)	
IIIA	8 (15.4%)	5 (9.6%)	
IIIB, IIIC	2 (3.8%)	3 (5.7%)	
IVA, IVB	9 (17.3%)	32 (61.5%)	
BCLC stage, n (%)			<0.001
A	20 (38.5%)	4 (7.7%)	
B	13 (25.0%)	8 (15.4%)	
C	16 (30.8%)	31 (59.6%)	
D	3 (5.8%)	9 (17.3%)	
Tumor size (cm)	6.42±4.41	11.06±5.73	0.043
Tumor number, n (%)			0.430
Single	25 (48.1%)	21 (40.4%)	
Multiple	27 (51.9%)	31 (59.6%)	
Portal vein thrombosis, n (%)	14 (26.9%)	26 (50.0%)	0.016
Vascular invasion, n (%)	5 (9.7%)	5 (9.7%)	1.0
Mean duration of follow-up (months)	9.5±11.1	6.12±7.85	0.076

*TSUVmax: maximal standardized uptake value of the tumor (TSUVmax); MSUVmean: mean standardized uptake value of the mediastinum; HBV: hepatitis B virus; HCV: hepatitis C virus; MELD: Model for End-Stage Liver Disease; AFP: alpha-fetoprotein; AST: aspartate transaminase; ECOG PS score: Eastern Cooperative Oncology Group Performance Status; TNM stage: Tumor, Node, and Metastasis stage; BCLC stage: Barcelona Clinic Liver Cancer stage.

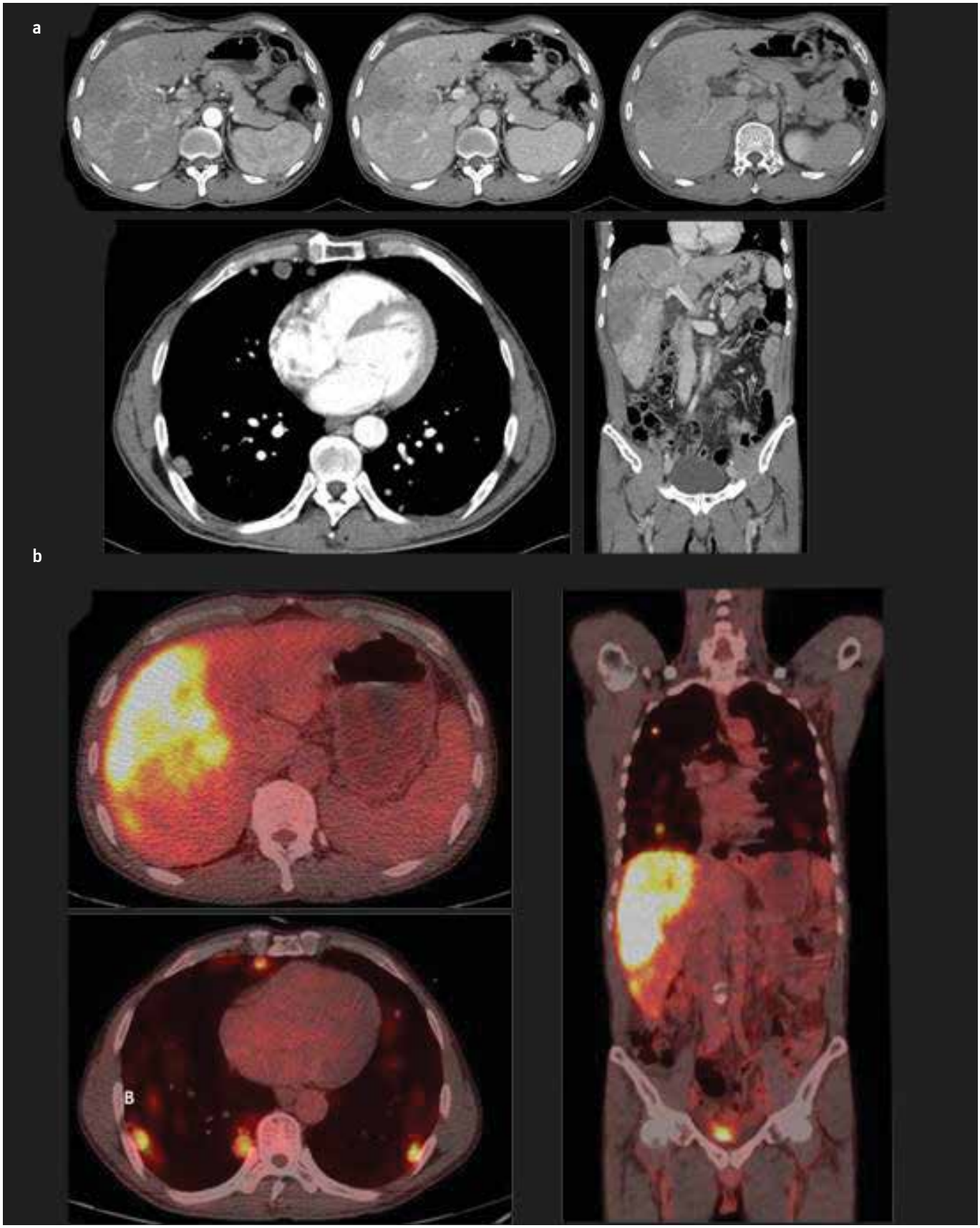

Figure 1. a, b. A case of hepatocellular carcinoma (HCC) with a high TSUVmax/MSUVmean ratio. **(a)** Dynamic computed tomography (CT) of the abdomen and chest showing infiltrative HCC with multiple lung metastases. **(b)** ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) exhibiting high ^{18}F-FDG uptake in the HCC (TSUVmax=10.5, TSUVmax/MSUVmean=7.50). SUV, standardized uptake value (SUV); TSUVmax/MSUVmean, ratio of the maximal tumor SUV to the mean mediastinum SUV.

was more common in the high TSUVmax/MSUVmean group, whereas lower stage disease (<IIIB) was more prevalent in the low TSUVmax/MSUVmean ratio group (p<0.001). A similar pattern was observed in relation to the BCLC stage because stage A and B disease was more common in the low TSUVmax/MSUVmean ratio group than in the high TSUVmax/MSUVmean ratio group, in which prevalent stage C and D disease was more prevalent (p<0.001). Portal vein thrombosis was also more frequent in the high TSUVmax/MSUVmean group (p=0.016). A case of HCC with a high TSUVmax/MSUVmean ratio is shown in Figure 1.

All of the tumors were larger than 1 cm. A larger tumor size was associated with a higher TSUVmax/MSUVmean ratio (Table 2). The mean TSUVmax/MSUVmean ratio was 2.75±1.88 in HCC of less than 5 cm, 4.09±2.61 in tumors between 5 and 10 cm, and 5.45±3.34 in HCC larger than 10 cm. Advanced tumor stage was also related to a higher TSUVmax/MSUVmean ratio (Table 2). According to the TNM stage, stage I–II disease had a TSUVmax/MSUVmean ratio of 3.08±2.63, stage IIIA disease had a ratio of 3.46±2.08, stage IIIB–IIIC disease had a ratio of 5.49±3.44, and stage IV disease had a ratio of 5.51±2.93. In the BCLC staging system, the TSUVmax/MSUVmean ratio was 2.41±1.95 in stage A disease, 3.82±2.98 in stage B disease, and 5.06±2.94 in stage C or D disease.

Overall survival according to TSUVmax/MSUVmean ratio

Thirty-nine patients (37.5%) died during the follow-up period. The median survival time in expired patients was 4 months. The mortality rate during the follow-up period in patients with a high TSUVmax/MSUVmean ratio (≥3.1) was 48.1%, whereas the mortality rate was 23.1% (p=0.021) in patients with a low TSUVmax/MSUVmean ratio (<3.1). In the univariate analysis, patients with a low SUV ratio had a significantly longer survival period than those with a high SUV ratio (Figure 2). Univariate analysis also found that AFP (p<0.001), TNM stage (p<0.001), BCLC stage (p<0.001), tumor number (p=0.003), vascular invasion (p=0.004), and portal vein thrombosis (p=0.005) were also significantly associated with mortality (Table 3). However, in the multivariate analysis, only TSUVmax/MSUVmean was associated with mortality (p=0.024).

Recurrence after transarterial chemoembolization and TSUVmax/MSUVmean ratio

Among the enrolled patients, 47 (45.2%) subjects underwent TACE. Patients with a higher TSUVmax/MSUVmean ratio were more likely to have recurrence after TACE (18/19, 94.7%) than those with a lower TSUVmax/MSUVmean ratio (18/28, 64.3%, p=0.016). Although tumor progression-free survival after TACE was shorter in the high SUV ratio group, it was not significantly different between the two groups (104 vs. 137 days, p=0.345).

DISCUSSION

^{18}F-FDG-PET has been considered to be a very useful noninvasive tool for diagnosis, tumor staging, and monitoring of treatment responses in various malignancies (16,17). Recent studies have shown that PET/CT is useful in assessing tumor characterization. Low ^{18}F-FDG uptake is seen in well-differentiated HCC, whereas high ^{18}F-FDG uptake is observed in moderately to poorly differentiated HCC (18,19). After the uptake

Table 2. TSUVmax/MSUVmean ratio according to tumor size and stage

	TSUVmax/MSUVmean (mean±SD)	p value
Tumor size		<0.001
<5 cm	2.75±1.88	
≥5 cm, <10 cm	4.09±2.61	
≥10 cm	5.45±3.34	
TNM stage		0.001
I, II	3.08±2.63	
IIIA	3.46±2.08	
IIIB, IIIC	5.49±3.44	
IVA, IVB	5.51±2.93	
BCLC stage		0.001
A	2.41±1.95	
B	3.82±2.98	
C, D	5.06±2.94	

*TSUVmax: maximal standardized uptake value of the tumor (TSUVmax); MSUVmean: mean standardized uptake value of the mediastinum; TNM stage: Tumor, Node, and Metastasis stage; BCLC stage: Barcelona Clinic Liver Cancer stage.

Table 3. Univariate and multivariate analysis for factors that influence mortality

		Univariate			Multivariate		
Factors	**Unfavorable status**	**Hazard ratio**	**95% CI**	**p value**	**Hazard ratio**	**95% CI**	**p value**
TSUVmax/MSUVmean ratio ≥ 3.1	≥3.1	3.24	1.64–6.43	0.001	2.44	1.13–5.27	0.024
AFP (IU/mL)	>400	4.66	2.31–9.39	<0.001	1.98	0.88–4.44	0.100
TNM stage	III/IV	7.70	3.19–18.57	<0.001	2.72	0.72–10.28	0.141
BCLC stage	C/D	5.06	2.30–11.12	<0.001	1.06	0.35–3.19	0.916
Tumor Number	Multiple	2.98	1.45–6.12	0.003	1.82	0.83–3.96	0.134
Vascular invasion	Present	3.19	1.44–7.04	0.004	1.94	0.79–4.80	0.151
Portal vein thrombosis	Present	2.55	1.33–4.88	0.005	1.05	0.52–2.12	0.885

*CI: confidence interval; TSUVmax: maximal standardized uptake value of the tumor (TSUVmax); MSUVmean: mean standardized uptake value of the mediastinum; AFP: alpha-fetoprotein; TNM stage: Tumor, Node, and Metastasis stage; BCLC stage: Barcelona Clinic Liver Cancer stage.

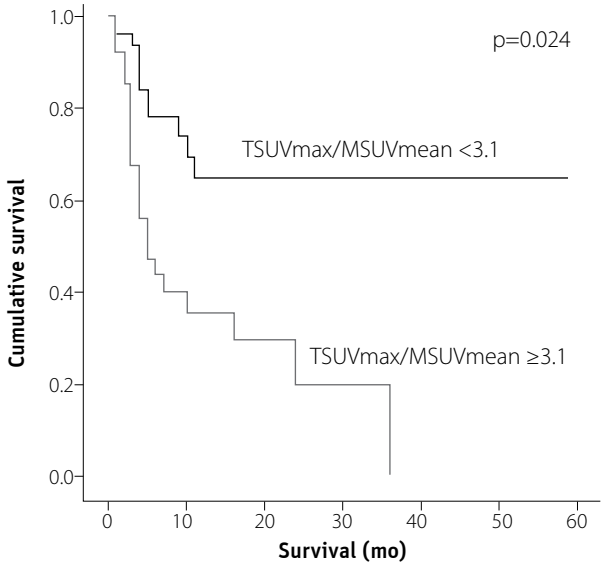

Figure 2. Overall survival rates in low and high TSUVmax/MSUVmean level groups. Cumulative survival rate was higher in the low TSUVmax/MSUVmean group (<3.1) than that in the high TSUVmax/MSUVmean group (≥3.1) (p=0.024). SUV, standardized uptake value (SUV); TSUVmax/MSUVmean, ratio of the maximal tumor SUV to the mean mediastinum SUV.

of ^{18}F-FDG by the cancer cells via facilitative glucose transporters, particularly type 1 (Glut 1), it is phosphorylated by hexokinase to FDG-6-phosphate. FDG-6-phosphate cannot proceed down the glycolytic or oxidative pathways to be metabolized. While FDG-6-phosphate can be dephosphorylated by glucose-6-phoshatase (G6Pase) and transported out from normal cells, G6Pase expression is significantly decreased in cancer cells and FDG-6-phosphate is trapped in the cell, resulting in accumulation and related higher SUV measurements. This difference in the activity of glucose-6-phosphatase (G6Pase) explains the divergence in the ^{18}F-FDG uptake rates in relation to the degree of differentiation of the HCC. Well-differentiated HCC has a higher G6Pase activity than moderately to poorly differentiated HCC, resulting in low ^{18}F-FDG uptake (20,21).

This study examined the value of ^{18}F-FDG-PET/CT in predicting the prognosis of HCC. Our study is a comprehensive study that assessed the association of all known prognostic factors of HCC with ^{18}F-FDG uptake of the tumor. High ^{18}F-FDG tumor uptake significantly correlated with tumor burden such as the biomarkers AFP, AST, and tumor characteristics such as tumor size and portal vein thrombosis, which are considered predictive factors of the aggressiveness of HCC (22). ^{18}F-FDG uptake was also associated with advanced stages in both TNM and BCLC staging systems, which are established prognostic factors. ^{18}F-FDG uptake had a significant correlation with overall survival. In addition, the increase in ^{18}F-FDG uptake in HCC was associated with recurrence after TACE.

In this study, the TSUVmax/MSUVmean ratio was evaluated as a prognostic factor in HCC. Previous studies have reported tumor to non-tumor (background liver) SUV ratio as a more useful parameter than the SUV of tumors in predicting the prognosis of HCC (23,24). However, most patients with HCC have underlying liver cirrhosis or chronic hepatitis and ~20%–56% of patients even have previously undiagnosed liver cirrhosis (25,26). Because ^{18}F-FDG uptake is altered by underlying liver cirrhosis or chronic liver disease, background liver SUV can also be affected, and sometimes increased uptake of the liver tumor may even be concealed by background liver cirrhosis (27,28). In addition, many patients have diffuse, multinodular, or massive HCCs (29), making it difficult to obtain background liver SUV because of the small remnant non-tumor liver volume available. Alternatively, the SUV of the mediastinum, which is often used as another background parameter in various malignancies (30-32), can be used in the presence of liver cirrhosis or HCC. Furthermore, mediastinum SUV is not affected by body weight or scan time, which affects liver SUV values (33). These findings suggest the preference of background mediastinum SUV values over liver SUV values in HCC patients.

Our principal finding is that an increased TSUVmax/MSUVmean ratio, with a cutoff value of 3.1, was significantly related to more aggressive tumor burden characterized by higher AFP, AST, tumor size, and portal vein thrombosis. Increased TSUVmax/MSUVmean ratio also correlated well with higher stages of disease in both the TNM and BCLC staging systems. These findings are compatible with other studies using tumor SUV or the tumor to non-tumor SUV ratio as parameters to predict the tumor characteristics (24,34,35).

Furthermore, our results demonstrate that an increased TSUVmax/MSUVmean ratio before treatment is an independent predictor of survival in HCC. In the univariate analysis, increased TSUVmax/MSUVmean ratio, increased AFP level, TNM and BLCL stages, tumor number, vascular invasion, and portal vein thrombosis were all significant factors that influenced survival rates. However, in the multivariate analysis, only an increased TSUVmax/MSUVmean ratio was determined as an independent prognostic factor. Thus, the TSUVmax/MSUVmean ratio of ^{18}F-FDG-PET/CT may provide additional information in predicting the prognosis of patients with HCC. Contrary to other studies, TNM and BCLC stages were not independent factors for survival in our study. This may be explained by the fact that our study had a relatively short follow-up period.

Previous studies have pointed out the predictive value of ^{18}F-FDG uptake for evaluating the response after treatment in HCC patients (23,24). We found that the TSUVmax/MSUVmean ratio correlated with recurrence rates after TACE. Although either the BCLC staging system or the Advanced Liver Cancer Prognostic System (ALCPS) has been used to aid in the selection of treatment modalities or prediction of prognosis in HCC, none of these systems are perfect in assessing the biological activity of HCC. Because ^{18}F-FDG uptake reflects the metabolic activity of the tumor, which is a mark of histological differentiation (34), ^{18}F-FDG-PET/CT may compensate the drawback of these systems.

The present study has some limitations inherent to a retrospective study. First, the number of HCC cases for each treatment modality was relatively small. The recurrence rate after therapies other than TACE could not be analyzed because of the small sample size, although the recurrence rate after TACE increased significantly in the high ^{18}F-FDG uptake group. Second, our study had a relatively short follow-up period. However, a significant dif-

ference in cumulative survival was observed before the mean follow-up duration of 8 months. A large-scale, prospective study is required to confirm our results in the future.

In conclusion, the present study shows that the TSUVmax/MSUVmean ratio correlates well with factors in association with the biological behavior of HCC and can serve as a predictive factor for overall survival. Thus, ^{18}F-FDG-PET/CT could be a useful modality in providing prognostic information for HCC.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of our university and was performed in compliance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - E.C.; Design - C.H.J.; Supervision - S.K.C.; Resource - E.C.; Materials - C.H.J.; Data Collection &/or Processing - S.K., D.J.S., W.S.C.; Analysis &/or Interpretation - E.C., C.H.J.; Literature Search - E.C., C.H.J.; Writing - E.C., C.H.J.; Critical Reviews - S.K.C.

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