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ORIGINAL ARTICLE

Prognostic implication of ^{18}F FDG-PET in patients with extrahepatic metastatic hepatocellular carcinoma undergoing systemic treatment, a retrospective cohort study

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Abstract
Purpose The role of ^{18}F FDG-PET in hepatocellular carcinoma (HCC) has not been firmly established. We conducted this study to investigate the clinical implication of SUVmax on ^{18}F FDG-PET as a prognostic factor in patients with HCC, especially in the metastatic setting.
Methods HCC patients with extrahepatic metastatic lesions were enrolled that were evaluated by ^{18}F FDG-PET before palliative systemic therapy, between January 2002 and December 2009 at the Seoul National University Hospital. We retrospectively analyzed the clinical outcome and the value of the SUVmax.
Results A total of 25 patients (men, 88.0%) were enrolled. The response rate and disease control rate was 18.2% (95% CI: 2.1–34.3) and 32.0% (95% CI: 16.3–56.5), respectively. The progression-free survival (PFS) and overall survival (OS) were 2.3 months (95% CI: 1.1–3.4) and 14.2 months (95% CI: 9.1–19.2), respectively. The univariate analysis of OS showed that SUVmax and alphafetoprotein (AFP) were significant prognostic factors ($P = 0.023$ and $P = 0.006$, respectively). The multivariate analysis of OS showed that SUVmax and AFP were significant prognostic factors ($P = 0.008$ and $P = 0.006$, respectively). SUVmax and AFP were independent prognostic factors for PFS, too ($P = 0.010$ and $P = 0.016$, respectively). When the patients were divided according to the SUVmax and AFP, the patients with an SUVmax < 4.9 and an AFP ≤ 400 ng/ml showed longer OS and PFS than the patients with SUVmax ≥ 4.9 or AFP > 400 ng/ml (26.7 months vs. 9.3 months, $P < 0.001$ and 5.6 months vs. 1.7 months, $P = 0.012$, respectively).
Conclusions The SUVmax of the ^{18}F FDG-PET has a prognostic value for OS and PFS in patients with metastatic HCC undergoing systemic therapy. The combined analysis of the SUVmax with AFP might provide more detailed prognostic information.

Keywords Positron emission tomography · Standardized uptake value · Hepatocellular carcinoma · Systemic therapy · Prognostic factor

Introduction

^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F FDG-PET) has been widely used in patients with a variety of cancers. The clinical usefulness of the FDG-PET has been documented for various malignancies such as lung cancer, breast cancer, lymphoma, head and neck cancer, and colorectal cancer. During the early development of PET imaging, the ^{18}F FDG-PET was mainly used for diagnostic purposes. It has played an important role in the detection of recurrence or distant metastasis and the staging workup of malignancies such as lung cancer, breast cancer, and lymphomas [1–4]. The emerging data have shown that PET imaging may be useful for the prediction of the treatment response and/or clinical outcomes

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associated with chemotherapy as well as other treatment modalities [5, 6]. Its prognostic efficacy has been studied in many different tumors including esophageal cancer, breast cancer, head and neck cancer, and pancreatic cancer [7–11].

However, the role of ^{18}F FDG-PET in hepatocellular carcinoma (HCC) has not been firmly established. The irregular activity of glucose-6-phosphatase in the hepatocytes of patients with HCC has been associated with variability of FDG uptake in HCC. The sensitivity of ^{18}F FDG-PET in patients with HCC has been reported to be 55–61% [12, 13]. Since this limitation of ^{18}F FDG-PET, other molecules such as ^{11}C-acetate, ^{11}C-choline, and 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) have been tried to detect HCC more sensitively and accurately [14–16].

However, one report showed that the diagnostic sensitivity of PET for extrahepatic metastatic lesions in metastatic HCC was extremely high (100%) [17]. In addition, another report showed that the fusion PET/CT was superior to conventional computed tomography as a diagnostic tool for the HCC with extrahepatic metastases [18]. Some researchers demonstrated that the dual tracer PET using ^{18}F-FDG and ^{11}C-acetate also showed a more accurate diagnostic efficacy in metastatic HCC [19]. These reports might reflect the fact that the pathology of extrahepatic HCC metastases usually shows poor differentiation [20].

Although there is no confirmed report that ^{18}F FDG-PET is useful for the initial diagnosis and staging workup of HCC, there are some data on the correlation between the prognosis and PET findings in patients with HCC. Previous studies have reported on the role of ^{18}F FDG-PET imaging for the prognosis of clinical outcomes in patients with HCC receiving surgery with curative intent [21, 22]. However, few studies have evaluated whether the PET was useful for the prognosis of patients with HCC in the unresectable metastatic setting. A few studies have also demonstrated a correlation between the maximum standardized uptake value (SUVmax) of ^{18}F FDG-PET and overall survival in patients with HCC [13, 23]. The clinical implication of ^{18}F FDG-PET imaging for response to chemotherapy in metastatic HCC has not yet been explored.

Several prognostic factors have been identified in patients with HCC. According to previous reports, the most important prognostic factor in HCC is the alphafetoprotein (AFP) level. In addition, the presence of extrahepatic metastasis, macroscopic vascular invasion and the Child-Pugh score are prognostic factors in patients with HCC. The goal of this study was to examine the prognostic implications of PET and determine its predictive role with regard to response to systemic treatment in patients with measurable extrahepatic metastatic HCC lesions.

Materials and methods

Patients

Twenty-five patients with HCC and extrahepatic metastatic lesions were consecutively enrolled that were evaluated by ^{18}F FDG-PET before palliative systemic therapy was started, between January 2002 and December 2009 at the Seoul National University Hospital. All 25 patients were diagnosed with HCC by (a) a pathologically defined or >2-cm mass in a cirrhotic liver and typical features of HCC on one dynamic imaging study or AFP level > 200 ng/ml, (b) a 1- to 2-cm mass in a cirrhotic liver and typical features of HCC on two dynamic imaging studies [computed tomography (CT) scan and magnetic resonance imaging with contrast], according to the American Association for the Study of Liver Disease guidelines [24]. Data were collected including age, gender, etiology, Child-Pugh classification, PET image findings, AFP levels, treatment modalities other than systemic treatment, regimen of systemic treatment, response rate, overall survival, and progression-free survival (PFS). Among these factors, the data on the Child-Pugh classification and AFP levels were collected within 2 weeks of the PET study. The response to treatment was evaluated every two cycles with a CT scan or earlier if there were clinical signs of progression. The RECIST (response evaluation criteria in solid tumors) criteria were used to estimate the antitumor response. Toxic effects were evaluated according to the National Cancer Institute-Common Toxicity Criteria version 3.0. The study population was divided into two groups by the SUVmax in order to explore the clinical associations of the ^{18}F FDG-PET findings. The study population was divided at the median value of SUVmax and compared.

^{18}F FDG-PET

After 8 h of fasting, 5.18 MBq/kg (0.14 mCi/kg) of FDG was injected. Then, all patients rested for 1 h. A whole-body ^{18}F FDG-PET scan was taken from the skull base to the proximal thigh. For the whole-body emission scan, 9-bed positions were examined at 3 min per each step. The obtained images were reconstructed onto a square matrix, corrected for attenuation, and integrated. SUV was calculated as follows: SUV = (radioactivity per unit volume)/(injected dose per body weight). The circular region of interest (ROI) was drawn around the metastatic lesion; SUVmax was defined as the peak SUV value on the pixel within the ROI, and SUVmean was measured as the average SUV value estimated based on a 25% isocontour within ROI, respectively. We measured and analyzed the SUVmax and SUVmean of all hottest lesions. To reflect the tumor burden, we also calculated the mean value of SUVmax (mean SUVmax) and the sum of SUVmax of all hot lesions.

Statistics

Statistical analysis of the data was performed using SPSS version 17.0 for Windows (Chicago, IL) and SAS version 9.1 (Cary, NC). The chi square and Fisher's exact test were used to compare the frequencies in the two groups. The PFS was defined as the time interval from the first cycle of chemotherapy to the date that disease progression or any cause of death was first observed. The overall survival (OS) was defined as the time interval between the first cycle of systemic treatment and death due to any cause or the last clinical follow-up. The PFS and OS were assessed by the Kaplan–Meier method, and differences between the curves were analyzed using the log-rank test. To check the assumption of linearity between log (hazard ratio (HR)) and continuous independent variables in Cox regression, fractional polynomial analysis was performed [25]. For survival analysis, variables with a P value < 0.20 in univariate analysis were included in a multivariate analysis, which were further confirmed using the Cox's stepwise proportional hazard model. A two-sided P value of < 0.05 was considered statistically significant. We received consultation from a statistician of the Medical Research Collaborating Center (MRCC) at Seoul National University Hospital.

Ethics

This study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB No: H-0911-021-300). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed.

Results

Patient characteristics

A total of 25 patients (22 men and 3 women) with a median age of 53 years (range, 34–70) were enrolled.

Nineteen patients of 25 patients (76%) were diagnosed as HCC by pathologic findings, and the others (six patients, 24%) were diagnosed by imaging findings and/or serum AFP level. The underlying etiology of HCC was hepatitis B in 22 patients, non-viral hepatitis in two patients, and hepatitis C in 1 patient. A total of 24 patients were Child-Pugh A and one patient was Child-Pugh B. The most commonly involved sites were lungs (60%), lymph nodes, including regional and distant lymph nodes (44%), and bone (20%). The AFP level was elevated in 15 patients and within normal range (< 20 ng/ml) in the other (10) patients despite metastatic disease, and the median AFP level was 75.4 ng/ml (range, 1.6–75400). Intrahepatic HCC viable lesions were present in 14 patients, and macrovascular invasion was present in 4 patients (Table 1). Abnormal FDG uptake was not observed in two patients with lung metastasis but was observed in another 23 patients.

Table 1 Patient characteristics

Age, median (range)	53 (34–70 years)
Gender, *n* (%)	
Male	22 (88)
Female	3 (12)
Etiology	
HBV	22 (88)
HCV	1 (4)
NBNC	2 (8)
Child-Pugh	
A	24 (96)
B	1 (4)
Other treatment after chemotherapy	
TACE	8 (32)
Palliative radiation therapy	2 (8)
Metastasectomy	4 (4)
Macrovascular invasion	4 (16)
Intrahepatic viable HCC lesion	14 (56)
Lung metastasis only	7 (28)
Lesion showing SUVmax	
Liver	6 (24)
Regional lymph node	3 (12)
Distant lymph node	3 (12)
Lung	4 (16)
Bone	3 (12)
Other site	4 (16)
SUVmax, median (range)	4.9 (1.1–17.9)
SUVmean	3.1 (1.0–10.3)
Mean SUVmax	3.8 (0.8–10.7)
Sum of SUVmax	15.0 (1.5–214.6)
AFP level	75.4 (2–75400 ng/ml)

HBV hepatitis B virus, *HCV* hepatitis C virus, *NBNC* non-HBV non-HCV etiology, *SUV* standardized uptake value, *SUVmax* maximum SUV, *mean SUVmax* mean value of SUVmax of all hot lesions, *SUVmean* average SUV inside the region of interest of the hottest lesion, *TACE* transarterial chemoembolization

The two patients without abnormal FDG uptake had multiple lung metastases. One patient had six metastatic lung lesions smaller than 1 cm. The other patient had multiple lesions over 30 sites of small metastatic nodules, of which the sizes of the largest ones were 1.5, 1.1, and 1.0 cm, which showed the significant FDG uptake in uncorrected scan.

The median SUVmax was 4.9 (range, 1.1–17.9), and the site with the highest SUVmax was the liver in six patients, lymph nodes in six patients, lung in four patients, bone in

three patients, adrenal gland in two patients, abdominal wall in one patient, and peritoneum in one patient. Of these 23 lesions showing highest SUVmax, intrahepatic lesions showed higher SUVmax, while metastatic lung lesions had a little lower SUVmax (Table 2). All patients received palliative systemic treatment within 8 weeks (0–8 weeks, median 20 days). After patients progressed with the systemic treatment, two patients received additional palliative radiotherapy, four patients received palliative surgery, and eight patients received transarterial chemoembolization (TACE) after they completed the systemic chemotherapy (Table 1).

Systemic treatment

All patients in this study received palliative systemic treatment. Nineteen patients among the 25 patients were treated with fluoropyrimidine and platinum combination, and the others were treated with targeted agents such as sorafenib (four patients) and sunitinib (two patients). Most (20) patients received chemotherapy as the first-line treatment, and five patients received it as second-line palliative treatment. The best response was a complete remission in one patient, partial response in three patients, stable disease in four patients, and progressive disease in 14 patients. The response rate was 18.2% (95% CI: 2.1–34.3), and the disease control rate was 32.0% (95% CI: 16.3–56.5).

The median follow-up duration from the initiation of palliative chemotherapy was 9.6 months (2.2–35.1 months). The median overall survival and median PFS were 14.2 months (95% CI: 9.1–19.2) and 2.3 months (95% CI: 1.1–3.4), respectively. Sixteen patients were died at the time of the last follow-up (Table 3).

Table 3 Patterns and outcomes of systemic treatment

	No of patients (%)
Type of drug	
Cytotoxic drug	
FP	5 (20)
XP	7 (28)
TS-1/platinum	3 (12)
FOLFOX	2 (8)
Gemox	1 (4)
iFAM	1 (4)
Target drug	
Sorafenib	4 (16)
Sunitinib	2 (8)
Line	
1st line	20 (80)
2nd line	5 (20)
Cycle (range)	2 (1–17)
Best response	
Complete response	1 (4)
Partial response	3 (12)
Stable disease	4 (16)
Progressive disease	14 (56)
Not available	3 (12.0)
Response rate	18.2% (95% CI: 2.1–34.3)
Disease control rate	32.0% (95% CI: 16.3–56.5)
Progression-free survival	2.3 months (95% CI: 1.1–3.4)
Overall survival	14.2 months (95% CI: 9.1–19.2)

FOLFOX 5-fluorouracil/leucovorin/oxaliplatin, *FP* 5-fluorouracil/cisplatin, *Gemox* gemcitabine/oxaliplatin, *iFAM* infusional 5-fluorouracil/adriamycin/mitomycin, *XP* capecitabine/cisplatin

Analysis according to SUVmax

To compare the characteristics descriptively according to the SUVmax, patients were divided by the median value of SUVmax (SUVmax < 4.9 and SUVmax ≥ 4.9). The baseline characteristics, laboratory and PET imaging findings, and treatment profiles did not show statistically significant differences. The overall response rate and disease control rate were 20.0 and 30.8% in group A (SUVmax < 4.9) and 16.7 and 33.3% in group B (SUVmax ≥ 4.9) (Table 4).

Overall survival and PFS analysis

Two patients without ^{18}F FDG hot uptake were not included in the survival analysis because the value of SUV for analysis was unavailable. The fractional polynomial analysis

Table 2 ^{18}F FDG uptake pattern of the HCC lesions showing the highest SUVmax

	Number of pts	SUVmax, mean (range)	SUVmean, mean (range)	SUVmean/SUVmax, mean (range)
Liver	6	8.7 (3.0–17.9)	5.4 (2.4–9.5)	0.65 (0.53–0.79)
Lymph node	6	7.5 (3.3–10.6)	4.4 (2.6–7.1)	0.62 (0.40–0.78)
Lung	4	3.9 (1.1–7.9)	3.1 (1.0–6.2)	0.79 (0.69–0.87)
Bone	3	6.2 (3.1–8.6)	3.8 (2.1–7.0)	0.67 (0.34–0.82)
Adrenal gland	2	7.1 (4.0–10.3)	4.9 (3.1–6.8)	0.72 (0.66–0.77)
Abdominal wall	1	3.9	2.6	0.67
Peritoneum	1	3.1	1.3	0.41

SUVmax maximum SUV, *SUVmean* average SUV by a 25% isocontour in the region of interest

Table 4 Comparison according to SUVmax

	Group A (SUVmax < 4.9)	Group B (SUVmax ≥ 4.9)	*P* value
No. of patients	13	12	
Age, median (range)	53 (37–62 years)	54 (34–70 years)	0.91
Sex, *n* (%)			
Male	10 (76.9%)	12 (100%)	0.22
Female	3 (23.1%)	0	
Etiology			
HBV	11 (91.7%)	9 (81.5%)	0.73
HCV	0	1 (9.1%)	
NBNC	1 (8.3%)	1 (9.1%)	
Child-Pugh			
A	13 (100%)	11 (91.7%)	0.48
B	0	1 (8.3%)	
Macrovascular invasion	2 (15.4%)	2 (16.7%)	0.93
Other treatment after chemotherapy			
TACE	3 (23.1%)	5 (41.7%)	0.21
Radiation therapy	1 (7.7%)	1 (8.3%)	
Debulking surgery	1 (7.7%)	2 (25.0%)	
Lesion showing SUVmax			
Liver	3 (23.1%)	3 (25.0%)	0.43
Regional lymph node	0	3 (25.0%)	
Distant lymph node	1 (7.7%)	2 (16.7%)	
Lung	3 (23.1%)	1 (8.3%)	
Bone	1 (7.7%)	2 (16.7%)	
Lung metastasis only	5 (38.5%)	2 (16.7%)	0.38
Number of extrahepatic metastasis			
<5	8 (61.5%)	4 (33.3%)	
≥5	5 (38.5%)	8 (66.7%)	0.16
Size of largest metastatic lesion			
<2 cm	6 (46.2%)	4 (33.3%)	
≥2 cm	7 (53.8%)	8 (66.7%)	0.51
SUVmax, median (range)	3.3 (1.1–4.6)	9.6 (4.9–17.9)	
SUVmean	2.5 (1.0–3.1)	6.4 (2.3–10.3)	
AFP	43.8 (1.6–20910 ng/ml)	82.8 (3.0–75400 ng/ml)	0.34
Type of systemic treatment agent, n (%)			
Cytotoxic			0.16
FP	0	5 (41.7%)	
XP	6 (46.2%)	1 (8.3%)	
TS-1/platinum	1 (7.7%)	2 (16.7%)	
FOLFOX	1 (7.7%)	1 (8.3%)	
Gemox	0	1 (8.3%)	
iFAM	0	1 (8.3%)	
Targeted			
Sorafenib	3 (23.1%)	1 (8.3%)	
Sunitinib	2 (15.4%)	0	
Line			
1st line	10 (76.9%)	10 (83.3%)	1.0
2nd line	3 (23.1%)	2 (16.7%)	

Table 4 continued

	Group A (SUVmax < 4.9)	Group B (SUVmax ≥ 4.9)	*P* value
Best response			
Complete response	1 (7.7%)	0	0.90
Partial response	1 (7.7%)	2 (16.7%)	
Stable disease	2 (15.4%)	2 (16.7%)	
Progressive disease	6 (46.2%)	8 (66.7%)	
Not available	3 (23.1%)	0	
Overall response rate	20.0%	16.7%	1.0
Disease control rate	30.8%	33.3%	1.0

FOLFOX 5-fluorouracil/leucovorin/oxaliplatin, *FP* 5-fluorouracil/cisplatin, *Gemox* gemcitabine/oxaliplatin, *iFAM* infusional 5-fluorouracil/adriamycin/mitomycin, *XP* capecitabine/cisplatin

which was performed for the analysis of OS showed that the most appropriate pattern of associations between SUVmax as well as an age and log (HR) was a linear association pattern. In the analysis for PFS, the most appropriate association pattern between SUVmax and log (HR) was also a linear association.

The univariate analysis of the OS showed that a higher SUVmax, AFP over 400 ng/ml, and other than lung metastasis only had statistically significant shorter survival ($P = 0.023$, $P = 0.006$, and $P = 0.041$, respectively) (Fig. 1; Table 5). The multivariate analysis of the OS showed that higher SUVmax was a significant poor prognostic factor (relative risk per value of 1.0: 1.26, 95% CI: 1.06–1.48, $P = 0.008$), and an AFP over 400 ng/ml was also significant (relative risk: 5.79, 95% CI: 1.65–20.33, $P = 0.006$). However, the presence of intrahepatic viable HCC lesions did not show statistical power as an independent poor prognostic factor in multivariate analysis ($P = 0.082$) (Table 6). The median OS was 23.0 months (95% CI: 9.4–36.5) in group A (SUVmax < 4.9) and 11.8 months (95% CI: 8.8–14.8) in group B (SUVmax ≥ 4.9), respectively. Combining AFP with the SUVmax showed that patients with an SUVmax < 4.9 and AFP ≤ 400 ng/ml showed longer OS than the other patients (26.7 months vs. 9.3 months, $P < 0.001$) (Fig. 1c). Among the other patients, the patients with an AFP ≤ 400 ng/ml and an SUVmax ≥ 4.9 showed a similar OS compared to the patients with an AFP > 400 ng/ml (11.8 months vs. 9.3 months, $P = 0.55$) (Fig. 1d).

The univariate analysis of the PFS showed that a higher SUVmax was a significant poor prognostic factor for PFS ($P = 0.021$), and an AFP over 400 ng/ml also showed a marginal significance ($P = 0.05$). The multivariate analysis of the PFS showed that a higher SUVmax was an independent poor prognostic factor for PFS (relative risk per value of 1.0: 1.26, 95% CI: 1.06–1.48, $P = 0.008$), and an AFP over 400 ng/ml was also an independent poor prognostic factor (relative risk: 3.91, 95% CI: 1.29–11.87, $P = 0.016$).

When the patients were divided according to the SUVmax and AFP, the patient group with an SUVmax < 4.9 and an AFP ≤ 400 ng/ml showed a longer PFS than the patient group with an SUVmax > 4.9 or an AFP > 400 ng/ml (5.6 months vs. 1.7 months, $P = 0.012$) (Table 7). The patients with AFP ≤ 400 ng/ml and SUVmax > 4.9 did not show the significant difference in PFS compared to the patients with AFP > 400 ng/ml and/or SUVmax > 4.9 (2.6 months vs. 1.7 months, $P = 0.64$) (Table 7).

Predictive role of PET

The response to chemotherapy could be evaluated in 22 patients, and the data on the response to chemotherapy in three patients were not available due to loss to follow up. In group A, the response to chemotherapy was evaluated in ten patients, and the response rate was 20.0% (95% CI: −4.8–44.8), and the disease control rate was 30.8% (95% CI: 9.6–70.4). In group B, the response could be evaluated in all patients, and the response rate was 16.7% (95% CI: −4.4–37.8), and the disease control rate was 33.3% (95% CI: 6.7–60.0). In the analysis of the response rate (RR) and disease control rate (DCR), there were no significant predictive factors identified (data not shown).

The analysis of the response to cytotoxic chemotherapy showed a response rate of 12.5 and 9.1% in group A and group B, respectively. Among the six patients that received targeted agents, data on response were available in five patients. One patient with an SUVmax of 10.0 showed a partial response, another patient with an SUVmax of 3.0 showed partial response, and three patients with an SUVmax less than 4.9 showed no response. In our cohort, only four patients showed response to systemic chemotherapy. Two patients with an SUVmax less than 4.9 showed no progression until 25.2 and 22.9 months. One of these two patients showed a complete clinical remission. Furthermore, these two patients showed a longer response duration

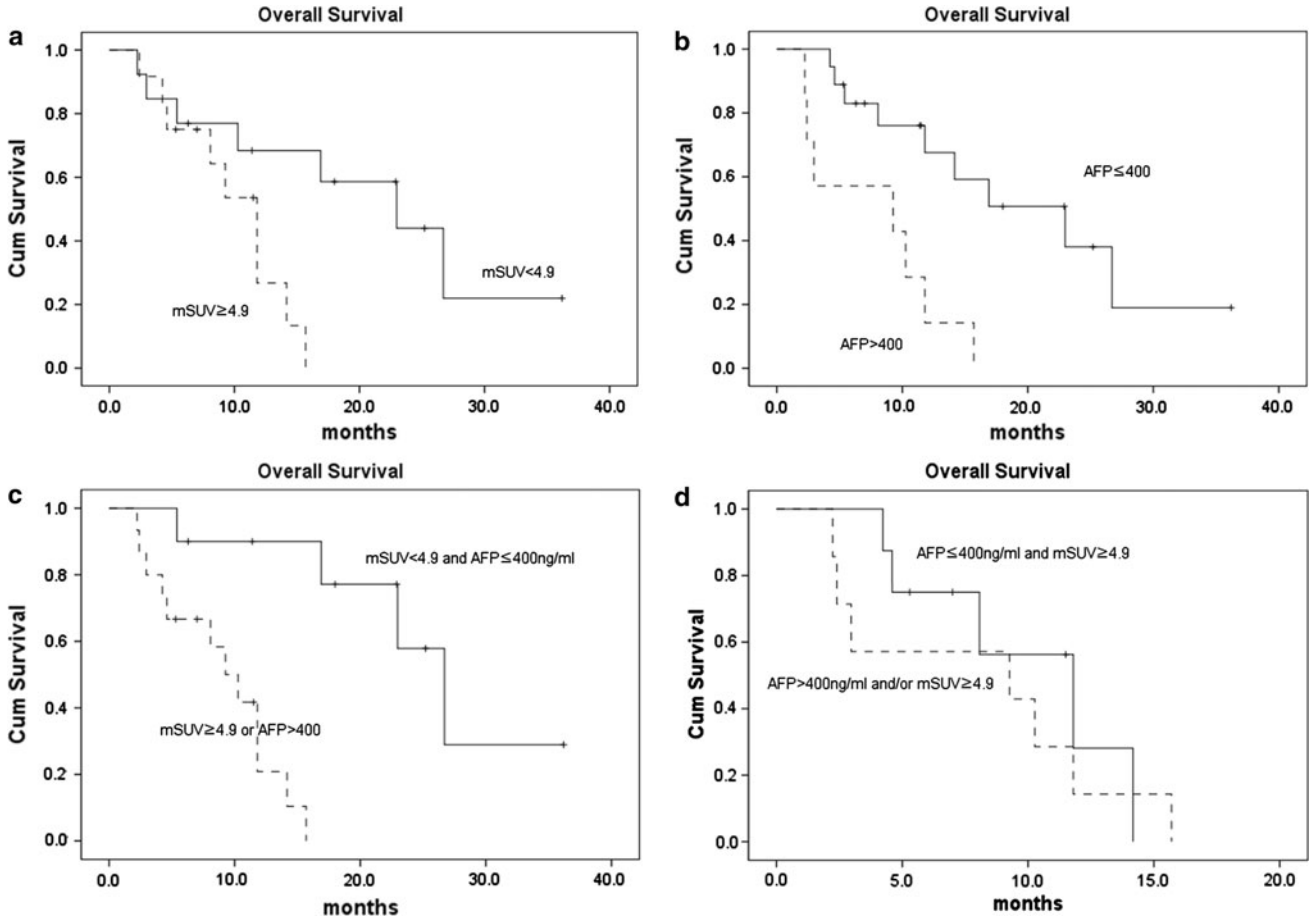

Fig. 1 **a** Overall survival of the 25 patients according to the standardized uptake value ($P = 0.023$). **b** Overall survival according to the AFP levels ($P = 0.002$). **c** Overall survival between both lower groups (SUVmax < 4.9 and AFP ≤ 400) and the other groups (SUVmax ≥ 4.9 or AFP > 400) ($P < 0.001$). **d** Overall survival between the subgroup with AFP ≤ 400 ng/ml and SUVmax ≥ 4.9 and the subgroup with an AFP > 400 ng/ml and/or SUVmax ≥ 4.9 ($P = 0.55$)

compared to the two patients with an SUVmax higher than 4.9. (25.2 and 22.9 months vs. 9.3 and 7.0 months).

Discussion

The results of this study showed that the SUVmax was an independent prognostic factor for the OS and PFS in patients with metastatic HCC. The serum AFP level, known to be a strong prognostic factor in patients with HCC [26], was also significant on the multivariate analysis. The combination of the AFP and SUVmax might provide more accurate prognostic information with the FDG-PET imaging findings added to the serum tumor marker levels. The patients with a lower value of both SUVmax and AFP showed the best prognosis when compared to the patients with higher SUVmax or AFP values. Furthermore, the patients with a higher SUVmax, although with a lower AFP level, had a similar prognosis compared to the patients with a high AFP level. This data suggests that the serum AFP level, which has been a traditional prognostic marker, is still meaningful and that the SUVmax also has powerful prognostic implications, especially when combined with the AFP in the patients with metastatic HCC.

According to one report [27], about 22% of HCC patients with extrahepatic metastasis showed normal range of serum AFP level; PET finding might be helpful to predict the prognosis in these patients.

The findings of our study are consistent with a few prior reports suggesting that the SUVmax is a prognostic factor in patients with HCC. One report showed that the ^{18}F FDG-PET played a prognostic role in tumor recurrence after liver transplantation in patients with hepatocellular carcinoma [22].

To date, there have been fewer than five studies have reported an association between the SUVmax on the ^{18}F FDG-PET and prognosis in patients with HCC with regard to OS and tumor recurrence before surgery including curative resection and liver transplantation [12, 21, 28]. Several studies have reported that the SUV was a prognostic factor

Table 5 Univariate analysis of OS and PFS

Variables	Overall survival			Progression-free survival		
	RR	95% CI	*P* value	RR	95% CI	*P* value
Age	1.048	0.98–1.12	0.17	0.97	0.91–1.03	0.26
Sex (male)	3.24	0.42–24.77	0.26	1.22	0.28–5.36	0.80
Etiology (non-viral)	0.35	0.044–2.77	0.32	1.14	0.69–1.89	0.62
Child ≥ B	1.34	0.17–10.49	0.78	0.75	0.098–5.78	0.79
Macrovascular invasion	0.99	0.27–3.55	0.98	1.00	0.29–3.52	1.00
TACE	0.84	0.29–2.44	0.75	0.45	0.10–1.97	0.29
Radiation therapy	0.91	0.20–4.09	0.90	1.39	0.31–6.25	0.67
Debulking surgery	0.77	0.22–2.77	0.69	1.09	0.30–4.00	0.90
Type of chemotherapy (targeted therapy)	0.46	0.10–2.08	0.31	0.77	0.25–2.39	0.66
AFP > 400	4.68	1.55–14.13	0.006	2.72	1.00–7.39	0.05
SUVmax	1.17	1.02–1.34	0.023	1.19	1.03–1.37	0.021
SUVmean	1.18	0.97–1.42	0.099	1.23	1.01–1.50	0.038
Intrahepatic viable HCC	2.65	0.84–8.40	0.098	1.37	0.52–3.59	0.52
Lung metastasis only	0.21	0.047–0.94	0.041	1.16	0.38–3.55	0.80
Size of largest extrahepatic metastasis (>2 cm)	1.50	0.52–4.35	0.46	0.85	0.33–2.19	0.73
Number of extrahepatic metastasis (≥5)	0.91	0.34–2.48	0.86	1.34	0.50–3.60	0.56

Table 6 Multivariate analysis of OS and PFS

Variables	Overall survival			Progression-free survival		
	RR	95% CI	*P* value	RR	95% CI	*P* value
AFP > 400	5.79	1.65–20.33	0.006	3.91	1.29–11.87	0.016
SUVmax	1.26	1.06–1.48	0.008	1.25	1.05–1.48	0.010

Table 7 Combined analysis of OS and PFS according to the SUVmax and AFP

	Overall survival			Progression-free survival		
	Median (months)	95% CI	*P* value	Median (months)	95% CI	*P* value
SUVmax < 4.9 and AFP ≤ 400	26.7	20.9–32.5	<0.001	5.6	0.0–12.3	0.012
SUVmax ≥ 4.9 or AFP > 400	9.3	5.7–12.8		1.7	0.7–2.7	
AFP ≤ 400 and SUVmax ≥ 4.9	11.8	6.0–17.6	0.55	2.6	0.6–4.7	0.64
AFP > 400	9.3	0.0–25.4		1.7	1.1–2.3	

for the OS in patients with HCC including a small subpopulation of patients with extrahepatic metastases [12, 13, 29]. Two studies recently reported that not the SUV but rather the tumor-to-non-tumor ratio (TNR) was a significant prognostic factor for OS in patients with HCC [30, 31]. However, the heterogeneity of the study populations in these investigations makes it difficult to generalize the clinical role of the SUVmax on the ^{18}F FDG-PET among patients with HCC and extrahepatic metastases. One recent study showed a correlation between the SUVmax on the ^{18}F FDG-PET and survival in patients with unresectable hepatocellular carcinoma receiving non-surgical therapy [32]. This study used a dividing point of the SUVmax similar to our criterion (SUV = 5.0), and the results showed only the "post-therapeutic visual PET diagnosis (positive or negative)" as a factor that was statistically significant for the OS. The prognostic significance of the post-therapeutic SUV or AFP levels was negative in this study. In this study, the subgroup that received pre-therapeutic FDG-PET imaging was analyzed. The resulting categories were the high–high, high–low, low–high, and low–low subgroups according to the sequential uptake patterns at the pre-therapeutic and post-therapeutic PET studies. However, unexpectedly, survival was the best for the high–low subgroup,

and the low–low subgroup had the second longest survival. Our retrospective cohort had two patients without FDG hot uptake of the metastatic lesion. There was no statistically significant survival gain in patients without FDG uptake when compared to the patients with FDG uptake of the metastatic lesion. This result might have been due to the small number of patients and the uneventful situation where the two patients did not die during all of our follow-ups.

^{18}F FDG has a different baseline uptake according to different organs, and the tumor-to-normal tissue ratio (TNR) has been a useful measure to differentiate tumors. However, this value is not commonly described in the reading of PET scans and is therefore not very useful as a reference for the clinician. We also found that the mean value as well as the sum of SUVmax of all hot lesions in ^{18}F FDG-PET had significant prognostic efficacy to predict the OS in univariate analysis; furthermore, the sum of SUVmax was also an independent prognostic factor in multivariate analysis. These two values were also independent prognostic factors for PFS, too (data not shown).

The mean value or the sum of SUVmax of all hot lesions might be more appropriate to reflect the metastatic burden. However, we used the simple SUVmax of the hottest single lesion instead of the mean value or the sum of SUVmax of all the hottest lesions, because we thought the simple concept could be applied to the clinic more conveniently.

Although a previous study showed that the assessment of SUVmean might be a little more reproducible than that of SUVmax in malignant tumors [33], SUVmax might be more appropriate to reflect the prognostic nature of malignant tumor considering the tumor heterogeneity and possible errors in the definition of ROI. For example, a SUVmean of lesions with necrotic center and relatively thin rim of viable tumor tissue might be underestimated. In addition, SUVmean might be lower for larger ROI and have larger random errors for smaller ROI [34]. Our result showed that SUVmax rather than SUVmean was more prognostic for OS in the metastatic HCC patients who received palliative systemic treatment.

We used the liver lesions as well as extrahepatic lesions as hottest lesions in the analysis because it is well known that the presence of an intrahepatic viable HCC lesion is a prognostic factor in the patients with metastatic HCC. However, the result that analyzed using only extrahepatic lesions as hottest lesions was also consistent with the result presented in our manuscript (data not shown).

The findings of this study showed that the SUVmax regardless of the metastatic organ was a powerful prognostic factor. These findings have practical implications for ^{18}F FDG-PET scanning in patients with stage IV HCC and extrahepatic metastases. We clinicians might be able to select the modality of palliative treatment such as palliative brain radiation therapy, palliative surgery of bone metastasis, or compression fracture according to the expected lifetime of the patients through the initial ^{18}F FDG-PET finding.

A few recent studies showed that PET using new molecules such as ^{11}C-acetate or ^{18}F-FLT also showed prognostic meaning for survival in the patients with HCC [14, 29]. These studies suggest that there is a probability that further studies might reveal the prognostic meaning of new modalities of molecular imaging for OS in metastatic HCC.

Earlier studies on the ^{18}F FDG-PET focused on its diagnostic and staging efficacy. However, more recently its predictive role during early assessment of the treatment response and the prediction of clinical outcome have become a more common focus of study. The ^{18}F FDG-PET has already been incorporated into the main assessment of the response criteria for patients with lymphoma [35]. In addition, several studies including a small population that received PET imaging showed that it might play a predictive role in patients undergoing systemic chemotherapy with a few cancers [23]. In these reports, the main factor predicting the treatment response was not the pre-chemotherapy ^{18}F FDG-PET findings but the post-chemotherapy ^{18}F FDG-PET findings or the change in the SUV before and after the treatment [36, 37].

The predictive role of PET is not only useful for targeted therapy such as imatinib mesylate for the treatment of gastrointestinal stromal tumors and bevacizumab for colorectal cancer [38, 39], but also in conventional chemotherapy for non-small-cell lung cancer and breast cancer [40, 41]. The predictive role of PET in the response evaluation of the systemic chemotherapy in patients with extrahepatic metastatic HCC has not been previously examined. However, the results of this study on the role of the pretreatment PET study for the evaluation of the treatment response of systemic treatment were not definitive. Our findings did not show a predictive role of PET in the subgroup analysis according to the subtype of chemotherapeutic agents. However, when we analyzed the patients excluding those who received targeted agents to exclude the bias resulting from the type of chemotherapy, an SUVmax was also significant prognostic factor for OS and PFS (data not shown).

This data suggests that the pretreatment ^{18}F FDG-PET study may not predict the response to systemic treatment. Our data showed that the response duration and PFS of the patients with lower SUVmax were longer than those of the patients with a higher SUVmax, which is opposite to the results in patients with non-small-cell lung cancer [42]. Since the benefit of the drug cannot be assessed appropriately through the evaluation of response rate in some cases, the concept of disease control rate is frequently used in the interpretation of the effect of the drug. However, our data showed that the disease control rate as well as response rate was similar in both groups according to SUVmax. So, our

result showing the longer response duration and PFS in the patients with lower SUVmax despite the similar response or disease control rate suggests that SUV reflects the biology of metastatic HCC. That is, the HCC with low SUV could be considered as less aggressive disease, which also showed better survival.

The limitations of this study include the following. The sample size was small, and this likely affected our statistical findings. In addition, the study design was retrospective and therefore included biases that could be reduced with a prospective study. Despite these limitations, our results suggest that the SUVmax is a potent prognostic factor associated with the PFS as well as OS in patients with HCC and extrahepatic metastases. This is the first study to investigate the prognostic value of the SUVmax on ^{18}F FDG-PET in patients with metastatic HCC receiving systemic treatment. Further well-designed large prospective studies are required to further elucidate the clinical importance of the ^{18}F FDG-PET in metastatic hepatocellular carcinoma more clearly.

Conflict of interest None.

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