Potential and Clinical Significance of ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for Evaluating Liver Cancer Response to Lenvatinib Treatment

Daiki Yamashige^{a, b} Yusuke Kawamura^{a, b} Masahiro Kobayashi^{a, b}
Junichi Shindoh^{b, c} Yuta Kobayashi^{b, c} Satoshi Okubo^{b, c} Nozomu Muraishi^{b, c}
Akira Kajiwaru^{a, b} Soichi Iritani^{a, b} Shunichiro Fujiyama^{a, b} Tetsuya Hosaka^{a, b}
Satoshi Saitoh^{a, b} Hitomi Sezaki^{a, b} Norio Akuta^{a, b} Fumitaka Suzuki^{a, b}
Yoshiyuki Suzuki^{a, b} Kenji Ikeda^{a, b} Yasuji Arase^{a, b} Masaji Hashimoto^{b, c}
Hiromitsu Kumada^{a, b}

^aDepartment of Hepatology, Toranomon Hospital, Tokyo, Japan; ^bOkinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan; ^cHepatobiliary-Pancreatic Surgery Division, Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan

Keywords

¹⁸F-fluorodeoxyglucose positron emission tomography/
computed tomography · Hepatocellular carcinoma ·
Lenvatinib · Tyrosine kinase inhibitor

Abstract

Background: The sensitivity of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) in hepatocellular carcinoma (HCC) is low; however, clinical evidence demonstrating its prognostic value in patients with HCC has recently been reported. This study aimed to assess the value of ¹⁸F-FDG-PET/CT as a tool for evaluating the response of HCC to lenvatinib treatment. **Methods:** We evaluated 11 consecutive patients with HCC diagnosed by dynamic CT or magnetic resonance imaging combined with ¹⁸F-FDG-PET/CT from April 2018 to December 2019. The tumor-to-normal liver ratio (TLR) of the target tumor was measured before and during the course of lenvatinib treatment with ¹⁸F-FDG-PET/CT (pre and post analysis,

respectively), with a TLR ≥ 2 classified as PET-positive HCC. At the time of each evaluation, we also used the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, the modified RECIST (mRECIST), and the tumor marker alpha-fetoprotein (AFP). **Results:** Of 11 patients, 3 (27%) and 8 (73%) had an objective response to lenvatinib treatment at the time of post-analysis by RECIST 1.1 and mRECIST, respectively. There were 3 (27%) and 7 (64%) patients with PET-positive HCC at the time of pre- and post-analysis, respectively. There was a significant correlation between the rates of change in AFP and TLR during lenvatinib treatment ($r = 0.69$, $p = 0.019$). Based on these results, we were able to perform liver resection on 4 patients with PET-positive HCC as conversion therapy. Three samples from these patients showed poorly differentiated tumors. **Conclusion:** ¹⁸F-FDG-PET/CT has potential as an evaluation tool for describing biological tumor behavior and reflecting disease progression, location, and treatment response. This modality may provide useful information for considering prognosis and subsequent therapy.

© 2020 The Author(s)
Published by S. Karger AG, Basel

Introduction

Lenvatinib is the first approved molecular-targeted agent for first-line treatment of unresectable advanced hepatocellular carcinoma (HCC) worldwide [1]. It is an oral multikinase inhibitor that inhibits the proliferation of cancer cells and angiogenesis, leading to a decrease in tumor volume and intratumoral arterial feeding. The modified Response Evaluation Criteria in Solid Tumors (mRECIST), which depend on intratumoral arterial enhancement, are commonly used to evaluate the response of HCC to treatment [2]. However, the true viability of HCC during lenvatinib treatment remains unclear.

^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) reflects the glucose metabolism of cancer cells, but its sensitivity in HCC has been reported to be lower than in other solid tumors [3, 4]. Thus, the usefulness of ^{18}F -FDG-PET/CT in HCC is limited. However, there is evidence that ^{18}F -FDG-PET/CT-positive HCC is strongly associated with poor histological differentiation [5]. Recently, we reported the utility of ^{18}F -FDG uptake in HCC as a useful predictor of an extremely rapid response to lenvatinib [6].

Several years ago, Harimoto et al. [7] reported that increased fibroblast growth factor receptor (FGFR) 2 expression correlated significantly with poor histological differentiation, a higher incidence of portal vein invasion, and a high AFP level. Lenvatinib, an inhibitor of vascular endothelial growth factor receptor 1–3, FGFR1–4, platelet-derived growth factor receptor- α , Ret, and Kit, was reported to be noninferior to sorafenib with respect to overall survival in patients with untreated advanced HCC [8, 9]. Therefore, potential FGFR inhibition by lenvatinib may have influenced this rapid treatment response.

Usually, treatment response is assessed with dynamic CT or MRI, which depend only on tumor blood flow, especially with mRECIST. However, a decrease in tumor blood flow does not always mean tumor necrosis, and the mechanism of action of lenvatinib is to decrease tumor blood flow by inhibiting angiogenesis. Therefore, this tool remains controversial for the evaluation of lenvatinib treatment response from a clinical standpoint.

Until now, no data regarding the change in accumulation of ^{18}F -FDG during lenvatinib treatment have been reported. Therefore, in this study, we assessed the value of ^{18}F -FDG-PET/CT as a tool for evaluating lenvatinib treatment response by comparing it with other tools, such as mRECIST, RECIST 1.1, and the tumor marker α -fetoprotein (AFP).

Patients and Methods

Study Population

From April 2018 to December 2019, 91 patients received systemic anticancer treatment with lenvatinib for unresectable HCC at the Department of Hepatology, Toranomon Hospital, Tokyo, Japan.

The following inclusion criteria were used in this retrospective study: (1) dynamic CT or magnetic resonance imaging (MRI) performed prior to initiation of lenvatinib; (2) a tumor showing hyperenhancement in the arterial phase of dynamic CT or MRI; (3) ^{18}F -FDG-PET/CT performed prior to the introduction of lenvatinib; (4) triple-phase dynamic CT or MRI and ^{18}F -FDG-PET/CT performed to evaluate the treatment response to lenvatinib; (5) Child-Pugh class A liver function at the time of lenvatinib initiation; (6) Barcelona Clinic Liver Cancer (BLCL) stage A–C categorization; (7) patients with unresectable HCC who did not want to undergo local ablation or chemoembolization therapy for various reasons (i.e., tumor size, number, and location; extrahepatic metastasis; transcatheter arterial chemoembolization [TACE] failure/refractoriness [10]; and other complications); (8) no treatment history with lenvatinib; (9) treatment interval >28 days since previous tyrosine kinase inhibitor (sorafenib or regorafenib) therapy; and (10) observation period of 8 weeks or more. Ultimately, 11 patients were enrolled in the current study.

Diagnosis of HCC

The diagnosis of HCC was based predominantly on imaging analysis using dynamic CT or MRI. When a liver nodule showed hyperenhancement in the arterial phase of the dynamic study and washout in the portal or delayed phase, the nodule was diagnosed as HCC.

Imaging Analysis of HCC Using ^{18}F -FDG-PET/CT

Within 1 month before the initiation of lenvatinib, ^{18}F -FDG-PET/CT was performed using a dedicated whole-body PET scanner (Biograph mCT Flow40; Siemens Healthcare, Germany). With SYNAPSE VINCENT v4 software for semiquantitative analysis, the volume of interest was drawn along the outline of the tumor, and the maximum standardized uptake value (SUV_{max}) and mean SUV (SUV_{mean}) in each intra- and extrahepatic target tumor were calculated. Of the lesions measured, that with the highest ^{18}F -FDG uptake was selected and used to calculate the tumor-to-normal liver ratio (TLR). Next, to measure normal liver activity, 3 non-overlapping spherical 1-cm³ volumes of interest were drawn in the liver (2 in the right lobe and 1 in the left) on the axial PET images, avoiding the HCC areas seen on dynamic CT. The TLR was calculated using the following equation: $\text{TLR} = \text{SUV}_{\text{max}}$ of the tumor / SUV_{mean} of the normal liver. Based on previous reports, we defined HCC with a $\text{TLR} \geq 2$ as FDG-PET-positive HCC to indicate high malignant potential.

Lenvatinib Treatment and Assessment of Adverse Events

Lenvatinib (Lenvima[®]; Eisai, Tokyo, Japan) was given orally (8 mg/day to patients <60 kg, or 12 mg/day to patients >60 kg). Treatment was discontinued in the case of any unacceptable or serious adverse events (AEs) or significant clinical tumor progression. According to the guidelines for the administration of lenvatinib, the dose should be reduced or treatment interrupted if a patient develops grade >3 AEs or any unacceptable drug-related grade 2 AEs.

Table 1. Baseline characteristics of the patients with HCC treated with lenvatinib and evaluated by ^{18}F -FDG-PET/CT

Case No.	Age, years	Sex	Etiology	AFP, $\mu\text{g/L}$	BCLC stage	CPS	Pretreatment image analysis using ^{18}F -FDG-PET/CT	
							SUV _{max}	TLR
1	79	M	Others	153	B	5	3.86	1.40
2	67	M	Alcohol	2.0	B	6	2.53	1.29
3	67	M	HBV	6,687	B	5	3.45	1.49
4	80	M	Others	9.40	B	5	8.72	3.66
5	83	M	HCV	25.0	C	5	6.24	2.81
6	65	F	HCV	373.0	A	6	4.30	1.45
7	69	F	HCV	126	A	5	3.52	1.25
8	59	M	HCV	5.9	C	5	6.44	3.20
9	66	M	HCV	13	C	5	2.60	1.25
10	77	F	Other	20	B	5	3.13	1.25
11	59	M	Alcohol	0.8	B	6	3.77	1.71

HCC, hepatocellular carcinoma; ^{18}F -FDG-PET/CT, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CPS, Child-Pugh score; SUV_{max}, maximum standardized uptake value; TLR, tumor-to-normal liver ratio; HBV, hepatitis B virus; HCV, hepatitis C virus.

AEs were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 [11]. If a drug-related AE occurred, a dose reduction or temporary interruption was implemented until the AE improved to grade 1 or 2, according to the guidelines provided by the manufacturer.

Treatment Response Evaluation

The treatment response was evaluated according to RECIST 1.1 [12] and mRECIST [2]. We assessed the best tumor response during 2–12 weeks using dynamic CT or MRI.

The treatment response was assessed independently by an expert hepatologist (Y. Kawamura) and an expert hepatobiliary surgeon (J. Shindoh) who were blinded to the clinical data. Discrepancies between these two examiners were resolved by consensus review including an additional reviewer (K. Ikeda).

Follow-Up Protocol

Physicians examined the patients every 1–2 weeks after the initiation of lenvatinib, and biochemical laboratory and urine tests were also performed. After the initiation of lenvatinib, the patients underwent dynamic CT or MRI to evaluate the best treatment response at 2–12 weeks. After the first evaluation of the treatment response, dynamic CT or MRI was performed every 1–3 months. Post- ^{18}F -FDG-PET/CT analysis was performed when tumor viability was indefinite even though CT, MRI, and a tumor marker were used. This time was defined as the time of post-analysis.

Method of Evaluation at the Time of Post- ^{18}F -FDG-PET/CT Analysis

Within 1 month of the post- ^{18}F -FDG-PET/CT analysis, dynamic CT or MRI was performed and tumor response was evaluated. According to RECIST 1.1 and mRECIST assessment, the target lesion was assessed by anatomic size and intratumoral arterial

enhancement. In this study, “disease control” was defined as successful tumor control without progressive disease (PD) state at the time of post-analysis of lenvatinib treatment with or without additional sequential therapies. Changes in AFP and TLR values were calculated using the following mathematical formulae:

$$\Delta\text{TLR} = [\text{TLR value at the time of post-analysis}] - [\text{TLR value at the time of pre-analysis}]$$
$$\Delta\text{AFP} = [\text{AFP value at the time of post-analysis}] - [\text{AFP value at the time of pre-analysis}]$$
$$\Delta\text{TLR} (\%) = \Delta\text{TLR} / [\text{TLR value at the time of pre-analysis}]$$
$$\Delta\text{AFP} (\%) = \Delta\text{AFP} / [\text{AFP value at the time of pre-analysis}]$$

Statistical Analysis

Statistical analysis was performed with IBM SPSS software (v26.0; SPSS Inc., Chicago, IL, USA). Data are expressed as the median and range. Correlations were analyzed with the Spearman correlation test. p values <0.05 were considered to indicate statistical significance.

Results

Patient Demographics

We enrolled 11 patients using ^{18}F -FDG-PET/CT for evaluating the treatment response to lenvatinib. Table 1 shows the baseline characteristics of the 11 patients. There were 8 men and 3 women; their median age was 67 years (range, 59–83). Two patients had BCLC stage A, 6 patients had BCLC stage B, and 3 patients had BCLC stage C disease. The median value of AFP before lenvatinib

Fig. 1. Relationship between evaluation with dynamic CT (RECIST 1.1 and mRECIST) and the tumor-to-normal liver standardized uptake value ratio (TLR) measured by ^{18}F -FDG-PET/CT. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

treatment was 20 $\mu\text{g/L}$ (range, 0.8–6,687). The median values of SUV_{max} and TLR on ^{18}F -FDG-PET/CT before lenvatinib treatment were 3.77 (range, 2.53–8.72) and 1.45 (range, 1.25–3.66), respectively.

Evaluation of the Initial Treatment Response at 2–12 Weeks by Dynamic CT

According to the RECIST 1.1 assessment conducted at 2–12 weeks, no patient had a complete response (CR), 6 patients had a partial response (PR), 5 patients had stable disease (SD), and no patient had PD. According to mRECIST assessment, 3 patients had a CR, 6 had a PR, and 2 had SD. No patient had PD (Table 2). Among the 11 patients, 6 and 9 patients had an objective response by RECIST 1.1 and mRECIST, respectively.

Evaluation at the Time of Post-Analysis

According to the RECIST 1.1 assessment conducted at the time of post-analysis, no patient had a CR, 3 patients had a PR, 6 had SD, and 2 had PD. According to mRECIST assessment, 2 patients had a CR, 6 had a PR, and 3 had SD. No patient had PD (Table 2). Among the 4 patients with a $\Delta\text{TLR} < 0$, 3 patients had an objective response according to RECIST 1.1 and mRECIST, respectively. In contrast, among the 7 patients with a $\Delta\text{TLR} \geq 0$, no and 5 patients had an objective response by RECIST 1.1 and mRECIST, respectively (Fig. 1). Nine patients had good cancer control with lenvatinib and other additional therapies (mainly TACE, $n = 6$) at the time of post-analysis.

Fig. 2. Correlation of tumor-to-normal liver ratio (TLR) and alfa-fetoprotein (AFP) between pre- and post-analysis.

Correlation of TLR and AFP between Pre- and Post-Analysis

The median change in TLR and AFP was 0.78 (range, –0.91 to 3.96) and 6.7 $\mu\text{g/L}$ (range, –9.0 to 27,764), respectively. The median rate of change in TLR and AFP was 27.5% (range, –53.6 to 282) and 114% (range, –53.8 to 2,001), respectively. In 4 patients, TLR values were decreased. The median interval between pre- and post- ^{18}F -FDG-PET/CT analysis was 10.6 months (range, 2.0–17.5). There was a significant correlation between the rates of change in AFP and TLR ($r = 0.69$; $p = 0.019$) (Fig. 2). Example images for 2 patients are shown in Figures 3 and 4.

Medical Treatment

Among the 11 patients, 3 experienced a change in tyrosine kinase inhibitor to ramucirumab, 4 patients underwent liver resection, and 2 patients received TACE as subsequent therapy. Two patients continued lenvatinib treatment, and 1 patient died a few days after post-analysis.

Histological Tumor Differentiation of Liver Resection Samples

Among the 11 patients, 4 (cases 3, 4, 5, and 8) underwent liver resection, and all 4 cases had a TLR > 2 at the time of post-analysis (Table 3). One case had a moderately differentiated tumor, but all other cases had poorly differentiated tumors.

Fig. 3. Upregulation of FDG uptake during lenvatinib treatment: a case presentation. **a** Dynamic CT image at pre-treatment analysis. **b** Dynamic CT image at post-treatment analysis. **c** ^{18}F -FDG-PET/CT image at pre-treatment analysis. **d** ^{18}F -FDG-PET/CT image at post-treatment analysis. Baseline and follow-up imaging analysis during lenvatinib treatment of a 67-year-old male patient with HCC (case 2). These tumors were in stable disease with a decrease in arterial blood flow, and there was no significant increase in tumor size (**a**, **b**). However, there was higher tumor uptake in the second scan (**d**) than in the first scan (**c**), indicating no actual tumoral necrosis with lenvatinib treatment (13.3 months) and a poor prognosis. ^{18}F -FDG-PET/CT during therapy with a molecular-targeted agent provided more information on HCC. ^{18}F -FDG-PET/CT, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography; HCC, hepatocellular carcinoma.

Fig. 4. Downregulation of FDG uptake during lenvatinib treatment: a case presentation. **a** Dynamic CT image at pre-treatment analysis. **b** Dynamic CT image at post-treatment analysis. **c** ^{18}F -FDG-PET/CT image at pre-treatment analysis. **d** ^{18}F -FDG-PET/CT image at post-treatment analysis. Baseline and follow-up imaging analysis during lenvatinib treatment of a 59-year-old male patient with HCC (case 8). These tumors were in complete response with the disappearance of intratumoral arterial enhancement, and there was no significant increase in tumor size (**a**, **b**). The AFP tumor marker also did not change. There was lower tumor uptake in the second scan (**d**) than in the first scan (**c**), but it still remained. This indicated that the tumor survived, even though the patient had received lenvatinib treatment (7.3 months). Thus, we were able to perform liver resection as conversion therapy. The histological diagnosis was poorly differentiated HCC. ^{18}F -FDG-PET/CT, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

Table 2. Correlation of ¹⁸F-FDG-PET/CT images and AFP tumor marker during lenvatinib treatment

Case No.	Initial treatment response at 2–12 weeks using dynamic CT		Evaluation at the time of post-analysis			Changes in values				Lenvatinib dose between analysis			Additional treatment			
	RECIST1.1	mRECIST	RECIST1.1	mRECIST	disease control	TLR	ΔTLR	%	AFP, μg/L	ΔAFP, μg/L	%	interval, months	initial dose, mg	RDI, %	pre- to post-analysis	after post-analysis
1	PR	CR	PD	PR	-	5.37	3.96	282	3,214	3,061	2,001	10.6	12	45	TACE	Death
2	PR	PR	SD	SD	+	2.42	1.13	88	6.1	4.1	205	13.3	8	52	None	None
3	SD	SD	SD	SD	+	2.62	1.13	76	34,451	27,764	415	6.7	8	100	TACE	RAM, operation
4	PR	CR	SD	CR	+	4.67	1.01	28	12.1	2.7	29	6.5	12	72	None	Operation
5	SD	PR	SD	PR	+	3.71	0.90	32	16.0	-9.0	-36	2.0	8	100	None	Operation
6	SD	SD	SD	PR	+	2.22	0.78	54	17,275	16,902	4,531	17.3	12	24	TACE	RAM
7	SD	PR	PD	PR	-	1.45	0.20	16	286	160	127	17.5	8	51	TACE	RAM
8	PR	CR	PR	CR	+	3.10	-0.10	-3.2	12.6	6.7	114	7.3	8	100	None	Operation
9	PR	PR	PR	PR	+	1.09	-0.16	-13	6.0	-7.0	-54	5.4	12	84	None	TACE
10	SD	PR	SD	SD	+	0.82	-0.43	-35	32.5	12.5	63	11.4	8	27	TACE	TACE
11	PR	PR	PR	PR	+	0.79	-0.91	-54	0.6	-0.2	-25	13.3	12	43	TACE	None

¹⁸F-FDG-PET/CT; ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; CT, computed tomography; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST, Response Evaluation Criteria in Solid Tumors; TLR, tumor-to-normal liver ratio; AFP, alpha-fetoprotein; RDI, relative dose intensity; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TACE, transcatheter arterial chemoembolization; RAM, ramucitumab.

Table 3. Relationships between histological tumor differentiation, AFP tumor marker, and imaging findings by ¹⁸F-FDG-PET/CT in patients with HCC who underwent surgical resection

Case No.	At the time of post-analysis		Pathological tumor differentiation
	TLR	AFP, ng/dL	
3	2.62	34,451	Moderate
4	4.67	12.1	Poor
5	3.71	16.0	Poor
8	3.10	12.6	Poor

AFP, alpha-fetoprotein; ¹⁸F-FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; HCC, hepatocellular carcinoma; TLR, tumor-to-normal liver ratio.

Discussion

This study investigated the value of ¹⁸F-FDG-PET/CT as a tool for evaluating the response to lenvatinib treatment compared with mRECIST, RECIST 1.1, and AFP. Our results suggest that the rate of change in TLR is associated with the tumor marker AFP and pathological tumor differentiation. To the best of our knowledge, this is the first study focusing on treatment response using ¹⁸F-FDG-PET/CT in patients with HCC treated with lenvatinib.

RECIST is a general method for evaluating treatment response based on tumor shrinkage [13, 14]. However, the treatment response of HCC is poorly correlated with the clinical outcome by RECIST for many molecular-targeted agents and interventional therapies [15, 16]. In 2008, the American Association for the Study of Liver Diseases (AASLD) developed mRECIST, which depends on intra-tumoral arterial enhancement, and mRECIST has been the main tool for evaluating the treatment response of HCC. However, it may also be difficult to evaluate the tumor response by mRECIST during lenvatinib treatment because its mechanism of action is to decrease the number of intra-tumoral feeding arteries to inhibit angiogenesis and proliferation of HCC. In this study, among 11 patients, 6 and 9 had an objective response by RECIST 1.1 and mRECIST at 2–12 weeks, respectively, with similar outcomes at the time of post-analysis; 3 and 8 patients had an objective response by RECIST 1.1 and mRECIST, respectively (Table 2). In addition, among the 7 patients with a ΔTLR ≥ 0, responses were judged differently by RECIST 1.1 and mRECIST (Fig. 1). This may indicate that the evaluation of response by mRECIST during lenvatinib treatment was an overestimation and uncertain from a clinical standpoint.

Although the sensitivity of ^{18}F -FDG-PET/CT in HCC is low, previous studies about its predictive value for poor prognosis have been published [3, 15, 17, 18]. On the other hand, the TLR has been reported as a useful predictor of an extremely rapid response to lenvatinib [6]. However, researchers have focused on the prognostic and predictive value, and there have been few studies investigating the treatment response. In our study, we evaluated treatment response using ^{18}F -FDG-PET/CT before and after lenvatinib treatment. The results showed that patients with a decreased TLR primarily experienced objective responses by RECIST 1.1 and mRECIST (Fig. 1), and a significant correlation was observed between the rates of change in AFP and TLR during lenvatinib treatment ($r = 0.69$, $p = 0.019$) (Fig. 2). This means that the TLR may serve as a surrogate marker of lenvatinib treatment response. In addition to the reflection on total treatment response, imaging analysis using ^{18}F -FDG-PET/CT demonstrates the localization of the tumor, unlike tumor markers. Therefore, we were able to perform liver resection in 4 cases using ^{18}F -FDG-PET/CT as conversion therapy.

^{18}F -FDG-PET/CT is also a good predictor of tumor differentiation and biological properties in HCC [5, 19–23]. High-histological-grade HCC has increased glucose transporter and hexokinase activity, which are positively correlated with FDG uptake [5, 24, 25]. In our study, 4 liver resection samples with a TLR >2 had greater malignant pathology regardless of the AFP value. Based on the results of our previous studies, 1 had a moderately differentiated tumor and 3 had poorly differentiated tumors (Table 3).

Among the 11 patients, 3 (27%) had PET-positive HCC at the time of pre-analysis, but 7 (64%) had PET-positive HCC at the time of post-analysis. Considering that the sensitivity of ^{18}F -FDG-PET/CT for HCC diagnosis was reported to be about 50% or lower [20, 26], on the other hand, there were many cases presented as PET-positive HCC at the time of post-analysis and the number of patients with PET-positive HCC increased during lenvatinib treatment. This result means that the tumoral biological condition might convert aerobiosis to anaerobiosis for survival under the action of lenvatinib, inhibiting angiogenesis to decrease intratumoral arterial blood flow and proliferation of HCC. ^{18}F -FDG-PET/CT has the potential to be an evaluation tool for describing biological tumor behavior and reflecting disease progression, location, and treatment response. This modality could provide useful information in considering prognosis and conversion therapy (Fig. 3, 4).

There are several limitations to this study. First, the sample size is small, resulting in statistical bias and inac-

curate conclusions. Second, the diagnosis of HCC was based exclusively on imaging analysis. Third, patients underwent different therapies (mainly TACE, $n = 6$) before post-analysis, which may have influenced their outcomes. Fourth, although FDG-PET/CT analysis is an optional imaging tool, for various reasons, it is not as easy to perform as other types of imaging such as CT or MRI, and it has a relatively high cost, with a small number and uneven distribution of required instruments. Therefore, our findings should be interpreted with caution due to these limitations.

Conclusion

During lenvatinib treatment, response evaluation based on intratumoral blood flow was sometimes uncertain. Evaluation with ^{18}F -FDG-PET/CT depends not on intratumoral blood flow but on actual biological tumor behavior. In addition to the reflection of treatment response as a tumor marker, ^{18}F -FDG-PET/CT shows tumoral localization. Therefore, this modality may provide valuable information that could impact individual decision-making on the most appropriate subsequent therapy.

Acknowledgments

This work was supported in part by grants from the Ministry of Health, Labor and Welfare in Japan and the Japan Agency for Medical Research and Development.

Statement of Ethics

Ethics approval and consent to participate: this retrospective non-intervention study was approved by the Institutional Review Board of Toranomon Hospital (protocol No. 1438-H/B). The study was performed in accordance with the Declaration of Helsinki. Because of the anonymous nature of the data and the opt-out disclosed on our institution's homepage (https://www.crc-toranomonhosp.jp/wp-content/uploads/2020/01/rinken_1438HB_2.pdf), the requirement for additional informed consent to participate in this study was deemed unnecessary according to the Japanese national regulation “Ethical Guidelines for Medical and Health Research Involving Human Subjects” (<https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukousei-kagakuka/0000080278.pdf>).

Conflict of Interest Statement

Y. Kawamura, M. Kobayashi, J. Shindoh, and H. Kumada report receiving honoraria from Eisai. The other authors declare no conflicts of interest.

Funding Sources

This study was funded by the Okinaka Memorial Institute for Medical Research and the Japanese Ministry of Health, Labor and Welfare.

Author Contributions

D. Yamashige: study concept and design, acquisition of data, statistical analysis, and drafting of the manuscript. Y. Kawamura: study concept and design, acquisition of data, statistical analysis.

M. Kobayashi: acquisition of data and statistical analysis. J. Shin-doh: acquisition of data, statistical analysis, and critical revision of the manuscript. Y. Kobayashi: acquisition of data. S. Okubo: acquisition of data. A. Kajiwarra: acquisition of data. K. Kasuya: acquisition of data. S. Iritani: acquisition of data. S. Fujiyama: acquisition of data. T. Hosaka: acquisition of data. S. Saitoh: acquisition of data. H. Sezaki: acquisition of data. N. Akuta: acquisition of data. F. Suzuki: acquisition of data. Y. Suzuki: acquisition of data. K. Ikeda: acquisition of data, statistical analysis, and study supervision. Y. Arase: acquisition of data. M. Hashimoto: acquisition of data. H. Kumada: acquisition of data.

References

- 1 Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *J Gastroenterol*. 2017;52(4):512–9.
- 2 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010 Feb;30(1):52–60.
- 3 Sung PS, Park HL, Yang K, Hwang S, Song MJ, Jang JW, et al. 18F-fluorodeoxyglucose uptake of hepatocellular carcinoma as a prognostic predictor in patients with sorafenib treatment. *Eur J Nucl Med Mol Imaging*. 2018;45(3):384–91.
- 4 Hong CM, Ahn BC, Jang YJ, Jeong SY, Lee SW, Lee J. Prognostic value of metabolic parameters of 18F-FDG PET/CT and apparent diffusion coefficient of MRI in hepatocellular carcinoma. *Clin Nucl Med*. 2017 Feb;42(2):95–9.
- 5 Seo S, Hatano E, Higashi T, Hara T, Tada M, Tamaki N, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography predicts tumor differentiation, P-glycoprotein expression, and outcome after resection in hepatocellular carcinoma. *Clin Cancer Res*. 2007 Jan;13(2 Pt 1):427–33.
- 6 Kawamura Y, Kobayashi M, Shindoh J, Kobayashi Y, Kasuya K, Sano T, et al. 18F-fluorodeoxyglucose uptake in hepatocellular carcinoma as a useful predictor of an extremely rapid response to lenvatinib. *Liver Cancer*. 2020;9(1):84–92.
- 7 Harimoto N, Taguchi K, Shirabe K, Adachi E, Sakaguchi Y, Toh Y, et al. The significance of fibroblast growth factor receptor 2 expression in differentiation of hepatocellular carcinoma. *Oncology*. 2010;78(5–6):361–8.
- 8 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–73.
- 9 Matsuki M, Hoshi T, Yamamoto Y, Ikemori-Kawada M, Minoshima Y, Funahashi Y, et al. Lenvatinib inhibits angiogenesis and tumor fibroblast growth factor signaling pathways in human hepatocellular carcinoma models. *Cancer Med*. 2018;7(6):2641–53.
- 10 Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, et al. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. *Oncology*. 2014;87(Suppl 1):22–31.
- 11 National Cancer Institute. Cancer Therapy Evaluation Program. Adverse Events/CTCAE [Internet]. Available from: https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.
- 12 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228–47.
- 13 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981 Jan;47(1):207–14.
- 14 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000 Feb;92(3):205–16.
- 15 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008 Jul;359(4):378–90.
- 16 Forner A, Ayuso C, Varela M, Rimola J, Hesseimer AJ, De Lope CR, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are Response Evaluation Criteria in Solid Tumors reliable? *Cancer*. 2009;115(3):616–23.
- 17 Song MJ, Bae SH, Lee SW, Song DS, Kim HY, Yoo IR, et al. 18F-fluorodeoxyglucose PET/CT predicts tumour progression after transarterial chemoembolization in hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging*. 2013;40(6):865–73.
- 18 Lee JH, Park JY, Kim DY, Ahn SH, Han KH, Seo HJ, et al. Prognostic value of 18F-FDG PET for hepatocellular carcinoma patients treated with sorafenib. *Liver Int*. 2011 Sep;31(8):1144–9.
- 19 Hatano E, Ikai I, Higashi T, Teramukai S, Torizuka T, Saga T, et al. Preoperative positron emission tomography with fluorine-18-fluorodeoxyglucose is predictive of prognosis in patients with hepatocellular carcinoma after resection. *World J Surg*. 2006;30(9):1736–41.
- 20 Trojan J, Schroeder O, Raedle J, Baum RP, Herrmann G, Jacobi V, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. *Am J Gastroenterol*. 1999 Nov;94(11):3314–9.
- 21 Lee JD, Yun M, Lee JM, Choi Y, Choi YH, Kim JS, et al. Analysis of gene expression profiles of hepatocellular carcinomas with regard to 18F-fluorodeoxyglucose uptake pattern on positron emission tomography. *Eur J Nucl Med Mol Imaging*. 2004 Dec;31(12):1621–30.
- 22 Khan MA, Combs CS, Brunt EM, Lowe VJ, Wolverson MK, Solomon H, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. *J Hepatol*. 2000 May;32(5):792–7.
- 23 Ho CL, Yu SCH, Yeung DWC. 11C-acetate PET imaging in hepatocellular carcinoma and other liver masses. *J Nucl Med*. 2003;44(2):213–21.
- 24 Torizuka T, Tamaki N, Inokuma T, Magata Y, Sasayama S, Yonekura Y, et al. In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. *J Nucl Med*. 1995;36(10):1811–7.
- 25 Lee M, Jeon JY, Neugent ML, Kim JW, Yun M. 18F-fluorodeoxyglucose uptake on positron emission tomography/computed tomography is associated with metastasis and epithelial-mesenchymal transition in hepatocellular carcinoma. *Clin Exp Metastasis*. 2017;34(3–4):251–60.
- 26 Kornberg A, Friess H. 18F-fluorodeoxyglucose positron emission tomography for diagnosis of HCC: implications for therapeutic strategy in curative and non-curative approaches. *Therap Adv Gastroenterol*. 2019 Mar;12:1756284819836205.