Pretreatment Positron Emission Tomography with ^{18}F -Fluorodeoxyglucose May Be a Useful New Predictor of Overall Prognosis Following Lenvatinib Treatment

Yusuke Kawamura^{a,b} Masahiro Kobayashi^{a,b} Junichi Shindoh^{b,c} Yuta Kobayashi^{b,c}
Satoshi Okubo^{b,c} Nozomu Muraishi^{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

Hepatocellular carcinoma · Lenvatinib · Malignant potential · Poorly differentiated · ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography

Abstract

Background and Aim: The aim of this study was to identify the utility of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) as a predictor of overall prognosis in patients with hepatocellular carcinoma treated with lenvatinib. **Methods:** Forty-eight consecutive patients who received lenvatinib treatment were reviewed. The oncological aggressiveness of tumors estimated using ^{18}F -FDG-PET/CT was investigated by the analysis of progression-free survival (PFS), post-progression survival (PPS), and overall survival (OS). Multivariate analysis was used to identify potential confounders for OS during lenvatinib therapy. **Results:** Using the Modified Response Evaluation Criteria in Solid Tumors, a tumor-to-normal liver ratio (TLR) ≥ 2 , indicating higher oncological aggressiveness in HCCs, was associated with a better objective response to lenvatinib than a TLR < 2 (78 vs. 62%), resulting in a similar PFS

($p = 0.751$). Because of a significantly worse PPS, OS with a TLR ≥ 2 was poor compared to a TLR < 2 ($p = 0.012$). Multivariate analysis confirmed that a TLR ≥ 2 was associated with poor OS (hazard ratio, 2.709; 95% CI, 1.140–6.436; $p = 0.024$). Analysis of 24 patients who received a repeat ^{18}F -FDG-PET/CT showed that daily changes expressed as $\Delta\text{TLR} \times 10^3/\text{day}$ over the treatment course tended to be different among the types of subsequent treatment. A R0 resection and lenvatinib-TACE sequential therapy provided good disease control (median, -4.593 and -0.024 , respectively) compared with other treatments (median, 5.278) ($p = 0.075$). **Conclusion:** Lenvatinib has acceptable disease control regardless of estimated tumor differentiation. A high TLR (≥ 2) is a poor prognostic factor of OS following lenvatinib treatment, while $\Delta\text{TLR} \times 10^3/\text{day}$ provides useful information of disease control status.

© 2021 The Author(s)
Published by S. Karger AG, Basel

Introduction

Recently, prior to its approval elsewhere in the world, lenvatinib became available in Japan as a new molecular targeted agent for first-line treatment of unresectable ad-

Table 1. Clinical profiles and laboratory data of patients with HCC treated with lenvatinib*

<i>Patient characteristics and laboratory data</i>	
Patients, <i>n</i>	48
Gender, males:females, <i>n</i>	34:14
Age, median (range), years [†]	70.5 (53–90)
Body mass index, median (range), kg/m ²	22.3 (11.9–34.8)
Body weight <60:≥60 kg	25:23
HCV:HBV:non-B, non-C	20:7:21
Performance status 0:1, <i>n</i> (%)	46 (96):2 (4)
Platelet count, ×10 ³ /L (range) [†]	157.5 (52–305)
Albumin, g/dL (range) [†]	3.9 (3.0–4.9)
Total bilirubin, mg/dL (range) [†]	0.8 (0.3–1.6)
Prothrombin activity, % (range) [†]	88.4 (64.9–124.8)
AST, IU/L (range) [†]	31.5 (15–125)
AFP, g/L (range) [†]	87.8 (0.8–55,372.0)
DCP, AU/L (range) [†]	79.5 (13.0–28,282.0)
Child-Pugh score 5:6, <i>n</i> (%)	33 (69):15 (31)
mALBI score (1:2a:2b:3), <i>n</i> (%)	20 (42):16 (33):12 (25):0 (0)
Initial dose of lenvatinib, 8:12 mg, <i>n</i> (%)	25 (52):23 (48)
Reduced starting dose of lenvatinib, <i>n</i> (%)	0 (0)
History of TKI treatment, <i>n</i> (%)	5 (10)
<i>Tumor characteristics</i>	
Largest tumor diameter, median (range), mm [†]	27.8 (10.7–115.0)
Number of tumors, <i>n</i> (range)	3 (1–>200)
Macrovascular invasion, <i>n</i> (%)	6 (13)
Extrahepatic metastasis, <i>n</i> (%)	20 (42)
BCLC stage A:B:C, <i>n</i> (%)	5 (10):19 (40):24 (50)
TACE failure/refractoriness, <i>n</i> (%)	27 (56)
<i>Image findings of ¹⁸F-FDG-PET/CT</i>	
TLR ≥ 2.0, <i>n</i> (%)	27 (56)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; AST, aspartate aminotransferase; DCP, des-γ-carboxyprothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IU, international units; mALBI, modified albumin-bilirubin; non-B, non-C, neither HBV nor HCV infection present; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TLR, tumor-to-normal liver ratio; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography. The composition ratio is rounded off to the first decimal place, and therefore the total will not necessarily be 100. [†] Data expressed as median (range).

vanced hepatocellular carcinoma (HCC) [1, 2]. Based on several clinical reports, the utility of lenvatinib to treat high malignant potential HCCs (e.g., poorly differentiated type and non-simple nodular type) was recently established [3, 4]. Regarding the imaging features of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT), ¹⁸F-FDG-PET/CT positivity has been reported to be associated strongly with poorly differentiated HCC [5]. Therefore, a ¹⁸F-FDG-PET/CT-positive HCC is usually a negative predictor of the response to various treatments (i.e., surgical resection, TACE, and sorafenib) [6–9]. Recently, we reported a high treatment response rate for lenvatinib in patients who had

¹⁸F-FDG-PET/CT-positive HCC [10]. However, the usefulness of ¹⁸F-FDG-PET/CT for predicting the prognosis of patients treated with lenvatinib has not been evaluated sufficiently. Moreover, the utility of a repeat ¹⁸F-FDG-PET/CT during the course of treatment remains unclear.

Therefore, the main aim of this study was to evaluate the relationship between the tumor-to-normal liver ratio (TLR) and ¹⁸F-FDG-PET/CT, and examine the overall prognosis of patients following the administration of lenvatinib. We also performed an additional analysis to evaluate the utility of a repeat ¹⁸F-FDG-PET/CT on selection of subsequent treatments.

Patients and Methods

Study Population

From October 2010 to January 2021, 114 patients received systemic anticancer treatment using lenvatinib for an unresectable HCC at the Department of Hepatology, Toranomon Hospital, Tokyo, Japan. The inclusion criteria for the study were as follows: (1) dynamic CT or magnetic resonance imaging (MRI) performed prior to initiation of lenvatinib, (2) a tumor showing hyperenhancement in the arterial phase of a dynamic CT or MRI, (3) ^{18}F -FDG-PET/CT performed prior to initiation of lenvatinib, (4) Child-Pugh class A liver function at the time of lenvatinib initiation, (5) BCLC stage A–C tumor(s), (6) an unresectable HCC with the patient not wanting to undergo local ablation or chemoembolization therapy for various reasons (i.e., tumor size, number, and location; extrahepatic metastasis; TACE failure/refractoriness [11]; and various complications), (7) no treatment history of lenvatinib, and (8) an observation period of ≥ 4 weeks. A total of 48 patients met these inclusion criteria. The study was approved by the Institutional Review Board of our hospital (protocol number: 1438-H/B).

Diagnosis of HCC

The diagnosis of HCC was based predominantly on the image analysis using dynamic-CT or MRI that was governed by a protocol reported elsewhere [4, 12]. When a liver nodule showed hyperattenuation in the arterial phase and washout in the portal or delayed phase in the dynamic study, the nodule was diagnosed as an HCC.

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

Within 1 month before the initiation of lenvatinib, a ^{18}F -FDG-PET/CT was performed using a dedicated whole-body PET scanner (Biograph mCT Flow40, Siemens Healthcare, Germany). Synapse Vincent software ver. 4 (Fujifilm Medical Systems, Japan) was used for the semi-quantitative analysis, with the volume of interest drawn along the outline of the tumor, and the maximum SUV (SUV-max) and mean SUV (SUV-mean) in each intra- and extra-hepatic target tumor then calculated. Of the lesions measured, the one with the highest ^{18}F -FDG uptake was selected and used to calculate the TLR. We next measured normal liver activity by drawing 3 non-overlapping spherical 1 cm³-sized VOIs on the axial PET images of the liver (2 in the right lobe and 1 in the left lobe), avoiding the HCC areas seen on the dynamic CT. The TLR was calculated using the following equation: $\text{TLR} = \text{SUV-max of the tumor} / \text{SUV-mean of the normal}$

Table 2. Evaluation of the early treatment response after initiation of lenvatinib, grouped according to the imaging findings of ^{18}F -FDG-PET/CT and analysis of imaging features using mRECIST

^{18}F -FDG-PET/CT TLR	Response evaluation using mRECIST, n (%)			
TLR ≥ 2.0 (n = 27)	CR	PR	SD	PD
	4 (15)	17 (63)	4 (15)	2 (7)
	OR			
	21 (78)			
TLR <2.0 (n = 21)	CR	PR	SD	PD
	1 (5)	12 (57)	6 (29)	2 (10)
	OR			
	13 (62)			

CR, complete response; CT, computed tomography; HU, Hounsfield units; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; OR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TLR, tumor-to-normal liver ratio; PET, positron emission tomography; FDG, fluorodeoxyglucose. The composition ratio is rounded off to the first decimal place, and therefore the total will not necessarily be 100.

liver. Based on previous reports [6, 9, 13], we selected a $\text{TLR} \geq 2$ to indicate a high malignant potential.

Lenvatinib Treatment and Adverse Event Assessment

Lenvatinib (Levima®, Eisai, Tokyo, Japan) was administered orally at 8 mg/day to patients weighing <60 kg or 12 mg/day to those weighing ≥ 60 kg. Treatment was discontinued when any unacceptable or serious adverse events (AEs) or significant clinical tumor progression was observed. According to the guidelines for administration of lenvatinib, the drug dose should be reduced or the treatment interrupted if a patient develops grade ≥ 3 AEs or any unacceptable drug-related grade 2 AEs. AEs were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 [14]. In accordance with the guidelines provided by the manufacturer, when a drug-related AE occurred, dose reduction or temporary interruption was maintained until the symptom resolved to either grade 1 or 2.

Treatment Response Evaluation

Treatment response was evaluated according to the Modified Response Evaluation Criteria in Solid Tumors

Fig. 1. Survival outcomes according to the TLR value on ^{18}F -FDG-PET/CT prior to the introduction of lenvatinib. PFS rate (**a**), PPS rate (**b**), and OS rate (**c**). TLR, tumor-to-normal liver ratio; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PFS, progression-free survival; PPS, post-progression survival; OS, overall survival.

(mRECIST) [15] that was used as an auxiliary. We assessed the best tumor response during the 2- to 12-week period. 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 2 examiners were resolved by consensus review including an additional reviewer (K. Ikeda).

Assessment of Immunonutritional Status Using the Controlling Nutritional Status Score

As described previously, the Controlling Nutritional Status (CONUT) score used to assess immunonutritional status was calculated from the sum of the following 3 parameters [16, 17]: (1) albumin levels of 3.5, 3.0–3.49, 2.5–2.99, and <2.5 g/dL were scored as 0, 2, 4, and 6 points, respectively; (2) total lymphocyte counts of $\geq 1,600$, 1,200–1,599, 800–1,199, and <800 cells/ μL were scored as 0, 1, 2, and 3 points, respectively; and (3) total cholesterol levels of ≥ 180 , 140–179, 100–139, and <100 mg/dL were scored as 0, 1, 2, and 3 points, respectively. Nutritional status was classified into the following 4 groups: normal (0–1), slight undernutrition (2–4), moderate undernutrition (5–8), and severe undernutrition (9–12).

Follow-Up Protocol

Physicians examined the patients every 1–2 weeks after initiation of lenvatinib, and laboratory biochemical and urine tests were also performed. After initiation of lenvatinib, the patients underwent a dynamic-CT to evaluate their early treatment response during the 2- to 12-week period. A dynamic-CT or MRI was performed every 1–3 months after the first evaluation of best treatment response. Follow-up ^{18}F -FDG-PET/CT was performed according to the physician's decision or patient's preference because this imaging modality was considered optional for evaluating treatment responses.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software (ver. 27.0 SPSS Inc., IL, USA). Data were expressed as the median and range. Differences in background features between each parameter were analyzed using either the χ^2 test, Fisher exact test, or Kruskal-Wallis test. p values <0.05 were considered statistically significant. Progression-free survival (PFS) and post-progression survival (PPS) after introduction of lenvatinib were estimated by the Kaplan-Meier method, with the values compared using the log-rank test.

To identify the factors associated with OS after initiation of lenvatinib, a multivariate analysis was performed using a

Table 3. Predictive factors for OS

	<i>p</i> value*	Coefficients [†]	SE	Wald χ^2	HR	95% CI
¹⁸ FDG-PET/CT positive (TLR ≥ 2)	0.024	0.997	0.441	5.096	2.709	1.140–6.436
Tumor number +1 nodule	0.001	0.021	0.006	10.540	1.021	1.008–1.034
Age +1 year	0.044	0.054	0.027	4.061	1.055	1.001–1.112
<i>CONUT score</i>						
Normal nutrition						
Light undernutrition	0.260	1.167	1.036	1.269	3.211	0.422–24.440
Moderate undernutrition	0.068	1.951	1.071	3.321	7.037	0.863–57.371

AFP, alpha-fetoprotein; 95% CI, 95% confidence interval; CT, computed tomography; HR, hazard ratio; SE, standard error; TACE, transarterial chemoembolization; TLR, tumor-to-normal liver ratio; FDG, fluorodeoxyglucose; PET, positron emission tomography; OS, overall survival; CONUT, controlling nutritional status. Multivariate Cox regression was applied using stepwise backward selection. Of the potential predictors, factors showing a marginal association ($p < 0.15$) with OS after the introduction of lenvatinib in the univariate analysis were included in the initial model. The factors that showed no or limited statistically significant association ($p > 0.1$) adjusted for the remaining factors in the model were then deleted from the model in a stepwise fashion. The 18 variables tested were as follows (p values in univariate analysis): age (0.077), gender (0.608), body mass index (0.177), etiology (HCV vs. others) (0.602), serum albumin (0.194), serum total bilirubin (0.352), prothrombin activity (0.859), platelet count (0.713), serum aspartate aminotransferase (0.098), serum AFP (0.092), plasma des-gamma carboxyprothrombin (0.061), tumor diameter (0.002), tumor number (<0.001), macrovascular invasion (0.006), extrahepatic metastasis (0.058), ¹⁸FDG-PET/CT positive (TLR ≥ 2) (0.015), TACE failure/refractoriness (0.423), and CONUT score (slight undernutrition 0.191 and moderate undernutrition 0.042). * Based on the likelihood test adjusted for the other factors in the final model. [†]Estimated coefficient for the variable and the associated standard error.

Cox proportional hazards model. In this multivariate analysis, the integrated score was excluded in order to detect the true factors. All factors that were at least marginally associated with OS ($p < 0.15$) in the univariate analysis were entered into a stepwise Cox regression analysis and significant variables selected by the stepwise method. A two-tailed p value <0.05 was considered to be statistically significant.

Results

Overview

Table 1 summarizes the baseline characteristics of the study population. The median age was 70.5 years, and 34 (71%) of the patients were male. The median size of the largest tumor was 27.8 mm (range, 10.7–115 mm), and the median number of tumors was 3 (range, 1–>200). Of the 48 patients, 5 (10%) with BCLC stage A disease received lenvatinib because of the location of the tumor, TACE failure/refractoriness, and the patient's preference; 24 (50%) patients presented with BCLC stage C disease (macrovascular invasion [$n = 6$] (Vp2, $n = 3$; Vp3, $n = 1$; Vp3 and Vv2, $n = 1$; and Vp4, $n = 1$), while 20 had extrahepatic metastasis. Five patients (10%) had a history of

Fig. 2. Adjusted OS curves with lenvatinib treatment, analyzed using the TLR value. TLR, tumor-to-normal liver ratio; OS, overall survival; HR, hazard ratio.

treatment with other TKIs and 27 patients (56%) had a TACE failure/refractoriness status. Twenty-seven patients had died at the time of the database lock (January

Fig. 3. Swimmers plots of patients treated with lenvatinib, stratified by TLR value and BCLC stage. TLR, tumor-to-normal liver ratio; BCLC, Barcelona Clinic Liver Cancer; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; TACE, transarterial chemoembolization.

4, 2021), with the median duration of lenvatinib administration being 8 months and a median observation period of 12.5 months.

Treatment Response and Survival Outcomes after Initiation of Lenvatinib according to the TLR Value on ^{18}F -FDG-PET/CT

A cut-off TLR of 2 was used in this study to define a HCC with a high malignant potential. In the evaluation of the treatment response based on the TLR value calculated by mRECIST, the ORR of each TLR value (≥ 2 or < 2) was 78 and 62%, respectively. There was no significant difference in the objective response between each TLR value ($p = 0.230$) (Table 2).

Figure 1 shows the survival outcomes according to the TLR value. Although there was no difference in PFS between the 2 groups ($p = 0.751$) (Fig. 1a), survival after progression was markedly worse when a patient present-

ed with a TLR ≥ 2 prior to the introduction of lenvatinib ($p < 0.001$) (Fig. 1b). As a result, the cumulative survival after introduction of lenvatinib was significantly different between the 2 groups ($p = 0.012$) (Fig. 1c).

Predictors of Unfavorable Overall Survival after Introduction of Lenvatinib

Table 3 summarizes the results of the multivariate analysis for unfavorable overall survival (OS) during lenvatinib therapy using pretreatment variables. Of the 18 variables tested, ^{18}F -FDG-PET/CT positivity (TLR ≥ 2) (hazard ratio [HR], 2.709; 95% CI, 1.140–6.436; $p = 0.024$), increased tumor number (HR, 1.021; 95% CI, 1.008–1.034; $p = 0.001$), and increasing age (HR, 1.055; 95% CI, 1.001–1.112; $p = 0.044$) were associated significantly with a poor OS, while an insufficient CONUT score (moderate undernutrition HR, 7.037; 95% CI, 0.863–57.371; $p = 0.068$) showed a tendency for a low OS. The adjusted OS

Fig. 4. OS rate after initiation of lenvatinib, grouped according to whether or not subsequent treatment was administered during the course of treatment. OS, overall survival; TACE, transarterial chemoembolization.

curves showed clear differences according to each TLR value (TLR ≥ 2 or < 2) (Fig. 2).

Overall Prognosis of Lenvatinib-Treated Patients according to the BCLC Stage and TLR Value

Figure 3 shows the overall prognosis of the lenvatinib-treated patients, grouped according to the BCLC stage and TLR value. In total, 9 patients received a R0 resection as subsequent treatment during the treatment course, with 8 of these patients (89%) classified as BCLC stage C with a TLR ≥ 2 . Moreover, 12 patients received lenvatinib-TACE sequential therapy (in this treatment procedure, lenvatinib was administrated continuously before and after TACE) as the initial subsequent treatment, with 11 of these patients (92%) receiving TACE after diagnosis of the PD state and the remaining patient in the PR state receiving scheduled sequential TACE. All of these patients were classified as BCLC stage A/B.

In addition, 14 patients received multi-molecular targeted agent sequential therapy, with 5 of these patients (36%) receiving atezorizumab plus bevacizumab as a second- or third-line treatment. Finally, 6 patients acquired drug-free, complete cancer control after additional treatment; 4 (67%) had a R0 resection, and 2 (33%) received lenvatinib-TACE sequential therapy with or without radiation therapy (stereotactic radiation therapy).

The Effect of Subsequent Treatment after Lenvatinib Initiation and Changes in the TLR Values during the Course of These Treatments

Figure 4 shows the cumulative survival after introduction of lenvatinib. In this figure, the subsequent treatments were stratified into the following 4 groups: R0 resection ($n = 9$); lenvatinib-TACE sequential therapy ($n = 12$); other subsequent treatments (including R2 resection [$n = 5$], TACE without restarting lenvatinib after the procedure [$n = 2$], radiation therapy [$n = 6$], other molecular targeted agents [$n = 3$]); and no subsequent treatment ($n = 11$). The results showed that there was a significant difference in cumulative survival rate among the subsequent treatment types ($p < 0.001$). The groups of patients who successfully received subsequent treatment (37 patients, 77%), especially the R0 resection and lenvatinib-TACE sequential therapy group ($n = 21$), showed a better OS than the group who received no subsequent treatment. In this study, 24 patients received repeat ^{18}F -FDG-PET/CT, with the conversion rate of TLR < 2 to TLR ≥ 2 as shown in Figure 5. In the R0 resection group, 1 patient showed a positive to negative TLR change prior to resection (Fig. 6). In the TACE group, 4 of 8 patients (50%) showed a negative to positive TLR change during the course of treatment. Table 4 shows the analysis of the changes in the TLR value during the course of each treat-

Initial main subsequent treatment	Initial ¹⁸ F-DG-PET/CT	The conversion rate [†] between TLR <2 and ≥2
R0 resection <i>n</i> = 9	TLR <2 <i>n</i> = 1 (11%) TLR ≥2 <i>n</i> = 8 (89%)	1 / 1 (100%) 1 / 5 (20%)
R2 resection <i>n</i> = 5	TLR <2 <i>n</i> = 0 (0%) TLR ≥2 <i>n</i> = 5 (100%)	0 / 3 (0%)
TACE <i>n</i> = 14	TLR <2 <i>n</i> = 12 (86%) TLR ≥2 <i>n</i> = 2 (14%)	4 / 8 (50%) 0 / 1 (0%)
Radiation therapy <i>n</i> = 6	TLR <2 <i>n</i> = 2 (33%) TLR ≥2 <i>n</i> = 4 (67%)	1 / 1 (100%) 0 / 3 (0%)
Other MTA therapy <i>n</i> = 3	TLR <2 <i>n</i> = 2 (67%) TLR ≥2 <i>n</i> = 1 (33%)	1 / 2 (50%)
No subsequent treatment <i>n</i> = 11	TLR <2 <i>n</i> = 4 (36%) TLR ≥2 <i>n</i> = 7 (64%)	

*MTA, molecular target agent; PD, progressive disease; TACE, transarterial chemoembolization
[†]The conversion rate was calculated based on patients who received a 2nd ¹⁸F-FDG-PET/CT in each group

Fig. 5. Background and breakdown of initial subsequent treatment, and conversion rate between TLR <2 and ≥2. The conditions of R0 and R2 resections were as follows: the R0 resection was selected when no new lesion was observed during the treatment period (at least 8 weeks) and adequate disease control of the primary target nodules was achieved, while the R2 resection was a salvage resection to control life-threatening rapid progression of a target nodule. The breakdown of TACE was as follows: the majority of patients received TACE to control the PD state during lenvatinib treatment (*n* = 13); only 1 patient received scheduled TACE combined with lenvatinib to enhance the TACE effect. The breakdown of radiation was as follows: 2 patients received SBRT, 2 patients received IMRT

of the intrahepatic target nodule, 1 patient received IMRT for lung metastasis, and 1 patient received combination therapy of PBT and SBRT for bone metastasis. The breakdown of MTA therapy was as follows: each patient received ramucirumab, sorafenib, and regorafenib as initial subsequent therapy. Finally, the breakdown of no subsequent treatment was as follows: 2 patients with a partial response continued lenvatinib, while 9 other patients could not continue lenvatinib due to decreasing residual liver function or progression of the tumor. TLR, tumor-to-normal liver ratio; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; TACE, transarterial chemoembolization; MTA, molecular target agent; PD, progressive disease.

ment. The $\Delta\text{TLR} \times 10^3/\text{day}$ tended to differ among the groups, with the R0 resection group having a greater decrease in the TLR value.

Discussion

¹⁸F-FDG-PET/CT is considered a useful method for predicting the degree of histological differentiation on imaging analysis. ¹⁸F-FDG-PET/CT positivity has been reported to be associated strongly with poorly differentiated HCCs [5] and, therefore, is often a negative predictor of the response to various treatments [6–9]. On the other hand, as we reported previously [10], the current study confirmed that ¹⁸F-FDG-PET/CT positivity (TLR ≥2) correlated with a higher response to lenvatinib (Table 2)

and had a similar PFS as a ¹⁸F-FDG-PET/CT-negative result (TLR <2). In addition a ¹⁸F-FDG-PET/CT-positive HCC was associated with a significantly worse PPS, resulting in a shorter OS (Fig. 1). These results showed lenvatinib decreased the rate of tumor growth and extended PFS, regardless of the tumor TLR values. However, the estimated PPS of ¹⁸F-FDG-PET/CT-positive HCC (TLR ≥2) was extremely poor and therefore we predicted that the prognosis of a patient with a ¹⁸F-FDG-PET/CT-positive HCC (TLR ≥2) would not exceed that of a patient with a ¹⁸F-FDG-PET/CT-negative HCC (TLR <2). Multivariate analysis also revealed ¹⁸F-FDG-PET/CT positivity (TLR ≥2) was associated significantly with poor OS. Given that ¹⁸F-FDG-PET/CT positivity correlates strongly with poor differentiation, the present results suggest that PPS is dependent predominantly on the malignant

Fig. 6. Changes in tumor blood flow and viability during lenvatinib treatment. The time course shows a marked decrease in tumor blood flow including tumor thrombus of an infiltrative type HCC during lenvatinib treatment. Finally, ^{18}F -FDG accumulation showed a marked decrease. The red arrow shows the tumor thrombus in each image, and the red dotted arrow indicates a marked decrease in tumor blood flow and ^{18}F -FDG accumulation. FDG, fluorodeoxyglucose; HCC, hepatocellular carcinoma; PET, positron emission tomography; CT, computed tomography.

Table 4. Imaging features of repeated ^{18}F -FDG-PET/CT between each subsequent therapy during the duration of lenvatinib treatment

Initial main subsequent treatment (<i>n</i>)	Initial ¹⁸ F-FDG-PET/CT	Changes in values		Analysis interval (days)	Additional treatment between pre- to post-analysis	
		TLR	ΔTLR**		ΔTLR ×10 ³ /d***	no, (<i>n</i>) %
R0 resection (6)	3.195 (1.203–5.992)	−0.606 (−1.050–4.543)	−4.593 (−12.577–42.856)	128.5 (60–220)	(5) 83	(1) 17
Lenvatinib-TACE sequential therapy (9)	1.448 (1.248–2.449)	−0.007 (−0.574–3.704)	−0.024 (−1.539–12.470)	320.0 (80–495)	(3) 33	(6) 67
Other subsequent treatment (9)	2.280 (1.183–3.930)	1.029 (−0.181–2.623)	5.278 (−1.111–8.798)	207.0 (55–328)	(3) 33	(6) 67

TACE, transarterial chemoembolization; TLR, tumor-to-normal liver ratio; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography. $^{**}p = 0.103$. $^{***}p = 0.075$. † Data expressed as median (range).

potential of the tumor and may not be prolonged even when an objective response is achieved with lenvatinib.

In this study, 37 of 48 patients (77%) received subsequent treatment after lenvatinib initiation, and as shown in Fig. 3, various subsequent treatments were performed during the course of treatment. Receiving subsequent treatment also resulted in a significant improvement in OS after initiation of lenvatinib (Fig. 4).

Similar to the findings of previous studies lenvatinib-TACE sequential therapy showed good survival benefits in this study [18, 19]. Therefore, the most important clinical messages in this study are that it is necessary to consider various subsequent treatments (resection, sequential TACE and radiation therapy combined with multi-molecular targeted agent sequential therapy) and that it is also important

to control treatment intensity in order to maintain sufficient residual liver function when considering these subsequent treatments. Recently, another study reported a relationship between the CONUT score and OS in patients treated with lenvatinib [20]. Similarly, multivariate analysis in our study showed that a CONUT score indicating moderate undernutrition was associated with a tendency to low OS ($p = 0.068$). The CONUT score is a useful predictive factor of OS and therefore may be useful for considering early changes to other subsequent treatments.

In our study, 24 patients received a repeat ^{18}F -FDG-PET/CT, with $\Delta\text{TLR} \times 10^3/\text{day}$ tending to differ among subsequent treatment groups. Moreover, the R0 resection group showed a greater decrease in TLR value, with 5 of 6 patients (83%) not receiving additional treatment in the

interval between analyses. On the other hand, in the lenvatinib-TACE sequential therapy group, 6 of 9 patients (67%) received additional treatment in the interval between analyses, and $\Delta\text{TLR} \times 10^3/\text{day}$ was well maintained at a low level compared with that observed in the other subsequent treatment group. Based on these results, observation of daily changes expressed as $\Delta\text{TLR} \times 10^3/\text{day}$ may provide useful information on disease control status. In order to evaluate the meaning of changes in TLR during the course of treatment, a large-scale multicenter study is required in the future.

This study had some limitations. First, it was a retrospective, single-center study of a relatively small number of series. Second, the diagnosis of HCC was based exclusively on imaging analysis. Third, the follow-up period of the trial was relatively short compared to that of the global Phase III REFLECT trial [2] (median follow-up period of 12.5 vs. 27.7 months, respectively). It was therefore not possible to carry out a high-quality prognostic analysis. Fourth, although ^{18}F -FDG-PET/CT analysis is an optional imaging tool, for various reasons it cannot be performed easily compared to other types of imaging such as CT or MRI. These reasons include the relatively high cost and the small number and uneven distribution of the instruments required for the scans. Therefore, a large-scale multicenter study is necessary to evaluate the utility of ^{18}F -FDG-PET/CT for predicting the overall prognosis and response of HCC to lenvatinib.

In conclusion, lenvatinib showed a good treatment response in unresectable ^{18}F -FDG-PET/CT-positive HCC and had acceptable disease control regardless of the estimated tumor differentiation. Taken together, these results indicate that a high TLR (≥ 2) is a prognostic factor of poor OS in lenvatinib treatment, with changes in $\text{TLR} \times 10^3/\text{day}$ having the potential to provide useful information on disease control status.

Acknowledgment

This work was supported, in part, by grants from the Ministry of Health, Labour and Welfare in Japan, the Taiju Life Social Welfare Foundation, and the Program for Basic and Clinical Research on Hepatitis, Japan Agency for Medical Research and Development.

Statement of Ethics

This retrospective, nonintervention study was approved by the Institutional Review Board, Toranomon Hospital (protocol number: 1438-H/B). The study was performed in accordance

with the Declaration of Helsinki. Because the data were anonymized, and the opt-out option was 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 regulations "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (<https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagaku-ka/0000080278.pdf>).

Conflict of Interest Statement

1. Yusuke Kawamura, MD, PhD, reports honoraria from Eisai.
  2. Masahiro Kobayashi, MD, reports honoraria from Eisai.
  3. Junichi Shindoh, MD, PhD, reports honoraria from Eisai.
  4. Hiromitsu Kumada, MD, PhD, reports honoraria from Eisai.
- The other authors declare no conflicts of interest.

Funding Sources

This work was supported by Okinaka Memorial Institute for Medical Research and the Japanese Ministry of Health, Labour and Welfare.

Author Contributions

1. Yusuke Kawamura, MD, PhD: study concept and design, acquisition of data, statistical analysis, and drafting of manuscript.
2. Masahiro Kobayashi, MD: acquisition of data and statistical analysis.
3. Junichi Shindoh, MD, PhD: acquisition of data and critical revision.
4. Yuta Kobayashi, MD: acquisition of data.
5. Satoshi Okubo, MD, PhD: acquisition of data.
6. Nozomu Muraishi, MD: acquisition of data.
7. Soichi Iritani, MD: acquisition of data.
8. Shunichiro Fujiyama, MD: acquisition of data.
9. Tetsuya Hosaka, MD: acquisition of data.
10. Satoshi Saitoh, MD: acquisition of data.
11. Hitomi Sezaki, MD: acquisition of data.
12. Norio Akuta, MD, PhD: acquisition of data.
13. Fumitaka Suzuki, MD, PhD: acquisition of data.
14. Yoshiyuki Suzuki, MD, PhD: acquisition of data.
15. Kenji Ikeda, MD, PhD: acquisition of data, statistical analysis, and study supervision.
16. Yasuji Arase, MD, PhD: acquisition of data.
17. Masaji Hashimoto, MD, PhD: acquisition of data.
18. Hiromitsu Kumada, MD, PhD: acquisition of data.

All authors had access to the data and participated in the writing of this manuscript.

References

- 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;52:512–9.
- Kudo M, Finn RS, Qin S, Han K-H, 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;391:1163–73.
- Kudo M, Han K-H, Ye S-L, Zhou J, Huang Y-H, Lin S-M, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific primary liver cancer expert consensus statements. *Liver Cancer*. 2020;9:245–60.
- Kawamura Y, Kobayashi M, Shindoh J, Kobayashi Y, Kasuya K, Sano T, et al. Pretreatment heterogeneous enhancement pattern of hepatocellular carcinoma may be a useful new predictor of early response to lenvatinib and overall prognosis. *Liver Cancer*. 2020;9:275–92.
- 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;13:427–33.
- Kitamura K, Hatano E, Higashi T, Seo S, Nakamoto Y, Yamanaka K, et al. Preoperative FDG-PET predicts recurrence patterns in hepatocellular carcinoma. *Ann Surg Oncol*. 2012;19:156–62.
- 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;40:865–73.
- 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;45:384–91.
- 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;30:1736–41.
- 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;9:84–92.
- Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, et al. Transarterial chemoembolization failure/refractoriness: JSH-LESGJ criteria 2014 update. *Oncology*. 2014;87(Suppl 1):22–31.
- Kawamura Y, Ikeda K, Shindoh J, Kobayashi Y, Kasuya K, Fujiyama S, et al. No-touch ablation in hepatocellular carcinoma has the potential to prevent intrasubsegmental recurrence to the same degree as surgical resection. *Hepatology*. 2019;49:164–76.
- Hyun SH, Eo JS, Lee JW, Choi JY, Lee KH, Na SJ, et al. Prognostic value of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with Barcelona Clinic Liver Cancer stages 0 and A hepatocellular carcinomas: a multicenter retrospective cohort study. *Eur J Nucl Med Mol Imaging*. 2016;43:1638–45.
- National Cancer Institute. Division of Cancer Treatment and Diagnosis. Cancer therapy evaluation program. Adverse events/CTCAE. Available from: https://ctep.cancer.gov/protocol_Development/electronic_applications/ctc.htm#ctc_40. Accessed 2018 Dec 23.
- Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30:52–60.
- de Ulíbarri IJ, González-Madroño A, de Villar NG, González P, González B, Mancha A. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp*. 2005;20:38–45.
- Harimoto N, Yoshizumi T, Inokuchi S, Itoh S, Adachi E, Ikeda Y, et al. Prognostic significance of preoperative controlling nutritional status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma: a multi-institutional study. *Ann Surg Oncol*. 2018;25:3316–23.
- Kudo M, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and child-pugh a liver function: a proof-of-concept study. *Cancer*. 2019;11:1084.
- Kawamura Y, Kobayashi M, Shindoh J, Kobayashi Y, Okubo S, Tominaga L, et al. Lenvatinib-transarterial chemoembolization sequential therapy as an effective treatment at progression during lenvatinib therapy for advanced hepatocellular carcinoma. *Liver Cancer*. 2020;9(6):756–70.
- Shimose S, Kawaguchi T, Iwamoto H, Tanaka M, Miyazaki K, Ono M, et al. Controlling nutritional status (CONUT) score is associated with overall survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib: a multicenter cohort study. *Nutrients*. 2020;12:1076.