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

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**Keywords**

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

**Abstract**

**Background and Aim:** The aim of this study was to identify the utility of \(^{18}\text{F}-\text{fluorodeoxyglucose}\) positron emission tomography/computed tomography (\(^{18}\text{F}-\text{FDG-}\text{PET/CT}\)) 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 \(^{18}\text{F}-\text{FDG-}\text{PET/CT}\) 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 \(^{18}\text{F}-\text{FDG-}\text{PET/CT}\) showed that daily changes expressed as ΔTLR × 10\(^3\)/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 ΔTLR × 10\(^3\)/day provides useful information of disease control status.

**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-
advanced 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 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 during the course of treatment remains unclear.
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) 18F-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 18F-FDG-PET/CT

Within 1 month before the initiation of lenvatinib, a 18F-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 18F-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: TLR = SUV-max of the tumor/SUV-mean of the normal liver. Based on previous reports [6, 9, 13], we selected a TLR ≥ 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

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

<table>
<thead>
<tr>
<th>18F-FDG-PET/CT TLR</th>
<th>Response evaluation using mRECIST, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR ≥2.0 (n = 27)</td>
<td>CR</td>
</tr>
<tr>
<td>4 (15)</td>
<td>17 (63)</td>
</tr>
<tr>
<td>OR</td>
<td>21 (78)</td>
</tr>
<tr>
<td>TLR &lt;2.0 (n = 21)</td>
<td>CR</td>
</tr>
<tr>
<td>1 (5)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>OR</td>
<td>13 (62)</td>
</tr>
</tbody>
</table>

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.
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 ≥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 18F-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 χ² 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
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 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), $^{18}$FDG-PET/CT positive (TRL ≥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.

### 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 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

<table>
<thead>
<tr>
<th>Table 3. Predictive factors for OS</th>
<th>$p$ value*</th>
<th>Coefficients†</th>
<th>SE</th>
<th>Wald $\chi^2$</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$FDG-PET/CT positive (TRL ≥2)</td>
<td>0.024</td>
<td>0.997</td>
<td>0.441</td>
<td>5.096</td>
<td>2.709</td>
<td>1.140–6.436</td>
</tr>
<tr>
<td>Tumor number +1 nodule</td>
<td>0.001</td>
<td>0.021</td>
<td>0.006</td>
<td>10.540</td>
<td>1.021</td>
<td>1.008–1.034</td>
</tr>
<tr>
<td>Age +1 year</td>
<td>0.044</td>
<td>0.054</td>
<td>0.027</td>
<td>4.061</td>
<td>1.055</td>
<td>1.001–1.112</td>
</tr>
</tbody>
</table>

CONUT score

<table>
<thead>
<tr>
<th>Normal nutrition</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Light undernutrition</td>
<td>0.260</td>
<td>1.167</td>
<td>1.036</td>
<td>1.269</td>
<td>3.211</td>
<td>0.422–24.440</td>
</tr>
<tr>
<td>Moderate undernutrition</td>
<td>0.068</td>
<td>1.951</td>
<td>1.071</td>
<td>3.321</td>
<td>7.037</td>
<td>0.863–57.371</td>
</tr>
</tbody>
</table>

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), $^{18}$FDG-PET/CT positive (TRL ≥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.
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 presented 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
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 18F-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-
The $\Delta$TLR $\times 10^3$/day tended to differ among the groups, with the R0 resection group having a greater decrease in the TLR value.

**Discussion**

$^{18}$F-FDG-PET/CT is considered a useful method for predicting the degree of histological differentiation on imaging analysis. $^{18}$F-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 $^{18}$F-FDG-PET/CT positivity (TLR $\geq 2$) correlated with a higher response to lenvatinib (Table 2) and had a similar PFS as a $^{18}$F-FDG-PET/CT-negative result (TLR <2). In addition a $^{18}$F-FDG-PET/CT-positive HCC was associated significantly with poor OS. Given that $^{18}$F-FDG-PET/CT positivity correlates strongly with poor differentiation, the present results suggest that PPS is dependent predominantly on the malignant

**Fig. 5.** Background and breakdown of initial subsequent treatment, and conversion rate between TLR <2 and $\geq 2$. 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 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.
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 \(^{18}\text{F-FDG-PET/CT}\), 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

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

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

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).
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 ΔTLR × 10^3/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 ΔTLR × 10^3/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 TLR × 10^3/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-Seisakujuouhou-10600000-Daijinkanboukouseikagakuka/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.
5. The other authors declare no conflicts of interest.

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**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.
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References