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Outcomes of the Sequential Treatment of Unresectable Hepatocellular Carcinoma Using Lenvatinib

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Clinical study

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Abstract

Background/Aim: The chemotherapeutic landscape for hepatocellular carcinomas (HCCs) has changed dramatically with the availability of several treatment options. This study aimed to assess the long-term outcomes of lenvatinib treatment and analyze its feasibility in the sequential treatment of HCCs.

Patients and Methods: Eighty-five consecutive patients who received lenvatinib for unresectable HCCs were investigated retrospectively. Survival was assessed based on when the patients were first radiologically diagnosed with progressive disease. Among those with radiologically diagnosed stable or progressive disease at 3 months after lenvatinib administration, the cutoff α-fetoprotein (AFP) ratio (ratio of the AFP level after lenvatinib treatment to the pretreatment AFP level) that was predictive of survival was determined using receiver operating characteristic analysis.

Results: The median survival time (MST) was significantly worse among patients diagnosed with progressive disease at 1 month after treatment than among those diagnosed at 2–3 or 3–4 months after treatment [MSTs at 1, 2–3, and 3–4 months: 2.2, 10.2, and 17.3 months, respectively (p<0.001)]. An AFP ratio of 1.36 (computed using the AFP level at 3 months after lenvatinib treatment) was

significantly predictive of survival in patients with stable or progressive disease (26.3 *vs*. 11.3 months, *p*=0.0024).

Conclusion: The prognosis of patients on lenvatinib who develop early progressive disease is dismal. Thus, their treatment should be ceased or switched. The 3-month AFP ratio of 1.36 may be a potentially useful cutoff for considering a switch to other treatments in patients radiologically diagnosed with stable or progressive disease.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and a leading cause of cancer-related mortality worldwide (1, 2). Although cancer surveillance programs are conducted among patients at a high risk of HCCs, some patients are diagnosed at an advanced stage; such patients present with multicentric intrahepatic spread, portal vein thrombosis, huge tumor burden, and distant metastasis (3). According to the clinical practice guidelines, standard treatments for early, intermediate, and advanced tumors include potentially curative therapies (*i.e.*, resection, radiofrequency ablation, and liver transplantation), transarterial chemoembolization, and systemic drugs (multikinase and immune checkpoint inhibitors), respectively (4-6).

Until recently, sorafenib (an oral multikinase inhibitor) was the only systemic drug that was shown to extend overall survival (OS) when administered as first-line treatment in patients with unresectable HCCs (7). A randomized phase III trial in 2018 demonstrated that lenvatinib was non-inferior to sorafenib in terms of OS (8). Lenvatinib, another oral multikinase inhibitor, targets vascular endothelial growth factor receptors-1–3, fibroblast growth factor receptors-1–4, platelet-derived growth factor receptor-β, RET, and the *KIT* gene (7). Additionally, lenvatinib administration achieved a significant improvement in secondary outcomes such as progression-free survival, time-to-progression, and objective response rate (ORR) (3).

Since its approval as a first-line oral multikinase inhibitor, several real-world studies have investigated the efficacy and safety of lenvatinib as a first-line treatment for advanced HCCs (9-11). In 2020, a study noted that the OS and progression-free survival were better with atezolizumab plus bevacizumab than

with sorafenib; since then, this combination has been adopted as a first-line treatment (4, 12). However, recent reports have suggested that the efficacy of atezolizumab plus bevacizumab is limited according to the etiology (13). Furthermore, this combination is contraindicated according to the patient's status, such as in the case of immune conditions. Thus, from a clinical perspective, the role of lenvatinib remains essential in the sequential treatment of HCCs.

The present study aimed to perform a detailed analysis of the long-term outcomes of lenvatinib and to analyze its role in the sequential treatment of HCCs.

Patients and Methods

Patient inclusion

This retrospective, single-institutional, non-comparative, observational study included patients with advanced, unresectable HCCs who were treated with lenvatinib at the Kobe University Hospital between April 2018 and July 2020.

A diagnosis of unresectable HCCs was established based on the findings from histological examinations or radiological imaging (contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging); the diagnosis was further confirmed if the patients were staged B or C in the Barcelona Clinic Liver Cancer staging system.

Data on the patient's demographic and clinical characteristics were collected; these included the age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG-PS), Child-Pugh class, albumin-bilirubin (ALBI) grade (14), and modified ALBI (mALBI) grade (15).

This study was performed in accordance with the ethical standards laid down

by the Declaration of Helsinki and approved by the Institutional Review Board of Kobe University in 2020 (approval number: #180289).

Protocol and assessment

Patients with body weights >60 kg and ≤60 kg were initiated on 12 mg/day and 8 mg/day of oral lenvatinib (Eisai Co., Ltd., Tokyo, Japan), respectively (16). These doses were reduced or ceased depending on the clinical situation. Laboratory tests, including those for assessing the serum levels of α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKAII), were performed every 4–8 weeks.

In clinical settings, it is often debated whether the treatment regimen should be continued or changed when the tumor response is SD or PD. Thus, to address this issue, we computed the AFP and PIVKAII ratios only for patients with SD and PD. The AFP ratios were the ratios of the AFP levels at specific timepoints after lenvatinib introduction to the pretreatment AFP level; similarly, the PIVKAII ratios were the ratios of the PIVKAII levels at specific timepoints after lenvatinib introduction to the pretreatment PIVKAII level.

Radiological assessments for the tumor response were performed every 4–8 weeks; using the modified response evaluation criteria in solid tumors (mRECIST) (17, 18), the responses at 1 month, 2–3 months, and 3–4 months after lenvatinib treatment were evaluated. The mRECIST categorizes treatment responses into four types, namely complete responses (CRs), partial responses (PRs), stable disease (SD), and progressive disease (PD). The ORR represents a combination of CRs and PRs, while the disease control rate (DCR) represents

a combination of the ORR and SD. Particularly, to determine the correlations between the OS and the radiological tumor response, the OS of patients diagnosed as DCR and as having PD were compared at each time point (*i.e.,* 1 month, 2–3 months, and 3–4 months after lenvatinib treatment). The correlations between the OS and the period when PD was first diagnosed were evaluated. The degree of pathological differentiation of HCCs was determined based on findings from previously resected specimens or previously collected biopsies. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events Version 5.0 [CTCAE (v 5.0)].

Statistical analysis

Quantitative data are expressed as means ± standard deviations. Qualitative data are expressed as absolute numbers and percentages. Common statistical measures were used to describe the distribution of continuous and categorical variables. All statistical analyses were performed using the JMP 16 statistical package (SAS Institute, Cary, NC, USA). Continuous variables were compared using the Mann–Whitney U-test, while categorical variables were compared using the chi-square test and Fisher's exact probability test. OS was defined as the period from lenvatinib treatment initiation to death by any cause; survival curves were analyzed using the Kaplan–Meier approach and compared using the log-rank test. A receiver operating characteristic curve analysis was performed to determine the AFP cutoff for considering a change in the treatment regimen among patients with SD and PD. $p<0.05$ indicated statistical significance.

Results

Baseline characteristics

This study included 85 patients [mean age: 69.2 years; men: 68 (80.0%)]; their demographic and clinical characteristics are shown in Table I. Fifty-two patients (61.2%) had a history of hepatitis B or hepatitis C. Furthermore, a PS of 0 was observed in 61 patients (71.8%), while Child-Pugh class A was observed in 64 patients (75.3%). The average ALBI score was -2.3101. The median AFP level was 87 ng/ml; 35 out of all patients (41.2%) had baseline AFP levels ≥400 ng/ml. Similarly, the median PIVKAII level was 193 μg/ml; 25 out of all patients (29.4%) had baseline PIVKAII levels ≥1,000 μg/ml. Furthermore, 58 patients had a pathological history that was shown by records of previous treatment. Pathologically, the HCCs were classified as being either well and moderately differentiated (well/moderate; n = 44) or as being poorly differentiated, combined, or sarcomatoid (poor/combined/sarcomatoid; n = 14). Distant metastasis was discovered in 50 patients. Finally, 20 and 65 patients had Barcelona Clinic Liver Cancer stages of B and C, respectively.

Treatment outcomes

Changes in liver function were evaluated based on the ratio of the pretreatment ALBI score to the ALBI scores after lenvatinib treatment. The liver function tended to improve 3 months after lenvatinib administration. This improvement was significantly more pronounced in patients with an mALBI grade of 2b/3 (*i.e.*, those with poor liver function) than in those with an mALBI grade of 1/2a (ratio of the ALBI score at 3 months after treatment to the pretreatment ALBI score: 1.060 *vs.*

0.949, p=0.021).

The overall median survival time (MST) in the cohort was 16.4 months, and the 1- and 2-year survival rates were 61.8% and 37.8%, respectively (Figure 1). The OS did not differ significantly between patients with hepatitis B/C and those without (MST; 21.1 *vs*. 14.4 months, *p*=0.3707). However, the OS was significantly better in patients with an mALBI grade of 1/2a than in those with an mALBI grade of 2b/3 (MST; 26.5 *vs*. 11.8 months, *p*=0.002). A significant difference in survival was observed according to the pathological differentiation of the HCCs; the MST was significantly higher in patients with well/moderate HCCs than in those with poor/combine/sarcomatoid HCCs (28.8 *vs*. 11.8 months, *p*=0.018).

Tumor response according to the mRECIST and tumor marker ratios

Table II shows the results of the radiological evaluations performed at each timepoint after lenvatinib administration. Radiological evaluations were performed in 52, 42, and 41 patients at 1, 2–3, and 3–4 months after lenvatinib administration, respectively. The corresponding ORRs were 40.4%, 45.2%, and 39.1%, respectively, while the corresponding DCRs were 94.2%, 76.2%, and 65.9%, respectively. At each time point, the OS was longer in patients with DCR than in those with PD [MST; 1 month: 19.5 *vs*. 2.2 months [*p*<0.001; Figure 2A]; 2–3 months: 23.5 *vs*. 10.2 months (*p*=0.018; Figure 2B), and 3–4 months: 32.0 *vs*. 17.3 months (*p*=0.034; Figure 2C)]. However, among patients with PD, the OS was significantly worse in those first diagnosed with PD at 1 month after treatment as compared to those first diagnosed with PD at 2–3 or 3–4 months

after treatment [MST at 1, 2–3, and 4–5 months: 2.2, 10.2, and 17.3 months, respectively (p<0.001); Figure 3A]. However, no significant differences were observed in the OS between patients first diagnosed with PD 2–3 months after treatment and those first diagnosed with PD 3–4 months after treatment (MST: 10.2 *vs*. 17.3 months, p=0.653; Figure 3B).

In the receiver operating characteristic curve analysis, the area under the curve was 0.57738; a cutoff AFP ratio of 1.36075 was identified as indicative of considering a change in the treatment regimen. The MST differed significantly between patients with AFP ratios ≤1.36075 and those with AFP ratios >1.36075 [MST: 26.3 *vs*. 11.3 months (p=0.002); Figure 4]. A comparison of the demographic data based on the cutoff AFP ratio of 1.36075 is shown in Table III. The proportion of females was significantly higher for patients with AFP ratios >1.36075 than for those with AFP ratios ≤1.36075. Although not statistically significant, the proportion of mALBI grade 2b/3 was higher for patients with AFP ratios >1.36075 than for those with AFP ratios ≤1.36075.

Adverse events

After receiving lenvatinib, 84 out of 85 patients developed AEs. The most frequent AEs were fatigue, hypothyroidism, hypertension, elevated aspartate transaminase or alanine transaminase levels, loss of appetite, hepatic encephalopathy, the hand-foot syndrome, and proteinuria. Severe AEs, defined by grades 3 and 4 of the CTCAE (v 5.0), occurred in 40 patients. Overall, 53 severe AEs were confirmed, and the most frequent events were proteinuria, fatigue, hypertension, and elevated aspartate transaminase or alanine

transaminase levels. There were no significant differences in the incidences of all AEs and severe AEs between patients with mALBI grade 1/2a and those with mALBI grade 2b/3 (all AEs: p=0.332, severe AEs: p=0.107; Table IV).

Discussion

Compared to the cohort analyzed in the REFLECT trial, the cohort in the present study had a more impaired liver function (represented by Child-Pugh classes B and C); however, the OS was comparable between the two. This indicates acceptable medium-to-long-term outcomes following lenvatinib administration in patients with advanced, unresectable HCCs (7).

In the present study, the OS was observed to be shorter in patients radiologically diagnosed with PD at 1 month after lenvatinib administration (Figure 2). However, no significant differences were observed in the OS among patients diagnosed with PD thereafter (*i.e.*, at 2–3 months and at 3–4 months after lenvatinib administration). This indicates that observation of disease control on radiological imaging 1 month after lenvatinib treatment can be a crucial predictor of the post-treatment OS. Takahashi *et al.* reported that early tumor shrinkage was predictive of a prolonged OS (19). In this rapidly evolving era of multi-chemotherapy, the optimal time for discontinuing or switching a treatment regimen remains unknown and is a matter of concern. The present study indicated that lenvatinib continuation should be avoided when PD is recognized early, and physicians should consider changing the regimen immediately thereafter.

Meanwhile, lenvatinib can exert antitumor effects even if its dose is reduced

or the drug is withdrawn (20-22). Furthermore, the continuation of lenvatinib during the diagnosis of PD in the clinical course reportedly contributes to prolonged survival (23). Accordingly, it is important that decisions for continuing or changing the regimens be made on a case-by-case basis; however, there are no clear guidelines for the same. In patients with CRs and PRs, the regimen must undoubtedly be continued; however, this decision is more difficult in patients radiologically diagnosed with SD and PD. The present study has indicated that the ratio of the AFP levels at 3 months after lenvatinib treatment to the pretreatment AFP level can serve as a significant predictor of survival. This can be especially useful in resolving discrepancies between radiological findings and AFP transition. The factors with female and mALBI 2b/3 can be risk factors for increased AFP levels above the cutoff values. Further research on the accumulation of clinical cases is required for more clarity.

Liver function is an important factor for survival after treatment for HCCs, and maintenance of liver function during treatment is crucial. In the present study, no apparent liver function deterioration was observed after lenvatinib treatment. For all patients, the ALBI scores improved slightly from their baseline values at 3 months after lenvatinib administration. This trend was particularly remarkable in patients with impaired liver function (represented by an mALBI grade of 2b/3). There was a significant difference in the mALBI transition at 3 months after treatment between patients with mALBI 1/2a and those with mALBI 2b/3. Although the interpretation of this finding is difficult and cannot be applied to every clinical situation, lenvatinib administration is not necessarily associated with liver function deterioration, even among those with impaired liver function. Regarding

lenvatinib-associated AEs, no significant differences in the proportions of total and severe AEs were noted between patients with mALBI 1/2a and those with mALBI 2b/3 in the present study. Thus, these findings have indicated the potential feasibility and effectiveness of lenvatinib treatment in patients with impaired liver function.

Currently, the atezolizumab plus bevacizumab combination is administered as the first-line systemic chemotherapy for HCCs, and lenvatinib is positioned as the second-line treatment in the regimen (4). However, lenvatinib is clinically considered an alternative first-line treatment for patients without indications for atezolizumab plus bevacizumab. Considering the limited reported efficacy of immune checkpoint inhibitors in patients without viral infections (13) and the restrictions on their usage in patients with severe autoimmune diseases, lenvatinib is still positioned as an important key drug. The present study revealed no differences in the effectiveness of lenvatinib among those with and without viral infections; it also demonstrated the superior outcomes of well/moderate HCCs over those of poor/combined/sarcomatoid HCCs. These findings can help in the delivery of personalized medicine and broaden the therapeutic sensitivity of chemotherapeutic treatment.

Recently, the significance of a treatment sequence comprising the administration of tyrosine kinase inhibitors immediately after the administration of immune checkpoint inhibitors has been reported (24). Furthermore, the concept of “rechallenge chemotherapy,” *i.e*., the re-administration of the same regimen for chemo-resistant tumors, has also been presented as a promising therapeutic alternative (25). A phase II study revealed promising outcomes of a combination

of lenvatinib with pembrolizumab; this combination is expected to become a considerably viable option in the future (26). Accordingly, lenvatinib will continue to play a significant role in the sequential treatment of HCCs.

The limitations of the present study include its retrospective nature. Furthermore, the patients in this study constituted a highly selective cohort representing a relatively homogeneous population. However, despite these limitations, the present study, with its detailed assessments and clinically based evidence, will serve as a milestone in developing lenvatinib-based regimens.

In conclusion, lenvatinib treatment can be effective and tolerable in the sequential treatment of HCCs. Radiological and biological landmarks may help in the precise enhancement of lenvatinib treatment and contribute to the prolonged survival of patients with HCCs.

Conflicts of Interest

The Authors declare no conflicts of interest in connection with this manuscript.

Authors' Contributions

Study conception and design; Nakagawa D, Komatsu S. Data collection; Kido M, Kuramitsu K, Yamamoto A, Omiya S, Shimura Y. Article preparation and review; Yano Y, Goto T, Yanagimoto H, Toyama H, Ueda Y, Kodama Y. Supervision; Fukumoto T.

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Figure legends

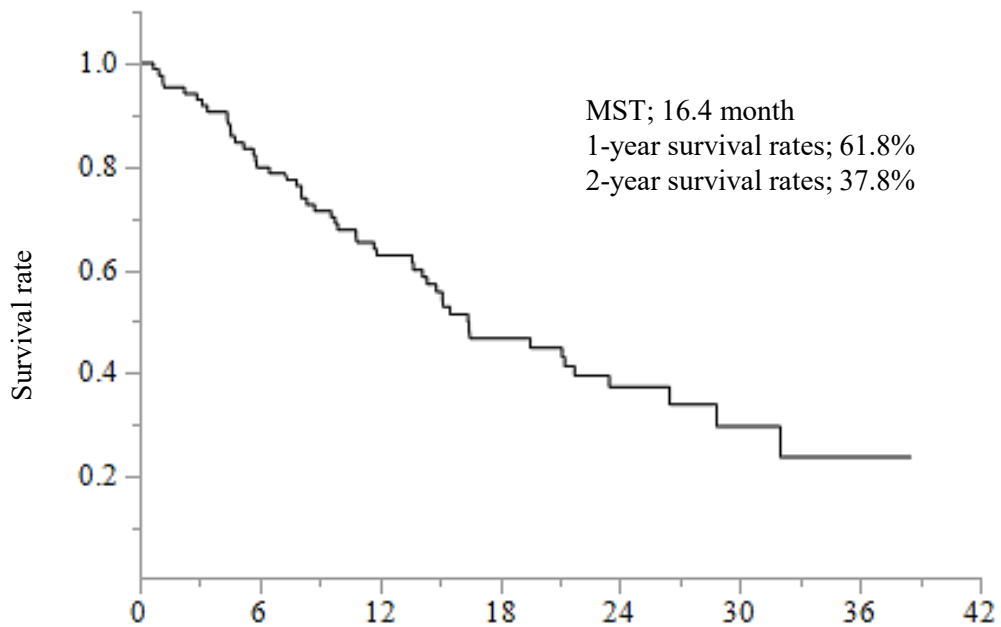
Figure 1. Overall survival of all patients after lenvatinib administration.

Figure 2. Overall survival rates according to the radiological evaluations performed using the modified RECIST. Survival was assessed as the “disease control rate” or “progressive disease” at each of the following timepoints. (A) One month after lenvatinib administration; (B) 2–3 months after lenvatinib administration; and (C) 3–4 months after lenvatinib administration. DCR: Disease control rate; PD: progressive disease.

Figure 3. Comparison of the overall survival rates among the timepoints when progressive disease was first diagnosed. (A) 1 month, 2–3 months, and 3–4 months after lenvatinib administration. (B) 2–3 months and 3–4 months after lenvatinib administration.

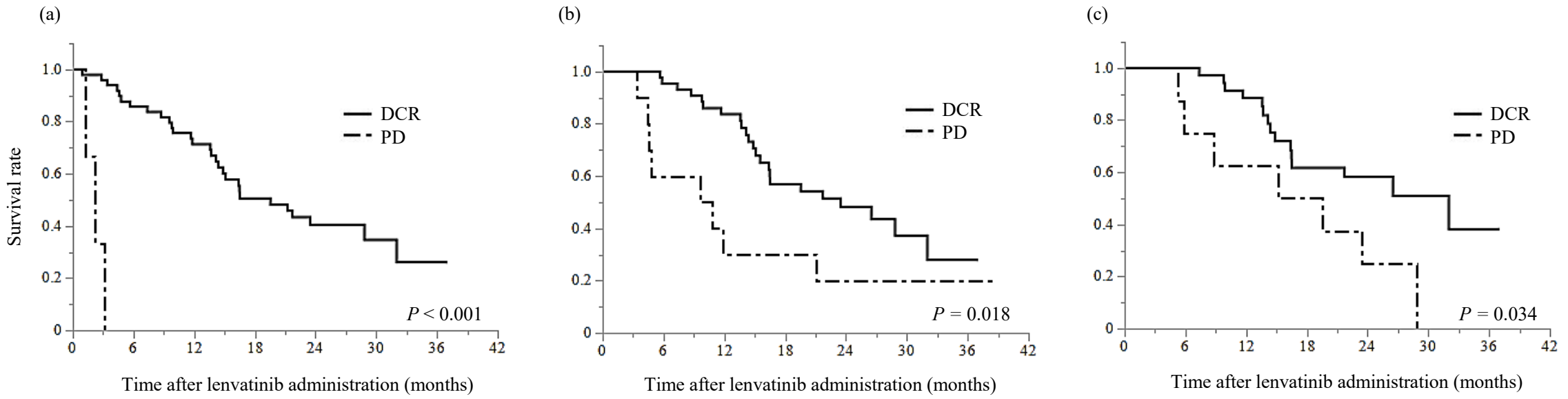
Figure 4. Overall survival rates according to the cutoff α-fetoprotein ratio (*i.e.*, the ratio of the α-fetoprotein level at 3 months after lenvatinib administration to the pretreatment α-fetoprotein level).

Figure 1



Number at risk	85	68	49	29	18	7	3	0

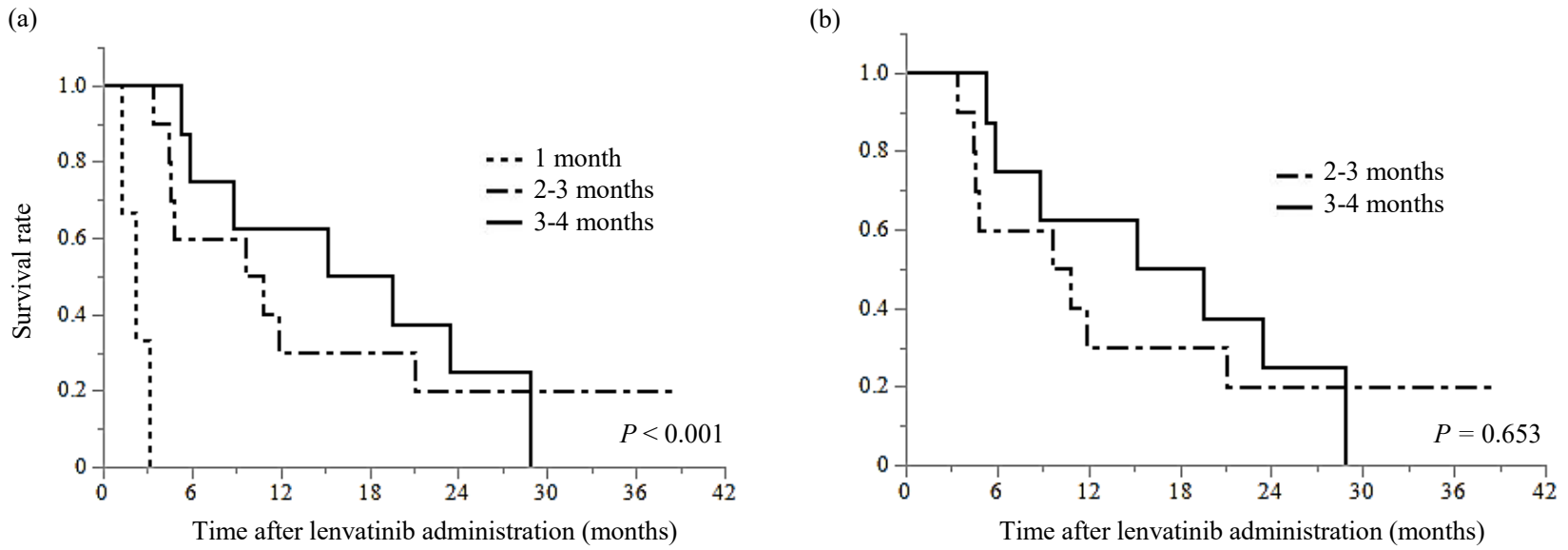
Figure 2



Number at risk

Group: DCR	49	43	35	22	15	6	2	0	43	42	35	22	16	6	2	0	35	35	30	19	14	6	2	0
Group: PD	3	0	0	0	0	0	0	0	10	7	4	4	3	2	2	0	8	8	6	5	3	0	0	0

Figure 3

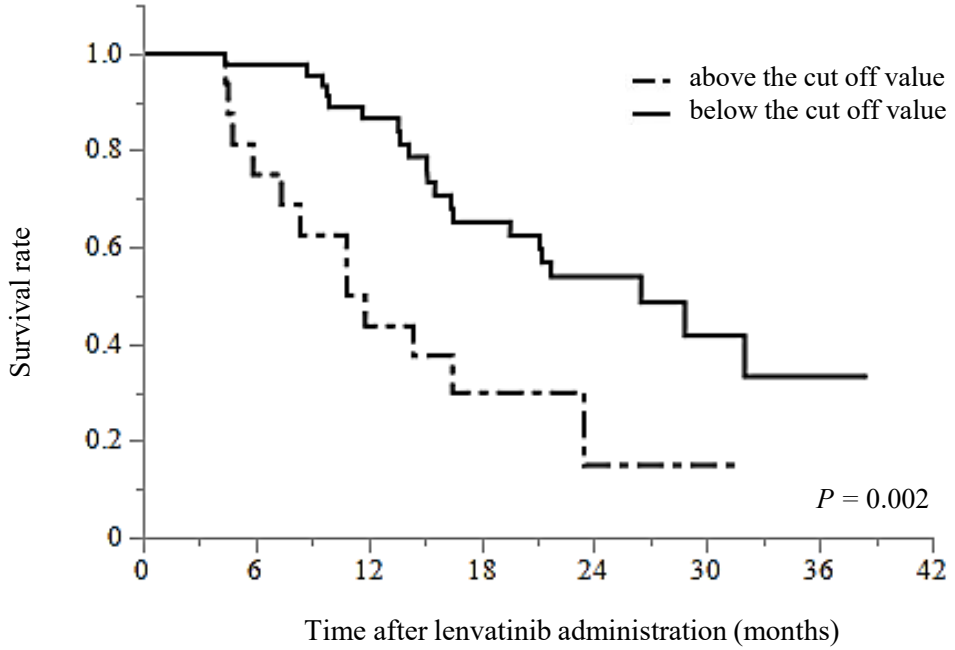


Number at risk

Group: 1 month	3	0	0	0	0	0	0	0
Group: 2-3 months	10	7	4	4	3	2	2	0
Group: 3-4 months	8	7	6	5	3	0	0	0

10	7	4	4	3	2	2	0
8	7	6	5	3	0	0	0

Figure 4



Number at risk

Group: above the cut off value	16	13	8	3	2	2	0	0
Group: below the cut off value	45	45	37	25	16	6	3	0

Table I. Patient characteristics.

Characteristics	All patients
Age, years, median (range)	71.5 (34-86)
Sex, n (%)	
Male	68 (80)
Female	17 (20)
ECOG-PS	
0 : 1 : 2	61 : 22 : 2
Original disease, n (%)	
HBV and/or HCV	52 (61.2)
Others	33 (38.8)
Child-Pugh classification, n (%)	
A	64 (75.3)
B	21 (24.7)
mALBI grade, n (%)	
1/2a	44 (51.8)
2b/3	41 (48.2)
AFP, ng/dl, median (range)	87 (2-554601)
PIVKA-II, mU/l, median (range)	193 (13-152517)
Pathological differentiation degree, n (%)	
Well and moderate	44 (51.8)
Poor, combine and sarcomatoid	14 (16.5)
None or unknown	27 (31.7)
Maximal tumor size, cm, median (range)	3.2 (0.5-18)
Region of tumor, n (%)	
Intrahepatic only	35 (41.2)
Extrahepatic only	20 (23.5)
Both	30 (35.3)
BCLC classification, n (%)	
B	20 (23.5)
C	65 (76.5)

ECOG-PS: Eastern cooperative oncology group performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; mALBI: modified albumin-bilirubin; AFP: α-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist II; BCLC: Barcelona Clinic Liver Cancer.

Table II. Radiological evaluations performed at each timepoint after lenvatinib administration.

	After 1 month (n = 52)	After 2-3 months (n = 42)	After 3-4 months (n = 41)
CR, n (%)	8 (15.4)	6 (14.2)	7 (17.1)
PR, n (%)	13 (25.0)	13 (31.0)	9 (22.0)
SD, n (%)	28 (53.8)	13 (31.0)	11 (26.8)
PD, n (%)	3 (5.8)	10 (23.8)	14 (34.1)
ORR (CR+PR), n (%)	21 (40.4)	19 (45.2)	16 (39.1)
DCR (CR+PR+SD), n (%)	49 (94.2)	32 (76.2)	27 (65.9)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate; DCR: disease control rate.

Table III. Comparison of demographic data based on the cutoff value of the α-fetoprotein (AFP) ratio.

	AFP ratio ≤ 1.36075 (n = 45)	AFP ratio > 1.36075 (n = 16)	*p*-Value
Age (years)*	69.9 (9.4)	70.9 (9.6)	0.7179
Sex ratio			0.0370
Male	37	10	
Female	8	6	
Original disease, n (%)			0.3130
HBV and/or HCV	29	8	
Others	16	8	
mALBI grade			0.0618
1/2a	29	6	
2b/3	16	10	
BCLC stage			0.5994
Stage B	11	5	
Stage C	34	11	
Treatment line			0.8216
First line	35	12	
Second or later line	10	4	
Macroscopic vascular invasion			0.3832
Yes	10	2	
No	35	14	
Distant metastases			0.3955
Yes	28	8	
No	17	8	
Intrahepatic maximal tumor size			0.6366
> 5 cm	11	3	
≤ 5 cm	34	13	

Values in parentheses are percentages unless indicated otherwise; *values are mean (standard deviation).

AFP: α-fetoprotein; HBV: hepatitis B virus; HCV: hepatitis C virus; mALBI: modified albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer.

Table IV. Adverse events.

	All cases (n = 85)	mALBI grade 1/2a (n = 44)	mALBI grade 2b/3 (n = 41)	*p*-Value
Any grades, n (%)	84 (98.8)	43 (97.7)	41 (100)	0.332
Grade 3/4, n (%)	40 (47.1)	17 (38.6)	23 (56.1)	0.107

mALBI: Modified albumin-bilirubin.