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ORIGINAL ARTICLE

Well-preserved liver function enhances the clinical impact of curative-intent subsequent treatment during lenvatinib treatment for unresectable hepatocellular carcinoma

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Abstract

Background The aims of this study were to evaluate the clinical impact of curative-intent subsequent treatment on overall prognosis in lenvatinib-treated hepatocellular carcinoma (HCC) patients.

Methods Eighty-three consecutive patients with intrahepatic target nodules who received lenvatinib were reviewed. The clinical impact of curative-intent subsequent treatments was investigated through analysis of overall survival (OS) according to pathological deterioration stratified by mALBI grade.

Results In patients with mALBI grade 1 and 2a liver function, R0 resection and lenvatinib-transarterial chemoembolization (lenvatinib-TACE) sequential therapy resulted in significantly better OS compared with other, non-curative-intent subsequent therapy and lack of additional treatment (median OS, 37.6 vs 29.0 months and 17.1 vs 8.9 months, respectively; $P < 0.001$). Multivariate analysis confirmed that use of R0 resection and lenvatinib-TACE sequential therapy were associated with better OS (hazard ratio [HR], 0.021; $P < 0.001$ and 0.108; $P < 0.001$) compared with other, non–curative-intent subsequent treatment (HR 0.256; $P = 0.010$). In contrast, in patients with mALBI grade 2b liver function, multivariate analysis confirmed higher treatment efficacy for non–curative-intent subsequent treatment with respect to OS (HR 0.041; $P < 0.001$) compared with R0 resection and lenvatinib-TACE sequential therapy (HR 0.057; $P = 0.027$ and 0.063; $P = 0.001$).

Conclusion Curative-intent subsequent treatment is more useful for HCC patients with better liver function (mALBI grade 1 and 2a) and intrahepatic target nodules who have received lenvatini b-based treatment.

Keywords Hepatocellular carcinoma · Lenvatinib · Subsequent treatment · Lenvatinib-transarterial chemoembolization sequential therapy

Abbreviations

AE	Adverse event
AFP	Alpha-fetoprotein
ALBI	Albumin-bilirubin
BCLC	Barcelona Clinic Liver Cancer
DCP	Des-γ-carboxyprothrombin
HCC	Hepatocellular carcinoma
mALBI	Modified albumin-bilirubin
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PPS	Post-progression survival RFA, radiofrequency ablation

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TACE Transarterial chemoembolization
TKI Tyrosine kinase inhibitor

Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, which, in turn, is the third most frequent type of cancer [1]. The Barcelona Clinic Liver Cancer (BCLC) system is widely used for staging HCCs [2–4], and various current treatment strategies depend on this staging algorithm. Molecularly targeted therapy is recommended as first-line treatment for advanced-stage HCC (BCLC stage C); and for intermediate-stage (BCLC stage B) HCC, transarterial chemoembolization (TACE) is recommended and is one of the most popular treatment options. BCLC intermediate-stage disease is quite heterogeneous, and can be further subclassified using the Up-to-7 criteria [5] and Child–Pugh score [6]. A recent report suggested that TACE is preferred for patients with tumors within the Up-to-7 criteria who have good liver function [7]. Moreover, in patients who exceed the Up-to-7 criteria and have a high tumor burden, upfront molecularly targeted therapy followed by TACE has been reported to be a useful treatment option in various clinical studies [8–14] and by the current AASLD guidelines [15]. However, the importance of intrahepatic tumor control in patients with extrahepatic tumor spread has also been reported [16–22].

Since the recent introduction of lenvatinib [23, 24], encouraging results have been reported regarding a highly synergic effect with TACE [9–12] and high treatment efficacy in patients with oncologically aggressive HCC [25–27]. However, the efficacy of subsequent treatments for various tumor and patient conditions (e.g., presence/absence of extrahepatic spread, macrovascular invasion, and liver function) after initiation of lenvatinib remains unclear. Therefore, in this study, we evaluated the efficacy of subsequent treatment following lenvatinib-based therapy in patients with HCC with intrahepatic target nodules and various degrees of liver function as determined by modified albumin-bilirubin (mALBI) grade.

Patients and methods

Study population

Between October 2010 and February 2022, among 137 consecutive patients who received systemic lenvatinib for unresectable HCC, 83 patients were selected based on the following inclusion criteria: (1) unenhanced and four-phase dynamic-computed tomography (CT) study performed within 1 month prior to initiation of lenvatinib, (2) tumor with hyperenhancement in the arterial phase of dynamic-CT, (3) dynamic-CT study performed to evaluate initial treatment response 2–12 weeks after initiation of lenvatinib, (4) Child–Pugh class A liver function at the time of lenvatinib initiation, (5) BCLC stage A-C tumor(s), (6) 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 spread, TACE refractoriness, and various complications), (7) no treatment history of lenvatinib, (8) at least one measurable target nodule in the liver, (9) a treatment interval of >28 days since previous tyrosine kinase inhibitor (TKI; sorafenib or regorafenib) therapy, and 10) an observation period of ≥ 4 weeks. All procedures were carried out in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. The study was approved by the Institutional Review Board of our hospital (protocol number; 1438-H/B).

Diagnosis of HCC

Diagnosis of HCC was predominantly based on image analysis using dynamic-CT. All patients underwent unenhanced and four-phase dynamic-CT using a 64-multidetector CT (MDCT) scanner (Aquilion 64, Canon Medical Systems, Tochigi, Japan) or 80-MDCT scanner (Aquilion one, Canon Medical Systems) using a protocol reported elsewhere [27]. When a liver nodule showed hyperattenuation in the arterial phase and washout in the portal or delayed phase on dynamic study, the nodule was diagnosed as HCC.

Imaging analysis of HCC and definitions of dynamic-CT enhancement patterns

Before treatment, HCC enhancement was classified into the following three patterns according to our CT enhancement classification (Supplementary Fig. 1), considering their strong association with macroscopic classification and histopathological differentiation in non-treated HCCs [28]: Type-2, homogeneous enhancement pattern with increased arterial blood flow; Type-3, heterogeneous enhancement pattern with a septum-like structure; and Type-4, heterogeneous enhancement pattern with irregularly shaped ring structures. This unique enhancement pattern classification was originally established in a surgically resected population, and its efficacy in prediction of oncological aggressiveness of HCC was later validated using a medical population treated by radiofrequency ablation (RFA) [29].

Enhancement patterns were assessed independently by an expert hepatologist (Y. Kawamura), expert hepatobiliary surgeon (J. Shindoh), and expert radiation oncologist (L. Tominaga) who were blinded to clinical data. Discrepancies

between examiners were resolved by consensus review including an additional reviewer (K. Ikeda). All target HCC nodules appeared to be hypervascular in the study; therefore, all nodules were classified by one of the three enhancement patterns described above (Type-2 to -4). The enhancement pattern that accounted for 70% of nodules was defined as the predominant enhancement pattern.

Lenvatinib treatment and assessment of adverse events

Lenvatinib (Lenvima®, Eisai, Tokyo, Japan) was administered orally to the majority of patients at a dose of either 8 mg/day for patients < 60 kg or 12 mg/day for patients ≥ 60 kg. Treatment was discontinued when any unacceptable or serious adverse events (AEs) occurred or significant clinical tumor progression was observed. According to the guidelines for administration of lenvatinib, the drug dose should be reduced or treatment interrupted when a patient develops grade ≥ 3 severe AEs or any unacceptable grade 2 drug-related AEs occur. AEs were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [30]. In accordance with the guidelines provided by the manufacturer, when a drug-related AE occurred, dose reduction or temporary interruption was maintained until symptoms resolved to either Grade 1 or 2.

Treatment protocol for subsequent TACE

Patients who subsequently received TACE during their treatment course either had TACE alone or lenvatinib-TACE sequential therapy. TACE was performed using a schedule and/or on-demand according to the tumor condition, with the decision to continue administration of lenvatinib during progressive disease (PD) based on liver function after TACE and physician judgment. In patients who received lenvatinib-TACE sequential therapy, lenvatinib was discontinued for 1 to 14 days (median, 3 days) before and 1 to 55 days (median, 10 days) after each TACE session, based the condition of the patient and the tumor. At the time of re-administration, the same starting dose was used as before TACE. TACE in both groups consisted of an intra-arterial injection of lipiodol plus warmed miriplatin (Miripla®, Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan), cisplatin (IA-call®, Nippon Kayaku, Tokyo, Japan), or epirubicin (Farmorubicin®, Pfizer, Tokyo, Japan). This was followed by injection of 1-mm gelatin particles (Gelpart®, Nippon Kayaku) mixed with contrast agent into the target blood vessel until complete obstruction of the tumor-feeding branch was achieved. In patients who received miriplatin, the injector containing miriplatin/lipiodol suspension and sterilized physiological saline was placed in a container and warmed to 60 °C, followed by injection of miriplatin (60 mg) suspended in 3.0 mL lipiodol. Injected miriplatin doses ranged from 50 to 100 mg. In patients who received cisplatin, 100 mg cisplatin was first dissolved in 70 mL saline. Then, cisplatin and lipiodol were divided into 7–10 parts, after which 7–10 mL cisplatin solution and 0.5–1 mL lipiodol were alternately repeatedly infused. The doses of cisplatin and lipiodol injected in each patient ranged from 60 to 100 mg cisplatin and from 3 to 5 mL lipiodol. For patients who received epirubicin, the agent was suspended with 2–5 mL lipiodol to prepare the contrast material, with ½–1/3 lipiodol, or was loaded to drug-eluting beads (DC Beads™, Boston Scientific, Marlborough, MA, USA) with 18–40 mg epirubicin per patient. In patients who received lenvatinib-TACE sequential therapy, all patients received miriplatin or epirubicin for the first TACE procedure after lenvatinib. Selection of anticancer agents (miriplatin, cisplatin, or epirubicin) was decided by the investigators. On-demand TACE was repeated until treatment failure due to progressive major vascular invasion, tumor-feeding artery disappearance due to repeat treatment, or deteriorated hepatic function.

Evaluation of treatment response

Treatment response was evaluated in accordance with the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [31]. We assessed the best tumor response over 2–12 weeks. Treatment response was assessed independently by an expert hepatologist (Y. Kawamura) and an expert hepatobiliary surgeon (J. Shindoh) who were blinded to the clinical data. Discrepancies between these two examiners were resolved by consensus review including an additional reviewer (K. Ikeda).

Definition of TACE failure

TACE failure was defined as an insufficient response after ≥ 2 consecutive TACE procedures evident during response evaluation on CT or magnetic resonance imaging (MRI) after 1–3 months, even in situations in which the chemotherapeutic agent had been changed and/or the feeding artery was redetermined. In addition, the appearance of a higher number of lesions in the liver than that recorded at the previous TACE procedure (other than the nodule being treated) was also defined as TACE failure/refractoriness [32].

Decision process regarding the timing and method of subsequent treatment

When the patients presented with a good treatment response or progressive disease based on imaging analysis, we discussed the timing and most suitable additional subsequent

treatment method according to each patient's tumor and hepatic reserve condition at a weekly multidisciplinary conference.

Assessment of hepatic functional reserve

The Child–Pugh classification [6] and ALBI grade [33] were used to assess hepatic functional reserve. The modified ALBI (mALBI) grade was based on the ALBI score, calculated from serum albumin and total bilirubin concentrations using the following formula: [ALBI score = ($\log_{10}$ bilirubin [μmol/L] × 0.66) + (albumin [g/L] × − 0.085)], defined by the following cut-off values: ≤ − 2.60 = Grade 1; > − 2.60 to ≤ − 2.27 = Grade 2a; > − 2.27 to ≤ − 1.39 = Grade 2b; and > − 1.39 = Grade 3[34].

Follow-up protocol

Physicians examined patients every 1–2 weeks after initiation of lenvatinib, and biochemical laboratory and urine tests were also performed. After initiation of lenvatinib, patients underwent dynamic-CT to evaluate early treatment response during the 2–12 week period. Dynamic-CT or -MRI was performed every 1–3 months after the first evaluation of best treatment response.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (ver. 28.0 SPSS Inc., IL, USA). Data were expressed as the median and range. Differences in background features between each parameter were analyzed by the chi-squared test, Fisher's exact test, or Mann–Whitney U test. *P*-values < 0.05 were considered to indicate statistical significance. Progression-free survival (PFS), post-progression survival (PPS), and overall survival (OS) after introduction of lenvatinib were estimated by the Kaplan–Meier method, with values compared using log-rank testing. For the PFS analysis, patients who received scheduled curative-intent sequential therapy (R0 resection and lenvatinib-TACE sequential therapy) were treated as censored cases.

To identify factors associated with OS after initiation of lenvatinib, a multivariate analysis was performed using a Cox proportional hazards model. In this analysis, in addition to pretreatment parameters, subsequent treatment was added as a possible factor for intervention. All factors that were at least marginally associated with OS ($P < 0.15$) in univariate analysis were entered into a stepwise Cox regression analysis. Significant variables were 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 72 years, and 62 (75%) patients were male. Four patients (5%) who were enrolled in a global Phase II study received a higher starting dose (12 mg) of lenvatinib. The median size of the largest tumor was 33.0 mm (range, 11–175 mm), and the median number of tumors was 4 (range, 1 to > 200). Of the 83 patients, 12 (14%) patients with BCLC stage A disease received lenvatinib due to tumor location, TACE failure/refractoriness, and patient preference, and 39 (47%) patients presented with BCLC stage C disease (macrovascular invasion [$n = 18$] (Vp2, $n = 10$; Vp2 and Vv1, $n = 1$; Vv2, $n = 1$; Vp3 and Vv3, $n = 1$; and Vp4, $n = 5$) and extrahepatic spread [$n = 25$]). Ten patients (12%) had a history of treatment with other TKIs, and 54 patients (65%) had a TACE failure/refractoriness status. The median number of TACE treatments was 3 (range, 0–20) before initiation of lenvatinib. The median (range) relative dose intensity (RDI) of lenvatinib was 100% (25–150%) at 2 weeks, 93% (29–150%) at 4 weeks, 86% (30–150%) at 8 weeks, and 74% (31–138%) at 12 weeks. Sixty patients had died at the time of database lock (February 23, 2022), with a median duration of lenvatinib administration of 6.6 months and median observation period of 15.3 months.

Treatment response after initiation of lenvatinib according to the dynamic-CT enhancement pattern

In the evaluation of the early treatment response based on the dynamic-CT enhancement pattern assessed by mRECIST, the objective response rate (ORR) of each enhancement pattern (Type-2, -3, -4) was 55, 78, and 86%, respectively. The ORR was significantly higher with the heterogeneous enhancement pattern than with the homogeneous enhancement pattern (81% vs. 55%, respectively) ($P = 0.036$) (Supplementary Table 1).

Overall prognosis of lenvatinib-treated HCC patients

Supplementary Fig. 2 shows the survival outcomes of lenvatinib-treated HCC patients. Median PFS was 6.4 months (Supplementary Fig. 2a), median PPS was 9.4 months (Supplementary Fig. 2b), and median OS was 17.1 months (Supplementary Fig. 2c).

Impact of general landmark predictive factors for OS of HCC

Figure 1 shows the impact of general HCC landmark predictive factors for OS. The presence of high tumor burden

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

Patient characteristics and laboratory data	
Number of patients	83
Sex, males:females, *n*	62:21
Age, years (range)[a]	72 (45–91)
Body mass index, kg/m^2 (range)	22.6 (11.9–34.8)
Body weight < 60 kg: ≥ 60 kg	41:42
HCV:HBV:NonB, NonC	39:14:30
Performance status 0:1, *n* (%)	78 (94%):5 (6%)
Platelet count, × 10^3/μL (range)[a]	131 (48–371)
Albumin, g/dL (range)[a]	3.7 (2.9–4.6)
Total bilirubin, mg/dL (range)[a]	1.0 (0.3–2.8)
Prothrombin activity, % (range)[a]	82.3 (64.9–124.8)
AST, IU/L (range)[a]	36 (15–351)
AFP, μg/L (range)[a]	91.0 (0.8–61,040.7)
DCP, AU/L (range)[a]	158.0 (9.0–96,035.0)
Child–Pugh score 5:6, *n* (%)	55 (66%):28 (34%)
mALBI score (1:2a:2b:3), *n* (%)	22 (27%):34 (41%):27 (33%):0 (0%)
Initial dose of lenvatinib, 4 mg:8 mg:12 mg [*n* (%)]	3 (4%):40 (48%):40 (48%)
Reduced starting dose of lenvatinib [*n* (%)]	8 (10%)
History of TKI treatment, *n* (%)	10 (12%)
Tumor characteristics	
Largest tumor diameter, mm (range)[a]	33.0 (11.0–175.0)
Number of tumors, *n* (range)	4 (1 to > 200)
Exceeding Up-to-7 criteria, *n* (%)	44 (53%)
Macrovascular invasion, *n* (%)	18 (22%)
Extrahepatic metastasis, *n* (%)	25 (30%)
BCLC stage A:B:C, *n* (%)	12 (14%):32 (39%):39 (47%)
TACE failure/refractoriness, *n* (%)	54 (65%)
Pretreatment dynamic-CT study enhancement pattern (number and ratio)	
Type -2; -3; -4, *n* (%)	20 (24%); 41 (49%); 22 (27%)

Ratios are rounded off to the first decimal place; therefore, the total will not necessarily be 100

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, *NonB, NonC*, neither HBV nor HCV infection present, *TACE*, transarterial chemoembolization, *TKI* tyrosine kinase inhibitor

[a]Data expressed as median (range)

(exceeding the Up-to-7 criteria, $P < 0.001$; Fig. 1a), macrovascular invasion (Fig. 1b, $P = 0.022$), predicted highly malignant tumor potential (dynamic-CT enhancement pattern Type-4, $P = 0.030$; Fig. 1d), and relatively worse residual liver function (vs. mALBI grade 1, $P = 0.022$; Fig. 1e) were associated with significantly worse OS. Furthermore, history of subsequent treatment with curative intent (lenvatinib-TACE sequential therapy and R0 resection, $P < 0.001$; Fig. 1f) during lenvatinib-based therapy was associated with significantly better OS. In contrast, no significant differences in OS were observed with respect to presence of extrahepatic spread ($P = 0.738$; Fig. 1c).

Impact of general HCC landmark predictive factors for OS stratified by mALBI grade

Supplementary Fig. 3 shows the impact of general HCC landmark predictive factors for OS in patients with mALBI grade 1 and 2a liver function. High tumor burden (exceeding the Up-to-7 criteria, $P = 0.012$; Supplementary Fig. 3a) and predicted highly malignant tumor potential (dynamic-CT enhancement pattern Type-4, $P = 0.005$; Supplementary Fig. 3d) were associated with significantly worse OS. In contrast, history of subsequent treatment with curative intent (lenvatinib-TACE sequential therapy

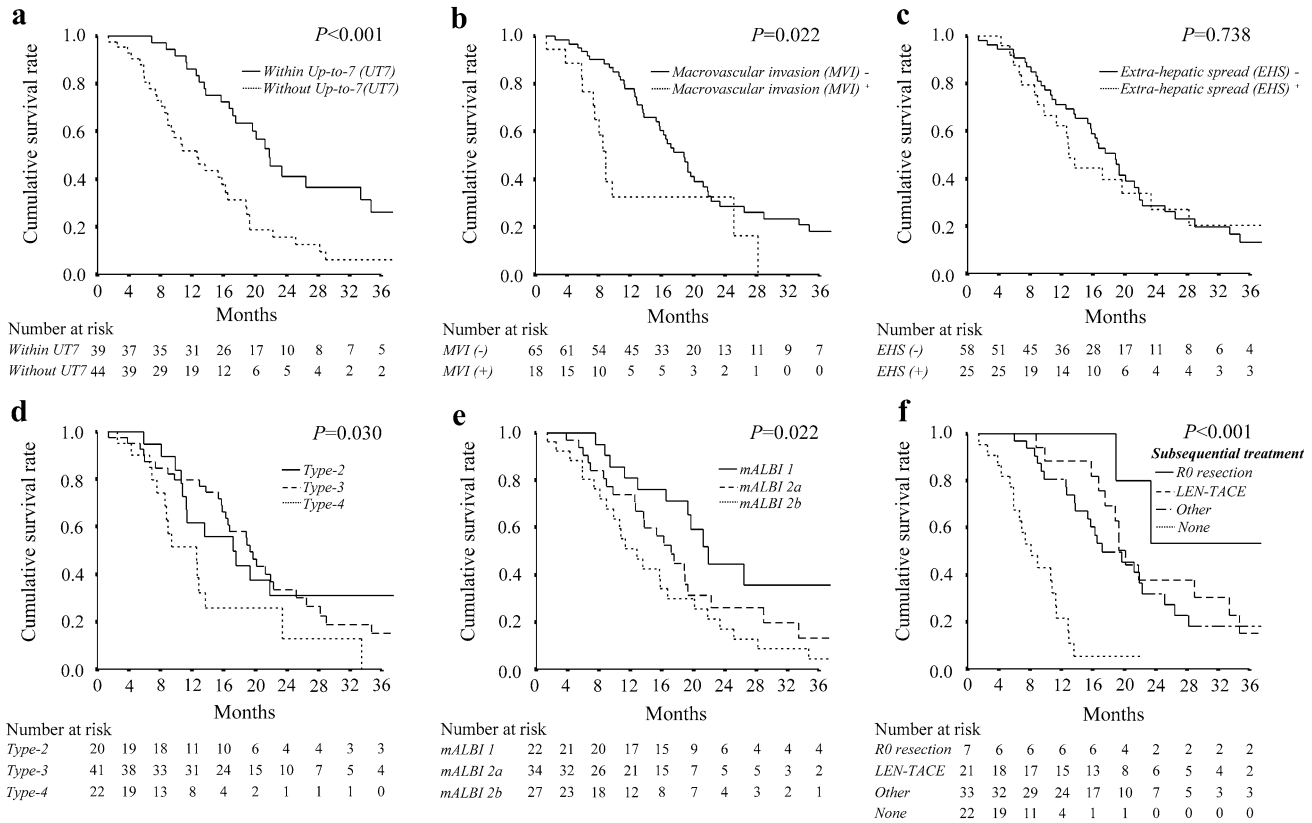

Fig. 1 Overall survival outcomes of all lenvatinib-treated HCC patients stratified by **a** tumor burden (estimated using the Up-to-7 criteria), **b** presence of macrovascular invasion, **c** presence of extrahepatic spread, **d** pretreatment dynamic-CT enhancement pattern, **e** mALBI grade, and **f** use of subsequent treatment during the treatment period. UT7, Up-to-7; MVI, microvascular invasion; EHS, extrahepatic spread; mALBI, modified albumin-bilirubin; LEN-TACE, lenvatinib-transarterial chemoembolization

and R0 resection, $P < 0.001$; Supplementary Fig. 3e) during the treatment period was associated with significantly better OS. Additionally, presence of macrovascular invasion showed marginal significance ($P = 0.064$; Supplementary Fig. 3b). However, with respect to extrahepatic spread, no significant differences in OS were observed ($P = 0.578$; Supplementary Fig. 3c).

Supplementary Fig. 4 shows the impact of general HCC landmark predictive factors for OS in patients with mALBI grade 2b liver function. Presence of high tumor burden (exceeding the Up-to-7 criteria, $P = 0.019$; Supplementary Fig. 4a) was associated with significantly worse OS. In contrast, history of subsequent treatment with curative intent (lenvatinib-TACE sequential therapy and R0 resection, $P < 0.001$; Supplementary Fig. 4e) during the treatment period was associated with significantly better OS. Finally, three predictive factors (Type-4 enhancement pattern, macrovascular invasion, and extrahepatic spread; Supplementary Fig. 4b–d) did not significantly impact OS.

Predictors of OS after introduction of lenvatinib stratified by mALBI grade

Table 2 summarizes the results of multivariate analysis for OS in patients with mALBI grade 1 and 2a liver function during lenvatinib-based therapy using pretreatment variables and use of subsequent treatment. Of the 14 tested variables, *Type-4* CT enhancement pattern (hazard ratio [HR] 3.970; 95% CI 1.192–13.221; $P = 0.025$), exceeding the Up-to7 criteria (HR 2.562; 95% CI 1.121–5.859; $P = 0.026$), and des-γ-carboxyprothrombin (DCP) level (HR 1.003; 95% CI 1.001–1.006; $P = 0.020$) were significantly associated with poor OS. In contrast, body mass index (BMI) (HR 0.876; 95% CI 0.777–0.988; $P = 0.031$) and sequential therapy (particularly lenvatinib-TACE sequential therapy and R0 resection) were associated with better OS (HR 0.108; 95% CI 0.030–0.392; $P < 0.001$ and HR 0.021; 95% CI 0.003–0.162; $P < 0.001$, respectively). Adjusted OS curves showed clear differences according to selection of subsequent treatment during lenvatinib-based therapy (Fig. 2).

Table 2 Predictive factors for overall survival among patients with mALBI grade 1 and 2a liver function

	*P**	Coefficients[a]	SE	Wald χ^2	HR	95% CI
Pretreatment dynamic-CT enhancement pattern						
Type-2						
Type-3	0.548	0.361	0.599	0.362	1.434	0.443–4.642
Type-4	0.025	1.379	0.614	5.046	3.970	1.192–13.221
Exceeding Up-to-7 criteria	0.026	0.941	0.422	4.972	2.562	1.121–5.859
DCP + 100 AU/L	0.020	0.003	0.001	5.418	1.003	1.001–1.006
BMI + 1 kg/m^2	0.031	− 0.132	0.061	4.648	0.876	0.777–0.988
Subsequent treatment during treatment period						
No subsequent treatment						
Other subsequent treatment	0.010	− 1.363	0.531	6.589	0.256	0.090–0.724
Lenvatinib-TACE sequential therapy	< 0.001	− 2.223	0.657	11.458	0.108	0.030–0.392
R0 resection	< 0.001	− 3.844	1.032	13.863	0.021	0.003–0.162

Multivariate Cox regression was applied using stepwise backward selection. Of the potential predictors, factors presenting marginal association ($P < 0.15$) with overall survival after the introduction of lenvatinib in univariate analysis were included in the initial model. Then factors that showed no or limited statistically significant association ($P > 0.1$) adjusted for the remaining factors in the model were deleted from the model in a stepwise fashion. The following 14 variables were tested (*P*-values in univariate analysis): age (0.219), sex (0.994), body mass index (0.017), etiology (HCV vs. others) (0.255), serum a-fetoprotein (< 0.001), plasma des- γ carboxyprothrombin (< 0.001), Up-to-7 criteria (within vs. exceeding) (0.015), macrovascular invasion (0.072), extrahepatic metastasis (0.579), neutrophil-to-lymphocyte ratio (0.150), pretreatment dynamic-CT enhancement pattern (Type-3, 0.294 and Type-4, 0.005), TACE failure/refractoriness (0.728), reduced starting dose of lenvatinib (0.345), and subsequent treatment during treatment period (other subsequent treatment, < 0.001; lenvatinib-TACE sequential therapy, < 0.001; and R0 resection, < 0.001)

*Based on the likelihood test adjusted for the other factors in the final model

[a]Estimated coefficient for the variable and the associated standard error

BMI body mass index, *95% CI* 95% confidence interval, *CT* computed tomography, *DCP* des-γ-carboxyprothrombin, *HR* hazard ratio, *mALBI* modified albumin-bilirubin, *SE* standard error, *TACE* transarterial chemoembolization

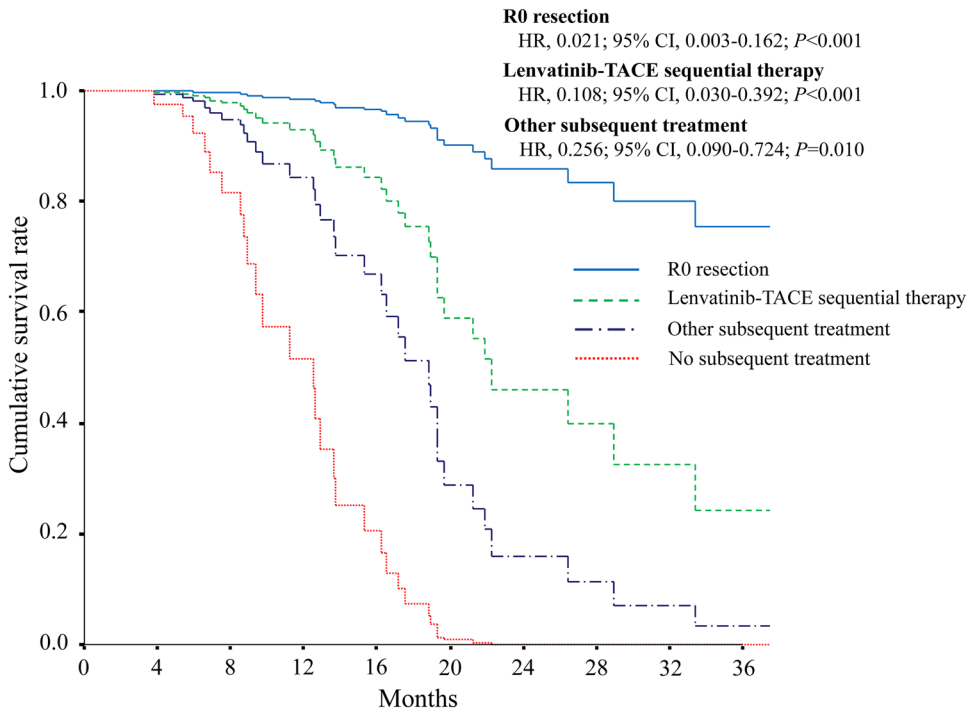

Fig. 2 Adjusted overall survival curves of lenvatinib-treated HCC patients with mALBI grade 1 and 2a liver function grouped according to subsequent treatment during the treatment period. *HR* hazard ratio, *CI* confidence interval, *TACE* transarterial chemoembolization

Table 3 Predictive Factors for Overall Survival among Patients with mALBI Grade 2b Liver Function

	*P**	Coefficients[a]	SE	Wald χ^2	HR	95% CI
DCP + 100 AU/L	0.018	0.006	0.002	5.586	1.006	1.001–1.010
Subsequent treatment during treatment period						
No subsequent treatment						
Other subsequent treatment	< 0.001	− 3.200	0.953	11.276	0.041	0.006–0.264
Lenvatinib-TACE sequential therapy	0.001	− 2.769	0.850	10.609	0.063	0.012–0.332
R0 resection	0.027	− 2.860	1.295	4.878	0.057	0.005–0.725

Multivariate Cox regression was applied using stepwise backward selection. Of the potential predictors, factors presenting marginal association ($P < 0.15$) with overall survival after the introduction of lenvatinib in univariate analysis were included in the initial model. Then factors that showed no or limited statistically significant association ($P > 0.1$) adjusted for the remaining factors in the model were deleted from the model in a stepwise fashion. The following 14 variables were tested (*P*-values in univariate analysis): age (0.827), gender (0.519), body mass index (0.424), etiology (HCV vs. others) (0.365), serum a-fetoprotein (0.016), plasma des- γ carboxyprothrombin (0.020), Up-to-7 criteria (within vs. without) (0.024), macrovascular invasion (0.515), extrahepatic metastasis (0.850), neutrophil-to-lymphocyte ratio (0.575), pretreatment dynamic-CT enhancement pattern (Type-3, 0.072 and Type-4, 0.742), TACE failure/refractoriness (0.670), reduced starting dose of lenvatinib (0.024), and subsequent treatment during treatment period (other subsequent treatment, < 0.001; lenvatinib-TACE sequential therapy, 0.003; and R0 resection, 0.028)

*Based on the likelihood test adjusted for the other factors in the final model

[a]Estimated coefficient for the variable and the associated standard error

95% CI 95% confidence interval, *DCP* des-γ-carboxyprothrombin, *HR* hazard ratio, *mALBI* modified albumin-bilirubin, *SE* standard error, *TACE* transarterial chemoembolization

Table 3 summarizes the results of multivariate analysis for OS in patients with mALBI grade 2b liver function during lenvatinib-based therapy using pretreatment variables and use of subsequent treatment. Of the 14 tested variables, DCP level (HR 1.006; 95% CI 1.001–1.010; $P = 0.018$) was significantly associated with poor OS. In contrast, use of sequential therapy (other subsequent treatment, lenvatinib-TACE sequential therapy, and R0 resection) was associated with better OS (HR 0.041; 95% CI 0.006–0.264; $P < 0.001$, HR 0.063; 95% CI 0.012–0.332; $P = 0.001$, and HR 0.057; 95% CI 0.005–0.725; $P = 0.027$, respectively). Adjusted OS curves for each subsequent treatment during lenvatinib-based therapy are shown in Fig. 3.

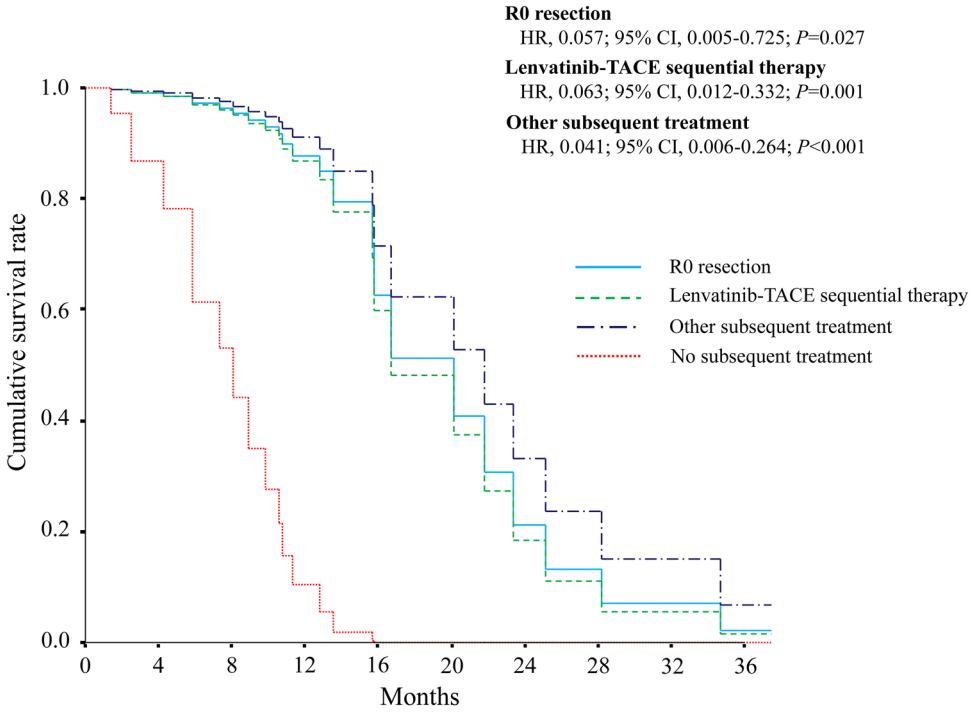

Fig. 3 Adjusted overall survival curves of lenvatinib-treated HCC patients with mALBI grade 2b liver function grouped according to subsequent treatment during the treatment period. *HR* hazard ratio, *CI* confidence interval, *TACE* transarterial chemoembolization

Clinical background of lenvatinib-treated patients who did and did not receive subsequent treatment stratified by mALBI grade

Supplementary Fig. 5 shows the distributions of subsequent treatments by mALBI grade. The percentage of patients who did not receive subsequent treatment was significantly higher among patients with mALBI grade 2b liver function ($P = 0.005$), while the percentages of patients who underwent subsequent treatment with curative intent were similar between groups (36% in patients with mALBI grade 1 and 2a liver function and 30% in patients with mALBI grade 2b liver function).

As shown in Supplementary Table 2, no significant differences (except liver function) in patient or tumor characteristics were observed between patients with mALBI grade 1/2a and 2b liver function.

Among patients with mALBI grade 1/2a liver function, the rates of extrahepatic spread and BCLC stage C disease were significantly higher in patients who did not receive subsequent treatment during the treatment period (Supplementary Table 3). In contrast, in patients with mALBI grade 2b liver function, serum DCP levels and the rate of exceeding the Up-to 7 criteria were significantly higher in patients who did not undergo subsequent treatment group during the treatment period (Supplementary Table 4).

Clinical features of patients with HCC treated with lenvatinib followed by subsequent treatment

As shown in Supplementary Table 5, at the time of initiation of subsequent treatment, almost 50% patients showed disease progression (PD state) with lenvatinib-TACE sequential therapy and other subsequent treatment. On the other hand, in the R0 resection group, all patients maintained an objective response at the time of conversion surgery. In addition, 5 of 7 (71%) patients experienced tumor recurrence during the follow-up period, and 4 of 5 (80%) patients received curative-intent subsequent treatment (R0 resection or RFA combined use super selective TACE) for early to intermediate-stage HCC recurrence. Moreover, these patients acquired cancer-free status again. Eight of 21 (38%) patients received Lenvatinib-TACE sequential therapy as scheduled TACE, while the remaining 13 (32%) patients received it as on-demand TACE. In addition, the breakdown of the other subsequent treatment group was as follows: 14 of 34 (41%) patients received TACE, 3 (9%) patients received transarterial chemoinfusion, 5 (15%) patients received R2 resection, 5 (15%) patients received stereotactic or intensity modulated radiation therapy, and the remaining 7 (21%) patients received molecularly targeted agents with or without an immune checkpoint inhibitor (sorafenib; $n = 2$, ramucirumab; $n = 1$, and atezolizumab plus bevacizumab; $n = 4$). The RDI at 8 weeks, in the lenvatinib-TACE sequential therapy group showed a relatively low median RDI (66.8%) compared with the median of the entire cohort RDI (86%). Regarding liver function at the time of initiation of subsequent treatment, the rate of mALBI grade 1 and 2a decreased except with a R0 resection.

Discussion

In this study, we evaluated tumor and liver function to maximize the efficacy of subsequent treatment during lenvatinib-based treatment of patients with HCC. As previously reported in the literature [16–22], the presence of extrahepatic spread did not have a significant clinical impact on OS of lenvatinib-treated HCC patients in the present study. However, macrovascular invasion was significantly associated with a poor prognosis in this patient population. Therefore, macrovascular invasion rather than extrahepatic spread appears to be an important prognostic factor in advanced HCC.

Since high tumor burden (e.g., exceeding the Up-to-7 criteria) is also a significant prognostic factor, management of intrahepatic HCC is extremely important for prolonging OS. Moreover, subsequent treatment during lenvatinib-based treatment, especially procedures with curative intent, resulted in significantly better prognoses in this study. Therefore, we should focus on the importance of subsequent treatment during lenvatinib-based treatment.

In addition, residual liver function estimated by mALBI grade had a clear impact on OS. Thus, when analyzing conditions for maximizing the efficacy of subsequent treatment during lenvatinib-based therapy, liver function stratified by mALBI grade must also be considered. Among patients with mALBI grade 1 and 2a liver function, pretreatment dynamic-CT enhancement pattern (Type-3 and -4), high tumor burden (exceeding the Up-to-7 criteria), and high DCP level were identified as negative prognostic factors. Type-3 and -4 enhancement patterns reflect highly malignant tumor potential, and as reported in our previous studies, lenvatinib demonstrated reasonable tumor control with respect to initial treatment response and PFS, regardless of malignant potential. However, the present results indicate that the sustained antitumor effect in tumors with high malignant potential was not sufficient to prolong PPS or OS [10, 27]. Furthermore, high BMI was identified as a positive predictive factor.

All subsequent treatments yielded significant positive effects on OS, especially those with curative intent (R0 resection and lenvatinib-TACE sequential therapy), among patients with mALBI grade 1 and 2a liver function (Fig. 2). In contrast, among patients with mALBI grade 2b liver function, no remarkable differences between subsequent treatment type (curative intent versus palliative intent) were

observed with respect to prolongation of OS; each showed a similar beneficial effect (Fig. 3).

In this study, we performed a multivariate analysis to identify factors that predicted OS, including subsequent treatment during lenvatinib-based therapy. In general, such analyses should be performed using only pretreatment data. However, it is well known that most patients who receive lenvatinib experience disease progression relatively early in the treatment course. Therefore, we need to consider various subsequent treatments during the treatment period in patients who have sufficient residual liver function and can receive RFA, surgical resection, radiation therapy, other molecularly targeted agents, or TACE with or without lenvatinib before initiation of lenvatinib. In addition, the adjusted OS curves showed a clear difference when lenvatinib was used based on subsequent treatment during the treatment period (Figs. 2 and 3).

Therefore, the most important clinical message from this study is as follows: it is necessary to consider lenvatinib-TACE sequential therapy as one of the first-line subsequent treatments when a patient has intrahepatic target nodules, as has been stated in previous reports [9–14], and it is important to control the treatment intensity to maintain sufficient residual liver function at the time additional subsequent treatment is given. As shown in Supplementary Fig. 5, the proportion of patients who could not receive optimal subsequent treatment when needed was significantly higher in patients with mALBI grade 2b liver function compared with those with mALBI grade 1 and 2a liver function ($P=0.005$). Moreover, for patients with insufficient liver function (mALBI grade 2b) who could receive treatment, all subsequent treatments showed similar beneficial effects (Fig. 3). Therefore, in the situations described above, we should select subsequent treatment depending on each patient's individual tumor and liver condition. From our results, we created a treatment strategy for subsequent treatment during lenvatinib treatment (Supplementary Fig. 6). The key decision-making factors were macrovascular invasion and liver function and it is necessary to select subsequent treatment according to these tumor and liver conditions. In addition, it is necessary to first consider intrahepatic tumor management using prioritized curative intent subsequent treatment including surgical resection. The timing of subsequent treatment is when the tumor is well controlled and a high RDI is maintained, especially in R0 resections. On the other hand, in lenvatinib-TACE sequential therapy, the treatment intensity should be modified according to the tumor and liver condition. In situations of good tumor control and maintenance of high RDI, curative intent lenvatinib-TACE sequential therapy is desirable. However, when tumor control appears to have deteriorated as a result of poor RDI, on-demand TACE should be considered. Finally, for patients with insufficient liver function (mALBI grade 2b) who could receive treatment, all subsequent treatments showed similar beneficial effects. Therefore, in this case, we should select the most appropriate subsequent treatment depending on each patient's individual tumor and liver condition.

Recently, other researchers have reported the utility of NLRs for predicting patient outcomes following lenvatinib treatment of HCC [35, 36]. However, in the present cohort, no significant differences in OS were observed. This difference may have been due to the small number of cases in the current study. In addition, it should be noted that previously reported NLR cut-off values for predicting patient outcomes differed between several studies [35–37], with changes in NLRs due to various patient conditions (e.g., infections and certain medications, particularly steroid-based immunosuppressive regimens). Therefore, more robust NLR cut-off values are desirable for use in daily clinical practice. In addition, the utility of the skeletal muscle mass index (SMI) for predicting patient outcomes following lenvatinib treatment of HCC has been reported [38, 39]. However, in this study, SMI data were not available. Therefore, we consider it necessary to perform additional analysis of SMI data to evaluate survival outcomes in future studies.

The majority of the cases evaluated in the present study were post-marketing cases, so long-term analysis has not yet been completed. A small number of patients in the present analysis were converted to surgery during lenvatinib-based therapy. Although surgical outcomes remain inconclusive due to the relatively short observation period and general impression of survival outcomes of R2 resection cases were not satisfactory. Therefore, future studies are needed to further clarify the impact of each treatment option during lenvatinib-based treatment.

Limitations of the present study include its retrospective nature, performance at a single center, and relatively small number of patients. In addition, the median follow-up period (15.3 months) was relatively short compared with that of the global phase III REFLECT trial (27.7 months) [24]. Furthermore, a variety of subsequent treatments were used because no established treatment strategy exists in the lenvatinib era, so it is difficult to clarify the actual impact of each treatment in this limited number of cases. Therefore, future studies using larger, multicenter cohorts with sufficiently long observation periods are needed to validate the present outcomes. An additional major limitation of the present study is lack of pathological data. However, the dynamic-CT enhancement patterns used in the present study were originally established by comparison with pathological data in a surgical population, and OS was significantly different according to enhancement patterns determined by 3 independent reviewers (Fig. 1d). The present results validated the utility of these CT enhancement criteria in prediction of oncological aggressiveness of tumors in the untreated population and among patients with recurrent

HCC, consistent with our previous work [27]. Given that each HCC nodule is histologically heterogeneous and it is not realistic to perform biopsy of all target nodules to confirm histological differentiation in actual clinical settings, the present outcomes confirm that CT enhancement patterns can be used as a substitute for estimation of oncological aggressiveness of HCC in the clinical population. Regarding the choice of subsequent treatment, some patients could not switch to lenvatinib-TACE sequential therapy due to decreased hepatic functional reserve during treatment, and this could be an issue of clinical management even if lenvatinib-TACE sequential treatment might offer beneficial survival effects. Thus, consideration of optimal sequential treatment timing and strategies should also be addressed in future clinical studies.

Conclusion

In conclusion, various subsequent therapies during lenvatinib-based treatment enable better OS among HCC patients with intrahepatic target nodules. Moreover, subsequent treatments with curative intent are more effective in patients with better liver function (mALBI grade 1 and 2a).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12328-022-01723-4.

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Data availability All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest Yusuke Kawamura, M.D., Ph.D. reports honoraria from Eisai Co., Ltd., Chugai Pharmaceutical Co., Ltd., and TERUMO CORPORATION. Junichi Shindoh, M.D., Ph.D. reports honoraria from Eisai Co., Ltd., and Chugai Pharmaceutical Co., Ltd. Hiromitsu Kumada, M.D., Ph.D. reports honoraria from Eisai Co., Ltd. The other authors declare no conflicts of interest.

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