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ORIGINAL ARTICLE

Prognostic Advantages of Individual Additional Interventions After Lenvatinib Therapy in Patients with Advanced Hepatocellular Carcinoma

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Abstract

Background Increasing number of patients with advanced hepatocellular carcinoma (HCC) has recently achieved salvage interventions after introduction of new biologic agents, while there are insufficient data to determine if such additional intervention(s) after treatment with newer biologic agents are truly advantageous for patients with advanced HCC.

Methods The clinical records of 107 consecutive patients who underwent lenvatinib treatment for advanced HCC were extensively reviewed and the prognostic advantages of individual additional treatments after lenvatinib treatment were investigated through a regression analysis considering time-dependent covariates.

Results Multivariate analysis revealed that R0 resection or curative-intent radiofrequency ablation (RFA) (hazard ratio [HR], 0.07; 95% CI, 0.01–0.32), transarterial chemoembolization or transarterial infusion therapy (HR, 0.39; 95% CI, 0.19–0.81), and subsequent line of systemic therapy (HR, 0.25; 95% CI, 0.10–0.63) were associated with improved disease-specific survival (DSS), while R2 resection or palliative-intent RFA showed no correlation with DSS. The best response during lenvatinib therapy, nutritional status, plasma des-gamma-carboxyprothrombin level, a baseline CT enhancement pattern, and BCLC stage were also selected as independent predictors for DSS. Among the various treatments performed after lenvatinib therapy, R0 resection also showed clear prognostic advantage in both progression-free survival (HR, 0.30; 95% CI, 0.16–0.58) and time-to-treatment failure (HR, 0.08; 95% CI, 0.02–0.39), suggesting that successful conversion to surgery may prolong survival outcomes through prolonged cancer-free interval in advanced HCC.

Conclusions Additional intervention(s)/treatment(s) after lenvatinib therapy for advanced HCC may have prognostic advantage in strictly selected populations. Successful conversion to curative resection may offer survival benefit with acceptable clinical outcomes.

Keywords Hepatocellular carcinoma · Conversion · Surgery · Chemotherapy · Lenvatinib

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. To date, surgical resection,[1,2] radiofrequency ablation (RFA),[3,4] and liver transplantation[5,6] have been shown to be effective for early-stage HCCs, and transarterial chemoembolization (TACE) has been a standard of care for many patients with multiple (> 3) HCCs. Despite the recent developments in screening methods, however, HCC is often diagnosed in its intermediate or advanced stage, and therefore, choice of treatment is relatively limited in actual clinical settings.

For patients with advanced HCC, there are as yet no established treatments other than systemic therapies. With

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the recent introduction of various molecular-targeted agents and multidisciplinary treatment approaches, however, successful conversion to curative-intent surgery has been achieved in an increasing number of patients, and the clinical outcomes of such aggressive approaches have been sporadically reported after the introduction of lenvatinib.[7–14] There are insufficient data to determine if additional interventions after treatment with newer molecular-targeted agents, such as lenvatinib, are truly advantageous for patients with advanced HCC.

Our group previously investigated the preliminary outcomes of 107 patients who had received lenvatinib treatment and reported that successful conversion to surgery or other additional treatments after lenvatinib therapy may offer prognostic advantage in selected patients.[13] However, because of the inherent immortal time bias and insufficient data with regard to the prognostic impact of "subsequent" treatments for relapse of the disease, it remains inconclusive as to whether curative-intent surgical intervention as part of a multidisciplinary approach is truly beneficial or not. In the present study, we sought to investigate the prognostic advantages of additional treatment(s) after lenvatinib therapy in patients with advanced HCC, with special attention paid to time-dependent covariates which change over the clinical course and the individual prognostic impacts of each of the additional interventions.

Methods

Study Population

This study was conducted using the updated data (updated on January 15, 2022) of 107 consecutive patients who were initiated on lenvatinib treatment between October 2010 and September 2020 at Toranomon Hospital and whose data were analyzed in our previous preliminary study,[13] to examine the mid-term efficacy of additional interventions after lenvatinib therapy. The study protocol was approved by the institutional review board (No. 1438-H/B) and the analysis was performed in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies in Japan.

Principle of Patient Management and Lenvatinib Therapy

Our basic management protocol for patients with advanced HCC is described in detail in our previous report.[13] In brief, the management protocol for each patient is determined at a multidisciplinary team meeting, in accordance with the Clinical Practice Guidelines for Hepatocellular Carcinoma published by the Japan Society of Hepatology.[15] All the patients enrolled in the present analysis had BCLC stage C disease or BCLC stage A/B disease with recurrent/advanced lesions who were not suitable candidates for TACE, and received lenvatinib therapy as the first-line treatment or as second-line treatment after sorafenib.

Lenvatinib treatment was initiated at the dose of 8 mg/day (for patients weighing < 60 kg) or 12 mg/day (for patients weighing ≥ 60 kg). The drug dose was reduced or the treatment was interrupted in the event of emergence of any grade 3 or more severe adverse events (AEs), or any unacceptable grade 2 AEs, until the symptom(s) resolved. The treatment was discontinued altogether in the event of emergence of any unacceptable or serious AEs, or when significant tumor progression was observed. AEs were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0.[16]

Imaging Assessment

To guide individual clinical management while avoiding unnecessary tumor biopsy, the dynamic CT enhancement pattern[17,18] at the baseline was used for predicting the oncological aggressiveness of tumor. In regard to the response evaluation, the best tumor response between 4 and 12 weeks of treatment was evaluated according to the mRECIST,[19] by serial imaging studies, with contrast-enhanced CT scan performed at 2 weeks, 4 weeks, 8 weeks, 12 weeks, and every 4–8 weeks thereafter.

Additional Interventions After Lenvatinib Treatment

Patients who showed disease progression after lenvatinib treatment received subsequent chemotherapy with agents such as sorafenib, regorafenib, ramucirumab, cabozantinib, or atezolizumab + bevacizumab. However, for selected patients who showed only "localized" progression within the liver or presented with only a few extrahepatic lesions, the additional interventions consisted of TACE, transarterial infusion chemotherapy (TAI), radiation therapy (RT), RFA (palliative-intent), or surgical resection (i.e., salvage surgery/palliative surgery), selected taking into account the oncological status and expected potential benefit of the additional treatment. For the small group of patients who showed good and/or sustained response to lenvatinib chemotherapy, resection with curative intent (i.e., conversion surgery) or curative-intent RFA was attempted. For patients who presented with relapse after such interventions, subsequent treatment was selected as appropriate, taking into account the technical feasibility, oncological status, and expected benefit of the treatment.

Statistical Analysis

Statistical analysis was performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/). Disease-specific survival (DSS) was defined as the time from the date of initiation of lenvatinib therapy to the date of death from HCC, time-to-treatment failure (TTF) was defined as the time from the date of initiation of lenvatinib therapy to the date of diagnosis of untreatable disease progression (i.e., of disease status suitable only for best supportive care) or death, and progression-free survival (PFS) was defined as the time from the date of initiation of lenvatinib therapy to progression of the disease confirmed in at least one imaging study. To account for any immortal bias, unadjusted associations between interventions after lenvatinib treatment and the outcomes were explored using the Kaplan–Meier method and a Cox proportional hazards model using time-dependent covariates. Adjusted associations between predictors (including various subsequent treatments after the initial intervention) and the outcomes were estimated by fitting a multivariate Cox proportional hazards model considering time-dependent covariates. Factors that were identified as showing at least marginal association in our preliminary study[13] were included in the initial multivariate analysis model, and factors that showed a statistically significant association at $P < 0.1$ were included in the final model after a backward elimination process.

Results

Baseline Characteristics

The baseline characteristics of the 107 patients are summarized in Table 1. All the patients were diagnosed as having unresectable or not optimally resectable HCC according to the criteria listed in Supplemental Table 1. The median duration of lenvatinib treatment was 5.0 months (range, 0.1–34.9 months), excluding the duration of adjuvant therapy after the interventions. Treatment interruption/discontinuation was required in 29 (27.1%) patients due to the emergence of severe AEs.

Response to Chemotherapy

The median relative dose intensity (RDI) after the initiation of lenvatinib treatment was as follows: 100% (interquartile range [IQR], 71.4–100%) at 2 weeks, 98.2% (IQR, 60.7–100%) at 4 weeks, 80.4% (IQR, 55.4–100%) at 8 weeks, and 73.0% (IQR, 51.1–100%) at 12 weeks. The best response evaluated between 4 and 12 weeks after the initiation of lenvatinib therapy was PR in 39 cases (36.4%), SD in 48 cases (44.9%), and PD in 14 cases (13.1%) according to the RECIST 1.1, and CR in 8 cases (7.5%), PR in 60 cases (56.1%), SD in 19 cases (17.8%), and PD in 14 cases (13.1%) according to the mRECIST; adequate response evaluation could not be conducted in 6 (5.6%) patients due to early (< 4 weeks) discontinuation of the treatment.

Survival Outcomes According to the "Initial" Additional Interventions After Lenvatinib Treatment

Additional interventions were eventually undertaken as an "initial" subsequent therapy after lenvatinib treatment in 64 (59.8%) patients, depending on the oncological status after treatment with lenvatinib. Details of the initial additional interventions performed in the 64 patients are as follows: R0 resection ($n = 9$, 8.4%); R2 resection ($n = 7$, 6.5%); TACE ($n = 38$, 36.4%); TACE + BAI ($n = 1$, 0.9%); TAI + BAI ($n = 1$, 0.9%); RT ($n = 7$, 6.5%); and RFA + TAI ($n = 1$, 0.9%). All non-surgical treatments were performed for controlling locally progressive disease after a median duration of lenvatinib treatment of 6.1 months (range, 0.6–30.2 months). The median duration of lenvatinib treatment prior to surgery in the surgical population was 4.2 months (range, 1.1–34.9 months). At the detection of progression or relapse of the disease, a variety of treatments were added, as appropriate. The subsequent treatments undertaken in the entire population are summarized in Fig. 1.

At a median follow-up period of 38.6 months (1.0–101.3 months), the estimated median OS of the patients in whom R0 resection was achieved first, who received other additional interventions first, in whom R2 resection was performed first, and who received subsequent lines of systemic therapies or no additional treatment were 19.0 months, 18.8 months, 8.9 months, and 9.3 months, respectively ($P < 0.0001$). The DSS durations in these 4 groups after excluding deaths from other causes were "not estimated," 19.3 months, 8.9 months, and 9.3 months, respectively ($P < 0.0001$).

The adjusted Kaplan–Meier curve constructed to examine the prognostic impact of the "initial" interventions considering the time-dependent covariates revealed a significantly longer DSS after R0 resection compared to the group that received no additional interventions as an initial treatment after lenvatinib therapy (hazard ratio [HR], 0.20; 95% CI, 0.05–0.75; $P = 0.018$) (Fig. 2).

Factors Associated with the Survival Outcomes After the Initiation of Lenvatinib Therapy

Given the wide variety of subsequent treatments after lenvatinib therapy (Fig. 1), the final survival outcomes of individual patients are difficult to be simply explained by the initial interventions after lenvatinib treatment alone. To

Table 1 Baseline characteristics

N	107
Age	73 (35–93)
Male gender	82 (76.6%)
Etiology (HB/HC/HB + HC/nBnC)	16 (15.0%)/54 (50.5%)/1 (0.9%)/36 (33.6%)
BCLC stage (A/B/C)	7 (6.5%)/40 (37.4%)/60 (56.1%)
Performance status (0/1/2)	94 (87.9%)/12 (11.2%)/1 (0.9%)
Child–Pugh class (A/B)	99 (92.5%)/8 (7.5%)
ALBI grade (1/2/3)	34 (31.8%)/72 (67.2%)/1 (0.9%)
CONUT undernutrition grade[a] (normal/mild/moderate/severe)	21 (19.6%)/64 (59.8%)/19 (17.8%)/3 (2.8%)
History of MTA administration	16 (15.0%)
Refractoriness to TACE[b]	76 (71.0%)
Intrahepatic disease	94 (87.9%)
Extrahepatic disease	44 (41.1%)
Maximum size (mm)	31 (11–175)
Number of tumor	4 (1–200)
Macroscopic portal invasion[c] (Vp0/Vp1/Vp2/Vp3/Vp4)	87 (81.3%)/3 (2.8%)/9 (8.4%)/2 (1.9%)/6 (5.6%)
Macroscopic venous invasion[c] (Vv0/Vv1/Vv2/Vv3)	99 (92.5%)/1 (0.9%)/1 (0.9%)/6 (5.6%)
Type 4 enhancement pattern[d]	23 (21.5%)
AFP level (ng/mL)	88 (1–61,041)
DCP level (mAu/mL)	215 (8–96,035)
Duration of treatment with lenvatinib[e] (months)	5.0 (0.1–34.9)
Discontinuation of lenvatinib due to adverse event during the treatment course	29 (27.1%)
Initial additional intervention	
R0 resection	9 (8.4%)
R2 resection	7 (6.5%)
Other non-surgical intervention	48 (44.9%)
None	43 (40.2%)

Figures represent median (range) unless indicated

[a]Undernutrition grade defined based on the CONUT score. [b]Defined based on the consensus statement. [c]Macroscopic vascular invasion defined by Liver Cancer Study Group of Japan. [d]Heterogeneous arterial enhancement pattern suggestive of poor differentiation. [e]Duration of adjuvant therapy after the interventions was excluded. Abbreviations: *HB*, hepatitis B; *HC*, hepatitis C; *BCLC*; Barcelona Clinic Liver Cancer; *CONUT*, controlling nutritional status; *MTA*, molecular targeted agent; *TACE*, transarterial chemoembolization; *AFP*, alpha-fetoprotein; *DCP*, des-gamma-carboxyprothrombin

clarify the "individual" prognostic influences of subsequent treatments after lenvatinib therapy, multivariate analysis was performed using time-dependent covariates.

In the analysis for the DSS, R0 resection or curative-intent RFA (HR, 0.07; 95% CI, 0.01–0.32), TACE or TAI (HR, 0.39; 95% CI, 0.19–0.81), and the subsequent line of systemic therapy (HR, 0.25; 95% CI, 0.10–0.63) were independently correlated with better survival outcomes, while R2 resection (i.e., salvage/palliative intervention) or addition of palliative-intent RFA were not associated with improved survival. The best response during lenvatinib therapy and a type 4 CT enhancement pattern at the baseline were identified as independent predictors of survival. Poor nutritional status (CONUT undernutrition grade moderate to severe), high plasma DCP levels, and the BCLC stage were also correlated with the DSS, even after changes in these parameters over the clinical course were taken into account (Table 2).

Exploratory analyses confirmed similar tendencies in both the TTF and PFS, though the prognostic advantage of "single session" treatment was evident only for R0 resection (HR, 0.08; 95% CI, 0.02–0.39 for TTR and HR, 0.30; 95% CI, 0.16–0.58 for PFS, respectively). The best response during lenvatinib therapy, high plasma DCP levels, and a type 4 CT enhancement pattern at the baseline were identified as significant predictors of both the TTF and PFS. Although BCLC stage and CONUT undernutrition grade were not found to be associated with the PFS, these factors were significantly correlated with the TTF, which directly determines the DSS (Table 3).

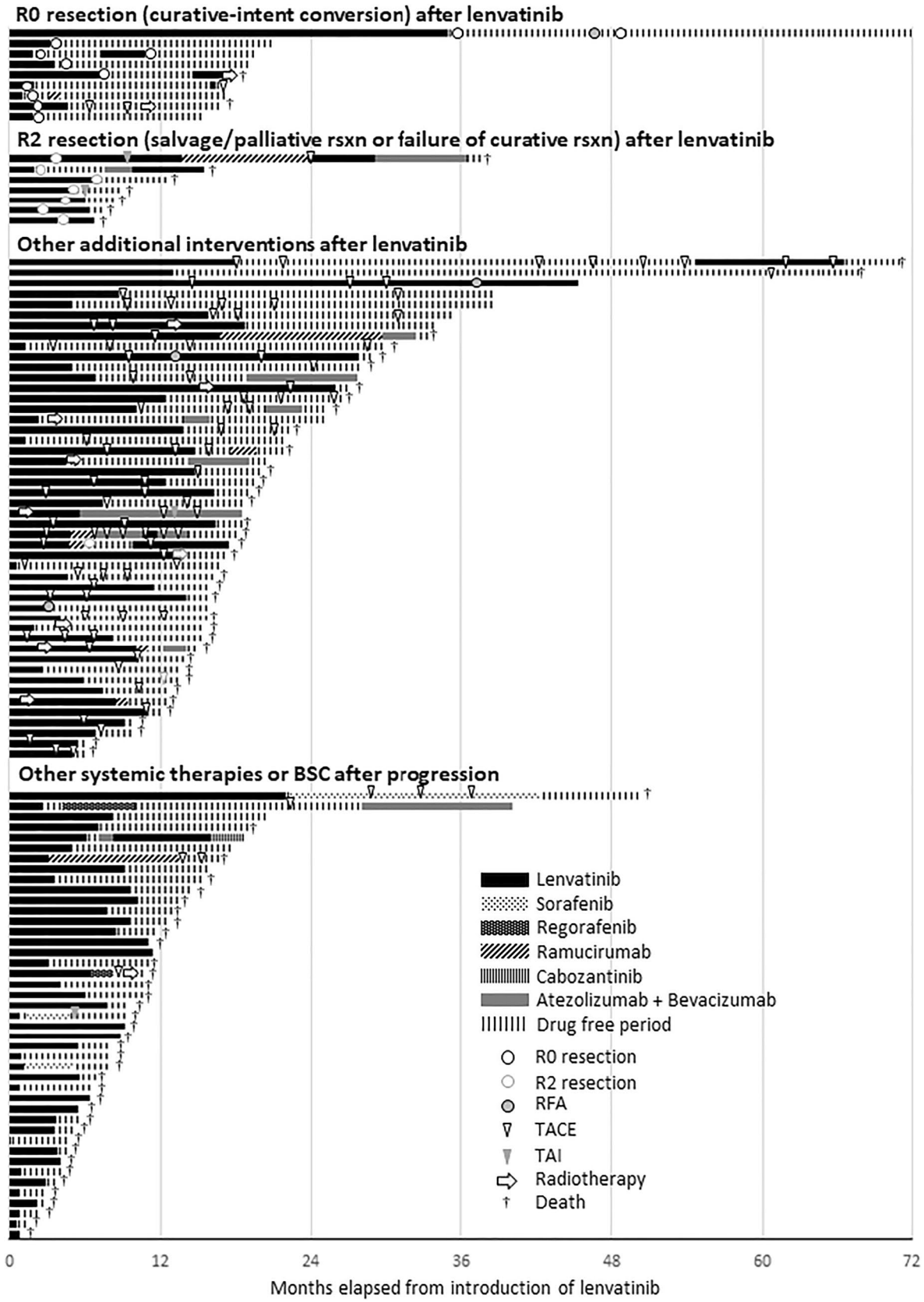
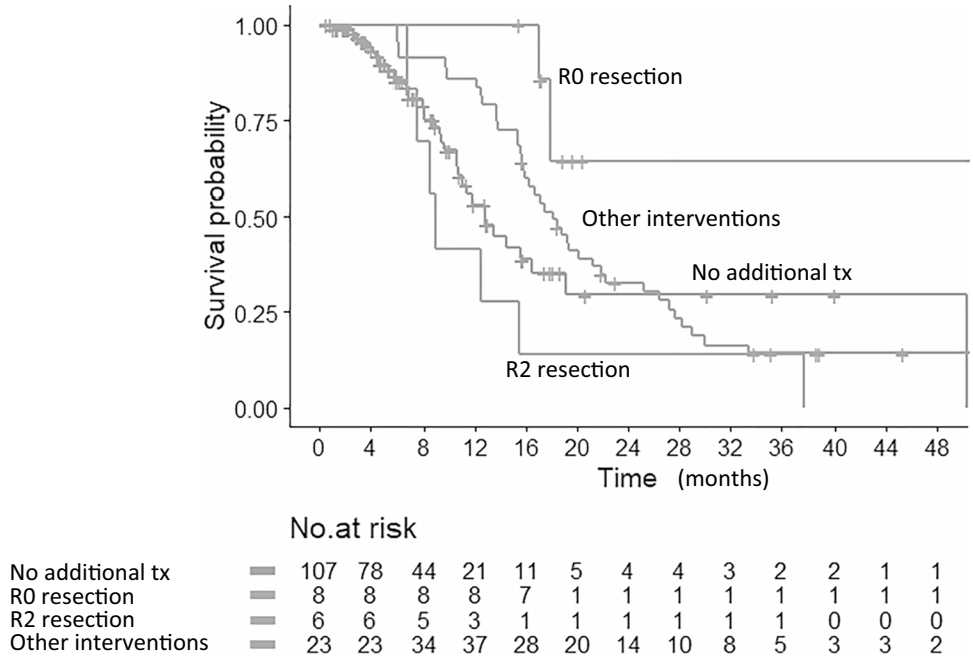


Fig. 1 Swimmer's plot for the detailed clinical courses of the 107 patients stratified by the initial treatments after lenvatinib



R0 resection: HR 0.20 (95% CI, 0.05-0.75), P=0.018
R2 resection: HR 1.83 (95% CI, 0.67-5.06), P=0.239
Other interventions: HR 0.78 (95% CI, 0.48-1.28), P=0.334

Fig. 2 Adjusted disease-specific survival curve according to the "initial" intervention after lenvatinib therapy

Discussion

This study was conducted to investigate the prognostic advantages of individual additional interventions after lenvatinib treatment in patients with advanced HCC. In a review of the detailed clinical courses of 107 consecutive patients, the individual prognostic advantages of R0 resection or curative-intent RFA, TACE/TAI, and of the subsequent line of systemic therapy after lenvatinib treatment were clarified through a regression analysis considering time-dependent covariates. It is worthy of note that the prognostic advantage of R0 resection or curative-intent RFA was obvious also in the exploratory analyses for TTF and PFS, suggesting that conversion to curative-intent surgery/ablation as a part of the multidisciplinary approach is probably beneficial from the point of view of prolonging the survival in patients with advanced HCC.

Since the introduction of sorafenib,[20,21] various biologic agents and immune checkpoint inhibitors have been tested and introduced for the treatment of HCC,[22–26] and the recent rapid progress in the field of systemic therapy is changing the landscape of multidisciplinary treatment for patients with advanced HCC. Because HCC is generally resistant to chemotherapy because of overexpression of drug transporter proteins, and presence of underlying liver disease also contributes toward reducing the efficacy of systemic therapies,[27] conversion of patients with advanced HCC to curative-intent treatment has remained rather difficult compared to patients with other malignancies, such as colorectal liver metastases, for decades. However, as shown by the results in the present study population, the chance of successful management with aggressive approaches, including curative-intent resection, appears to be available to quite a few patients. Actually, an increasing number of case reports of successful conversion surgery have been published since the introduction of lenvatinib,[7–12,28–33] and the optimal situation and timing of conversion surgery after lenvatinib treatment have come to be gradually understood. A multicenter prospective study was recently conducted to examine the efficacy of lenvatinib for conversion surgery, LENS-HCC (jRCTs031190057), and further clinically useful information is expected to be obtained in the near future.

A major issue in the management of HCC is the relatively high incidence of disease relapse, even after curative-intent treatment. Therefore, the actual impact of the so-called conversion surgery for HCC remains unclear because of the lack of a sufficient follow-up duration to clarify the true prognostic impact of such interventions in the reported outcomes. Because aggressive treatment of recurrence and a prolonged cancer-free interval after curative-intent treatment are reportedly associated with improved survival of patients with HCC,[34–37] it is important to clarify the details of the clinical course after treatment and look at the prognostic impacts of individual additional interventions after lenvatinib therapy.

Table 2 Factors associated with disease-specific survival

	*P**	Coefficient†	SE	HR	95% CI
Disease-specific survival					
Additional treatments					
R0 resection or curative-intent RFA	< 0.001	− 2.683	0.783	0.07	0.01–0.32
R2 resection or palliative-intent RFA	0.736	− 0.184	0.546	0.83	0.29–2.43
TACE or TAI	0.011	− 0.945	0.373	0.39	0.19–0.81
Radiotherapy	0.058	− 1.015	0.535	0.36	0.13–1.03
Subsequent systemic therapy	0.003	− 1.372	0.466	0.25	0.10–0.63
Best response during lenvatinib therapy (vs. mRECIST PD)					
mRECIST SD	< 0.001	− 1.579	0.390	0.21	0.10–0.44
mRECIST CR/PR	< 0.001	− 1.514	0.376	0.22	0.11–0.46
CONUT undernutrition grade at each intervention (vs. normal)					
Mild	0.408	0.502	0.607	1.65	0.50–5.43
Moderate to severe	0.020	1.427	0.614	4.17	1.25–13.89
DCP + 1log mAU/mL	0.008	0.281	0.106	1.32	1.08–1.63
Type 4 CT enhancement at baseline	0.002	1.004	0.320	2.73	1.46–5.11
BCLC stage at each intervention (vs. BCLC stage A)					
BCLC stage B	0.063	1.238	0.665	3.45	0.94–12.69
BCLC stage C	< 0.001	2.107	0.617	8.23	2.45–27.58

*Based on the likelihood test adjusted for the other factors in the final Cox proportional hazard model using time-dependent covariates. †Estimated coefficient for the variable and the associated robust standard error. Abbreviations: *SE*, standard error; *HR*, hazard ratio; *95% CI*, 95% confidence interval; *RFA*, radiofrequency ablation; *TACE*, transarterial chemoembolization; *TAI*, transarterial infusion therapy; *DCP*, des-gamma carboxyprothrombin

Note. Multivariate Cox regression using time-dependent covariates was applied with a stepwise backward selection. Initially, all the potential confounders were included in the model. Then, factors that showed no or limited statistically significant association ($P > 0.1$) with each prognostic indicator adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 9 factors tested were as follows: additional treatment, best response during lenvatinib therapy. CONUT undernutrition grade at each intervension, serum AFP level, plasma DCP level, type 4 CT enhancement pattern at baseline, BCLC stage at each intervention, chemotherapy line number, and number of TACE

The strength of the present analysis include (1) a sufficient follow-up duration of the population treated under a consistent treatment policy, and (2) statistical analysis conducted to exclude the influence of immortal time bias by taking into consideration time-dependent covariates based on the details of the clinical course. As shown in Fig. 2, updated data and statistical adjustment clearly indicate the pure prognostic advantage of R0 resection as the initial additional intervention after lenvatinib treatment for initially unresectable HCCs. Furthermore, the prognostic advantages of individual additional interventions after lenvatinib therapy (Table 2) were clarified by multivariate analysis for the first time in this study. R0 resection or curative-intent RFA obviously contributed to prolonged PFS, TTF, and DSS during the entire clinical course, and TACE/TAI and subsequent line of systemic therapies (i.e., other molecular-targeted agents or immune checkpoint inhibitors) were also shown to be beneficial to improve the survival. Although the contribution of TACE/TAI or subsequent systemic therapy for TTF or PFS was marginal, probably reflecting repetition or switching of these treatments over a relatively short period, the prognostic advantage of these additional treatments in terms of the DSS was evident, and these observations could serve as a rationale for an aggressive multidisciplinary approach for patients with advanced HCC. An additional important observation was that salvage/palliative R2 resection and palliative-intent RFA may not offer any prognostic advantage for patients with advanced HCC, confirming our previous preliminary report.[33] These outcomes suggest that any additional treatment should target the entire tumor burden, and that local control of the disease leaving other viable lesions might not yield any prognostic advantage.

The limitations of the present analysis include its retrospective nature and the inherent selection bias of treatment based on the patients' physical status, extent of the disease, biological behavior of tumor, or history of treatment. However, the present analysis was based on real-world prospectively collected data from patients with advanced HCC, and enabled analyses of the impacts of individual additional interventions after lenvatinib therapy, based on detailed observation of the clinical course and consistent treatment policy. In addition, while the

Table 3 Factors associated with TTF and PFS

	*P**	Coefficient†	SE	HR	95% CI
Time-to-treatment failure					
Additional treatments					
R0 resection or curative-intent RFA	0.002	−2.499	0.797	0.08	0.02–0.39
R2 resection or palliative-intent RFA	0.715	−0.188	0.513	0.83	0.30–2.26
TACE or TAI	0.429	−0.296	0.375	0.74	0.36–1.55
Radiotherapy	0.338	−0.735	0.767	0.48	0.11–2.16
Subsequent systemic therapy	0.110	−0.700	0.438	0.50	0.21–1.17
Best response during lenvatinib therapy (vs. mRECIST PD)					
mRECIST SD	< 0.001	−1.504	0.416	0.22	0.10–0.50
mRECIST CR/PR	< 0.001	−1.435	0.372	0.24	0.11–0.49
CONUT undernutrition grade at each intervention (vs. normal)					
Mild	0.464	0.418	0.571	1.52	0.50–4.65
Moderate to severe	0.010	1.452	0.565	4.27	1.41–12.93
DCP + 1log mAU/mL	0.002	0.336	0.109	1.40	1.13–1.73
Type 4 CT enhancement at baseline	0.006	0.827	0.302	2.29	1.26–4.13
BCLC stage at each intervention (vs. BCLC stage A)					
BCLC stage B	0.191	1.011	0.773	2.75	0.60–12.49
BCLC stage C	0.004	2.158	0.748	8.66	2.00–37.49
Progression-free survival					
Additional treatments					
R0 resection or curative-intent RFA	< 0.001	−1.201	0.336	0.30	0.16–0.58
R2 resection or palliative-intent RFA	0.623	−0.115	0.233	0.89	0.56–1.41
TACE or TAI	0.762	0.056	0.186	1.06	0.74–1.52
Radiotherapy	0.103	−0.625	0.383	0.54	0.25–1.13
Subsequent systemic therapy	0.025	−0.548	0.244	0.58	0.36–0.93
Best response during lenvatinib therapy (vs. mRECIST PD)					
mRECIST SD	0.092	−0.489	0.290	0.61	0.25–1.13
mRECIST CR/PR	0.033	−0.499	0.234	0.61	0.36–0.93
DCP + 1log mAU/mL	< 0.001	0.279	0.059	1.32	1.18–1.48
Type 4 CT enhancement at baseline	0.006	0.436	0.160	1.55	1.13–2.11

*Based on the likelihood test adjusted for the other factors in the final Cox proportional hazard model using time-dependent covariates. †Estimated coefficient for the variable and the associated robust standard error. Abbreviations: *SE*, standard error; *HR*, hazard ratio; *95% CI*, 95% confidence interval; *RFA*, radiofrequency ablation; *TACE*, transarterial chemoembolization; *TAI*, transarterial infusion therapy; *DCP*, des-gamma carboxyprothrombin

Note. Multivariate Cox regression using time-dependent covariates was applied with a stepwise backward selection. Initially, all the potential confounders were included in the model. Then, factors that showed no or limited statistically significant association ($P > 0.1$) with each prognostic indicator adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 9 factors tested were as follows: additional treatment, best response during lenvatinib therapy. CONUT undernutrition grade at each intervension, serum AFP level, plasma DCP level, type 4 CT enhancement pattern at baseline, BCLC stage at each intervention, chemotherapy line number, and number of TACE

present analysis enabled the prognostic contribution of individual treatments to be clarified while avoiding the influence of immortal time bias, clinical decision for additional treatment(s) or switching of treatment is not always influenced by the tumor progression status alone in actual clinical settings. Therefore, the present results, especially in relation to the TTF and PFS, should be interpreted with caution, because of the limitations of the statistical analysis. Nevertheless, a clear prognostic advantage of R0 resection in terms of all of the PFS, TTF, and DSS, even after adjustments for potential confounders, is an encouraging result, offering a potential rationale for aggressive surgical intervention in the era of multidisciplinary treatments for advanced HCC. In addition, although the cost-effectiveness analysis was difficult in the present study due to restriction of data availability, cost of individual subsequent treatment in the setting of post-lenvatinib therapy would be an important issue. The present results

may warrant future prospective study including cost-effectiveness analysis to guide treatment selection for patients with advanced HCC.

Conclusion

In conclusion, additional intervention(s)/treatment(s) after lenvatinib treatment for advanced HCC may have prognostic advantage in strictly selected populations. Successful conversion to curative resection may offer survival benefit with acceptable clinical outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11605-022-05388-9.

Declarations

Competing Interests Junichi Shindoh and Yusuke Kawamura receive honoraria from Eisai Pharmaceutical Co., Ltd. for this study. All other authors declare no competing interests.

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