Surgical intervention after lenvatinib treatment in patients with advanced hepatocellular carcinoma

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Abstract

Background

Survival efficacy and prognostic factors in patients with advanced hepatocellular carcinoma (HCC) who underwent surgical intervention after lenvatinib treatment is not well-understood.

Methods

Patients with advanced HCC who had lenvatinib treatment were retrospectively analyzed.

Results

Of 70 patients who were treated with lenvatinib, 14 patients underwent surgical intervention after lenvatinib treatment for 4–28 weeks. PFS was significantly longer in patients with surgical intervention than in patients with non-surgical treatment (median, 8.6 vs. 5.1 months, p = 0.019). Non-significant longer OS was also observed in patients with surgical intervention compared to patients with non-surgical treatment (median, unreached vs. 21.0 months, p = 0.206). In patients who underwent surgical intervention, 2 patients had a PR, and 12 had SD according to RECIST ver. 1.1 criteria. The serum AFP level was significantly lower after lenvatinib treatment than before lenvatinib treatment (median, 19.2 vs. 196.5 ng/mL, p = 0.0081). Eleven patients underwent curative surgery with a 14% major postoperative complication (Clavien–Dindo ≥ IIIa) rate. Patients who exhibited decreases in AFP levels or were within the normal range of AFP levels during lenvatinib treatment had significantly longer PFS (median, 8.6 vs. 3.0 months, p = 0.0009) and OS (median, unreached vs. 12.4 months, p = 0.012) than patients who had AFP levels beyond the normal range that did not decrease during lenvatinib treatment.

Conclusions

Surgical intervention after lenvatinib treatment for advanced HCC was associated with longer PFS. Patients exhibiting decreases in AFP levels or were within the normal limit of AFP levels may be good candidates for surgical intervention after lenvatinib treatment for advanced HCC.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fourth leading cause of cancer-related death(1). Surgical resection, local ablation, and liver transplantation for early-stage HCC are potentially curative therapies(2, 3). However, many patients with HCC already have advanced or metastatic disease at diagnosis or recurrence after curative locoregional therapies. Although systemic chemotherapy is indicated for these patients(4), systemic chemotherapy alone is not curative for these patients.

Conversion therapy is the treatment strategy making initially unresectable tumors amenable to resection and achieving locoregional therapy with curative intent. To date, the feasibility and efficacy of conversion

surgery for unresectable HCC remain debated. Sorafenib, the first systemic chemotherapy showing survival efficacy as a first-line treatment, provided a relatively low probability of conversion therapy of 1.4-5% due to its low response rate(5–7). Lenvatinib is the other multikinase inhibitor, targeting multiple kinase receptors including vascular endothelial growth factor receptors (VEGFR1–3), FGF receptors (FGFR1–4), PDGF receptor α (PDGFRα), KIT, and RET, for advanced HCC used as a 1st-line treatment that has shown noninferiority in overall survival (OS) to sorafenib(8). Because of the approximately 3 times higher objective response rate (ORR) of lenvatinib at 24.1% compared to sorafenib(8), a relatively high conversion rate of 11–60% after lenvatinib therapy has been reported.(9, 10) In addition, several prior studies reported the feasibility of conversion surgery after lenvatinib treatment, and some patients who underwent conversion surgery after lenvatinib had prolonged survival(6, 9, 10). However, the patients that gain a survival benefit from conversion therapy with lenvatinib treatment have not yet been identified. The safety of surgical intervention after lenvatinib is also not well understood. The present study aimed to assess the prognostic factors and safety in patients with advanced HCC who underwent surgical intervention after lenvatinib treatment.

Patients and Methods

Patients

This study was approved by the Institutional Review Board of Hyogo Medical University (No. 3944). Patients who underwent surgery for intrahepatic tumors and/or metastatic lesions after lenvatinib treatment from January 2018 through December 2021 were identified from an institutional database. The disease stage was defined according to the Barcelona Clinic Liver Cancer (BCLC) staging system(2). Six patients who had lenvatinib treatment ≤ 3 weeks due to adverse effect were excluded from this analysis (Fig. 1).

The treatment strategy was determined at the multidisciplinary tumor board conference based on the Clinical Practice Guidelines for HCC published by the Japan Society of Hepatology(3). Briefly, lenvatinib was indicated as a 1st-line treatment during the study period for Child–Pugh A or B patients with extrahepatic metastases, with 4 or more intrahepatic metastases that are not suitable for transarterial chemoembolization (TACE) and/or with macrovascular invasion that is oncologically or technically not applicable for surgery. Up-to-7 criteria was defined as previously reported(11).

Lenvatinib treatment for HCC

Patients received 12 mg/day (for bodyweight ≥ 60 kg) or 8 mg/day (for bodyweight < 60 kg) oral lenvatinib daily. The lenvatinib dose was interrupted and subsequently reduced to 8 mg and 4 mg/day or 4 mg every other day when grade 3 or greater adverse events according to the common terminology criteria for adverse events version 5.0 occurred. When lenvatinib treatment was discontinued due to adverse event or progressive disease, another systemic therapy such as sorafenib, regorafenib, cabozantinib, and ramucirumab, was administered if applicable.

Assessment of response to lenvatinib

Radiological assessment by contrast-enhanced computed tomography (CT) and/or Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI) was performed. The initial assessment of the efficacy of lenvatinib was performed within 2 to 4 weeks after initial administration and every 1–2 months thereafter during lenvatinib treatment. The objective response to lenvatinib was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 and modified RECIST (mRECIST).

The response to preoperative therapy was pathologically assessed based on the response evaluation criteria in cancer of the liver (RECICL), including treatment effect (TE) 4: tumor necrosis of 100%; TE3: tumor necrosis of 50–100%; TE2: effect other than TE3 or TE1; and TE1: tumor enlargement of ≥ 50% (12). Because tumor enlargement cannot be evaluated on pathology, pathological responses were classified from TE2 to TE4.

A decreasing trend at the alpha-fetoprotein (AFP) level and des-gamma-carboxy pro-thrombin (DCP) level was defined as a decreasing level of these tumor markers during lenvatinib treatment if these were beyond the normal limit at the beginning of lenvatinib treatment. Patients who had initially within normal limits of each tumor marker were evaluated as a same group of patients with decreasing trend. AFP and DCP levels were measured every month during lenvatinib treatment.

Initially, overall patients included in the current analysis were divided into 2 groups based on whether they underwent surgical intervention after lenvatinib treatment or not. Then, only the patients who underwent surgical intervention were evaluated to assess the prognostic factors and safety in patients with advanced HCC who underwent surgical intervention after lenvatinib treatment.

Surgery after lenvatinib treatment

Oncologically unresectable tumors classified as a partial response (PR) or stable disease (SD) based on RECIST ver1.1 or mRECIST that were maintained for at least 8 weeks or technically unresectable tumors that became resectable due to the response to lenvatinib treatment were considered amenable to curative resection, and the patient was considered a candidate for surgical intervention with a few exceptions. If patients had manageable extrahepatic metastases, noncurative surgery leaving the extrahepatic metastases in situ was performed if surgery was considered to contribute to prolonged survival or lenvatinib therapy could not be continued due to adverse effects. The indication for surgery was finally determined at the multidisciplinary tumor board conference based on tumor location, distribution, and response to lenvatinib. Ablation therapy for intrahepatic tumors and pulmonary metastases was also utilized if indicated. Major hepatectomy was defined as resection of four or more liver segments.

Assessment of clinical outcomes

Postoperative complications were assessed based on the Clavien–Dindo classification, and grades 3 and greater were considered major complications(13). Postoperative radiological assessments based on contrast-enhanced CT or EOB-MRI were performed every 2 to 4 months until patient death or loss to

follow-up. OS was measured from the date of the initial lenvatinib treatment. Progression-free survival (PFS) was defined as the time interval from the date of initial lenvatinib therapy to the date of recurrence after surgery in patients who underwent curative resection, date of tumor progression in patients with remaining tumor after noncurative surgery, or date of death due to any cause.

Statistical analysis

Categorical variables were summarized using frequencies and percentages and were compared using the χ2 test or Fisher's exact test where appropriate. Continuous variables were summarized using the median (range) and were compared using the Wilcoxon signed-rank test. The Wilcoxon signed-rank test was used to compare matched samples to assess whether their population median ranks differed. OS and PFS were estimated using the Kaplan–Meier method. A Cox regression model was used to identify risk factors for PFS and OS. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant. All statistical computations were performed using JMP pro15.2. (SAS Institute, Cary, NC).

Results

Study population and baseline characteristics

Of 70 patients who were treated with lenvatinib ≥ 4 weeks from January 2018 to December 2021, 14 patients (20.0%) underwent surgical intervention after lenvatinib therapy, including 10 patients with oncologically not suitable for upfront resection and 4 patients with technically unresectable (3 patients with insufficient remnant liver volume if all the tumors were removed, and 1 patient with tumor thrombosis reaching right atrium) (supplemental Table 1). Male-to-female ratio was significantly higher in the surgical intervention group (13/1, 92.9%/7.1%) than in the non-surgical treatment group (36/20, 64.3%/35.7%, p = 0.0037). The frequency of patients who had chemotherapy before lenvatinib treatment including sorafenib, adjuvant immune-checkpoint inhibitor as a clinical study, TACE, and hepatic artery infusion chemotherapy, was significantly lower in the surgical intervention group than in the non-surgical treatment group (28.6% vs. 69.6%, p = 0.012). The surgical intervention group had significantly higher incidence of non-viral underlying liver disease compared to the non-surgical treatment group (64.3% vs. 23.1%, p = 0.0027). Both baseline AFP level and DCP level were trend toward higher in the surgical intervention group than in the non-surgical treatment group (Table 1). Of the patients whose tumors were considered as unresectable according to diffuse bilobar liver involvement, all the patients in the surgical intervention group and 15 patients (55.6%) in the non-surgical treatment group were out of up-to-7 criteria.

Table 1
Baseline characteristics

	Surgical intervention (n = 14)	Non-surgical treatment (n = 56)	p
Age at surgery, y (range)	68 (25–90)	72 (39–89)	0.191
Sex			
Male	13 (92.9%)	36 (64.3%)	0.0037
Female	1 (7.1%)	20 (35.7%)	
Prior chemotherapy for target lesion			
No	10 (71.4%)	17 (30.4%)	0.012
Yes	4 (28.6%)	39 (69.6%)	
Sorafenib	0 (0)	2 (5.1%)	
TACE	1 (7.1%)	27 (69.2%)	
Sorafenib + TACE	0 (0)	4 (10.3%)	
HAIC	2 (14.3%)	4 (10.3%)	
Sorafenib + HAIC	1 (7.1%)	1 (2.6%)	
ICI	0 (0)	1 (2.6%)	
BCLC stage			0.299
A	0 (0)	3 (5.3%)	
B	4 (28.6%)	23 (41.1%)	
C	10 (71.4%)	30 (53.6%)	
Etiology			0.0027
HBV	3 (21.4%)	10 (17.9%)	
HCV	1 (7.1%)	32 (57.1%)	
HBV + HCV	1 (7.1%)	1 (1.8%)	
Nonviral	9 (64.3%)	13 (23.2%)	
Reason for unresectable			0.229
MVI	4 (28.6%)	6 (10.7%)	
Diffuse bilobar liver involvement	4 (28.6%)	27 (48.2%)	

	Surgical intervention (n = 14)	Non-surgical treatment (n = 56)	p
MVI with EHM	2 (14.3%)	3 (5.3%)	
Synchronous EHM	1 (7.1%)	10 (17.9%)	
Metachronous EHM	3 (21.4%)	10 (17.9%)	
Child–Pugh score, median (range)	5 (5–7)	6 (5–11)	0.097
Child–Pugh classification			
A	13 (92.3%)	44 (78.6%)	0.450
B	1 (7.1%)	10 (17.9%)	
C	0 (0)	2 (3.5%)	
ALBI score, median (range)	-2.50 (-3.07 to -1.65)	-2.25 (-3.24 to -0.81)	0.186
ALBI grade			
1	5 (35.7%)	16 (28.6%)	0.154
2a	6 (42.9%)	11 (19.6%)	
2b	3 (21.4%)	24 (42.9%)	
3	0	5 (8.9%)	
AFP level, ng/mL, median (range)	196.5 (2-643000)	31.2 (0.9-132000)	0.325
DCP level, mAu/mL, median (range)	3300 (17-332000)	413 (14-10200)	0.034
TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; ICI, XXXmmune-checkpoint inhibitor; BCLC, Barcelona Clinic Liver Cancer; MVI, macrovascular invasion; EHM, extrahepatic metastases; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy pro-thrombin			

Changes in liver function and tumor marker levels during lenvatinib therapy in patients with surgical intervention

The patients who had surgical intervention received a median of 8 weeks (4–28 weeks) of lenvatinib therapy. Changes in Child–Pugh score/classification, albumin-bilirubin (ALBI) score/grade, AFP level and DCP level during lenvatinib therapy are shown in Table 2. The ALBI score was significantly higher (median, -2.50 vs. -2.20, p = 0.019) and the AFP level was significantly lower (median, 196.5 vs. 19.2, p = 0.008) after lenvatinib therapy than before lenvatinib therapy. Before lenvatinib treatment, 4 patients had AFP levels within the normal limit, and the remaining 10 patients had AFP levels beyond the normal limit. Of these 10 patients, AFP levels were decreased in 8 patients during lenvatinib treatment. Three patients

had DCP levels within the normal limit before lenvatinib, and 7 of 11 patients whose DCP level before lenvatinib was beyond the normal limit had a downward trend in DCP levels during lenvatinib treatment. The ALBI grade in the majority of patients (4 of 5 patients with lenvatinib > 8 weeks and 5 of 9 patients with lenvatinib ≤ 8 weeks) deteriorated during lenvatinib, while the Child–Pugh classification was not (Table 2). No significant difference in the magnitude of change of the ALBI score was observed between patients with lenvatinib > 8 weeks and patients with lenvatinib ≤ 8 weeks. The best responses to lenvatinib were PR in 2 cases (14.3%) and SD in 12 cases (85.7%) according to RECIST ver. 1.1, and PR in 8 cases (57.1%) and SD in 5 cases (35.7%) according to mRECIST (Table 3).

Table 2
Changes in liver function and tumor marker levels during lenvatinib therapy

	Before lenvatinib	**After lenvatinib**	**p**
Child–Pugh score, median (range)	5 (5–7)	6 (5–7)	0.063
Child–Pugh classification			
A	13 (92.3%)	12 (85.7%)	
B	1 (7.1%)	2 (14.3%)	
ALBI score, median (range)	-2.50 (-3.07 to -1.65)	-2.20 (-3.02 to -0.95)	0.019
ALBI grade			
1	5 (35.7%)	1 (7.1%)	
2a	6 (42.9%)	4 (28.6%)	
2b	3 (21.4%)	8 (57.1%)	
3	0	1 (7.1%)	
AFP level, ng/mL, median (range)	196.5 (2-643000)	19.2 (1.2-643000)	0.0081
DCP level, mAu/mL, median (range)	3300 (17-332000)	2225 (14-269000)	0.31
ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy pro-thrombin			

Table 3
Response to lenvatinib and perioperative outcome

	Surgical intervention (n = 14)	Non-surgical treatment (n = 56)
Duration of lenvatinib treatment, weeks, median (range)	8 (4–49)	19 (4-150)
Response to lenvatinib by RECIST ver1.1		
CR		1 (1.8%)
PR	2 (14.3%)	10 (17.9%)
SD	12 (85.7%)	18 (21.1%)
PD		18 (32.1%)
Unevaluable		9 (16.1%)
Response to lenvatinib by mRECIST		
CR		2 (3.6%)
PR	8 (57.1%)	17 (30.4%)
SD	5 (35.7%)	11 (19.6%)
PD		16 (28.6%)
Unevaluable	1 (7.1%)	10 (17.9%)
Type of surgery		
Hepatectomy only	8 (57.1%)	
Hepatectomy with resection of EHM	3 (21.4%)	
Hepatectomy with RFA for lung metastases	1 (7.1%)	
Resection of EHM only	2 (14.3%)	
Type of hepatectomy		
Right hepatectomy	4 (33.3%)	
Extended left hepatectomy	3 (25.0%)	
Left hepatectomy	1 (8.3%)	
Extended anterior sectionectomy	2 (16.7%)	
Anterior sectionectomy	1 (8.3%)	
Partial hepatectomy	1 (8.3%)	
Curability of surgery		

	Surgical intervention (n = 14)	Non-surgical treatment (n = 56)
R0	10 (71.4%)	
R1	1 (7.1%)	
R2	3 (21.4%)	
Pathological response		
TE2	7 (50.0%)	
TE3	5 (35.7%)	
TE4	2 (14.3%)	
Length of postoperative stay, days	12 (6 ~ 53)	
Bleeding, g	627 (10 ~ 1940)	
Operative time, min	414 (136 ~ 604)	
Postoperative complication[†]		
II	3 (21.4%)	
IIIa	2 (14.3%)	
[†]II: ascites 2, portal thrombosis 1, IIIa: pleural effusion, bile leak		
PR, partial response; SD, stable disease; EHM, extrahepatic metastases; TE, treatment effect		

Perioperative outcome

The types of surgery after lenvatinib were hepatectomy in 9 patients, hepatectomy with intraoperative radiofrequency ablation for lung metastases in 1 patient, hepatectomy concomitant with metasectomy in 2 patients (1 had adrenalectomy and 1 had lymphadenectomy), and metasectomy only in 2 patients (l had lymphadenectomy and 1 had resection for peritoneal metastases). The median amount of intraoperative bleeding was 627 g (10-1940 g), and the operative time was 414 minutes (136–604 minutes). Only the patients who underwent hepatectomy had postoperative complications, including grade II in 3 patients (ascites in 2 cases and portal thrombosis in 1 case) and grade IIIa in 2 patients (pleural effusion in 1 case and bile leakage in 1 case). No postoperative mortality was observed. The pathological response to preoperative treatment was TE2 in 7 patients, TE3 in 5 patients and TE4 in 2 patients (Table 3).

Progression-free and Overall Survival according to surgical intervention

The median follow-up period after the initial administration of lenvatinib in patients who had surgical intervention and in patients with non-surgical treatment were 22.6 months and 16.1 months, respectively. PFS was significantly longer in patients with surgical intervention than in patients with non-surgical treatment (median, 8.6 vs. 5.1 months, p = 0.019, Fig. 2a). Non-significant longer OS was also observed in patients with surgical intervention compared to patients with non-surgical treatment (median, unreached vs. 21.0 months, p = 0.206, Fig. 2b).

Survival analysis in patients with surgical intervention

Patients exhibiting a decrease in AFP level during lenvatinib treatment or AFP levels initially within normal limits showed significantly longer PFS (median, 9.5 months vs. 3.0 months, p < 0.0001) and OS (1-year rate, 90.9% vs. 50.0%, p = 0.0018) than patients who did not meet these criteria (Fig. 3). Univariate analysis showed that a decrease in AFP during lenvatinib treatment or an AFP level initially within the normal limit was the only significant factor associated with both longer PFS (hazard ratio [HR], 2.28 $x10^{-7}$; p = 0.0027) and longer OS (HR, 0.058; p = 0.021). Additionally, BCLC stage C was significantly associated with worse PFS (HR, $1.11x10^{9}$; p = 0.029), and R2 resection was significantly associated with worse OS (HR, 5.31; p = 0.033) (Table 4).

Table 4
Factors associated with progression-free survival and overall survival

	Progression-free survival			Overall survival			
	HR	95% CI	p	HR	95% CI	p	1-year OS rate (%)
Prior therapy for target tumor							
No							78.8
Yes	2.28	0.44-12.0	0.329	2.23	0.25–20.1	0.475	100
BCLC stage							
B							100
C	1.22	0.30–4.95	0.78	$1.11x10^9$	-	0.029	78.8
Macrovascular invasion							
Absent							100
Present	2.98	0.78–11.4	0.11	6.02	0.67–54.1	0.109	66.7
Extrahepatic metastases							
Absent							87.5
Present	0.59	0.15–2.43	0.47	2.80	0.46-17.0	0.263	80.0
Etiology							
Viral							80.0
Nonviral	1.37	0.34–5.55	0.654	0.83	0.14–5.06	0.846	88.9
Response to lenvatinib by RECIST ver1.1							
PR							100
SD	1.92	0.24–15.5	0.54	1.02	0.11–9.30	0.984	82.5
Supplemental Table 1							
Summary of patients who underwent surgical intervention after lenvatinib treatment.							

	Progression-free survival			Overall survival			
Response to lenvatinib by mRECIST							
PR							85.7
SD	2.46	0.60–10.0	0.216	1.09	0.18–6.54	0.927	80.0
Pathological response							
TE2							85.6
TE3-4	0.53	0.13-2.00	0.343	1.39	0.23–8.40	0.720	85.7
Downtrend of AFP during lenvatinib							
No							50.0
Yes†	$2.28x10^{-7}$	-	0.0027	0.058	0.005–0.66	0.021	90.9
Down trend of DCP during lenvatinib							
No							75.0
Yes‡	0.45	0.11–1.87	0.274	0.61	0.10–3.69	0.602	88.9
R2 resection							
No							88.9
Yes	5.31	1.15–24.6	0.033	3.67	0.61–22.1	0.155	75.0
†Patients who had AFP within normal limit before lenvatinib were included in this cohort. ‡Patients who had DCP within normal limit before lenvatinib were included in this cohort.							
HR, hazard ratio; BCLC, Barcelona Clinic Liver Cancer; PR, partial response; SD, stable disease; TE, treatment effect; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy pro-thrombin							
Supplemental Table 1							
Summary of patients who underwent surgical intervention after lenvatinib treatment.							

Discussion

The current study investigated the prognostic factors in patients with advanced HCC who underwent surgical intervention after lenvatinib treatment and found that patients with a decreasing trend in AFP during lenvatinib treatment or patients with AFP levels within normal limits at the beginning of lenvatinib treatment had a significantly longer PFS and OS than patients who did not meet these criteria. The rate of conversion to surgical intervention after lenvatinib treatment was approximately 20%, and the major postoperative complication rate (≥ grade IIIa) was 14% with no mortality. Patients who had surgical intervention after lenvatinib treatment had significantly longer PFS and non-significant longer OS than those in patients who had non-surgical treatment.

Although advanced-stage HCC classified into BCLC stage C and a subgroup of intermediate-stage HCC classified into BCLC stage B (diffuse infiltrative extensive bilobar liver involvement) are considered indications for systemic therapy(2), several prior studies have shown the feasibility of conversion surgery after lenvatinib treatment(6, 9, 10). Shindoh et al. indicated the survival efficacy of R0 resection after lenvatinib treatment for advanced HCC, which was associated with a longer time to treatment failure and better disease-specific survival. The current analysis showed similar results of longer PFS and OS in patients who had surgical intervention after lenvatinib treatment compared to patients who only had lenvatinib treatment. Shindoh et al. also found that a downward trend in plasma DCP levels was a significant predictive factor for R0 resection after lenvatinib treatment(9). In the current analysis, male sex, no prior chemotherapy, non-viral underlying liver disease, and higher baseline DCP level were significantly associated with conversion to surgical intervention after lenvatinib treatment. The result of this study showing higher incidence of patients with no prior chemotherapy in the surgical intervention group may indicate that patients who have lenvatinib therapy as a second or later line treatment have less amenability to surgical intervention after lenvatinib therapy. Although no prior study regarding lenvatinib therapy for HCC showed such result, several study in patients with metastatic colorectal cancer described similar result(14, 15).

In addition, because no prior studies analyzed only patients who underwent surgical intervention after lenvatinib treatment, the current analysis investigated the factors associated with survival after conversion surgery. The current study found that a decrease in AFP level during preoperative lenvatinib treatment or an AFP level within normal limits before lenvatinib treatment was the only significant prognostic factor for both PFS and OS, while the DCP level was not. In addition, R0 resection was a significantly better prognostic factor for PFS but not OS although the number of patients who had R2 resection was small at 3 patients. Contrary to expectation, pathological response and radiological response to lenvatinib treatment were also not significantly associated with PFS and OS. As we cannot conclude anything about these results due to the small sample size of the current analysis, further studies with large number of samples are needed. Therefore, among patients who receive lenvatinib treatment for unresectable HCC, conversion resection should be considered if the pre-lenvatinib AFP level is normal or the AFP level is decreased during lenvatinib and if R0 resection is expected.

The safety of surgical intervention after lenvatinib treatment, especially in terms of chemotherapy-associated liver injury, is of great interest to liver surgeons. In the current analysis, the median ALBI score

was significantly higher after lenvatinib treatment, indicating the deterioration of liver function during lenvatinib treatment. ALBI grade also deteriorated in 9 of 14 patients (64%), although Child–Pugh grade worsened in only 1 patient. However, the lenvatinib treatment duration was not associated with the magnitude of deterioration of the ALBI score. These data are in agreement with a prior study which analyzed changes in ALBI during lenvatinib treatment in patients with unresectable HCC(16). That study showed that ALBI score at the end of lenvatinib treatment was significantly higher than that at the baseline, but each of that at 4 weeks, 8 weeks and 12 weeks was similar compared to the baseline(16). As liver function at the end of treatment is also affected by tumor progression and worsening of underlying liver disease, the association of lenvatinib treatment duration with deterioration of liver function may be limited. In addition, the major postoperative complication rate of the current cohort at 14.3% was similar to the results of prior studies in patients who underwent major hepatectomy for HCC or repeat hepatectomy for recurrent liver cancer(17–19). Therefore, surgical intervention after lenvatinib treatment could be safely performed.

Combination immunotherapy is an alternative treatment option to a multikinase inhibitor when considering downstaging for future surgical intervention. In 2020, the IMbrave150 study demonstrated the superiority of combination therapy consisting of atezolizumab and bevacizumab in survival compared to sorafenib(20). Tremelimumab plus durvalumab also showed longer OS than sorafenib in the HIMALAYA study(21). As a result of these studies, atezolizumab and bevacizumab therapy and tremelimumab plus durvalumab therapy have been recommended as a first choice of first-line systemic therapy in patients with advanced HCC(2, 20). Although no large series of case studies has been reported to date, conversion surgery after these combination immunotherapies for advanced HCC is highly expected. However, as no patients who had combination immunotherapies before surgical intervention were included in this study, whether the results of the current analysis can be extrapolated to surgical intervention after combination immunotherapy is unclear. Future studies focusing on conversion surgery after combination immunotherapy will address this issue.

The limitation of the current study is its retrospective nature and the relatively small cohort of patients, which may have resulted in selection bias. Because of the low number of events in terms of progression and death, multivariate analysis could not be performed. As this is the first study evaluating prognostic factors in patients who underwent surgical intervention after lenvatinib, further study based on a large number of cases may be needed to confirm the results of the current study. In addition, as patients who had progressive disease during lenvatinib treatment were not amenable to surgical intervention, these patients were included in the non-surgical treatment group. This also could be a selection bias leading to shorter survival in patients with non-surgical treatment. Another limitation is the equivocalness of the definition of “conversion” in HCC treatment. Although the current analysis only included patients with initially technically or oncologically unresectable HCC, multikinase inhibitors might be used as neoadjuvant settings in clinical practice. Because resectable, borderline resectable and unresectable HCC are not well defined in HCC, clear and widely acceptable definitions might be needed(22).

In conclusion, surgical intervention after lenvatinib treatment for advanced HCC was safe with no postoperative mortality. Surgical intervention after lenvatinib treatment may be associated with longer PFS. Patients with a decreasing trend in AFP during lenvatinib treatment or a normal level of AFP at the beginning of lenvatinib treatment may be good candidates for surgical intervention after lenvatinib treatment.

Declarations

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Figures

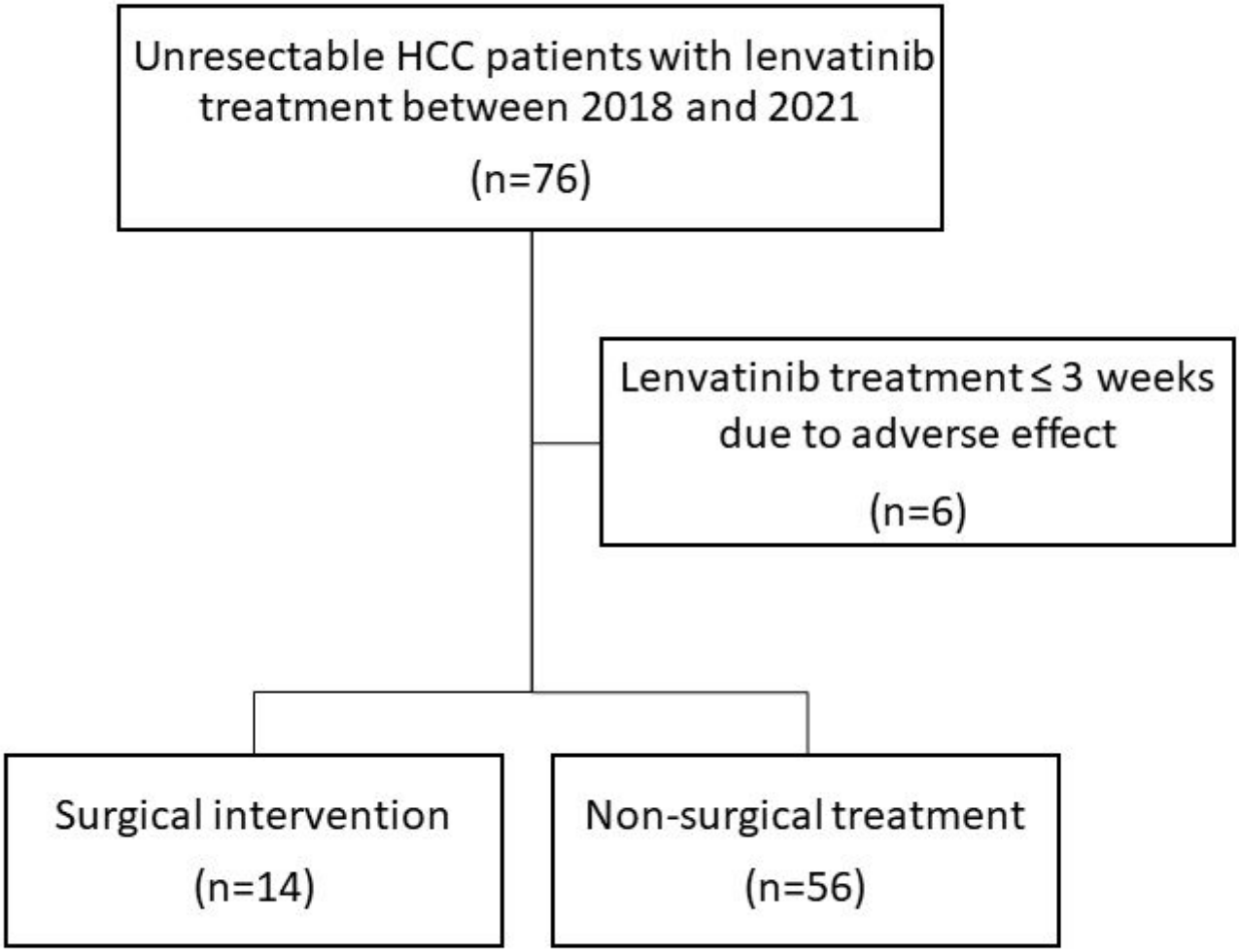

Figure 1

Patients included in the current analysis.

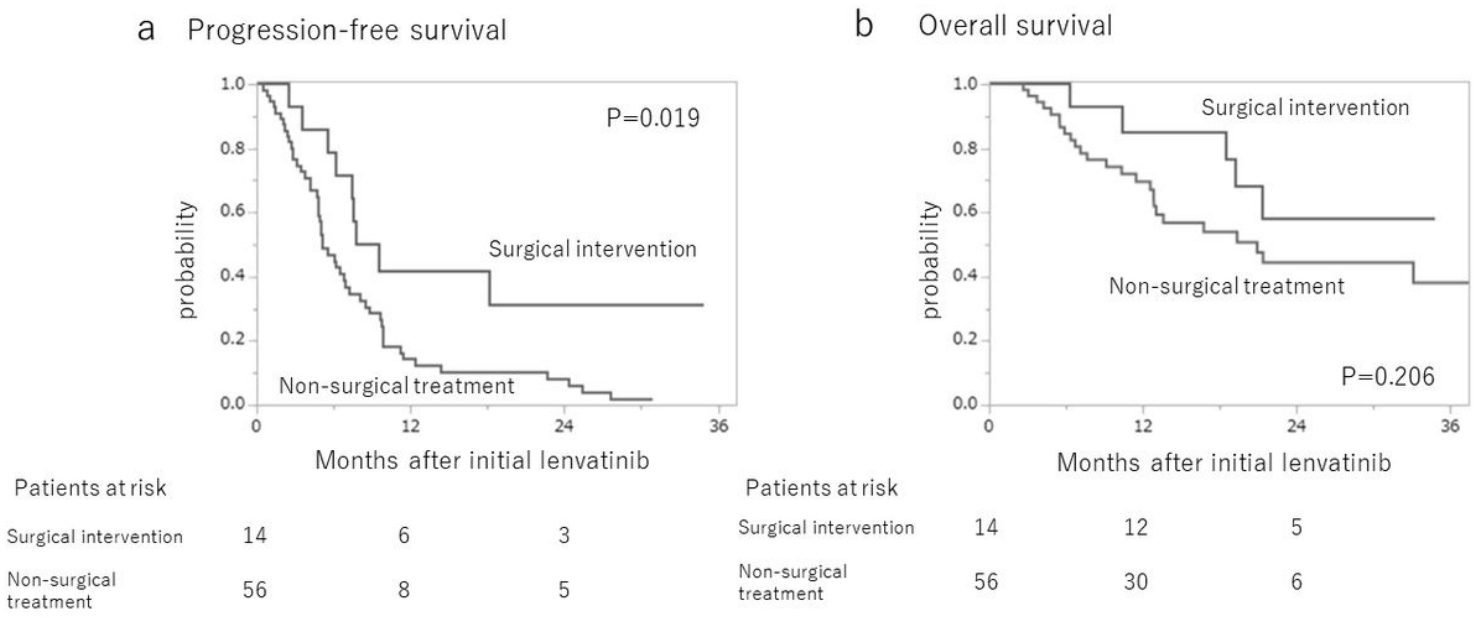

Figure 2

Progression-free survival (a) and overall survival (b) after lenvatinib treatment according to surgical intervention.

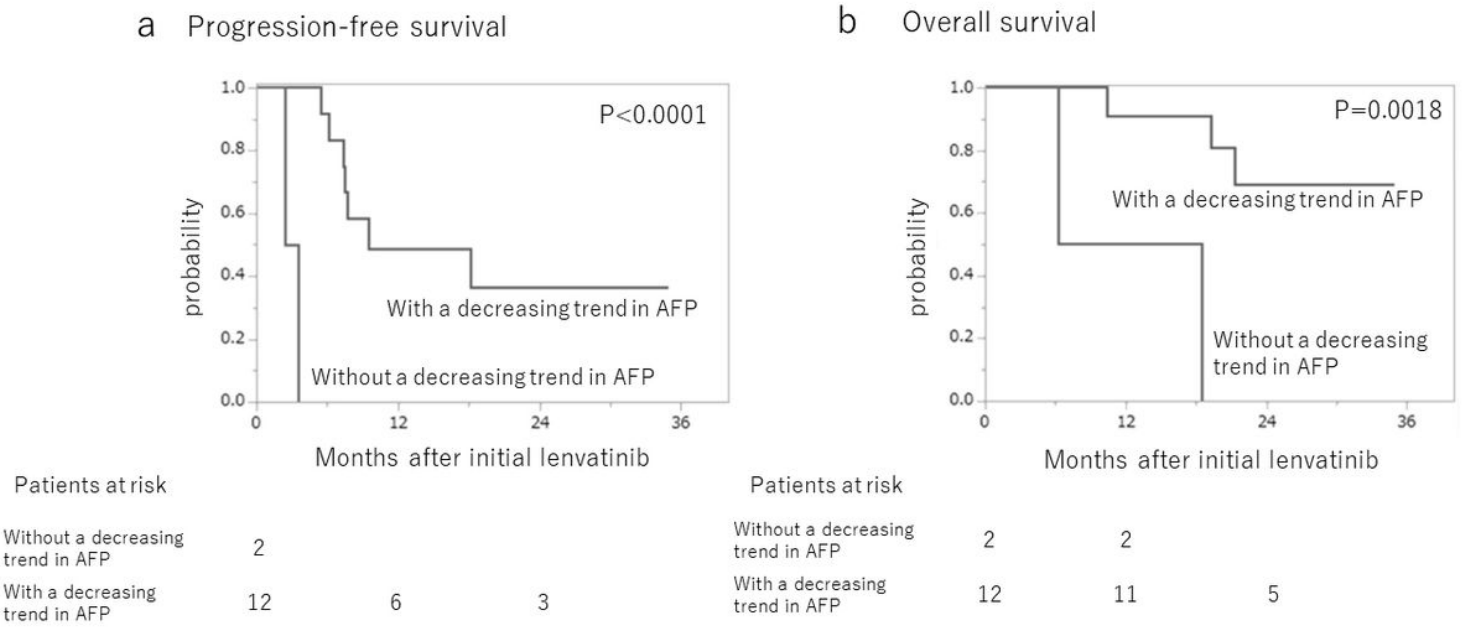

Figure 3

Progression-free survival (a) and overall survival (b) according to the trend of APF levels during lenvatinib treatment in patients with surgical intervention. The group exhibiting decreases in AFP levels included patients who had normal AFP levelsbefore lenvatinib treatment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaltable1.xlsx