Survival Benefits From Adjuvant Lenvatinib for Patients With Hepatocellular Carcinoma and Microvascular Invasion After Curative Hepatectomy

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Mu-Gen Dai[1,2], Si-Yu Liu[2], Wen-Feng Lu[3], Lei Liang[4] and Bin Ye[1]

[1]Department of Gastroenterology, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui, China. [2]Department of Laboratory Medicine, The Key Laboratory of Imaging Diagnosis and Minimally Invasive Interventional Research of Zhejiang Province, Lishui Hospital of Zhejiang University, Lishui, China. [3]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China. [4]General Surgery, Cancer Center, Department of Hepatobiliary & Pancreatic Surgery and Minimally Invasive Surgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, China.

ABSTRACT

BACKGROUND: The long-term prognosis of patients with hepatocellular carcinoma (HCC) after surgery remains far from satisfactory, especially in patients with microvascular invasion (MVI). This study aimed to evaluate the potential survival benefit from adjuvant lenvatinib for patients with HCC and MVI.

METHODS: Patients with HCC after curative hepatectomy were reviewed. All patients were divided into 2 groups according to adjuvant lenvatinib. Propensity score matching (PSM) analysis was used to reduce selection bias and make the results more robust. Survival curves are shown by the Kaplan-Meier (K-M) analysis and compared by the Log-rank test. Univariate and multivariate Cox regression analyses were performed to determine the independent risk factors.

RESULTS: Of 179 patients enrolled in this study, 43 (24%) patients received adjuvant lenvatinib. After PSM analysis, 31 pairs of patients were enrolled for further analysis. Survival analysis before and after PSM analysis showed a better prognosis in the adjuvant lenvatinib group (all $P < .05$). The adverse events associated with oral lenvatinib were acceptable. Multivariate Cox regression analysis showed that adjuvant lenvatinib was an independent protective factor for improving overall survival (OS) (hazard ratio [HR] = 0.455, 95% confidence interval [CI] = 0.249-0.831, P = .001) and recurrence-free survival (RFS) (HR = 0.523, 95% CI = 0.308-0.886, P = .016).

CONCLUSIONS: Postoperative adjuvant targeted therapy can improve the long-term prognosis of patients with HCC and MVI. Therefore, in clinical practice, oral lenvatinib should be recommended for patients with HCC and MVI to decrease tumor recurrence and improve long-term survival.

KEYWORDS: Hepatocellular carcinoma, adjuvant therapy, lenvatinib, recurrence, overall survival

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CORRESPONDING AUTHOR: Lei Liang, General Surgery, Cancer Center, Department of Hepatobiliary & Pancreatic Surgery and Minimally Invasive Surgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, No.158, Shangtang road, 310000, Hangzhou, Zhejiang, China. Email: liangl1992@hotmail.com

Bin Ye, Department of Gastroenterology, The Fifth Affiliated Hospital of Wenzhou Medical University, No.289, Kuocang Road, Liandu District, 323000, Lishui, Zhejiang, China. Email: 408252097@qq.com

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the third most common leading cause of tumor-related death.[1] The similarity between morbidity and mortality (830 000 deaths per year) highlights the poor prognosis associated with HCC.[2] Hepatectomy, liver transplantation, and radiofrequency ablation (RFA) represent the main curative treatment for patients with HCC. However, RFA generally focuses on the small tumor (≤3 cm) far from large blood vessels, and liver transplantation mainly focuses on tumors within the Milan criteria.[3] Importantly, most patients with HCC were diagnosed at an advanced stage in practice. Hepatectomy, thus, is still the first choice of curative treatment if the tumor is technically resectable.[4-6] Unfortunately, due to the high recurrence rate, the long-term prognosis of patients after surgery remains poor.[7] Despite the identification of some clinicopathological-associated risk factors that are significantly associated with HCC prognosis, there is still a lack of effective postoperative anti-recurrence therapy, especially for high-risk patients.

Microvascular invasion (MVI) was defined as the presence of cancer cell nests in the vascular lumen lined with endothelial cells under the microscope, mainly with small branches of portal veins (including intracapsular vessels).[8] Many studies have

demonstrated that MVI is associated with aggressive biological features of HCC, which has been established as a risk factor for early recurrence and poor outcomes.[9-11] Attempts are made to improve the prognosis of patients with HCC and MVI by anatomic hepatectomy or wide resection (⩾1 cm), but the long-term prognosis was still far from satisfactory.[12,13] Therefore, how to improve the long-term prognosis of patients with HCC complicated with MVI is an urgent clinical problem.

Nowadays, targeted therapy has made gratifying achievements in the treatment of unresectable HCC.[14] Sorafenib has been the first line of treatment for a decade,[7,15,16] and new treatments are ineffective and have not increased the therapeutic benefit until the introduction of lenvatinib, which was approved based on its non-inferiority against sorafenib.[17] Based on the molecular mechanism of the targeted therapy of HCC by lenvatinib, whether it can be used for decreasing the recurrence rate after hepatectomy is still unclear, especially for patients with HCC and MVI. This study, thus, aimed to evaluate the potential survival benefit from postoperative lenvatinib for patients with HCC and MVI.

Patients and Methods

Patients

The information of the consecutive patients diagnosed with HCC who underwent curative-intent hepatectomy (R0) was collected between January 2019 and January 2022 at Lishui Center Hospital and Zhejiang Provincial People's Hospital. The clinical diagnosis of HCC was confirmed by histopathology in each case. R0 resection was defined as the complete resection of all tumors with a microscopic free margin. Patients were excluded who (1) had recurrent HCC; (2) were less than 18 years old; (3) received neoadjuvant or other adjuvant therapies, including transcatheter arterial chemoembolization (TACE), radiotherapy, and systemic therapy; (4) died or recurrence within 3 months after surgery; and (5) cannot tolerate targeted therapy or received treatment for less than 6 months.

Ethics approval and consent to participate

This study was performed according to the Declaration of Helsinki, and all patients enrolled in this study provided informed consent and were approved by the Ethics Committee of Lishui Center Hospital and Zhejiang Provincial People's Hospital (no. QT2021430, December 29, 2021).

Surgery and adjuvant target therapy

All patients underwent preoperative multidisciplinary team discussion. The criteria for resectable HCC are based on tumor location and size, liver function, and future residual liver volume. Both open and laparoscopy surgery are options of treatment. All patients with HCC and MVI were informed of the option of targeted therapy to prevent tumor recurrence. The dosage of lenvatinib is determined by body weight (bw), 8 mg per day for bw < 60 kg and 12 mg per day for bw ⩾ 60 kg, respectively. If a patient has a serious adverse event that is intolerable during the administration of lenvatinib, it is necessary to discontinue the administration of lenvatinib.

Follow-up and data collection

All patients were followed up at each participating hospital. Follow-up was conducted until October 2022. Postoperative surveillance included physical examination, serum alpha-fetoprotein (AFP) level, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and chest every 2 months in the first 6 months, and then every 3 months in the next 18 months. After that, 6 months per time thereafter. The definition of recurrence was the new appearance of an extrahepatic or intrahepatic tumor nodule. Treatment for the recurrent HCC was undertaken at the treating surgeon's discretion according to the general condition of the patient, pattern of recurrent disease, and residual hepatic functional reserve. The options for treatment included curative therapy (such as local RFA, liver transplantation, and re-resection), palliative therapy (such as TACE, radiotherapy, systemic therapy with chemotherapy, targeted or immunotherapy), or best supportive treatment, either alone or in combination.

The collected variables collected: age, sex, performance status (PS), and the American Society of Anesthesiologists (ASA) score, etiology of liver disease, cirrhosis, portal hypertension, Child-Pugh grade, alanine aminotransferase (ALT), aspartate aminotransferase (AST), AFP, tumor diameter, tumor number, tumor differentiation, resection margin, blood transfusion, intraoperative blood loss, the scope of hepatectomy (minor or major), and operation time. The cut-off values of all continuous variables are based on previous studies.

Statistical Analysis

Categorical variables were represented by numbers (n, %), and compared by either χ^2 test or the Fisher exact test, as appropriate. Propensity score matching (PSM) analysis was used to reduce the bias of confounding factors with a caliper of 0.01.[18] Overall survival (OS) and recurrence-free survival (RFS) were calculated using the Kaplan-Meier (K-M) analysis by Log-rank test, and multivariate Cox regression was used to determine whether adjuvant lenvatinib was an independent prognosis factor. Variables with $P < .1$ in univariable analysis were enrolled into the multivariable analysis. R 4.2.2 (http://www.r-project.org/) was used for the statistical analysis. $P < .05$ was considered statistically significant.

Results

Baseline characteristics

All 179 patients who underwent R0 resection for newly diagnosed HCC were included. Among them, 43 (24%) patients

with MVI received adjuvant lenvatinib. Although baseline characteristics showed no statistical differences in the distribution of relevant variables between the 2 groups (all $P > .05$), patients with multiple tumors (32.6% vs 19.9%, $P = .097$), better liver function, and younger age (11.6% vs 22.8%, $P = .130$) were more likely to receive adjuvant lenvatinib after hepatectomy (Table 1). To decrease the selection bias, PSM was performed and created 31 pairs of patients. After PSM, all variables showed no statistical difference between the 2 groups (all $P > .05$).

Adverse events of lenvatinib

During follow-up, 43 patients received lenvatinib for more than half a year, and 29 (67.4%) patients suffered adverse events. The median duration of oral lenvatinib was 8 months (range = 6-12 months). Hypertension and palmar-plantar erythrodysesthesia syndrome (PPES) were the most common adverse events, and 9 (20.9%) patients experienced CTCAE grade 3 adverse events. Among the 9 patients, 6 patients reduced the dose of oral lenvatinib, and 3 patients alleviated their symptoms by taking related medications orally. None fatal adverse event was reported.

Overall survival and recurrence-free survival

The median follow-up time was 32.0 months. Among the 108 patients who experienced tumor recurrence, the majority (87 patients, 64.0%) belonged to the without lenvatinib group whereas only 48.8% (21 patients) were from the with lenvatinib group. Looking further at the recurrence pattern, it was observed that 62 (71.3%) patients in the without lenvatinib group had local recurrence and 25 (28.7%) had intrahepatic distal recurrence, in contrast to the with lenvatinib group where 14 (66.7%) patients had local recurrence and 7 (33.3%) had intrahepatic distal recurrence. No patients with extrahepatic metastasis were reported.

In the entire cohort, the median survival time was 34.0 months, and the 1-, 2-, and 3-year OS was 86%, 67%, and 46%, respectively. The median RFS was 23.0 months and the 1-, 2-, and 3-year RFS was 74%, 47%, and 39%, respectively. According to adjuvant lenvatinib, 179 patients were stratified into with and without lenvatinib groups: 43 (24%) and 136 (76%) patients. In with lenvatinib group, the 1-, 2-, and 3-year OS and RFS were 92%, 79%, and 66%, and 86%, 63%, and 47%, respectively. Accordingly, without the lenvatinib group, the 1-, 2-, and 3-year OS and RFS were 84%, 63%, and 43%, and 70%, 49%, and 36%, respectively (Table 2). K-M curves showed that adjuvant lenvatinib can increase the OS ($P = .004$) and RFS ($P = .020$) (Figure 1A and B). In the PSM cohort, K-M curves also showed that adjuvant lenvatinib can increase the OS ($P = .048$) and RFS ($P = .044$) (Figure 1A and B).

Univariable and multivariable Cox regression analysis

Variables with a $P < .1$ in univariable analysis were incorporated into multivariable Cox regression analysis. The results showed that adjuvant lenvatinib was an independent prognosis factor for improving OS (hazard ratio [HR] = 0.455, 95% confidence interval [CI] = 0.249-0.831, $P = .001$) and RFS (HR = 0.523, 95% CI = 0.308-0.886, $P = .016$) (Tables 3 and 4). In addition, independent predictors associated with OS and RFS after HCC resection among patients with MVI treated with or without adjuvant lenvatinib included portal hypertension, Child-Pugh grade B, preoperative AFP level, tumor size, tumor number, and resection margin (Figure 2).

Discussion

In this study, 179 patients with HCC and MVI were included for analysis. Among them, 43 patients with HCC and MVI received adjuvant lenvatinib, whereas 136 patients were not. To eliminate the potential bias caused by the differences in baseline characteristics and make the results more robust, PSM was performed, and created 31 pairs of patients. Survival analysis showed a favorable OS and RFS for patients with lenvatinib compared with patients without lenvatinib. The multivariable analysis also demonstrated that adjuvant lenvatinib was an independent prognosis factor of improving OS (HR = 0.455, 95% CI = 0.249-0.831, $P = .001$) and RFS (HR = 0.523, 95% CI = 0.308-0.886, $P = .016$). In other words, adjuvant lenvatinib can reduce nearly 50% risk of recurrence and death.

The success of the Sorafenib HCC Assessment Randomized Protocol (SHARP) and Asia Pacific trials prompted the approval of sorafenib as a first-line targeted therapy for unresectable HCC, ushering in the era of systemic therapy.[7,15,16] Sorafenib is a novel multitarget anti-tumor drug and a small-molecule multikinase inhibitor. Both in vivo and in vitro studies have shown that sorafenib destroys tumor micro-vessels and ultimately inhibits tumor growth by inhibiting anti-tumor neovascularization and cell proliferation. Based on the molecular mechanism of sorafenib, researchers have used it for postoperative anti-recurrence therapy, especially for patients with MVI.[30,31] In 2018, Kudo et al[17] performed an RCT phase 3 non-inferiority trial (REFLECT) to compare lenvatinib vs sorafenib in the first-line treatment of patients with unresectable HCC. Although lenvatinib was non-inferior to sorafenib for OS, lenvatinib was associated with obvious improvements compared with sorafenib in all secondary endpoints: longer time to progression and progression-free survival, higher objective response rate. Since then, lenvatinib has been used more widely in advanced HCC. However, there is still a lack of research on anti-recurrence therapy after hepatectomy. In this study, the results demonstrated that lenvatinib can reduce postoperative recurrence and improve long-term survival in patients with HCC and MVI after curative hepatectomy.

Table 1. Comparison of clinical characteristics between the 2 groups stratified by postoperative adjuvant lenvatinib for patients with hepatocellular carcinoma and MVI.

VARIABLES (N, %)	BEFORE PSM			AFTER PSM		
	WITH LENVATINIB (N = 43)	WITHOUT LENVATINIB (N = 136)	*P*	WITH LENVATINIB (N = 31)	WITHOUT LENVATINIB (N = 31)	*P*
Baseline characteristics						
Sex, men	39 (90.7)	118 (86.8)	.602	31 (100)	27 (87.1)	.113
Age, >60 years	5 (11.6)	31 (22.8)	.130	6 (19.4)	5 (16.1)	1.000
ASA score, >2	1 (2.3)	10 (7.4)	.465	2 (6.5)	1 (3.2)	1.000
Performance status ⩾1	9 (20.9)	39 (28.7)	.430	4 (12.9)	8 (25.8)	.335
Etiology of liver disease, HBV	38 (88.4)	120 (88.2)	.611	25 (80.6)	26 (83.9)	1.000
Cirrhosis	26 (60.5)	89 (65.4)	.587	17 (54.8)	21 (67.7)	.434
Portal hypertension	23 (53.5)	69 (50.7)	.861	8 (25.8)	9 (29.0)	1.000
Child-Pugh grade, B	3 (7.0)	17 (12.5)	.413	3 (9.7)	3 (9.7)	1.000
Preoperative AST level > 80 U/L	5 (11.6)	23 (16.9)	.479	3 (9.7)	3 (9.7)	1.000
Preoperative ALT level >80 U/L	4 (9.3)	22 (16.2)	.328	2 (6.5)	1 (3.2)	1.000
Tumor-related variables						
AFP >400 ng/L	26 (60.5)	88 (64.7)	.716	20 (64.5)	21 (67.7)	1.000
Maximum tumor size >5 cm	23 (53.5)	75 (55.1)	.862	18 (58.1)	18 (58.1)	1.000
Multiple tumors ⩾2	14 (32.6)	27 (19.9)	.097	7 (22.6)	10 (32.3)	.570
Poor tumor differentiation	26 (60.5)	100 (73.5)	.125	15 (48.4)	23 (74.2)	.067
Perioperative variables						
Resection margin <1 cm	20 (46.5)	85 (62.5)	.076	18 (58.1)	16 (51.6)	.799
Major hepatectomy	15 (34.9)	48 (35.3)	.557	10 (32.3)	8 (25.8)	.780
Intraoperative blood loss >600 mL	6 (14.0)	32 (23.5)	.206	6 (19.4)	4 (12.9)	.731
Blood transfusion	9 (20.9)	40 (29.4)	.330	5 (16.1)	6 (19.4)	1.000
Operation time >180 min	25 (58.1)	72 (52.9)	.601	17 (54.8)	16 (51.6)	1.000

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; HBV, hepatitis B virus; MVI, microvascular invasion; PSM, propensity score matching.

As a note, anti-recurrence therapy after hepatectomy has also been reported by many researchers.[24] Transcatheter arterial chemoembolization is the first-line treatment for advanced liver cancer, but it is also often used as a means of postoperative anti-recurrence therapy for HCC, which has been widely used clinically, especially in Asian countries.[25-27] Liang et al[27] performed a meta-analysis by enrolling 24 studies with 6977 patients to evaluate the effect of TACE on postoperative anti-recurrence therapy. The results showed that TACE can reduce HCC recurrence and improve OS, especially for patients with HCC with portal vein tumor thrombus (PVTT) or MVI, or multinodular HCC. However, all enrolled patients were from Asian countries. Furthermore, the efficacy of TACE in anti-recurrence treatment is still controversial, especially for patients in Western countries. Moreover, there are also studies trying to reduce tumor recurrence through postoperative adjuvant radiotherapy or traditional Chinese medicine, but the effect is still not exact.[28,29]

The success of the Sorafenib HCC Assessment Randomized Protocol (SHARP) and Asia Pacific trials prompted the approval of sorafenib as a first-line targeted therapy for unresectable HCC, ushering in the era of systemic therapy.[7,15,16] Sorafenib is a novel multitarget anti-tumor drug and a small-molecule multikinase inhibitor. Both in vivo and in vitro

Table 2. Comparison of survival outcomes between the 2 groups stratified by postoperative adjuvant lenvatinib for patients with hepatocellular carcinoma and MVI.

VARIABLES	BEFORE PSM			AFTER PSM		
	WITH LENVATINIB (N=43)	WITHOUT LENVATINIB (N=136)	*P*	WITH LENVATINIB (N=31)	WITHOUT LENVATINIB (N=31)	*P*
Number of death (%)	17 (39.5)	79 (58.1)	.037	8 (25.8)	13 (41.9)	.283
OS						
Median OS (months)	>42	31	.012	>42	28	.006
1-year OS	92%	84%	.030	97%	93%	1.000
2-year OS	79%	63%	.012	90%	73%	.025
3-year OS	66%	43%	.014	65%	48%	.038
Number of recurrences (%)	21 (48.8)	87 (64.0)	.107	14 (45.2)	19 (61.3)	.309
Recurrence-free survival (RFS)						
Median RFS (months)	35	24	.038	40	33	.035
1-year RFS	86%	70%	.101	97%	77%	.026
2-year RFS	63%	49%	.014	73%	50%	.035
3-year RFS	47%	36%	.036	52%	30%	.015

Abbreviations: MVI, microvascular invasion; OS, overall survival; PSM, propensity score matching; RFS, recurrence-free survival.

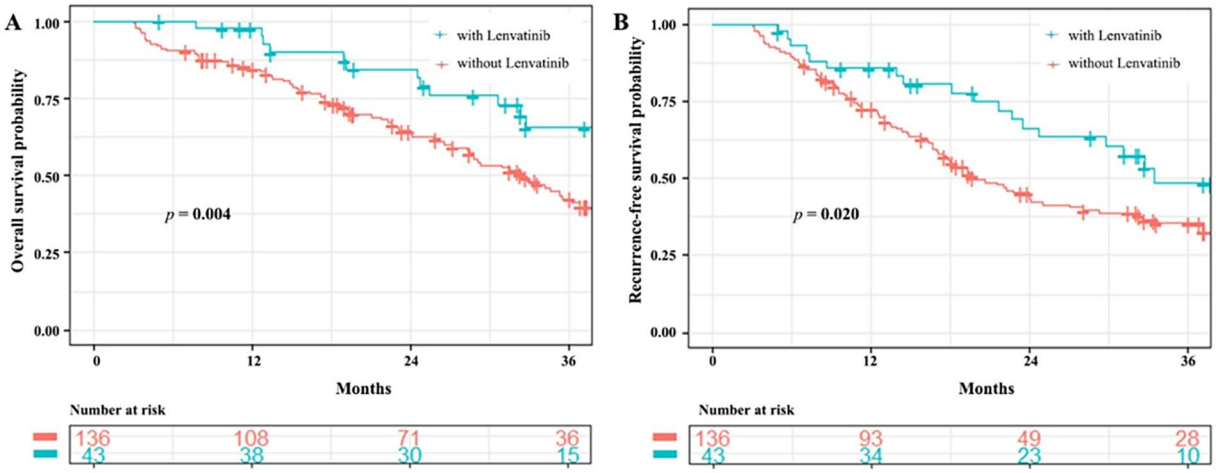

Figure 1. Kaplan-Meier analysis for survival in patients with HCC and MVI after hepatectomy stratified by adjuvant lenvatinib. (A) Overall survival. (B) Recurrence-free survival.
HCC indicates hepatocellular carcinoma; MVI, microvascular invasion.

studies have shown that sorafenib destroys tumor micro-vessels and ultimately inhibits tumor growth by inhibiting anti-tumor neovascularization and cell proliferation. Based on the molecular mechanism of sorafenib, researchers have used it for postoperative anti-recurrence therapy, especially for patients with MVI.[30,31] In 2018, Kudo et al[17] performed an RCT phase 3 non-inferiority trial (REFLECT) to compare lenvatinib vs sorafenib in the first-line treatment of patients with unresectable HCC. Although lenvatinib was non-inferior to sorafenib for OS, lenvatinib was associated with obvious improvements compared with sorafenib in all secondary endpoints: longer time to progression and progression-free survival, higher objective response rate. Since then, lenvatinib has been used more widely in advanced HCC. However, there is still a lack of research on anti-recurrence therapy after hepatectomy. In this study, the results demonstrated that lenvatinib can reduce postoperative recurrence and improve long-term survival in patients with HCC and MVI after curative hepatectomy.

Table 3. Univariable and multivariable Cox regression analyses of risk factors associated with overall survival for patients with hepatocellular carcinoma and MVI.

VARIABLES	UV HR (95% CI)	*P*	MV HR (95% CI)	*P**
Sex, men	1.108 (0.573-2.143)	.761		
Age, >60 years	1.457 (0.793-2.678)	.225		
ASA score, >2	1.177 (0.514-2.695)	.700		
Performance status, ⩾1	1.414 (0.923-2.166)	.111		
Etiology of liver disease, HBV	1.036 (0.537-2.000)	.915		
Cirrhosis	0.933 (0.602-1.446)	.756		
Portal hypertension, yes	2.243 (1.466-3.434)	.001	2.162 (1.352-3.457)	.001
Child-Pugh grade, B	1.702 (0.962-3.011)	.067	2.215 (1.207-4.065)	.010
ALT level, >80 U/L	1.324 (0.790-2.218)	.287		
AST level, >80 U/L	1.357 (0.800-2.302)	.257		
AFP level, >400 μg/L	2.254 (1.435-3.539)	.001	1.433 (1.097-2.290)	.033
Tumor size, >5 cm	2.635 (1.679-4.138)	.001	2.470 (1.561-3.906)	.001
Tumor number, ⩾2	1.845 (1.175-2.896)	.008	1.936 (1.212-3.093)	.006
Poor tumor differentiation	1.132 (0.714-1.794)	.599		
Resection margin, <1 cm	2.297 (1.482-3.560)	.001	1.765 (1.107-2.815)	.017
Extent of hepatectomy	1.408 (0.924-2.147)	.111		
Blood loss, >600 mL	1.330 (0.827-2.139)	.239		
Blood transfusion, yes	1.168 (0.919-2.411)	.141		
Operation time, ⩾180 min	1.230 (0.905-2.329)	.148		
With lenvatinib	0.436 (0.242-0.784)	.006	0.455 (0.249-0.831)	.001

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; CI, confidential interval; HBV, hepatitis B virus; HR, hazard ratio; MV, multivariable; MVI, microvascular invasion; UV, univariable.
*$P < .1$ in univariable analyses were entered into multivariable Cox analyses.

Some limitations should be considered in this study. As a retrospective study, there is some inherent bias, including variables that could not be standardized or identified, patients lost to follow-up, etc. In addition, all patients were from China and most of them had a background of hepatitis B virus (HBV) infection (more than 88%). Whether the results can be applied to predominantly hepatitis C virus (HCV)–related HCC needs further study. Future efforts should seek to validate the results, especially from the West, where the most common type of HCC is HCV-related but not HBV-related. In addition, previous studies have shown that the therapeutic efficacy of lenvatinib varies among HCC patients with different etiologies, although this conclusion remains a topic of debate. Recently, Sacco et al[32] concluded that patients affected by HCC with non-viral etiology treated with lenvatinib exhibit longer survival than those with viral etiology. Accordingly, when classifying postoperative patients, it is important to consider the potential influence of different etiologies on therapeutic efficacy. Similar consideration should also be given to patients with underlying medical conditions, such as concurrent diabetes[33] or those undergoing oral statin therapy,[34] as these factors may have an impact on the progression of HCC. Moreover, perioperative mortality can bias the apparent effect of adjuvant treatment in non-RCT studies. To partially compensate for this bias, we excluded patients who died within 90 days after hepatectomy. However, it is important to notice that this exclusion may have subjected the results to a different type of bias resulting from conditional survival, in which all patient prognoses improve as these individuals were presumed to have already survived a period since receiving lenvatinib. Further validation, especially multicenter RCT, still needed to be conducted.

Table 4. Univariable and multivariable Cox regression analyses of risk factors associated with recurrence-free survival for patients with hepatocellular carcinoma and MVI.

VARIABLES	UV HR (95% CI)	*P*	MV HR (95% CI)	*P**
Sex, men	1.190 (0.618-2.288)	.603		
Age, >60 years	1.280 (0.739-2.218)	.378		
ASA score, >2	1.378 (0.604-3.146)	.446		
Performance status, ⩾1	1.229 (0.817-1.850)	.322		
Etiology of liver disease, HBV	1.029 (0.563-1.880)	.926		
Cirrhosis	1.065 (0.704-1.611)	.767		
Portal hypertension, yes	2.245 (1.506-3.348)	.001	2.032 (1.320-3.128)	.001
Child-Pugh grade, B	1.927 (1.143-3.250)	.014	2.387 (1.376-4.140)	.002
ALT level, >80 U/L	1.334 (0.810-2.195)	.257		
AST level, >80 U/L	1.459 (0.895-2.379)	.130		
AFP level, >400 μg/L	2.741 (1.766-4.255)	.001	1.737 (1.098-2.748)	.018
Tumor size, >5 cm	2.365 (1.557-3.592)	.001	1.969 (1.286-3.013)	.002
Tumor number, ⩾2	1.899 (1.246-2.897)	.003	1.915 (1.229-2.985)	.004
Poor tumor differentiation	1.152 (0.749-1.771)	.520		
Resection margin, <1 cm	2.138 (1.443-3.304)	.001	1.634 (1.053-2.534)	.028
Extent of hepatectomy	0.781 (0.505-1.209)	.267		
Blood loss, >600 mL	1.221 (0.782-1.905)	.380		
Blood transfusion, yes	1.404 (0.930-2.118)	.106		
Operation time, ⩾180 min	1.188 (0.804-1.755)	.387		
With lenvatinib	0.551 (0.331-0.916)	.022	0.523 (0.308-0.886)	.016

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; CI, confidential interval; HBV, hepatitis B virus; HR, hazard ratio; MV, multivariable; MVI, microvascular invasion; UV, univariable.
*$P < .1$ in univariable analyses were entered into multivariable Cox analyses.

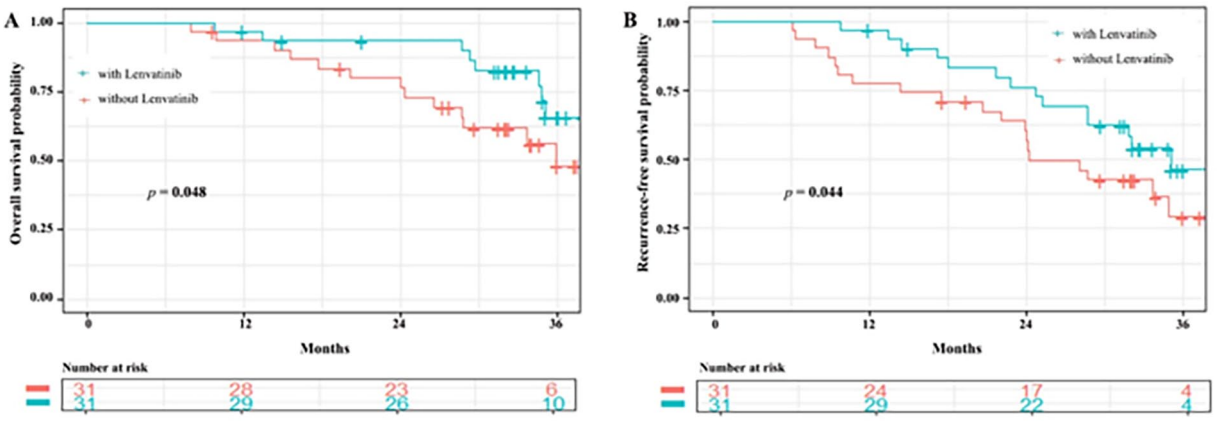

Figure 2. After PSM, Kaplan-Meier analysis for survival in patients with HCC and MVI after hepatectomy stratified by adjuvant lenvatinib. (A) Overall survival. (B) Recurrence-free survival.
HCC indicates hepatocellular carcinoma; MVI, microvascular invasion; PSM, propensity score matching.

Conclusions

In conclusion, this study demonstrated that lenvatinib can reduce postoperative recurrence and improve long-term survival in patients with HCC and MVI after curative hepatectomy. Therefore, in clinical practice, oral-targeted therapy should be recommended for patients with HCC and MVI.

Ethics Approval and Consent to Participate

This study was performed according to the Declaration of Helsinki, and all patients enrolled in this study provided informed consent and were approved by the Ethics Committee of Lishui Center Hospital and Zhejiang Provincial People's Hospital (no. QT2021430, December 29, 2021).

Author Contributions

M-GD, S-YL and W-FL contributed equally to this work. Dr LL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. BY contributed to study concept and design. M-GD, S-YL, and W-FL contributed to acquisition, analysis, or interpretation of data. M-GD, S-YL, and W-FL contributed to drafting of the manuscript. BY contributed to critical revision of the manuscript for important intellectual content. Lei Liang contributed to statistical analysis. LL, BY, and M-GD obtained funding. Lei Liang contributed to administrative, technical, or material support. BY contributed to study supervision.

ORCID iDs

Lei Liang https://orcid.org/0000-0003-3294-2978
Bin Ye https://orcid.org/0000-0001-6473-0369

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72:7-33.
3. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl*. 2011;17:S44-S57.
4. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76:681-693.
5. Kabir T, Tan ZZ, Syn NL, et al. Laparoscopic versus open resection of hepatocellular carcinoma in patients with cirrhosis: meta-analysis. *Br J Surg*. 2021;109:21-29.
6. Liang L, Xing H, Zhang H, et al. Surgical resection versus transarterial chemoembolization for BCLC intermediate stage hepatocellular carcinoma: a systematic review and meta-analysis. *HPB (Oxford)*. 2018;20:110-119.
7. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69:182-236.
8. Roayaie S, Blume IN, Thung SN, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. *Gastroenterology*. 2009;137:850-855.
9. Rodríguez-Perálvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. *Ann Surg Oncol*. 2013;20:325-339.
10. Lei Z, Li J, Wu D, et al. Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the Milan criteria. *JAMA Surg*. 2016;151:356-363.
11. Liang L, Li C, Wang MD, et al. Development and validation of a novel online calculator for estimating survival benefit of adjuvant transcatheter arterial chemoembolization in patients undergoing surgery for hepatocellular carcinoma. *J Hematol Oncol*. 2021;14:165.
12. Liao K, Yang K, Cao L, et al. Laparoscopic anatomical versus non-anatomical hepatectomy in the treatment of hepatocellular carcinoma: a randomised controlled trial. *Int J Surg (London, England)*. 2022;102:106652.
13. Shi C, Zhao Q, Liao B, et al. Anatomic resection and wide resection margin play an important role in hepatectomy for hepatocellular carcinoma with peritumoural micrometastasis. *ANZ J Surg*. 2019;89:E482-E486.
14. Huang A, Yang XR, Chung WY, Dennison AR, Zhou J. Targeted therapy for hepatocellular carcinoma. *Signal Transduct Target Ther*. 2020;5:146.
15. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378-390.
16. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:25-34.
17. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391:1163-1173.
18. Kane LT, Fang T, Galetta MS, et al. Propensity score matching: a statistical method. *Clin Spine Surg*. 2020;33:120-122.
19. Zhang XP, Wang K, Wei XB, et al. An eastern hepatobiliary surgery hospital microvascular invasion scoring system in predicting prognosis of patients with hepatocellular carcinoma and microvascular invasion after R0 liver resection: a large-scale, multicenter study. *Oncologist*. 2019;24:e1476-e1488.
20. Erstad DJ, Tanabe KK. Prognostic and therapeutic implications of microvascular invasion in hepatocellular carcinoma. *Ann Surg Oncol*. 2019;26:1474-1493.
21. Liu L, Shui Y, Yu Q, et al. Narrow-margin hepatectomy resulted in higher recurrence and lower overall survival for R0 resection hepatocellular carcinoma. *Front Oncol*. 2020;10:610636.
22. Su CM, Chou CC, Yang TH, Lin YJ. Comparison of anatomic and non-anatomic resections for very early-stage hepatocellular carcinoma: the importance of surgical resection margin width in non-anatomic resection. *Surg Oncol*. 2021;36:15-22.
23. Shi M, Guo RP, Lin XJ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. *Ann Surg*. 2007;245:36-43.
24. Yang J, Liang H, Hu K, et al. The effects of several postoperative adjuvant therapies for hepatocellular carcinoma patients with microvascular invasion after curative resection: a systematic review and meta-analysis. *Cancer Cell Int*. 2021;21:92.
25. Ke-Wei L, Tian-Fu W, Xi L, et al. The effect of postoperative TACE on prognosis of HCC with microscopic venous invasion. *Hepatogastroenterology*. 2012;59:1944-1946.
26. Liu S, Guo L, Li H, et al. Postoperative adjuvant trans-arterial chemoembolization for patients with hepatocellular carcinoma and portal vein tumor thrombus. *Ann Surg Oncol*. 2018;25:2098-2104.
27. Liang L, Li C, Diao YK, et al. Survival benefits from adjuvant transcatheter arterial chemoembolization in patients undergoing liver resection for hepatocellular carcinoma: a systematic review and meta-analysis. *Therap Adv Gastroenterol*. 2020;13:1756284820977693.
28. Chen Q, Shu C, Laurence AD, et al. Effect of Huaier granule on recurrence after curative resection of HCC: a multicentre, randomised clinical trial. *Gut*. 2018;67:2006-2016.
29. Ward TJ, Madoff DC, Weintraub JL. Interventional radiology in the multidisciplinary management of liver lesions: pre- and postoperative roles. *Semin Liver Dis*. 2013;33:213-225.
30. Esagian SM, Kakos CD, Giorgakis E, Burdine L, Barreto JC, Mavros MN. Adjuvant transarterial chemoembolization following curative-intent hepatectomy versus hepatectomy alone for hepatocellular carcinoma: a systematic review and meta-analysis of randomized controlled trials. *Cancers (Basel)*. 2021;13:2984.
31. Huang Y, Zhang Z, Zhou Y, Yang J, Hu K, Wang Z. Should we apply sorafenib in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy? *Onco Targets Ther*. 2019;12:541-548.
32. Sacco R, Ramai D, Tortora R, et al. Role of etiology in hepatocellular carcinoma patients treated with lenvatinib: a counterfactual event-based mediation analysis. *Cancers (Basel)*. 2023;15:381.
33. Shen GL, Lu Y, Liang L, et al. Impact of diabetes mellitus on the long-term prognosis of patients with hepatocellular carcinoma after hepatectomy. *Expert Rev Gastroenterol Hepatol*. 2022;16:473-478.
34. Facciorusso A, Abd El Aziz MA, Singh S, et al. Statin use decreases the incidence of hepatocellular carcinoma: an updated meta-analysis. *Cancers (Basel)*. 2020;12:874.