Efficacy and safety of lenvatinib for preventing tumor recurrence after liver transplantation in hepatocellular carcinoma beyond the Milan criteria

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Background: Lenvatinib is one of the first-line treatments for unresectable hepatocellular carcinoma (HCC). However, data are lacking on lenvatinib in the postoperative setting.

Methods: This retrospective analysis enrolled 242 patients with HCC who underwent liver transplantation (LTx). Eligible patients were divided into 2 groups according to their use of adjuvant lenvatinib following LTx (lenvatinib, n=42; control, n=200). The primary outcome measures were overall survival (OS), time to recurrence (TTR), and safety. Kaplan-Meier analysis was applied to calculate the OS, while a competing risk model was used to estimate the cumulative incidence of recurrence.

Results: The lenvatinib group showed more advanced tumors and a higher proportion of HCC beyond the Milan criteria (P<0.001) than the control group. There were no significant differences in both the OS and TTR between the 2 groups. After focusing on the patients with HCC beyond the Milan criteria, baseline characteristics were similar in the lenvatinib group (n=38) and the control group (n=102). Competing risk analysis showed lenvatinib significantly prolonged TTR after LTx versus the control group [sub-hazard ratio (sHR), 0.40; 95% confidence interval (CI): 0.17 to 0.93; P=0.031]. In the multivariate competing risk model, adjuvant lenvatinib was an independent protective factor for tumor recurrence after LTx in patients with HCC beyond the Milan criteria (sHR, 0.33; 95% CI: 0.13 to 0.83; P=0.018). The rate of early recurrence within t2 years after LTx was also significantly decreased in the lenvatinib group (15.8% *vs.* 33.3%, P=0.041). However, the lenvatinib group exhibited comparable OS with the control group in patients with HCC beyond the Milan criteria. Treatment-related adverse events (TRAEs) and Grade ≥3 TRAEs occurred in 40 (95.2%) and 13 (31%) patients who received adjuvant lenvatinib, respectively. No treatment-related death was reported.

Conclusions: Postoperative lenvatinib administration may provide clinical benefits and is well tolerated in patients with HCC beyond the Milan criteria who undergo LTx.

Keywords: Lenvatinib; recurrence; hepatocellular carcinoma (HCC); liver transplantation (LTx); competing risk model

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Introduction

Hepatocellular carcinoma (HCC) is a common cancer worldwide and a leading cause of cancer-related death (1,2). Despite improvements in screening programs and diagnostic tools, only 30–40% of patients with HCC are eligible for curative treatments such as surgical resection, liver transplantation (LTx), and radiofrequency ablation (3). Among them, LTx, which has the advantages of removing tumor lesions completely and simultaneously restoring normal liver function, is considered the best option for patients with tumors meeting the Milan criteria (solitary tumor ≤5 cm or up to 3 nodules ≤3 cm) (4,5). Candidate selection for LTx has increasingly been extended to include patients with HCC beyond the Milan criteria; however, a substantial proportion of these patients experience postsurgical tumor recurrence, with 5-year overall survival (OS) and disease-free survival rates of 65% and 62%, respectively (6). Therefore, an urgent need exists for an effective adjuvant therapy to improve outcomes after LTx for patients with HCC beyond the Milan criteria.

Lenvatinib is a multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, platelet-derived growth factor (PDGF) receptor alpha, rearranged during transfection (RET) proto-oncogene receptor, and the receptor tyrosine kinase (KIT) (7-10). The phase III REFLECT trial demonstrated noninferiority of lenvatinib to sorafenib for OS in patients with unresectable HCC, as well as favorable progression-free survival and time to progression (11). Based on these findings, lenvatinib was approved as one of the first-line treatments for unresectable HCC. However, there is a lack of data available in the literature regarding the use of lenvatinib in patients with HCC who have undergone LTx, particularly for those with HCC beyond the Milan criteria.

In this study, the data of 242 consecutive HCC patients with LTx at our institute during the past 2 years were retrospectively analyzed, including 102 cases within the Milan criteria and 140 beyond the Milan criteria. The safety and efficacy of lenvatinib in preventing early recurrence and improving OS after LTx for HCC patients were further evaluated, especially for those beyond the Milan criteria. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1353/rc).

Methods

Patients

Consecutive patients with HCC beyond the Milan criteria who underwent LTx at Zhongshan Hospital from August 2018 to December 2020 were retrospectively enrolled. The inclusion criteria were as follows: HCC confirmed by pathological examination, no history of other tumor types, complete patient information, and no perioperative mortality. Patients were divided into 2 groups according to the use of lenvatinib for the prevention of recurrence after LTx. Tumor differentiation was assessed using the Edmondson grading system and liver function was evaluated using the Child-Pugh scoring system. The Guidelines of Primary Liver Cancer in China (12) were used to determine tumor stage. The Milan criteria and Fudan criteria were used to evaluate the prognosis of patients with HCC after LTx (5,12). Positron emission tomography computed tomography (PET-CT) examination was performed prior to transplantation in all patients to confirm the absence of extrahepatic metastasis. The preoperative treatments and surgical parameters, including duration of surgery, blood loss, and warm ischemic time, were collected. Patient selection is summarized in *Figure 1*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the committee of Zhongshan Hospital (No. B2020-402) and individual consent for this retrospective analysis was waived. All grafts used in transplantation were obtained from deceased donors, none of whom were executed prisoners.

LTx procedure and follow-up

A standard procedure was implemented for LTx (13). Triple-drug immunosuppressive therapy, including cyclosporine or tacrolimus combined with corticosteroids and/or mycophenolate mofetil (MMF), was administered after LTx, as described previously (14,15). Corticosteroids and MMF were discontinued 3 months after LTx, and most patients subsequently received tacrolimus monotherapy. Tacrolimus was substituted with rapamycin if patients showed renal insufficiency or inadequate blood concentration of tacrolimus. A 2-drug regimen of hepatitis B immunoglobulin combined with lamivudine or entecavir was used to prevent hepatitis B virus reactivation (15).

Follow-up assessments were conducted every month for the first 6 months after LTx and every 3 months

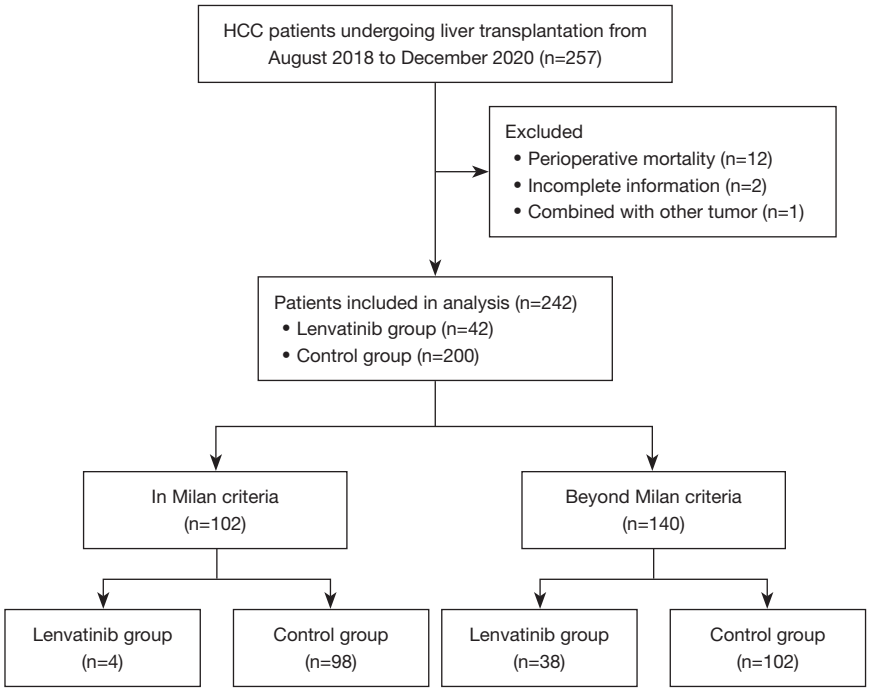

Figure 1 Flow chart of the study. HCC, hepatocellular carcinoma.

thereafter and consisted of serum alpha-fetoprotein (AFP), prothrombin induced by vitamin K absence-II (PIVKA-II), abdominal ultrasonography, chest computed tomography (CT), and enhanced magnetic resonance imaging (MRI). Suspected recurrence was confirmed by imaging examination (CT, MRI, bone scan, or PET-CT).

The OS was defined as the interval from the date of surgery to either the date of death or the last follow-up visit. Time to recurrence (TTR) was defined as the interval between LTx and the first recurrence or metastasis after LTx (13). When recurrence was confirmed, treatment options were discussed by a multidisciplinary team, and patients were given appropriate treatments, such as hepatectomy, radiofrequency ablation, transcatheter arterial chemoembolization, external beam radiotherapy, systemic chemotherapy, and/or tyrosine kinase inhibitors (TKIs; sorafenib, regorafenib, or lenvatinib), according to the pattern of recurrence, liver function, and general condition of the patient. Follow-up was terminated on 1 January 2022.

Post-LTx adjuvant lenvatinib treatment

After liver transplantation, the application of adjuvant lenvatinib was recommended for patients with a high risk of recurrence [multiple lesions, microvascular invasion (mVI), poor differentiation, or postoperative AFP/PIVKA-II positive], with the intention of reducing relapse and improving survival. The recommended duration of lenvatinib treatment was 2 years. Patients were treated with lenvatinib orally at a dosage of 8 mg/day (body weight <60 kg) or 12 mg/day (body weight ≥60 kg) starting 1 month after LTx. Treatment was withdrawn if there was unacceptable toxicity or upon patient request. Dose adjustments due to adverse events (AEs) were performed according to routine clinical practice. Any AEs during lenvatinib treatment were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (16).

Propensity score matching

To overcome the potential for confounding from selection bias between patients who did and did not receive adjuvant lenvatinib, propensity score matching (PSM) was conducted using R software v. 4.1.2 with "Matchit" package (https://www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria) (17). Based on clinical knowledge and experience, factors considered to have an influence on the

decision to use adjuvant lenvatinib and/or influence clinical outcomes included gender (male or female), age (≤50 or >50 years), hepatitis B surface antigen (HBsAg) status (negative or positive), AFP level (≤400 or >400 ng/mL), PIVKA-II (≤100 or >100 mAU/mL), Child-Pugh class (A or B/C), cirrhosis (no or yes), tumor size (≤5 or >5 cm), tumor number (solitary or multiple), Edmondson stage (I–II or III–IV), and mVI (no or yes). A 1:2 matching was applied using the nearest-neighbor matching algorithm to select matched pairs of patients.

Statistical analysis

Categorical variables were analyzed as frequency (%) and compared between groups via chi-square test. Continuous variables were summarized as median [interquartile range (IQR)] and compared using the Wilcoxon rank-sum test. The Kaplan-Meier method was used to calculate survival rates, and the log-rank test was applied to compare survival differences between groups. Univariate and multivariate Cox regression analyses were used to identify independent risk factors for OS and estimate the hazard ratio (HR). Variables with P<0.05 in the univariate model were selected for multivariate analysis. Since mortality ahead of relapse might have precluded recurrence in patients undergoing LTx, use of the usual Kaplan-Meier method would have misestimated the recurrence rate. Therefore, a competing risk analysis and the Fine-Gray test were applied to calculate and compare the cumulative incidence of recurrence, respectively (18). A multivariate competing model was used to identify the risk factors of recurrence after LTx and estimate the sub-hazard ratio (sHR) using the subdistribution analysis of competing risks (cmprsk) v. 2.2.11 package for R. Subgroup analyses were conducted using a competing risk model in patients stratified according to the clinical characteristics, including tumor size, tumor number, tumor differentiation, mVI, and postoperative AFP or PIVKA-II. All statistical tests were 2-tailed and a P-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.1.2.

Results

Patient baseline characteristics

Baseline characteristics of all included patients (n=242) are summarized in *Table 1*. A total of 42 (17.4%) patients received adjuvant lenvatinib after LTx, while 200 (82.6%) did not (control). Lenvatinib-treated patients showed a significantly larger tumor size (P=0.002), a higher PIVKA-II level (P=0.006), and a more advanced China Liver Cancer (CNLC) stage (P<0.001) compared with the control group.

Overall outcomes

The median follow-up time was 18.7 (range, 3.6 to 35.6) months. Overall, the 6-, 12-, and 24-month OS rates for all cases were 98.3%, 95.2%, and 88.0%, respectively (Figure S1A). In the competing risk analysis, the 6-, 12-, and 24-month cumulative incidence of recurrence were 5.4%, 13.4%, and 24.2%, respectively (Figure S1B). The clinical characteristics that had an impact on OS and TTR are shown in Table S1.

Among all cases, 23 (9.5%) died and 49 (20.2%) had tumor recurrence during follow-up. Tumor recurrence was observed in the liver (n=10), at extrahepatic sites (n=35), and at both intrahepatic and extrahepatic sites (n=4).

Efficacy of adjuvant lenvatinib in the whole cohort

There were no significant differences between the levantinib and control groups in postoperative OS [HR, 0.73; 95% confidence interval (CI): 0.25 to 2.13; P=0.562; *Figure 2A*] or TTR (sHR, 0.73; 95% CI: 0.33 to 1.57; P=0.441; *Figure 2B*). The 6-, 12-, and 24-month OS rates in the lenvatinib group were 97.6%, 95.2%, and 91.8%, compared with 98.5%, 95.2%, and 87.1% in the control group, respectively (*Figure 2A*). Competing risk analysis showed that the 6-, 12-, and 24-month cumulative incidences of recurrence in the lenvatinib group were 2.4%, 4.8%, and 21.4%, compared with 6.0%, 15.2%, and 24.7% in the control group, respectively (*Figure 2B*).

Efficacy of adjuvant lenvatinib in HCC within Milan criteria

Considering that patients beyond the Milan criteria experienced a high risk of recurrence after LTx, lenvatinib may achieve clinical benefits in these patients instead of in those who meet the Milan criteria. Thus, we further investigated the impact of adjuvant lenvatinib on patients who underwent LTx with HCC within and beyond the Milan criteria, respectively.

For patients within the Milan criteria (n=102), only 4 cases (3.9%) received adjuvant lenvatinib. There was no difference in OS (P=0.562; Figure S1C) or TTR (P=0.208;

Table 1 Baseline characteristics in patients with HCC undergoing liver transplantation

Variable	Items	All patients (n=242)			Patients beyond Milan criteria (n=140)		
		Control (n=200)	Lenvatinib (n=42)	P value	Control (n=102)	Lenvatinib (n=38)	P value
Gender	Male	173 (86.5)	40 (95.2)	0.113	90 (88.2)	36 (94.7)	0.410[a]
	Female	27 (13.5)	2 (4.8)		12 (11.8)	2 (5.3)	
Age (years)	≤50	99 (49.5)	21 (50.0)	0.953	49 (48.0)	20 (52.6)	0.629
	>50	101 (50.5)	21 (50.0)		53 (52.0)	18 (47.4)	
HBsAg	Negative	39 (19.5)	11 (26.2)	0.330	19 (18.6)	10 (26.3)	0.318
	Positive	161 (80.5)	31 (73.8)		83 (81.4)	28 (73.7)	
AFP (ng/mL)	≤400	161 (80.5)	34 (81.0)	0.946	76 (74.5)	31 (81.6)	0.381
	>400	39 (19.5)	8 (19.0)		26 (25.5)	7 (18.4)	
PIVKA-II (mAU/mL)	<100	104 (52.0)	12 (28.6)	0.006	39 (38.2)	10 (26.3)	0.189
	>100	96 (48.0)	30 (71.4)		63 (61.8)	28 (73.7)	
Child-Pugh class	A	128 (64.0)	33 (78.6)	0.069	69 (67.6)	30 (78.9)	0.191
	B-C	72 (36.0)	9 (21.4)		33 (32.4)	8 (21.1)	
Cirrhosis	No	32 (16.0)	7 (16.7)	0.915	23 (22.5)	7 (18.4)	0.597
	Yes	168 (84.0)	35 (83.3)		79 (77.5)	31 (81.6)	
Tumor size (cm)	≤5	159 (79.5)	24 (57.1)	0.002	61 (59.8)	20 (52.6)	0.445
	>5	41 (20.5)	18 (42.9)		41 (40.2)	18 (47.4)	
Tumor number	Single	74 (37.0)	9 (21.4)	0.053	9 (8.8)	6 (15.8)	0.380[a]
	Multiple	126 (63.0)	33 (78.6)		93 (91.2)	32 (84.2)	
Edmondson stage	I-II	111 (55.5)	20 (47.6)	0.351	51 (50.0)	18 (47.4)	0.782
	III-IV	89 (44.5)	22 (52.4)		51 (50.0)	20 (52.6)	
mVI	No	96 (48.0)	16 (38.1)	0.242	39 (38.2)	14 (36.8)	0.880
	Yes	104 (52.0)	26 (61.9)		63 (61.8)	24 (63.2)	
CNLC stage	I	107 (53.5)	10 (23.8)	<0.001	9 (8.8)	6 (15.8)	0.380[a]
	II	93 (46.5)	32 (76.2)		93 (91.2)	32 (84.2)	
Milan criteria	Within	98 (49.0)	4 (9.5)	<0.001	0	0	/
	Beyond	102 (51.0)	38 (90.5)		102 (100.0)	38 (100.0)	
Fudan criteria	Within	124 (62.0)	11 (26.2)	<0.001	26 (25.5)	7 (18.4)	0.381
	Beyond	76 (38.0)	31 (73.8)		76 (74.5)	31 (81.6)	
Preoperative TACE	No	134 (67.0)	24 (57.1)	0.222	55 (53.9)	22 (57.9)	0.674
	Yes	66 (33.0)	18 (42.9)		47 (46.1)	16 (42.1)	
Duration of surgery (minutes)		308.0 [278.0, 332.0]	308.0 [272.0, 329.3]	0.563	308.00 [284.0, 332.0]	305.0 [272.0, 330.0]	0.431[b]
Blood loss (mL)		800.0 [400.0, 1,500.0]	800.0 [600.0, 1,175.0]	0.433	900.0 [500.0, 1,500.0]	800.0 [600.0, 1,200.0]	0.82[b]
Warm ischemic time (minutes)		40.0 [36.0, 44.0]	40.0 [36.0, 45.0]	0.822	40.0 [36.3, 44.0]	39.5 [36.0, 45.0]	0.365[b]

Categorical variables were summarized as n (%); continuous variables were summarized as median [interquartile range]. [a], continuous correction. [b], Wilcoxon rank-sum test. AFP, alpha-fetoprotein; CNLC, China Liver Cancer Stage; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; mVI, microvascular invasion; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TACE, transarterial chemoembolization.

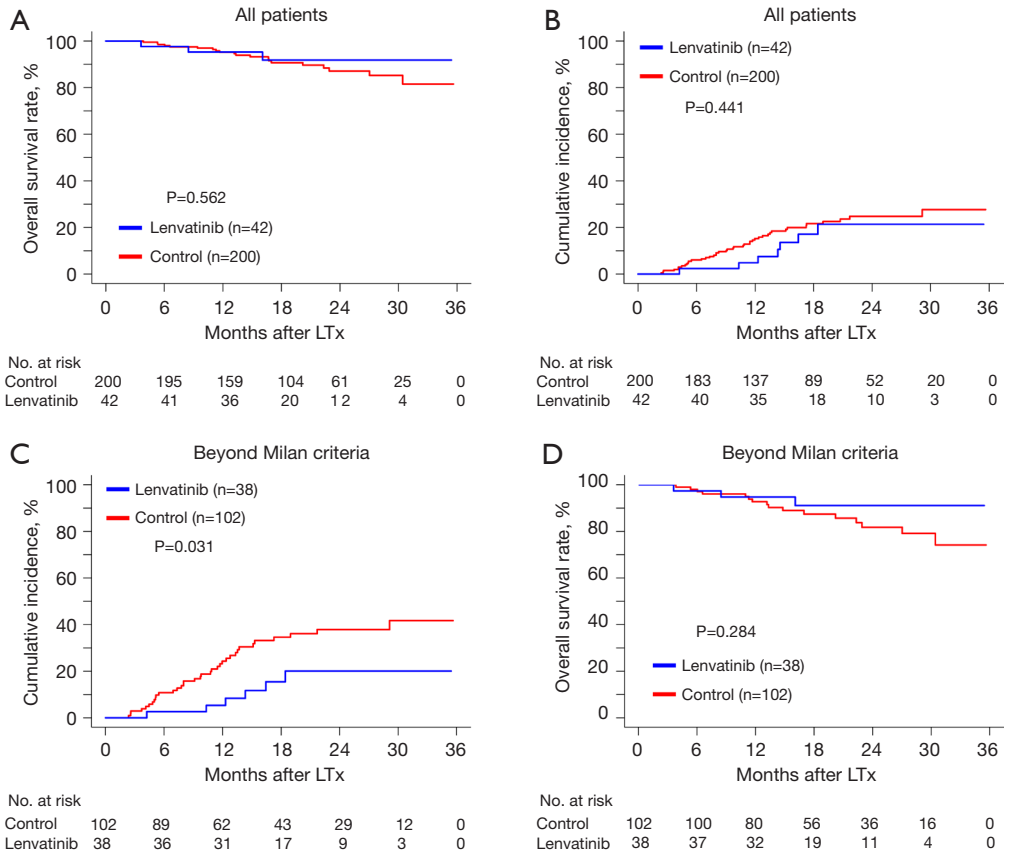

Figure 2 Efficacy of postoperative lenvatinib treatment in patients with HCC who underwent LTx. (A) Kaplan-Meier analysis of OS for all patients in the lenvatinib and control groups. (B) Competing risk analysis of the cumulative incidence of recurrence for all patients in the lenvatinib and control groups. (C) Competing risk analysis of the cumulative incidence of recurrence for patients with HCC beyond the Milan criteria in the lenvatinib and control groups. (D) Kaplan-Meier analysis of OS for patients with HCC beyond the Milan criteria in the lenvatinib and control groups. HCC, hepatocellular carcinoma; LTx, liver transplantation; OS, overall survival.

Figure S1D) between the lenvatinib group and the control group, using the Kaplan-Meier analysis and a competing risk analysis, respectively.

Efficacy of adjuvant lenvatinib in HCC beyond Milan criteria

Of the patients with HCC beyond the Milan criteria (n=140), 38 patients (27.1%) took lenvatinib as postoperative adjuvant therapy, and these patients showed a comparable baseline with those who did not use lenvatinib after LTx (*Table 1*). After using death without recurrence as a competing risk, patients who received lenvatinib had a significantly longer TTR than those in the control group (sHR, 0.40; 95% CI: 0.17 to 0.93; P=0.031; *Figure 2C*). The cumulative incidence of recurrence was also lower in the lenvatinib group versus the control group at 6 (2.6% *vs.* 10.7%), 12 (5.3% *vs.* 24.4%), and 24 (20.0% *vs.* 37.9%) months (*Figure 2C*). In the multivariate competing risk analysis that adjusted AFP, PIVKA-II, tumor size, Edmondson stage, and mVI, adjuvant lenvatinib was identified as an independent protective factor for recurrence after LTx and was associated with a 67% reduction in the risk of recurrence (sHR, 0.33; 95% CI: 0.13 to 0.83; P=0.018; *Table 2*).

In addition, there was similar OS in the lenvatinib group and the control group (HR, 0.57; 95% CI: 0.21 to 1.59; P=0.284; *Figure 2D*). The 6-, 12-, and 24-month survival rates in the lenvatinib group were 97.4%, 94.7%, and 91.1%, compared with 98.0%, 92.7%, and 81.8% in the control group, respectively (*Figure 2D*).

We also investigated the role of postoperative

Table 2 Univariate and multivariate competing risk analyses to identify independent risk factors for time to recurrence in patients with HCC beyond Milan criteria

Variable	Univariate analysis		Multivariate analysis	
	sHR (95% CI)	P value	sHR (95% CI)	P value
Gender (female)	0.89 (0.35–2.24)	0.810	NA	NA
Age (>50 years)	0.88 (0.48–1.62)	0.690	NA	NA
HBsAg (positive)	1.90 (0.75–4.78)	0.170	NA	NA
AFP (>400 ng/mL)	3.19 (1.72–5.91)	<0.001	2.33 (1.27–4.26)	0.006
PIVKA-II (>100 mAU/mL)	2.56 (1.18–5.56)	0.018	1.97 (0.85–4.57)	0.120
Child-Pugh class (B-C)	1.36 (0.69–2.65)	0.370	NA	NA
Cirrhosis (yes)	0.72 (0.37–1.41)	0.330	NA	NA
Tumor size (>5 cm)	1.72 (0.94–3.16)	0.078	NA	NA
Tumor number (multiple)	0.77 (0.30–2.02)	0.600	NA	NA
Edmondson stage (III-IV)	2.43 (1.25–4.72)	0.009	2.00 (1.00–4.00)	0.050
mVI (yes)	2.18 (1.05–4.53)	0.037	1.20 (0.52–2.79)	0.660
Preoperative TACE	1.27 (0.69–2.33)	0.450	NA	NA
Duration of surgery (minutes)	1.00 (0.99–1.00)	0.380	NA	NA
Blood loss (mL)	0.97 (0.93–1.01)	0.120	NA	NA
Warm ischemic time (minutes)	1.00 (1.00–1.00)	0.850	NA	NA
Lenvatinib (yes)	0.40 (0.17–0.92)	0.032	0.33 (0.13–0.83)	0.018

AFP, alpha-fetoprotein; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; NA, not applicable; mVI, microvascular invasion; PIVKA-II, protein induced by vitamin K absence or antagonist-II; sHR, sub-hazard ratio; TACE, transarterial chemoembolization.

lenvatinib treatment in reducing early tumor recurrence (≤2 years) after LTx, and found that early recurrences were significantly less frequent in the lenvatinib group (6/38, 15.8%) than in the control group (34/102, 33.3%; P=0.041; *Figure 3A*).

Furthermore, we performed PSM and matched 99 patients in a 1:2 ratio; 33 in the lenvatinib group and 66 matched controls. The clinical features of the 2 groups after PSM were well balanced (Table S2). As expected, the competing risk analysis showed a longer TTR in the lenvatinib group than the control group in the PSM cohort (sHR, 0.31; 95% CI: 0.12 to 0.78; P=0.013; Figure S2A). The early recurrence rates were also lower in the lenvatinib group than in the control group (15.2% *vs.* 40.9%; P=0.010; Figure S2B). Notably, the OS did not differ between the 2 groups, but there was a trend of longer OS in the lenvatinib group after PSM (HR, 0.40; 95% CI: 0.13 to 1.19; P=0.099; Figure S2C).

Subgroup analyses in HCC beyond Milan criteria

Compared with the control group, adjuvant lenvatinib significantly decreased the cumulative incidence of recurrence rate in patients with tumor size >5 cm (P=0.025), multiple tumors (P=0.020), Edmondson III–IV grade (P=0.018), and mVI (P=0.017) (*Figure 3B-3E*). Furthermore, patients with AFP >20 ng/mL or PIVKA-II >40 mAU/mL at 1 month after LTx could benefit from adjuvant lenvatinib (P=0.024, *Figure 3F*). The sHRs and 95% CIs for TTR in the exploratory subgroups are presented in Figure S3.

Safety of adjuvant lenvatinib

Among the 42 patients using lenvatinib, 27 patients discontinued. The median duration of adjuvant lenvatinib treatment was 13.0 months, with a range of 3.1 to 26.7 months. Treatment-related AEs (TRAE) are

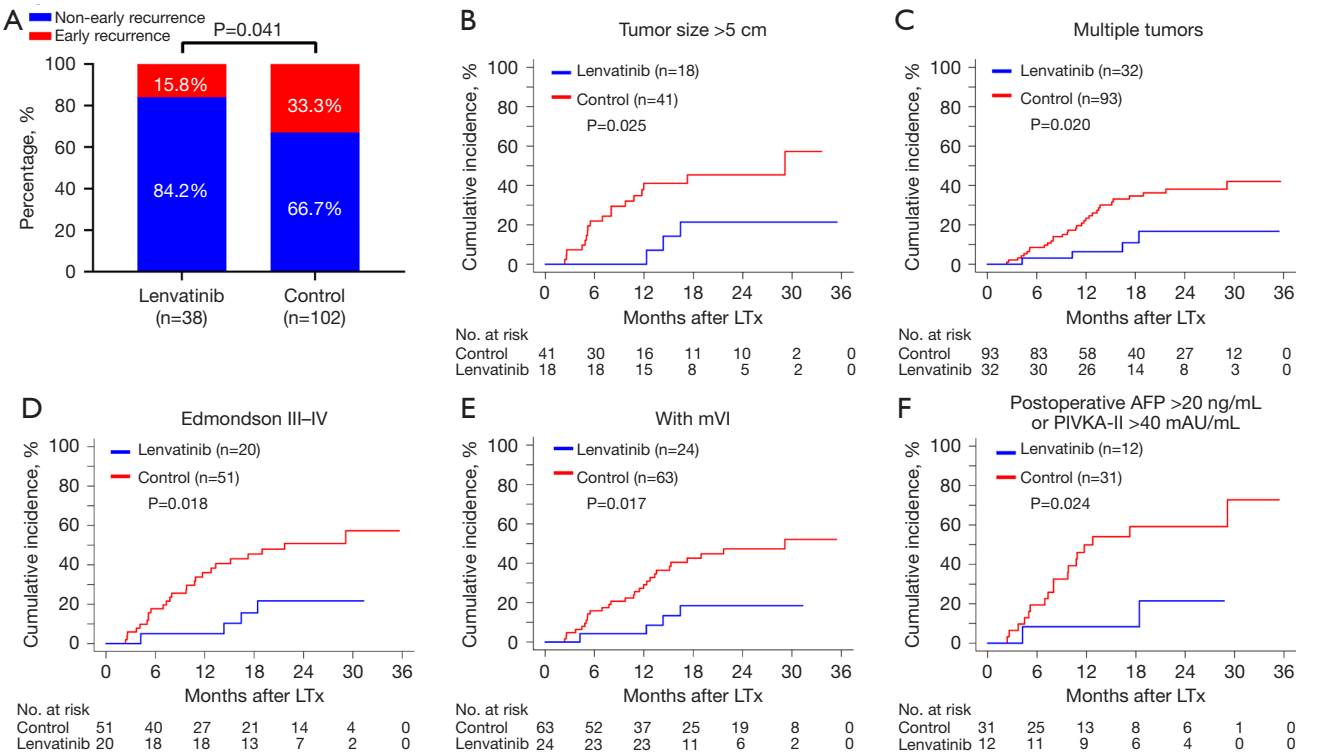

Figure 3 Competing risk analyses of recurrence rates in subgroups of patients with HCC who underwent LTx beyond the Milan criteria. (A) The correlation between adjuvant lenvatinib and early recurrence (≤2 years) in patients with HCC beyond the Milan criteria. (B-F) Competing risk analyses of recurrence rates for patients in the following subgroups: (B) tumor size >5 cm, (C) multiple tumors, (D) tumor differentiation III–IV, (E) mVI, (F) postoperative (1 month after LTx) AFP >20 ng/mL or PIVKA-II >40 mAU/mL. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; LTx, liver transplantation; mVI, microvascular invasion; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

summarized in *Table 3*. Any-grade TRAEs occurred in most patients (40/42, 95.2%), and grade ≥3 TRAEs occurred in approximately one third of patients (13/42, 31.0%). The most common TRAEs were hypertension (n=18, 42.9%), diarrhea (n=15, 35.7%), decreased appetite (n=10, 23.8%), and fatigue (n=10, 23.8%). Grade ≥3 TRAEs were hypertension (n=6, 14.3%), diarrhea (n=4, 9.5%), proteinuria (n=2, 4.8%), decreased appetite (n=1, 2.4%), and dysphonia (n=1, 2.4%). There were 3 patients (7.1%) who discontinued levantinib due to unbearable TRAEs and there were other patients who could tolerate the TRAEs after dose reduction (n=7, 16.6%), transient discontinuation (n=5, 11.9%), or symptomatic treatment (n=25, 59.5%). No treatment-related deaths were reported.

We also investigated whether adjuvant lenvatinib increased the postoperative complications of LTx. The incidence rates of infection, rejection, and bile duct stenosis in the lenvatinib group were comparable with those in the control group (4.8% *vs.* 4.0%, 4.8% *vs.* 2.0%, and 2.4% *vs.* 10.0%, respectively; all P>0.05).

Discussion

To our knowledge, this is the first large sample study of the use of lenvatinib as adjuvant treatment following LTx in patients with HCC. For all patients who underwent LTx with HCC, there were no significant differences in postoperative OS and TTR between patients who received adjuvant lenvatinib and those who did not. However, this observation was confounded because most patients in the lenvatinib group had tumors beyond the Milan criteria. Thus, further analysis focused on the patients with HCC beyond the Milan criteria, in which baseline characteristics were similar between the lenvatinib group and the control group. Interestingly, adjuvant lenvatinib significantly prolonged TTR and reduced the risk of tumor recurrence

Table 3 Treatment-related adverse events in patients who received postoperative lenvatinib

Event	Lenvatinib (n=42)	
	Any grade	Grade ≥3
Any	40 [95]	13 [31]
Hypertension	18 [43]	6 [14]
Diarrhea	15 [36]	4 [10]
Decreased appetite	10 [24]	1 [2]
Fatigue	10 [24]	0
Proteinuria	7 [17]	2 [5]
Palmar-plantar erythrodysesthesia	7 [17]	0
Decreased weight	6 [14]	0
Mucositis	6 [14]	0
Nausea	5 [12]	0
Dysphonia	4 [10]	1 [2]
Decreased platelet count	4 [10]	0
Rash	3 [7]	0
Bleed	3 [7]	0

Data are reported as n [%].

compared with the control group. The subsequent PSM analysis also validated the decreased recurrence rate in the lenvatinib group. The greatest benefits in reduction of tumor recurrence with adjuvant lenvatinib were seen in patients with tumor size >5 cm, multiple tumors, tumor differentiation grades III–IV, mVI, and postoperative AFP >20 ng/mL or PIVKA-II >40 mAU/mL. However, no significant difference in OS was observed between the groups, which might be due to the short follow-up time and relatively small sample size. Furthermore, the reserved liver function after LTx increased the probabilities of undergoing secondary resection and other locoregional therapy after recurrence. Notably, after further balancing the baselines via PSM, there emerged a trend toward better OS for the lenvatinib group.

It is well accepted that minimal residual disease is a major cause of metastasis and recurrence after LTx for HCC patients (19-22). We found that postoperative lenvatinib treatment significantly decreased the incidence of recurrence after LTx (sHR, 0.40; 95% CI: 0.17 to 0.93; P=0.031), which typically results from pre-operative occult micrometastases (23,24). The antitumor activity of lenvatinib has been associated with anti-angiogenesis and inhibition of tumor cell proliferation (25,26). Therefore, postoperative lenvatinib administration in patients with HCC may delay the appearance of new recurrent lesions via inhibition of tumor neovascularization and the proliferation of minimal residual disease.

Our data showed that lenvatinib was well tolerated in patients who underwent LTx, with a safety profile consistent with that previously reported in patients with advanced HCC in the REFLECT study (11). In the present study, patients had a similar rate of any grade TRAEs compared with those in the REFLECT study (95.2% *vs.* 93.9%), but a lower rate of grade ≥3 TRAEs (31.0% *vs.* 56.7%), which might be related to the improvement of liver function after LTx. In addition, it was shown that adjuvant lenvatinib did not increase the risk of complications after LTx.

The Milan criteria are the gold standard candidate selection criteria to minimize the risk of disease recurrence after LTx in patients with HCC (5,27). However, there are growing concerns that the Milan criteria may be too restrictive in view of the increasing candidate list, particularly in China (28,29). The eligibility criteria for LTx have been gradually expanded for HCC, and in China, around 50% of patients with HCC who receive LTx are beyond the Milan criteria (30,31). As a result, this will lead to a higher proportion of tumor recurrence after LTx (28.6% in our cohort within 2 years) (31,32).

The application of TKIs as adjuvant therapy in HCC after radical surgery remains controversial. Several pieces of evidence have demonstrated that TKIs, like sorafenib, improve the outcomes of HCC with a high risk of recurrence after radical resection or LTx (33-36). However, the phase III STORM trial failed to identify the clinical benefit of adjuvant sorafenib (37). In the present study, we initially found that postoperative lenvatinib administration could significantly reduce tumor recurrence (15.8% *vs.* 33.3%) and prolong median TTR (not reached *vs.* 14.6 months, P=0.019) after LTx for those HCC patients beyond the Milan criteria, compared with untreated controls. However, no significant difference in OS was observed, which might be related to the short follow-up time and small sample size, since lenvatinib only became available in China as recently as 2 years ago. Thus, our study indicated that postoperative lenvatinib administration could significantly decrease tumor recurrence for HCC patients beyond the Milan criteria who underwent LTx, especially early recurrence (within 2 years) after LTx.

The results also suggest some indications for patients within the Milan criteria. Firstly, the application of

lenvatinib after LTx was safe and did not increase the incidence of complications, indicating that lenvatinib could be used in LTx patients. Besides, our data showed that adjuvant lenvatinib therapy might reduce the recurrence rate of HCCs in patients with multiple lesions, mVI, poor differentiation, or postoperative positive AFP/PIVKA-II, offering the potential for lenvatinib to confer clinical benefit even to those patients within the Milan criteria. Further evidence from large-scale, prospective clinical trials is needed.

It is challenging to conduct a prospective study to explore treatment outcomes in patients with HCC who receive LTx, particularly for those beyond the Milan criteria. Therefore, we performed a retrospective study. However, the present study had several limitations inherent to the retrospective, single-center design, and small sample size. Consequently, the results should be interpreted with caution. A prospective, multicenter, randomized study with a large sample size is required to confirm the efficacy and safety of lenvatinib in this setting. Furthermore, the efficacy of other TKIs, such as sorafenib, in preventing recurrence after LTx was still unclear in the present study, and further studies are needed.

In conclusion, our study demonstrated that postoperative lenvatinib administration might be a promising modality to reduce tumor recurrence and improve the prognosis of HCC patients beyond the Milan criteria who undergo LTx. Meanwhile, lenvatinib is well tolerated in patients with HCC who receive LTx.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1353/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1353/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1353/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the committee of Zhongshan Hospital (No. B2020-402) and individual consent for this retrospective analysis was waived.

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