Adjuvant Lenvatinib in Combination with Transarterial Chemoembolization for Hepatocellular Carcinoma Patients with High-Risk of Postoperative Recurrence: A Prospective Cohort Study

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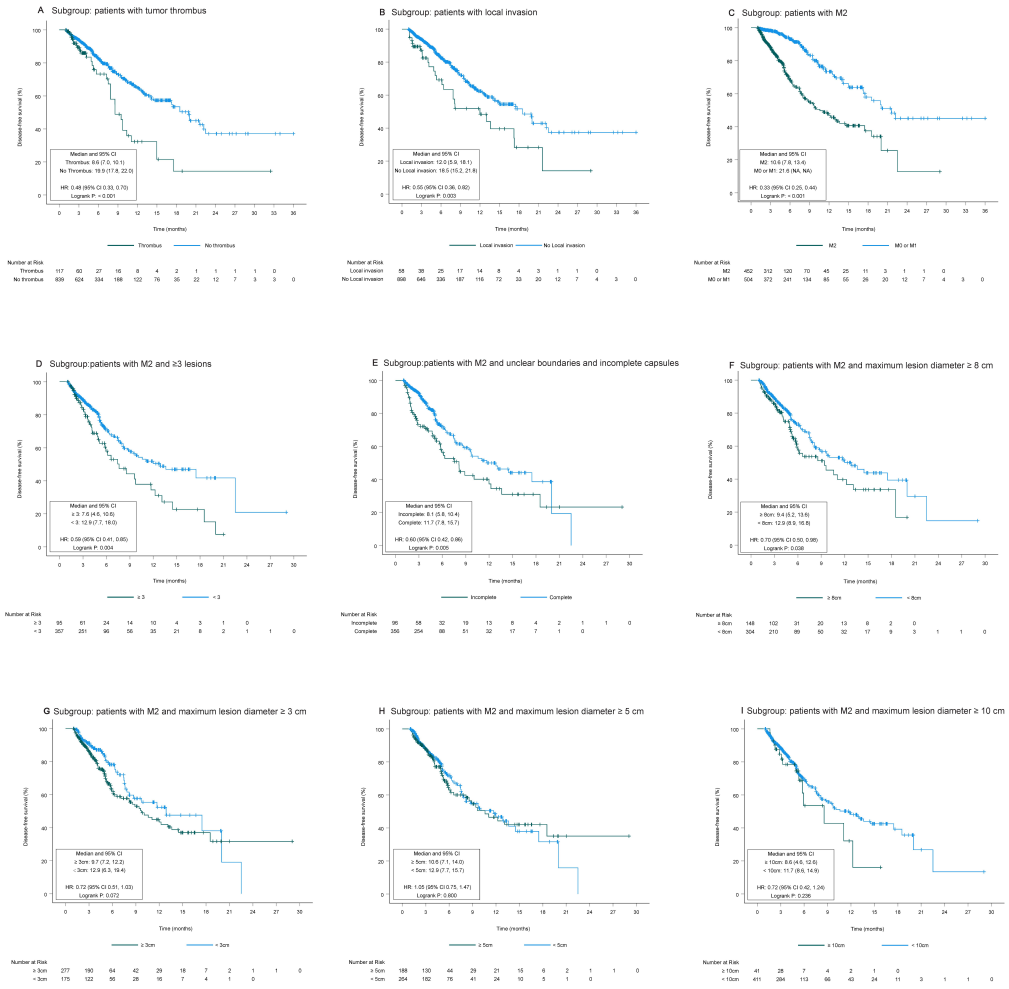

Fig. S1 Risk factors for DFS in patients receiving adjuvant TACE from the database. The risk factors for DFS in patients receiving adjuvant TACE were identified from the database involved 956 HCC patients in Huashan hospital from Jan 2015 to Dec 2017. The DFS was significantly poorer in patients with tumor thrombus (1A), local invasion (1B) and MVI M2 (1C) compared with patients without these factors when receiving adjuvant TACE. Among patients with MVI M2, ≥3 lesions (1D), unclear boundaries and incomplete capsules (1E), and maximum lesion diameter≥8 cm (1F) were further identified as risk factors strongly associated with poor DFS. Different cutoff values of maximum lesion diameter in patients with MVI M2 were also evaluated.

We found that the cutoff of 8 cm was an optimal predictive factor of DFS rather than 3cm, 5cm and 10cm (1G-1I).

Local invasion was defined as tumor rupture or invasion of adjacent organs.

DFS Disease free survival, *M0* Microvascular invasion classification 0, *M1* Microvascular invasion classification 1, *M2* Microvascular invasion classification 2, *HR* Hazard ratio; *CI* Confidence interval

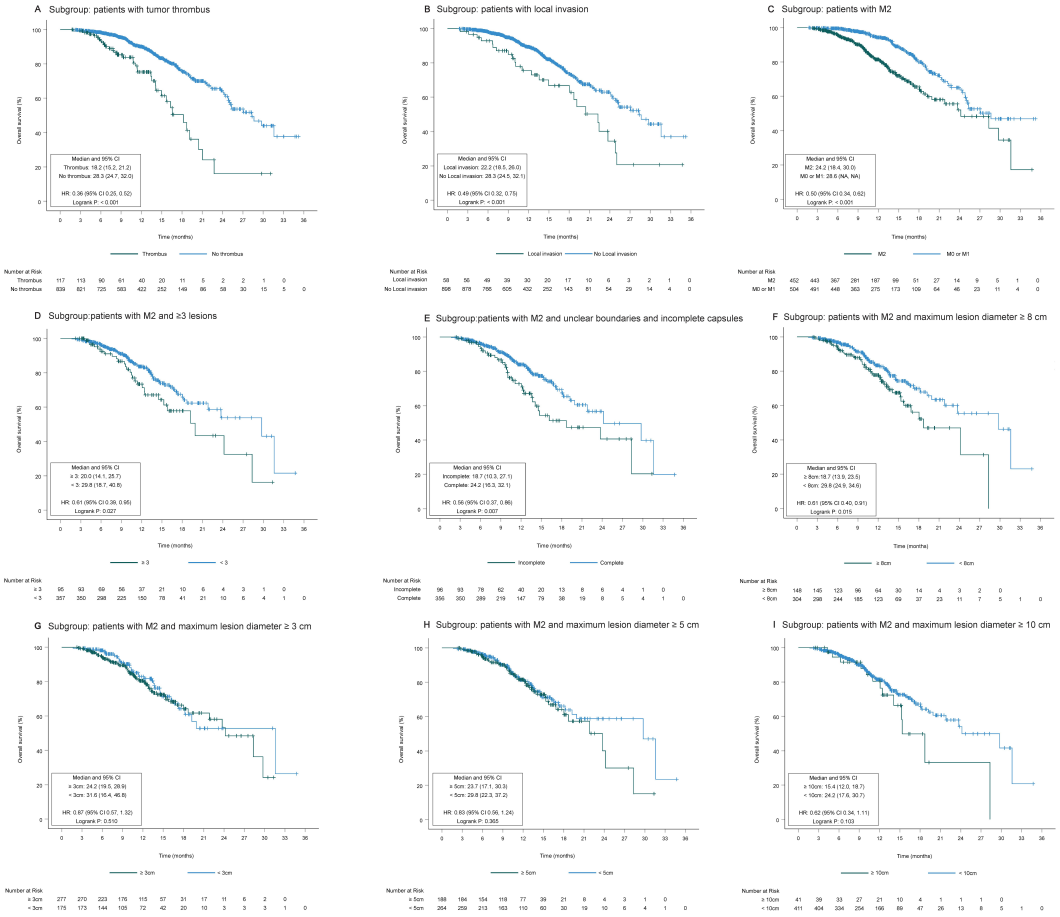

Fig. S2 Risk factors for OS in patients receiving adjuvant TACE from the database.

The risk factors for OS in patients receiving adjuvant TACE were identified from the database involved 956 HCC patients in Huashan hospital from Jan 2015 to Dec 2017. The identified risk factors for OS were consistent with that for DFS. Patients with tumor thrombus (2A), local invasion (2B), MVI M2 (2C) with any of the following situations: ≥3 lesions (2D), or unclear boundaries and incomplete capsules (2E) , or maximum lesion diameter≥8 cm (2F) showed significantly shorter overall survival than patients without these factors or other factors (2G-2I) from TACE treatment in the adjuvant setting.

Local invasion was defined as tumor rupture or invasion of adjacent organs.

OS Overall survival, *M0* Microvascular invasion classification 0, *M1* Microvascular invasion classification 1, *M2* Microvascular invasion classification 2, *HR* Hazard ratio; *CI* Confidence interval

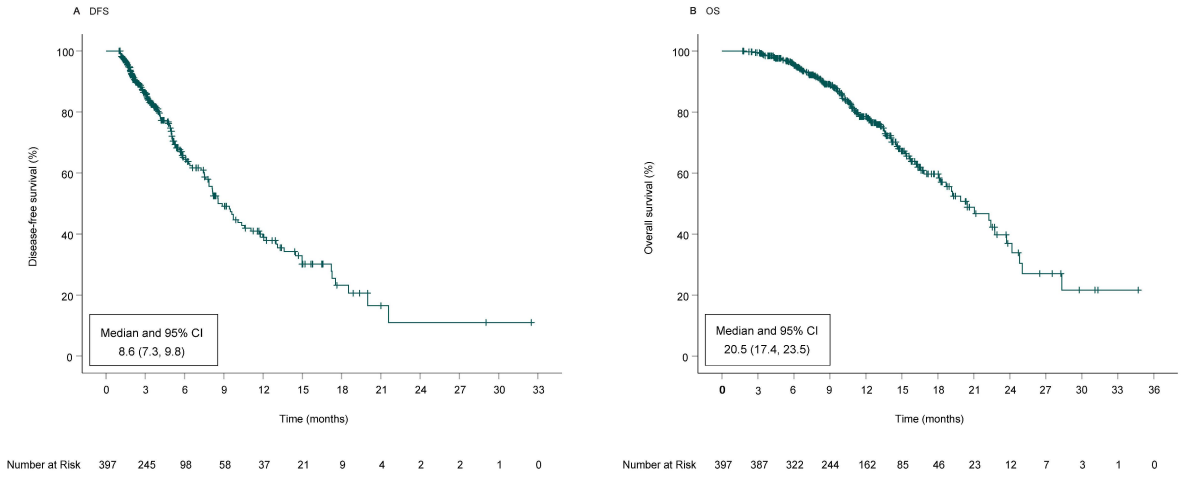

Fig.S3 DFS and OS in HCC patients with risk factors identified receiving adjuvant TACE. There were 397 patients with any of risk factors identified above in total from the database. The DFS was 8.6 months (95% CI, 7.3-9.8) and the OS was 20.5 months (95% CI, 17.4-23.5) in the defined population.

HR Hazard ration, *CI* Confidence interval

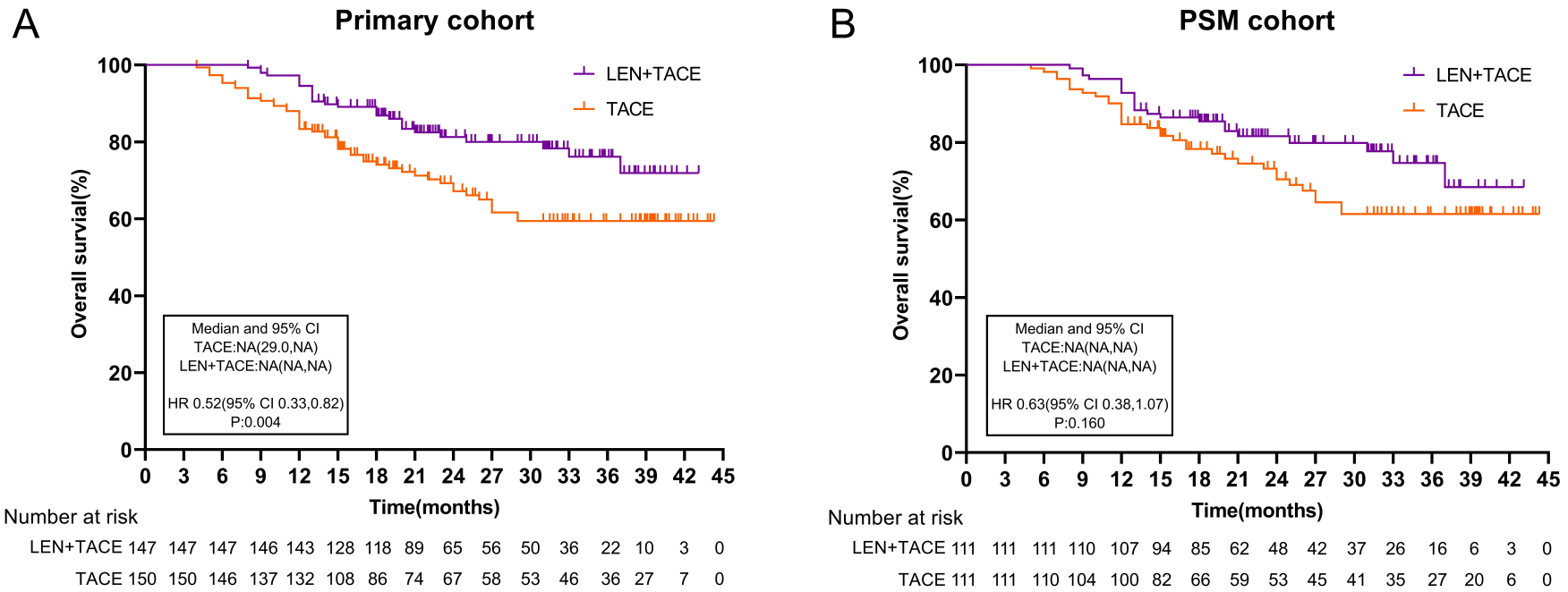

Fig.S4 Kaplan-Meier analysis of overall survival in primary and PSM cohort. (A) OS in primary cohort(P=0.004). (B) OS in PSM cohort (P=0.160).

Len Lenvatinib, *TACE* Transarterial chemoembolization, *HR* Hazard ratio; *CI* Confidence interval

Table S1 Propensity score analyses of DFS.

	HR (95% CI)	P value
Primary cohort analysis	0.70 (0.52,0.93)	0.014
Propensity-score analyses		
With matching	0.73(0.54,0.99)	0.041
With inverse probability weighting	0.69(0.57,0.85)	<0.001
With stratification	0.67(0.50,0.90)	0.008
With covariate adjustment	0.70(0.52,0.93)	0.016

HR Hazard ratio; CI Confidence interval

Table S2 Subsequent treatments after recurrence in the Len + TACE and TACE groups.

	Primary Cohort		PSM Cohort	
	Len + TACE (N = 147)	TACE (N = 150)	Len + TACE (N = 111)	TACE (N = 111)
Accepted subsequent treatments	**79 (53.7%)**	**83 (55.3%)**	**60 (54.1%)**	**63 (56.8%)**
Systemic treatment[†]	**50 (34.0%)**	**50 (33.3%)**	**37 (33.3%)**	**36 (32.4%)**
TKI	**9 (6.1%)**	**21 (14.0%)**	**5 (4.5%)**	**15 (13.5%)**
Regofenib	7 (4.8%)	3 (2.0%)	7 (6.3%)	2 (1.8%)
Sorafenib	7 (4.8%)	11 (7.3%)	3 (2.7%)	8 (7.2%)
Lenvatinib	2 (1.4%)	11 (7.3%)	2 (1.8%)	8 (7.2%)
Others[‡]	2 (1.4%)	1 (0.7%)	1 (0.9%)	1 (0.9%)
Anti-PD-1[§]	**10 (6.8%)**	**10 (6.7%)**	**9 (8.1%)**	**9 (8.1%)**
Anti-PD-1 + TKI/anti-VEGF	**32 (21.8%)**	**24 (16.0%)**	**24(21.6%)**	**17 (15.3%)**
Lenvatnib + anti-PD-1	21 (14.3%)	20 (13.3%)	14 (12.6%)	13 (11.7%)
Apatinib + camrelizumab	3 (2.0%)	1 (0.7%)	2 (1.8%)	1 (0.9%)
Atezolizumab + bevacizumab	2 (1.4%)	0 (0)	1 (0.9%)	0 (0.0%)
Sintilimab + bevacizumab biosimilar	2 (1.4%)	3 (2.0%)	1 (0.93%)	3 (2.7%)
Others[¶]	7 (4.8%)	1 (0.7%)	7 (6.3%)	0
Procedures[¶]	**61 (41.5%)**	**70 (46.7%)**	**47(42.3%)**	**56(50.5%)**
TACE	32 (21.8%)	55 (36.7%)	22 (19.8%)	46 (41.4%)
RFA	11 (7.5%)	8 (5.3%)	9 (8.1%)	5 (4.5%)
Hepatectomy	7 (4.8%)	2 (1.3%)	6 (5.4%)	1 (0.9%)
Liver transplantation	7 (4.8%)	2 (1.3%)	7 (6.3%)	2 (1.8%)
Radiotherapy	6 (4.1%)	6 (4.0%)	3 (2.7%)	5 (4.5%)
TACE + RFA	6 (4.1%)	1 (0.7%)	6 (5.4%)	1 (0.93%)
Best Supportive Care	**7 (4.8%)**	**17 (11.3%)**	**5 (4.5%)**	**10 (9.0%)**

Data presented as No. (%).

[†¶]Patients may have received more than one systemic treatment and/or procedure.

[‡] Other TKIs included apatinib and donafenib.

[§] Anti-PD-1 included sintilimab, camrelizumab, toripalimab, and tislelizumab.

[¶]Other anti-PD-1 + TKI/anti-VEGF included sorafenib + anti-PD-1, donafenib + anti-PD-1 and regofenib + anti-PD-1.

Len Lenvatinib, *TACE* Transarterial chemoembolization, *TKI* Tyrosine kinase inhibitor, *VEGF* Vascular endothelial growth factor; *RFA* Radiofrequency ablation