

# Transarterial Chemoembolization Combined with Lenvatinib plus PD-1 Inhibitor for Advanced Hepatocellular Carcinoma: A Retrospective Cohort Study

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## Research Article

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# Abstract

**Purpose** To investigate the efficacy and safety of transarterial chemoembolization (TACE) combined with lenvatinib plus PD-1 inhibitor (TACE-L-P) versus TACE combined with lenvatinib (TACE-L) for patients with advanced hepatocellular carcinoma (HCC).

**Methods** Data of advanced HCC patients treated with TACE-L-P or TACE-L from January 2019 to December 2020 were retrospectively analyzed. The differences in overall survival (OS), progression-free survival (PFS), tumor responses (based on modified Response Evaluation Criteria in Solid Tumors) and adverse events (AEs) were compared between the two groups. Potential factors affecting OS and PFS were determined.

**Results** A total of 81 patients were included in this study (41 received TACE-L-P and 40 received TACE-L). The patients in TACE-L-P group had prolonged OS (median, 16.9 vs. 12.1 months,  $p=0.009$ ), longer PFS (median, 7.3 vs. 4.0 months,  $p=0.002$ ) and higher objective response rate (56.1% vs. 32.5%,  $p=0.033$ ) and disease control rate (85.4% vs. 62.5%,  $p=0.019$ ) than those in TACE-L group. Multivariate analyses revealed that the treatment option of TACE-L, main portal vein invasion and extrahepatic metastasis were the independent risk factors for OS, while TACE-L and extrahepatic metastasis were the independent risk factors for PFS. In subgroup analyses, a superior survival benefit was achieved with TACE-L-P in patients with extrahepatic metastasis or tumor number  $>3$  but not in those with main portal vein invasion. The incidence and severity of AEs in TACE-L-P group were comparable to those in TACE-L group (any grade, 92.7% vs. 95.0%,  $p=1.000$ ; grade 3, 36.6% vs. 32.5%,  $p=0.699$ ).

**Conclusion** TACE-L-P significantly improved survival over TACE-L with an acceptable safety profile in advanced HCC patients, especially those with extrahepatic metastasis or tumor number  $>3$  but without main portal vein invasion.

## Introduction

Hepatocellular carcinoma (HCC), representing 75%-85% of primary liver cancer, is one of the most prevalent and fatal malignancies worldwide [1]. Although surgical resection, ablation and liver transplantation may provide curative potential for HCC, a majority of patients are diagnosed with advanced disease which is not amenable for these approaches and thus bear a poor prognosis with an expected median survival of 6-8 months [2-4].

The multikinase inhibitors sorafenib and lenvatinib are recommended as the first-line treatment of advanced HCC [2-4] on the basis of randomised trials demonstrating longer survival with sorafenib versus placebo [5, 6] and noninferiority of lenvatinib to sorafenib [7]. However, the efficacy of monotherapy with these drugs is modest, and only a small survival benefit of about 3 months can be achieved with oral sorafenib [8]. In this setting, transarterial chemoembolization (TACE) has been applied to providing local disease control in patients with acceptable liver function and tumor burden. It is supposed that the antiangiogenic agents in combination with TACE may effectively offset the post-TACE hypoxia-induced angiogenesis and, therefore, provide a superior antitumor effect for HCC [9, 10]. In fact, many studies have suggested improved outcomes of this combination treatment compared with the use of a single drug or TACE alone for advanced HCC [11-14]. But unfortunately, there still remained limited treatment responses with unsatisfied survival prolongation [11-13].

Recently, immune checkpoint inhibitors, including programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, have exhibited a promising clinical benefit to advanced HCC patients [15]. Although phase III trials for anti-PD-1 monotherapy failed to meet their primary survival endpoints [16, 17], the studies testing combined treatments with PD-1/PD-L1 inhibitor and antiangiogenic agent showed exciting results [18-20]. In a recent phase Ib study for evaluating the combination of lenvatinib and pembrolizumab (an anti-PD-1 antibody) in first-line treatment of unresectable HCC, an objective response rate (ORR) of 46.0% per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and a median overall survival (OS) of 22.0 months were achieved [20]. These impressive results suggested a promising therapeutic potential of the combination of lenvatinib plus PD-1 inhibitor in patients with HCC.

Since TACE possesses a local anticancer effect and may facilitate antitumor immunity but inevitably induces post-TACE angiogenesis [10, 21], and lenvatinib has an immunomodulatory effect on tumor microenvironment besides antiangiogenesis [22, 23], combining TACE and lenvatinib plus PD-1 inhibitor (TACE-L-P) may contribute to a synergistic anticancer activity for HCC. Accordingly, we hypothesized that the comprehensive therapy of TACE-L-P would be an effective treatment strategy for advanced HCC. Thus, we conducted this retrospective study to evaluate the efficacy and safety of TACE-L-P versus TACE combined with lenvatinib (TACE-L) in the patients with advanced HCC.

## **Materials And Methods**

### **Study design and patient selection**

This study was approved by our institutional review board, and written informed consent was obtained from every patient. Data of consecutive patients with advanced HCC who received TACE-L-P or TACE-L at our institution between January 2019 and December 2020 were prospectively collected and retrospectively analyzed.

The inclusion criteria for this study were as follows: (1) age between 18 and 75 years; (2) confirmed diagnosis with HCC [2, 24] accompanied by macrovascular invasion and/or extrahepatic metastasis; (3) tumor recurrence after curative resection or ablation was allowed; (4) Eastern Cooperative Oncology Group performance status (ECOG PS) of  $\leq 1$ ; and (5) Child-Pugh class A/B. Patients were excluded if they (1) had central nervous system metastasis; (2) had history of organ transplantation; (3) previously received TACE, hepatic arterial infusion chemotherapy (HAIC), radiotherapy or systemic therapy; (4) had other malignancies in addition to HCC; or (5) had severe medical comorbidities including severe cardiac, pulmonary, renal or coagulation dysfunction.

All laboratory test data were collected within 3 days before the initial treatment. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed within 7 days before the initial treatment.

### **TACE procedure**

The patients received either conventional TACE (cTACE) or drug-eluting bead TACE (DEB-TACE) according to their own choice. For cTACE, an emulsion of 5-20 mL Lipiodol (Guerbet, Paris, France) mixed with 20-60 mg

pirarubicin (Hisun Pfizer Pharmaceuticals, Fuyang, China) was administered into the tumor-feeding vessels, followed by embolization with polyvinyl alcohol particles (90-500  $\mu\text{m}$ ; Cook, Bloomington, Indiana, USA). For DEB-TACE, CalliSpheres (Hengrui Medical, Suzhou, China) or DC Bead (Biocompatibles, Farnham, Surrey, UK) with 100-300  $\mu\text{m}$  in diameter was used as the drug carrier and embolization agent. Typically, one vial of the beads was loaded with 60 mg pirarubicin. If blushed tumors were still visible after the embolization with one vial of beads, regular microspheres (8spheres, Hengrui Medical, Suzhou, China; Embosphere, Biosphere Medical, Roissy en France, France) with diameters of 100-700  $\mu\text{m}$  were additionally injected [25].

During TACE, superselective catheterization was performed, and the embolization end point was blood stasis of the tumor-feeding arteries. In patients with huge or bilobar multiple lesions, in order to reduce the risk of complications, the embolization end point was not achieved in the initial TACE but in the second or third TACE session [26]. In the case of arterioportal or arteriovenous fistula, the fistula would be embolized with 300-710  $\mu\text{m}$  polyvinyl alcohol particles before administration of the drug-oil emulsion or drug-loaded beads.

TACE was repeated “on demand” upon the demonstration of viable tumor by follow-up CT or MRI in patients without deteriorated performance status or organ function.

## Lenvatinib and PD-1 inhibitor administration

Lenvatinib (Eisai, Tokyo, Japan) and PD-1 inhibitor was initiated within 7 days after the first TACE. Lenvatinib at a dose of 12 mg (bodyweight  $\geq 60$  kg) or 8 mg (bodyweight  $< 60$  kg) was orally administered once a day. The PD-1 inhibitor sintilimab (Innovent Biologics, Suzhou, China), tislelizumab (BeiGene, Shanghai, China) or camrelizumab (Hengrui Pharma, Lianyungang, China) was injected intravenously at 200 mg once every 3 weeks. The interruption and discontinuation of drug administration depended on the presence and severity of toxicities according to the drug directions.

## Follow-up

Regular follow-up was conducted for all patients at a 3-6-week interval after the initial treatment. Each follow-up session included a detail history, physical examination, hematologic and biochemical tests, contrast-enhanced abdominal CT or MRI, chest CT, and other imaging examination if clinically indicated. The final follow-up ended on June 30, 2021.

During follow-up, the treatment of TACE-L-P or TACE-L was discontinued in cases of intolerable toxicity, progressive disease (PD) or change of treatment plan. And, the choice of the subsequent treatment, such as second-line targeted agent, PD-1 inhibitor (for the patients treated with TACE-L), radiotherapy (including iodine-125 seed brachytherapy), HAIC or best supportive care, was determined according to the results of discussion by our multidisciplinary team and the patients' request.

## Assessments and outcomes

OS and progression-free survival (PFS) were compared between TACE-L-P group and TACE-L group. OS was defined as the time from treatment initiation until death by any reason. PFS was defined as the time interval from treatment initiation to the first occurrence of PD or death, whichever occurred first.

Tumor responses were categorized as complete response (CR), partial response (PR), stable disease (SD) or PD according to mRECIST. Overall tumor response referred to the assessment of changes in tumor burden inside and outside the liver, while intrahepatic tumor response only included the assessment of changes in tumor burden inside the liver. ORR was defined as the percentage of patients who had a best tumor response rating of CR and PR. Disease control rate (DCR) was defined as the percentage of patients who had a best tumor response rating of CR, PR and SD.

Adverse events (AEs) related to treatments were recorded and assessed based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Postembolization syndrome (manifested by fever, abdominal pain, nausea, vomiting and increased white blood cell count) and transient abnormalities of liver enzyme after TACE [27, 28] were expected and would resolved within a short time, and therefore, they were not documented separately.

## Statistical Analyses

Categorical data were expressed as number of patients (percentage). Quantitative data were expressed as mean±standard deviation and median (range) for normally and non-normally distributed variables, respectively. Categorical data between the two groups were compared using  $\chi^2$  test or Fisher's exact test, as appropriate. Quantitative data were compared using Student's *t*-test or Mann-Whitney U test, as appropriate. Survival curves were analyzed by Kaplan-Meier method using log-rank test. Variables with  $p < 0.10$  in univariate analysis were entered into a multivariate analysis using Cox regression model to identify the independent prognostic factors for OS and PFS. All statistical analyses were performed with SPSS Statistics version 22 (IBM, Armonk, New York, USA). All statistical tests were two-tailed,  $p < 0.05$  was considered statistically significant.

## Results

### Study population

During the study period, 92 patients with advanced HCC who received TACE-L-P or TACE-L were screened for eligibility. Of these patients, 11 were excluded because they met the excluded criteria (Fig. 1). Finally, 81 patients were included in this study (41 in TACE-L-P group and 40 in TACE-L group). Detailed baseline characteristics of the patients were summarized in Table 1. In both groups, about half of the patients had more than 3 intrahepatic tumors at diagnosis. The mean largest tumor size of TACE-L-P group and TACE-L group was  $12.3 \pm 4.8$  cm and  $13.6 \pm 5.1$  cm, respectively. Two groups were comparable in the demographic, clinical and tumor characteristics.

Table 1  
Baseline characteristics of the patients

| Characteristic    | TACE-L-P group<br>( <i>n</i> =41) | TACE-L group<br>( <i>n</i> =40) | <i>p</i> value |
|-------------------|-----------------------------------|---------------------------------|----------------|
| Sex               |                                   |                                 | 0.309          |
| Female            | 4 (9.8)                           | 7 (17.5)                        |                |
| Male              | 37 (90.2)                         | 33 (82.5)                       |                |
| Age (years)       | 51.9±10.3                         | 54.6±11.0                       | 0.263          |
| ECOG PS           |                                   |                                 | 0.274          |
| 1                 | 8 (19.5)                          | 12 (30.0)                       |                |
| 0                 | 33 (80.5)                         | 28 (70.0)                       |                |
| HBsAg             |                                   |                                 | 0.779          |
| Positive          | 35 (85.4)                         | 35 (87.5)                       |                |
| Negative          | 6 (14.6)                          | 5 (12.5)                        |                |
| Child-Pugh class  |                                   |                                 | 0.309          |
| B                 | 4 (9.8)                           | 7 (17.5)                        |                |
| A                 | 37 (90.2)                         | 33 (82.5)                       |                |
| AFP level (µg/L)  |                                   |                                 | 0.733          |
| ≥400              | 21 (51.2)                         | 22 (55.0)                       |                |
| <400              | 20 (48.8)                         | 18 (45.0)                       |                |
| PIVKA-II (mAU/ml) |                                   |                                 | 0.517          |
| ≥400              | 27 (65.9)                         | 29 (72.5)                       |                |
| <400              | 14 (34.1)                         | 11 (27.5)                       |                |
| Recurrent tumor   |                                   |                                 | 0.362          |
| No                | 35 (85.4)                         | 31 (77.5)                       |                |
| Yes               | 6 (14.6)                          | 9 (22.5)                        |                |
| Number of tumors  |                                   |                                 | 0.439          |

Data were presented as *n* (%) or mean ± standard deviation

*TACE-L-P* transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, *TACE-L* transarterial chemoembolization combined with Lenvatinib, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *HBsAg* hepatitis B surface antigen, *AFP* α-fetoprotein level, *PIVKA-II* protein induced by vitamin K absence or antagonist-II, *TACE* transarterial chemoembolization, *cTACE* conventional transarterial chemoembolization, *DEB-TACE* drug-eluting bead transarterial chemoembolization

| Characteristic   | TACE-L-P group<br>(n=41) | TACE-L group<br>(n=40) | p value |
|--|--------------------------|------------------------|---------|
| >3   | 23 (56.1)                | 19 (47.5)              |         |
| ≤3   | 18 (43.9)                | 21 (52.5)              |         |
| Tumor distribution   |                          |                        | 0.939   |
| Bilobar  | 28 (68.3)                | 27 (67.5)              |         |
| Unilobar   | 13 (31.7)                | 13 (32.5)              |         |
| Largest tumor size (cm)  | 12.3±4.8                 | 13.6±5.1               | 0.218   |
| Main portal vein invasion  |                          |                        | 0.441   |
| Yes  | 15 (36.6)                | 18 (45.0)              |         |
| No   | 26 (63.4)                | 22 (55.0)              |         |
| Hepatic vein invasion  |                          |                        | 0.581   |
| Yes  | 12 (29.3)                | 14 (35.0)              |         |
| No   | 29 (70.7)                | 26 (65.0)              |         |
| Extrahepatic metastasis  |                          |                        | 0.585   |
| Yes  | 17 (41.5)                | 19 (47.5)              |         |
| No   | 24 (58.5)                | 21 (52.5)              |         |
| TACE technique   |                          |                        | 0.223   |
| cTACE  | 17 (41.5)                | 22 (55.0)              |         |
| DEB-TACE   | 24 (58.5)                | 18 (45.0)              |         |
| Data were presented as n (%) or mean ± standard deviation  |                          |                        |         |
| <p><i>TACE-L-P</i> transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, <i>TACE-L</i> transarterial chemoembolization combined with Lenvatinib, <i>ECOG PS</i> Eastern Cooperative Oncology Group Performance Status, <i>HBsAg</i> hepatitis B surface antigen, <i>AFP</i> α-fetoprotein level, <i>PIVKA-II</i> protein induced by vitamin K absence or antagonist-II, <i>TACE</i> transarterial chemoembolization, <i>cTACE</i> conventional transarterial chemoembolization, <i>DEB-TACE</i> drug-eluting bead transarterial chemoembolization</p> |                          |                        |         |

Patients in the TACE-L-P group underwent a total of 134 TACE procedures, with a median of 3 (range, 1-7). While patients in the TACE-L group underwent a total of 95 TACE procedures, with a median of 2 (range, 1-6). The mean duration of lenvatinib administration was 7.4±3.8 (range, 1.2-15.6) months in TACE-L-P group and 4.3±3.0 (range, 0.9-11.9) months in the TACE-L group ( $p<0.001$ ). In the TACE-L-P group, the cycles of PD-1 inhibitor injection ranged from 2 to 22, with a mean of 9.9. The categories of PD-1 inhibitor the patients received were as follows: sintilimab for 30 (73.2%), tislelizumab for 6 (14.6%) and camrelizumab for 5 (12.2%).

## Survival

The follow-up duration ranged from 4.6 to 29.8 months, with a median of 13.7 months. During follow-up, 27 patients (65.9%) in TACE-L-P group and 30 patients (75.0%) in TACE-L group died. Compared with the patients in TACE-L group, the patients in TACE-L-P group had significantly better survival outcomes (Fig. 2). The median OS was 16.9 (95% confidence interval [CI] 14.9-18.8) months in TACE-L-P group and 12.1 (95% CI 10.7-13.5) months in TACE-L group ( $p=0.009$ ). The median PFS was 7.3 (95% CI 6.0-8.7) months in TACE-L-P group and 4.0 (95% CI 2.7-5.3) months in TACE-L group ( $p=0.002$ ).

## Prognostic Factors Analysis

Based on the results of the univariate and multivariate analyses (Table 2), treatment option (TACE-L vs. TACE-L-P; hazard ratio [HR]=2.065, 95% CI 1.208-3.533,  $p=0.008$ ), extrahepatic metastasis (present vs. absent; HR=2.041, 95% CI 1.183-3.520,  $p=0.010$ ) and main portal vein invasion (yes vs. no; HR=1.867, 95% CI 1.089-3.200,  $p=0.023$ ) were identified as the independent prognostic factors for OS. In addition, treatment option (HR=2.243, 95% CI 1.344-3.743,  $p=0.002$ ) and extrahepatic metastasis (HR=2.244, 95% CI 1.365-3.689,  $p=0.001$ ) were also identified as the independent prognostic factors for PFS.

Table 2  
Analyses of prognostic factors for survival

| Factor            | Overall survival       |                |                       |                | Progression-free survival |                |                       |                |
|-------------------|------------------------|----------------|-----------------------|----------------|---------------------------|----------------|-----------------------|----------------|
|                   | Univariate analysis    |                | Multivariate analysis |                | Univariate analysis       |                | Multivariate analysis |                |
|                   | HR (95% CI)            | <i>p</i> value | HR (95% CI)           | <i>p</i> value | HR (95% CI)               | <i>p</i> value | HR (95% CI)           | <i>p</i> value |
| Sex               |                        |                |                       |                |                           |                |                       |                |
| Female/Male       | 1.459<br>(0.713-2.984) | 0.301          |                       |                | 0.951<br>(0.450-2.009)    | 0.895          |                       |                |
| Age (years)       |                        |                |                       |                |                           |                |                       |                |
| <60/≥60           | 1.118<br>(0.631-1.981) | 0.703          |                       |                | 0.971<br>(0.581-1.626)    | 0.912          |                       |                |
| ECOG PS           |                        |                |                       |                |                           |                |                       |                |
| 1/0               | 1.587<br>(0.897-2.809) | 0.113          |                       |                | 1.271<br>(0.748-2.162)    | 0.376          |                       |                |
| HBsAg             |                        |                |                       |                |                           |                |                       |                |
| Positive/Negative | 1.632<br>(0.699-3.810) | 0.257          |                       |                | 1.045<br>(0.533-2.046)    | 0.899          |                       |                |
| Child-Pugh class  |                        |                |                       |                |                           |                |                       |                |
| B/A               | 1.698<br>(0.800-3.606) | 0.168          |                       |                | 1.243<br>(0.631-2.448)    | 0.530          |                       |                |
| AFP level (µg/L)  |                        |                |                       |                |                           |                |                       |                |
| ≥400/<400         | 1.317<br>(0.779-2.225) | 0.304          |                       |                | 1.146<br>(0.718-1.828)    | 0.568          |                       |                |
| PIVKA-II (mAU/mL) |                        |                |                       |                |                           |                |                       |                |

Analyses were performed using Cox proportional hazard regression model

*HR* hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *HBsAg* hepatitis B surface antigen, *AFP* α-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist-II, *TACE-L* transarterial chemoembolization combined with lenvatinib, *TACE-L-P* transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, *TACE* transarterial chemoembolization, *cTACE* conventional transarterial chemoembolization, *DEB-TACE* drug-eluting bead transarterial chemoembolization

| Factor                    | Overall survival       |         |                        |         | Progression-free survival |         |                       |         |
|---------------------------|------------------------|---------|------------------------|---------|---------------------------|---------|-----------------------|---------|
|                           | Univariate analysis    |         | Multivariate analysis  |         | Univariate analysis       |         | Multivariate analysis |         |
|                           | HR (95% CI)            | p value | HR (95% CI)            | p value | HR (95% CI)               | p value | HR (95% CI)           | p value |
| ≥400/<400                 | 1.275<br>(0.714-2.274) | 0.411   |                        |         | 1.387<br>(0.829-2.319)    | 0.212   |                       |         |
| Recurrent tumor           |                        |         |                        |         |                           |         |                       |         |
| No/Yes                    | 1.480<br>(0.723-3.030) | 0.283   |                        |         | 1.013<br>(0.561-1.829)    | 0.965   |                       |         |
| Number of tumors          |                        |         |                        |         |                           |         |                       |         |
| >3/≤3                     | 1.528<br>(0.893-2.615) | 0.122   |                        |         | 1.177<br>(0.733-1.888)    | 0.500   |                       |         |
| Tumor distribution        |                        |         |                        |         |                           |         |                       |         |
| Bilobar/Unilobar          | 1.144<br>(0.647-2.022) | 0.643   |                        |         | 1.033<br>(0.623-1.711)    | 0.900   |                       |         |
| Largest tumor size (cm)   |                        |         |                        |         |                           |         |                       |         |
| ≥10/<10                   | 1.531<br>(0.857-2.733) | 0.150   |                        |         | 1.388<br>(0.836-2.304)    | 0.205   |                       |         |
| Main portal vein invasion |                        |         |                        |         |                           |         |                       |         |
| Yes/No                    | 1.638<br>(0.970-2.767) | 0.065   | 1.867<br>(1.089-3.200) | 0.023   | 1.025<br>(0.635-1.653)    | 0.920   |                       |         |
| Hepatic vein invasion     |                        |         |                        |         |                           |         |                       |         |

Analyses were performed using Cox proportional hazard regression model

HR hazard ratio, CI confidence interval, ECOG PS Eastern Cooperative Oncology Group Performance Status, HBsAg hepatitis B surface antigen, AFP α-fetoprotein, PIVKA-II protein induced by vitamin K absence or antagonist-II, TACE-L transarterial chemoembolization combined with lenvatinib, TACE-L-P transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, TACE transarterial chemoembolization, cTACE conventional transarterial chemoembolization, DEB-TACE drug-eluting bead transarterial chemoembolization

| Factor   | Overall survival    |         |                       |         | Progression-free survival |         |                       |         |
|--|---------------------|---------|-----------------------|---------|---------------------------|---------|-----------------------|---------|
|  | Univariate analysis |         | Multivariate analysis |         | Univariate analysis       |         | Multivariate analysis |         |
|  | HR (95% CI)         | p value | HR (95% CI)           | p value | HR (95% CI)               | p value | HR (95% CI)           | p value |
| Yes/No   | 1.263 (0.721-2.211) | 0.414   |                       |         | 1.315 (0.783-2.206)       | 0.300   |                       |         |
| Extrahepatic metastasis  |                     |         |                       |         |                           |         |                       |         |
| Yes/No   | 1.710 (1.013-2.888) | 0.045   | 2.041 (1.183-3.520)   | 0.010   | 2.125 (1.313-3.438)       | 0.002   | 2.337 (1.430-3.820)   | 0.001   |
| Treatment option   |                     |         |                       |         |                           |         |                       |         |
| TACE-L/TACE-L-P  | 1.987 (1.172-3.367) | 0.011   | 2.065 (1.208-3.533)   | 0.008   | 2.100 (1.288-3.425)       | 0.003   | 2.312 (1.404-3.808)   | 0.001   |
| TACE technique   |                     |         |                       |         |                           |         |                       |         |
| cTACE/DEB-TACE   | 1.188 (0.706-2.001) | 0.517   |                       |         | 1.311 (0.817-2.103)       | 0.262   |                       |         |
| Analyses were performed using Cox proportional hazard regression model   |                     |         |                       |         |                           |         |                       |         |
| <i>HR</i> hazard ratio, <i>CI</i> confidence interval, <i>ECOG PS</i> Eastern Cooperative Oncology Group Performance Status, <i>HBsAg</i> hepatitis B surface antigen, <i>AFP</i> α-fetoprotein, <i>PIVKA-II</i> protein induced by vitamin K absence or antagonist-II, <i>TACE-L</i> transarterial chemoembolization combined with lenvatinib, <i>TACE-L-P</i> transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, <i>TACE</i> transarterial chemoembolization, <i>cTACE</i> conventional transarterial chemoembolization, <i>DEB-TACE</i> drug-eluting bead transarterial chemoembolization |                     |         |                       |         |                           |         |                       |         |

Subgroup analyses of factors for OS indicated that TACE-L-P treatment could provide a superior survival benefit in patients with no main portal vein invasion, tumor number >3 or extrahepatic metastasis, but failed to have a clinical benefit in patients with main portal vein invasion, tumor number ≤3 or no extrahepatic metastasis (Fig. 3).

## Tumor Responses

Tumor responses for patients in the two groups were summarized in Table 3. The ORR of both overall tumor (56.1% vs. 32.5%,  $p=0.033$ ) and intrahepatic tumor (65.9% vs. 37.5%,  $p=0.011$ ) was higher in the TACE-L-P group than in the TACE-L group. A higher DCR was also achieved in TACE-L-P group when compared with TACE-L group (overall tumor: 85.4% vs. 62.5%,  $p=0.019$ ; intrahepatic tumor: 95.1% vs. 77.5%,  $p=0.021$ ).

Table 3  
Tumor responses for the patients

| Response   | TACE-L-P group<br>( <i>n</i> =41) | TACE-L group<br>( <i>n</i> =40) | <i>p</i> value |
|--|-----------------------------------|---------------------------------|----------------|
| Overall tumor  |                                   |                                 |                |
| CR, <i>n</i> (%)   | 4 (9.8)                           | 1 (2.5)                         |                |
| PR, <i>n</i> (%)   | 19 (46.3)                         | 12 (30.0)                       |                |
| SD, <i>n</i> (%)   | 12 (29.3)                         | 12 (30.0)                       |                |
| PD, <i>n</i> (%)   | 6 (14.6)                          | 15 (37.5)                       |                |
| ORR, %   | 56.1                              | 32.5                            | 0.033          |
| DCR, %   | 85.4                              | 62.5                            | 0.019          |
| Intrahepatic tumor   |                                   |                                 |                |
| CR, <i>n</i> (%)   | 5 (12.2)                          | 1 (2.5)                         |                |
| PR, <i>n</i> (%)   | 22 (53.7)                         | 14 (35.0)                       |                |
| SD, <i>n</i> (%)   | 12 (29.3)                         | 16 (40.0)                       |                |
| PD, <i>n</i> (%)   | 2 (4.9)                           | 9 (22.5)                        |                |
| ORR, %   | 65.9                              | 37.5                            | 0.011          |
| DCR, %   | 95.1                              | 77.5                            | 0.021          |
| <i>TACE-L-P</i> transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, <i>TACE-L</i> transarterial chemoembolization combined with lenvatinib, <i>CR</i> complete response, <i>PR</i> partial response, <i>SD</i> stable disease, <i>PD</i> progressive disease, <i>ORR</i> objective response rate, <i>DCR</i> disease control rate |                                   |                                 |                |

## Safety

In total, treatment-related AEs were observed in 76 of the 81 patients (93.8%), and no grade 4/5 AEs occurred (Table 4). The frequency and severity of AEs was similar between TACE-L-P group and TACE-L group (any grade, 92.7% vs. 95.0%,  $p=1.000$ ; grade 3, 36.6% vs. 32.5%,  $p=0.699$ ). The AEs related to TACE, including ascites, pleural effusion, inguinal hematoma and intrahepatic biliary dilatation/biloma, were mild ( $\leq$  grade 2) and occurred in 6 (14.6%) and 7 (17.5%) patients in TACE-L-P group and the TACE-L group ( $P=0.725$ ), respectively. The AEs related to lenvatinib and/or PD-1 inhibitor occurred in 38 (92.7%) and 37 (90.0%) patients in TACE-L-P group and TACE-L group ( $p=1.000$ ), respectively.

Table 4  
Treatment-related adverse events in the two groups

| Adverse events               | Any grade       |                 | <i>p</i> value | Grade 3         |                 |                |
|------------------------------|-----------------|-----------------|----------------|-----------------|-----------------|----------------|
|                              | TACE-L-P group  | TACE-L group    |                | TACE-L-P group  | TACE-L group    | <i>p</i> value |
|                              | ( <i>n</i> =41) | ( <i>n</i> =40) |                | ( <i>n</i> =41) | ( <i>n</i> =40) |                |
| Total                        | 38 (92.7)       | 38 (95.0)       | 1.000          | 15 (36.6)       | 13 (32.5)       | 0.699          |
| Related to TACE              | 6 (14.6)        | 7 (17.5)        | 0.725          | 0 (0.0)         | 0 (0.0)         | -              |
| New ascites                  | 3 (7.3)         | 2 (5.0)         | 1.000          | 0 (0.0)         | 0 (0.0)         | -              |
| Pleural effusion             | 2 (4.9)         | 2 (5.0)         | 1.000          | 0 (0.0)         | 0 (0.0)         | -              |
| Inguinal hematoma            | 2 (4.9)         | 3 (7.5)         | 0.675          | 0 (0.0)         | 0 (0.0)         | -              |
| Biliary injury <sup>a</sup>  | 1 (2.4)         | 2 (5.0)         | 0.616          | 0 (0.0)         | 0 (0.0)         | -              |
| Related to drug <sup>b</sup> | 38 (92.7)       | 37 (92.5)       | 1.000          | 15 (36.6)       | 13 (32.5)       | 0.699          |
| Hypertension                 | 16 (39.0)       | 14 (35.0)       | 0.708          | 9 (22.0)        | 8 (20.0)        | 0.829          |
| Weight loss                  | 14 (34.1)       | 11 (27.5)       | 0.517          | 1 (2.4)         | 0 (0.0)         | 1.000          |
| Diarrhea                     | 13 (31.7)       | 13 (32.5)       | 0.939          | 0 (0.0)         | 0 (0.0)         | -              |
| Hand-foot syndrome           | 11 (26.8)       | 13 (32.5)       | 0.576          | 0 (0.0)         | 0 (0.0)         | -              |
| Fatigue                      | 11 (26.8)       | 9 (22.5)        | 0.651          | 1 (2.4)         | 0 (0.0)         | 1.000          |
| Elevated AST                 | 11 (26.8)       | 8 (20.0)        | 0.468          | 0 (0.0)         | 1 (2.5)         | 0.494          |
| Decreased appetite           | 10 (24.4)       | 9 (22.5)        | 0.841          | 1 (2.4)         | 1 (2.5)         | 1.000          |
| Hypothyroidism               | 10 (24.4)       | 8 (20.0)        | 0.635          | 0 (0.0)         | 0 (0.0)         | -              |
| Elevated ALP                 | 9 (22.0)        | 11 (27.5)       | 0.563          | 0 (0.0)         | 0 (0.0)         | -              |
| Hypoalbuminemia              | 9 (22.0)        | 8 (20.0)        | 0.829          | 0 (0.0)         | 0 (0.0)         | -              |
| Abdominal pain               | 9 (22.0)        | 8 (20.0)        | 0.829          | 0 (0.0)         | 1 (2.5)         | 0.494          |

Data were presented as *n* (%)

<sup>a</sup>Included intrahepatic biliary dilatation and biloma, <sup>b</sup>referred to lenvatinib and/or PD-1 inhibitor

*TACE-L-P* transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, *TACE-L* transarterial chemoembolization combined with lenvatinib, *TACE* transarterial chemoembolization, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *TBi* total bilirubin, *GGT*  $\gamma$ -glutamyl transpeptidase

| Adverse events     | Any grade       |                 |                | Grade 3         |                 |                |
|--------------------|-----------------|-----------------|----------------|-----------------|-----------------|----------------|
|                    | TACE-L-P group  | TACE-L group    | <i>p</i> value | TACE-L-P group  | TACE-L group    | <i>p</i> value |
|                    | ( <i>n</i> =41) | ( <i>n</i> =40) |                | ( <i>n</i> =41) | ( <i>n</i> =40) |                |
| Pruritus           | 9 (22.0)        | 4 (10.0)        | 0.143          | 0 (0.0)         | 0 (0.0)         | -              |
| Elevated ALT       | 8 (19.5)        | 9 (22.5)        | 0.741          | 1 (2.4)         | 0 (0.0)         | 1.000          |
| Thrombocytopenia   | 8 (19.5)        | 8 (20.0)        | 0.956          | 1 (2.4)         | 2 (5.0)         | 0.616          |
| Neutropenia        | 8 (19.5)        | 6 (15.0)        | 0.591          | 2 (4.9)         | 2 (5.0)         | 1.000          |
| Proteinuria        | 8 (19.5)        | 6 (15.0)        | 0.591          | 0 (0.0)         | 0 (0.0)         | -              |
| Rash               | 8 (19.5)        | 4 (10.0)        | 0.228          | 0 (0.0)         | 0 (0.0)         | -              |
| Anemia             | 7 (17.1)        | 5 (12.5)        | 0.562          | 0 (0.0)         | 1 (2.5)         | 0.494          |
| Lymphopenia        | 7 (17.1)        | 4 (10.0)        | 0.353          | 1 (2.4)         | 0 (0.0)         | 1.000          |
| Elevated TBi       | 6 (14.6)        | 7 (17.5)        | 0.725          | 1 (2.4)         | 1 (2.5)         | 1.000          |
| Nausea             | 6 (14.6)        | 6 (15.0)        | 0.963          | 0 (0.0)         | 0 (0.0)         | -              |
| Elevated GGT       | 6 (14.6)        | 5 (12.5)        | 0.779          | 0 (0.0)         | 0 (0.0)         | -              |
| Ventosity          | 6 (14.6)        | 5 (12.5)        | 0.779          | 1 (2.4)         | 0 (0.0)         | 1.000          |
| Arthralgia         | 6 (14.6)        | 5 (12.5)        | 0.779          | 0 (0.0)         | 0 (0.0)         | -              |
| Vomiting           | 5 (12.2)        | 6 (15.0)        | 0.713          | 0 (0.0)         | 0 (0.0)         | -              |
| Gingival bleeding  | 5 (12.2)        | 6 (15.0)        | 0.713          | 0 (0.0)         | 0 (0.0)         | -              |
| Dysphonia          | 4 (9.8)         | 6 (15.0)        | 0.519          | 0 (0.0)         | 0 (0.0)         | -              |
| Edema              | 3 (7.3)         | 4 (10.0)        | 0.712          | 0 (0.0)         | 0 (0.0)         | -              |
| Elevated uric acid | 3 (7.3)         | 1 (2.5)         | 0.616          | 0 (0.0)         | 0 (0.0)         | -              |
| Insomnia           | 2 (4.9)         | 2 (5.0)         | 1.000          | 0 (0.0)         | 0 (0.0)         | -              |
| Infusion reaction  | 2 (4.9)         | -               | -              | 0 (0.0)         | -               | -              |
| Hyperglycemia      | 1 (2.4)         | 0 (0.0)         | 1.000          | 0 (0.0)         | 0 (0.0)         | -              |

Data were presented as *n* (%)

<sup>a</sup>Included intrahepatic biliary dilatation and biloma, <sup>b</sup>referred to lenvatinib and/or PD-1 inhibitor

*TACE-L-P* transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, *TACE-L* transarterial chemoembolization combined with lenvatinib, *TACE* transarterial chemoembolization, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *TBi* total bilirubin, *GGT*  $\gamma$ -glutamyl transpeptidase

| Adverse events  | Any grade       |                 |                | Grade 3         |                 |                |
|---|-----------------|-----------------|----------------|-----------------|-----------------|----------------|
|   | TACE-L-P group  | TACE-L group    | <i>p</i> value | TACE-L-P group  | TACE-L group    | <i>p</i> value |
|   | ( <i>n</i> =41) | ( <i>n</i> =40) |                | ( <i>n</i> =41) | ( <i>n</i> =40) |                |
| Pneumonitis   | 1 (2.4)         | 0 (0.0)         | 1.000          | 1 (2.4)         | 0 (0.0)         | 1.000          |
| Data were presented as <i>n</i> (%)   |                 |                 |                |                 |                 |                |
| <sup>a</sup> Included intrahepatic biliary dilatation and biloma, <sup>b</sup> referred to lenvatinib and/or PD-1 inhibitor   |                 |                 |                |                 |                 |                |
| <i>TACE-L-P</i> transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, <i>TACE-L</i> transarterial chemoembolization combined with lenvatinib, <i>TACE</i> transarterial chemoembolization, <i>AST</i> aspartate aminotransferase, <i>ALT</i> alanine aminotransferase, <i>ALP</i> alkaline phosphatase, <i>TBi</i> total bilirubin, <i>GGT</i> $\gamma$ -glutamyl transpeptidase |                 |                 |                |                 |                 |                |

Treatment-related AEs led to treatment interruption, dose reduction and treatment discontinuation of lenvatinib in 22 (53.7%), 21 (51.2%) and 3 (7.3%) patients, respectively, in the TACE-L-P group, and in 20 (50.0%), 20 (50.0%) and 3 (7.5%) patients, respectively, in the TACE-L group. Treatment-related AEs led to treatment interruption and discontinuation of PD-1 inhibitor in 10 (24.4%) and 6 (14.6%) patients in the TACE-L-P group, respectively. Discontinuation of both lenvatinib and PD-1 inhibitor because of AEs occurred in only 2 patients (4.9%).

## Discussion

Our study showed that TACE-L-P conferred a significant survival benefit when compared with TACE-L in patients with advanced HCC. This finding was associated with an increase in median OS from 12.1 months to 16.9 months, which might be attributed to the higher ORR and DCR and the longer PFS achieved in patients received TACE-L-P rather than TACE-L. Multivariate analyses also revealed that combining PD-1 inhibitor on the basis of TACE-L was an independent predictor for prolonged OS and PFS. These results indicated that the triple combination treatment of TACE-L-P might be a superior treatment option in advanced HCC patients. The reasons might be as follows: 1) TACE lead to an extensive local necrosis of the tumor and may subsequently elicit anticancer immune responses that may be further boosted with PD-1 inhibitors [10, 21]. 2) Lenvatinib is a multikinase inhibitor with antiproliferative and antiangiogenic activities [22], which may counteract the hypoxia-induced angiogenesis after TACE [9, 10] and can regulate the tumor immune microenvironment and enhance immune response of PD-1 inhibitor in HCC [22, 23]. Therefore, the combination of TACE, lenvatinib and PD-1 inhibitor may bring about a synergistic antitumor activity, contributing to improved clinical outcomes in advanced HCC patients.

In our study, the presence of main portal vein invasion or extrahepatic metastasis was identified as the independent risk factor for survival. These results were consistent with previous studies [29-32] and further confirmed that main portal vein invasion or extrahepatic spread had a profound adverse effect on prognosis in HCC patients. More notably, in subgroup analyses, a prolonged OS was observed with the treatment of TACE-L-P not in patients with main portal vein invasion but in those without main portal vein invasion, which implied that TACE-L-P might be better employed for HCC patients before the main portal trunk was involved so that an improved survival could be achieved. Furthermore, subgroup analyses also showed that TACE-L-P provided a

better OS than TACE-L in the patients with extrahepatic metastasis or tumor number >3 but not in those with no extrahepatic metastasis or tumor number  $\leq 3$ . The reasons might be that TACE exerted its antitumor property mainly by controlling intrahepatic lesions rather than extrahepatic metastases [9] and its effect on multiple tumors was also limited [33]. Thus, a treatment strategy combining TACE with a more potent systemic therapy was urgently needed for patients with extrahepatic metastasis or multiple tumors. Our results revealed the necessity of the additional treatment with PD-1 inhibitor to TACE-L for such patients.

In our study, all the AEs with the combination of TACE and lenvatinib with/without PD-1 inhibitor were manageable and consistent with previously reported data on each individual treatment [7, 10, 12, 34]. There were no new or unexpected AEs observed. Additionally, the incidence and severity of AEs in TACE-L-P group were comparable to those in TACE-L group. These results suggested that both the treatments of TACE-L-P and TACE-L were tolerable and combining PD-1 inhibitor with TACE-L did not significantly increase the risk of AEs compared with TACE-L, which revealed an acceptable safety profile of TACE-L-P.

Our study has some limitations. First, this study was a retrospective study, and the treatment option was individually determined based on the preference of the attending physician and the patient, which inevitably resulted in selection bias. Second, the sample size of this study was limited. The results of subgroup analyses should be cautiously interpreted. Third, the categories of PD-1 inhibitors were varied in the TACE-L-P group, which might lead to inconformity of the treatment procedure and influence the treatment outcomes. Consequently, validation of our findings by further randomized trials is necessary.

In conclusion, our study showed safety and promising outcomes with the treatment of TACE-L-P in patients with advanced HCC. These patients could benefit from TACE-L-P and had markedly better treatment responses and improved survival in comparison with TACE-L. These findings need to be confirmed in large sample, prospective randomized controlled trials.

## Declarations

**Data Availability** All data generated or analyzed during this study are available by contacting the corresponding author upon reasonable request.

**Ethics** The Institutional Review Board at the Second Affiliated Hospital of Guangzhou Medical University reviewed and approved the protocol (No. 2021-hg-ks-14). This study was performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from every patient included in this study.

**Plant Reproducibility** Not applicable.

**Clinical Trials Registration** Not applicable.

**Author Contributions** Mingyue Cai, Wensou Huang and Jingjun Huang conceived and designed the study with supervision from Kangshun Zhu. Mingyue Cai, Wensou Huang, Yongjian Guo, Jingwen Zhou and Kangshun Zhu provided the provision of study materials or patients. Wenbo Shi, Licong Liang, Liteng Lin, Bihui Cao, Ye Chen and Juan Zhou collected and assembled the data. Mingyue Cai, Jingjun Huang and Wenbo Shi

performed or supervised analyses. Mingyue Cai, Wensou Huang and Kangshun Zhu interpreted the results. Mingyue Cai, Jingjun Huang and Kangshun Zhu wrote the manuscript. All authors reviewed the manuscript and approved the final version.

**Conflict of Interest** All authors (Mingyue Cai, Wensou Huang, Jingjun Huang, Wenbo Shi, Yongjian Guo, Licong Liang, Jingwen Zhou, Liteng Lin, Bihui Cao, Ye Chen, Juan Zhou and Kangshun Zhu) have no conflict of interest to declare.

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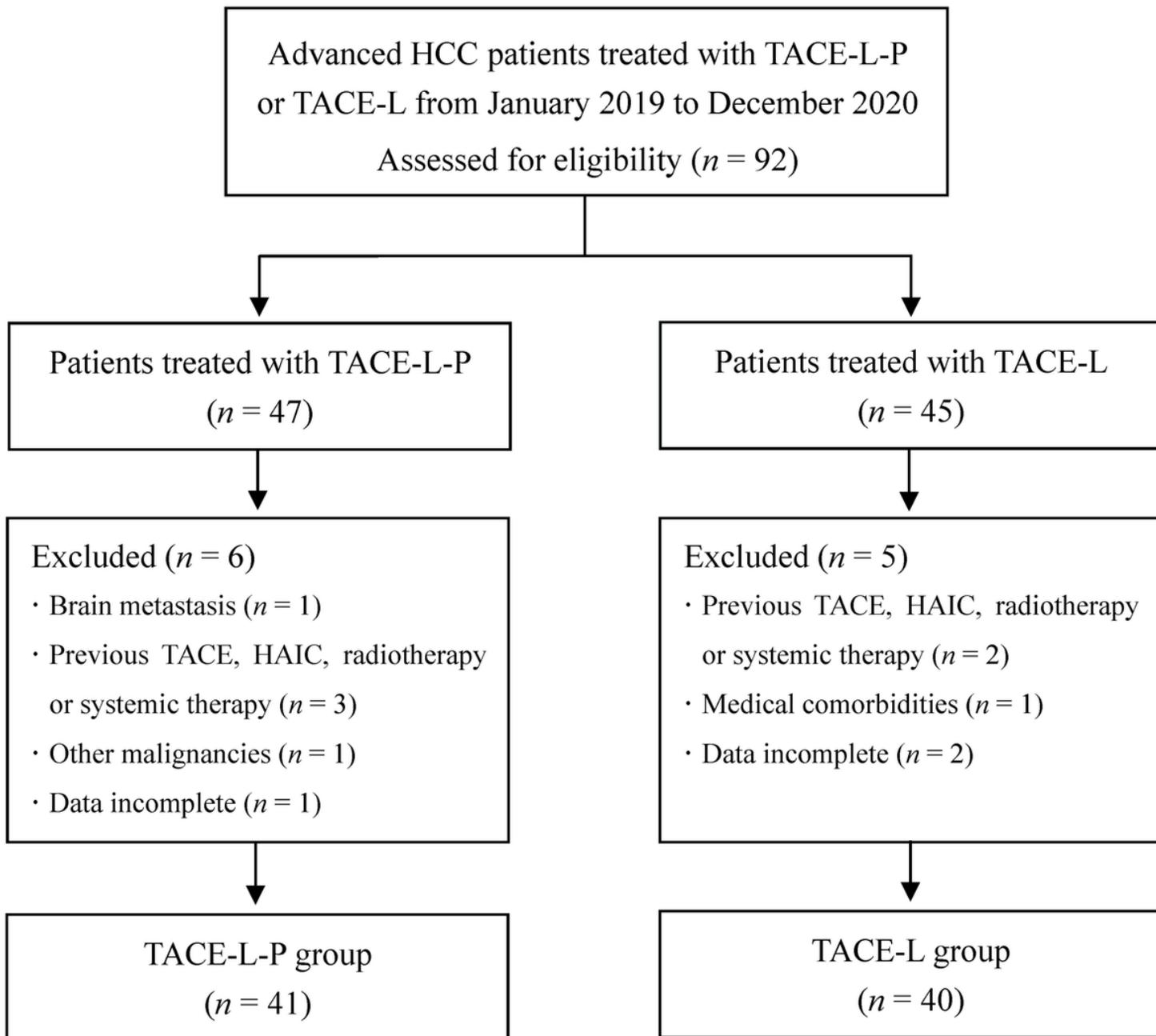
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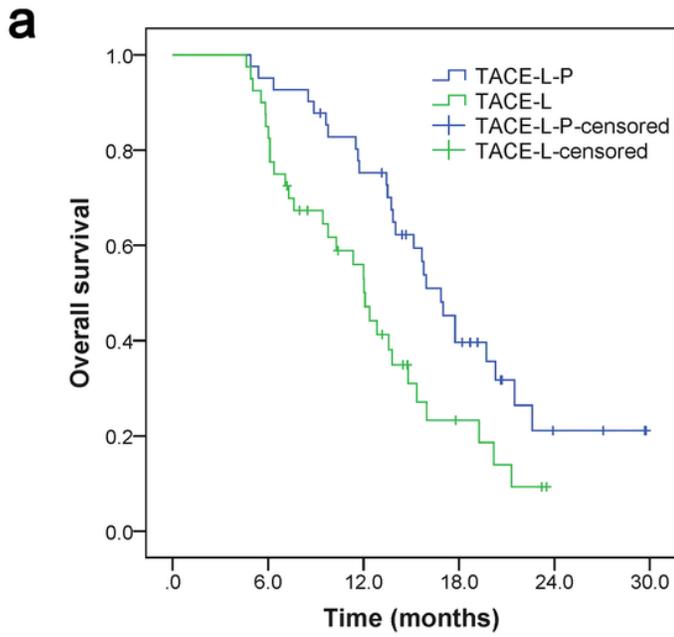
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## Figures

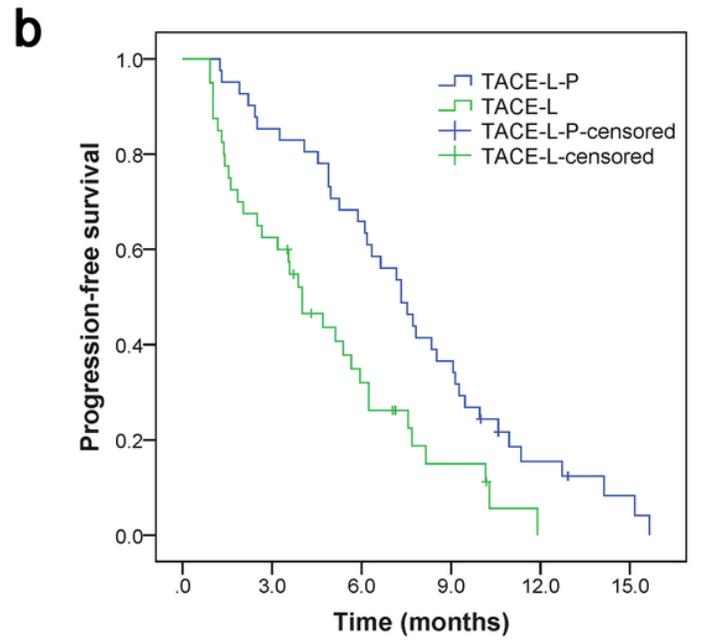


**Figure 1**

Flow diagram of patient enrollment. HCC: hepatocellular carcinoma. TACE-L-P: transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, TACE-L: transarterial chemoembolization combined with Lenvatinib, TACE: transarterial chemoembolization, HAIC: hepatic arterial infusion chemotherapy



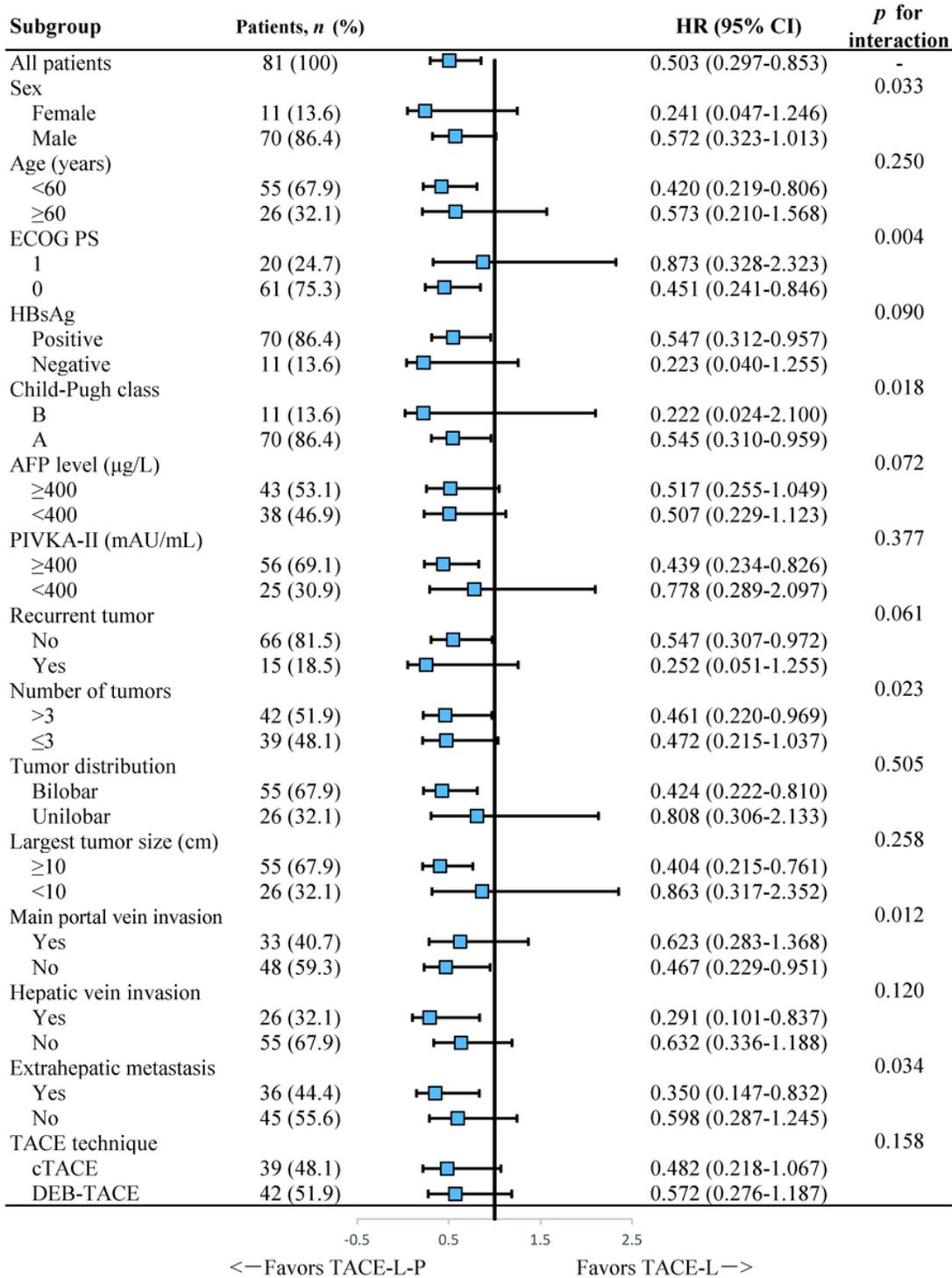
| Number at risk (censored) |        |        |        |        |       |       |
|---------------------------|--------|--------|--------|--------|-------|-------|
| Months                    | 0      | 6      | 12     | 18     | 24    | 30    |
| TACE-L-P                  | 41 (0) | 39 (1) | 30 (3) | 14 (7) | 3 (3) | 0 (0) |
| TACE-L                    | 40 (0) | 24 (4) | 19 (4) | 5 (2)  | 0 (0) | 0 (0) |



| Number at risk (censored) |        |        |        |        |       |       |
|---------------------------|--------|--------|--------|--------|-------|-------|
| Months                    | 0      | 3      | 6      | 9      | 12    | 15    |
| TACE-L-P                  | 41 (0) | 35 (0) | 27 (0) | 15 (2) | 5 (1) | 2 (0) |
| TACE-L                    | 40 (0) | 25 (3) | 11 (2) | 4 (1)  | 0 (0) | 0 (0) |

**Figure 2**

Kaplan-Meier analyses of survival outcomes according to treatment groups. Overall survival (a). Progression-free survival (b). TACE-L-P: transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor; TACE-L: transarterial chemoembolization combined with lenvatinib



**Figure 3**

Forest plot of the subgroup analyses for overall survival. HR: hazard ratio, CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HBsAg: hepatitis B surface antigen, AFP:  $\alpha$ -fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II, TACE: transarterial chemoembolization, cTACE: conventional transarterial chemoembolization, DEB-TACE: drug-eluting bead transarterial chemoembolization, TACE-L-P: transarterial chemoembolization combined with lenvatinib and PD-1 inhibitor, TACE-L: transarterial chemoembolization combined with lenvatinib