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ORIGINAL RESEARCH

Transarterial Chemoembolization, Molecular Targeted Treatments, and Programmed Death-(Ligand)1 Inhibitors, for Hepatocellular Carcinoma with Lung Metastasis: A Retrospective Cohort Study

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Background: Treatment options for patients with hepatocellular carcinoma (HCC) and lung metastases are diverse, requiring a personalized approach. Current CNLC guidelines recommend systemic therapy and focal radiation, emphasizing the roles of molecular targeted treatments (MTT) and programmed death-(ligand)1 (PD-[L]1) inhibitors. However, the efficacy of combining TACE with these treatments remains uncertain.

Purpose: To compare the efficacy and adverse reactions of TACE combined with MTT and PD-(L)1 versus MTT and (PD-[L]1) in patients with HCC and lung metastasis.

Materials and Methods: We retrospectively analyzed data from patients treated between January 2019 and May 2024 at the Affiliated Hospital of Southwest Medical University and West China Hospital of Sichuan University. Stabilized inverse probability weighting was employed to reduce bias. The primary outcome was overall survival (OS); secondary outcomes included progression-free survival (PFS) and objective response rate (ORR).

Results: Among 167 patients, 141 received TACE, MTT, and PD-(L)1, while 26 received MTT and PD-(L)1. The median follow-up times were 28 and 29 months, respectively. After weighting, baseline characteristics were well balanced. The median OS was significantly longer in the TACE group (15 months) compared to the MTT group (8 months; p=0.023), and PFS was also longer (8 months vs 5 months; p=0.038). For liver lesions, ORR was 42.6% in the TACE group and 46.2% in the MTT group (p=0.73); for lung lesions, ORR was 26.2% and 19.2%, respectively (p=0.449). Safety profiles were similar, except for a higher incidence of rash in the MTT group.

Conclusion: TACE combined with MTT and PD-(L)1 demonstrated better outcomes for patients with liver cancer and lung metastases compared to MTT and PD-(L)1 alone, without increasing complication rates, suggesting a promising first-line treatment option.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, molecular targeted treatments, tyrosine kinase inhibitor, programmed death-(ligand)1 inhibitors

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors worldwide. Although recent studies have shown a decreasing trend in the incidence of HCC, it is still one of the leading causes of cancer deaths.[1]

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Transarterial chemoembolization (TACE) is the most widely used local treatment for HCC, delivering chemotherapy drugs directly to the tumor blood vessels through a catheter, and concurrently using embolic agents to block the tumor's blood supply.[2] TACE can induce tumor cell necrosis and release tumor antigens, enhancing the immune response of CD8+ T cells to tumor-associated antigens, thereby boosting the anti-tumor immune response.[3] Additionally, it creates a local pro-vascular environment, improving the effectiveness of targeted drugs.[4] The TACTICS trial confirmed that TACE combined with sorafenib significantly improved PFS in patients with unresectable HCC compared to TACE alone. However, this combination did not translate into overall survival benefits.[5] EMERALD-1, a phase III randomized controlled trial, for the first time globally, confirmed that the combination of molecular targeted therapy (MTT) and (PD-[L]1) with TACE improves the PFS of patients with intermediate to advanced HCC who are suitable for embolization, compared to TACE alone.[6] These studies suggest that in the treatment of HCC, the combination of systemic therapy and locoregional treatment is more effective than local treatment alone.

IMbrave150, CARES-310, and ORIENT-32 studies have confirmed the combination of MTT and PD-1 inhibitor could improve the OS significantly for patients with unresectable HCC, established the position of the combination of MTT and (PD-[L]1) in the first-line treatment of advanced liver cancer.[7–9] Consequently, several authoritative guidelines, including BCLC, CNLC, and Japanese HCC guidelines, recommend systemic combination therapy represented by anti-angiogenic targeted therapy plus immune checkpoint inhibitors as the preferred treatment strategy for HCC patients with lung metastases.[10] However, the prognosis of HCC patients with lung metastases remains poor, with reported 1-year and 3-year survival rates of only 29.7% and 10.8%, respectively,[11] and a median survival time of approximately 9.6 months.[12] Although systemic therapy has become the standard of care, there is still insufficient clinical evidence regarding whether local therapy (such as TACE) could provide additional survival benefits when combined with systemic treatment for these patients with poor prognosis. Based on these insights, we hypothesize that TACE combined with MTT and (PD-[L]1) (TACE, MTT and (PD-[L]1) is a potentially effective treatment strategy for liver cancer patients with lung metastases. To validate this hypothesis, we conducted a retrospective cohort study to assess the efficacy and safety of TACE, MTT and (PD-[L]1) versus MTT and (PD-[L]1) in treating liver cancer patients with lung metastases.

Materials and Methods

Material

This retrospective study collected data from patients diagnosed with hepatocellular carcinoma (HCC) with lung metastases at the Affiliated Hospital of Southwest Medical University and West China Hospital of Sichuan University between January 1, 2019, and May 31, 2024.

The inclusion and exclusion criteria for patients are illustrated in Figure 1.

Inclusion Criteria

1. Confirmed HCC diagnosis according to CNLC 2024 diagnostic criteria.
2. Confirmed lung metastases by CT/MRI.
3. Child-Pugh grade A or B liver function.
4. Age ≥18 years.
5. Patients who received MTT and PD-(L)1 before or within three months after receiving TACE therapy, MTT and PD-(L)1 need to be administered at the same time, and patients in the TACE-MTT-PD-(L)1 group need to receive at least one cycle of MTT and PD-(L)1 combination therapy after initial TACE therapy, and there is no limit to the number of times patients can receive TACE.

Exclusion Criteria

1. Metastases beyond lung sites.
2. Incomplete key clinical information.
3. Severe comorbidities: Renal dysfunction (eGFR <30 mL/min), Coagulation disorders, Uncontrolled cardiovascular diseases.
4. Concurrent malignancies.
5. Patients deemed unsuitable for inclusion by the researchers.

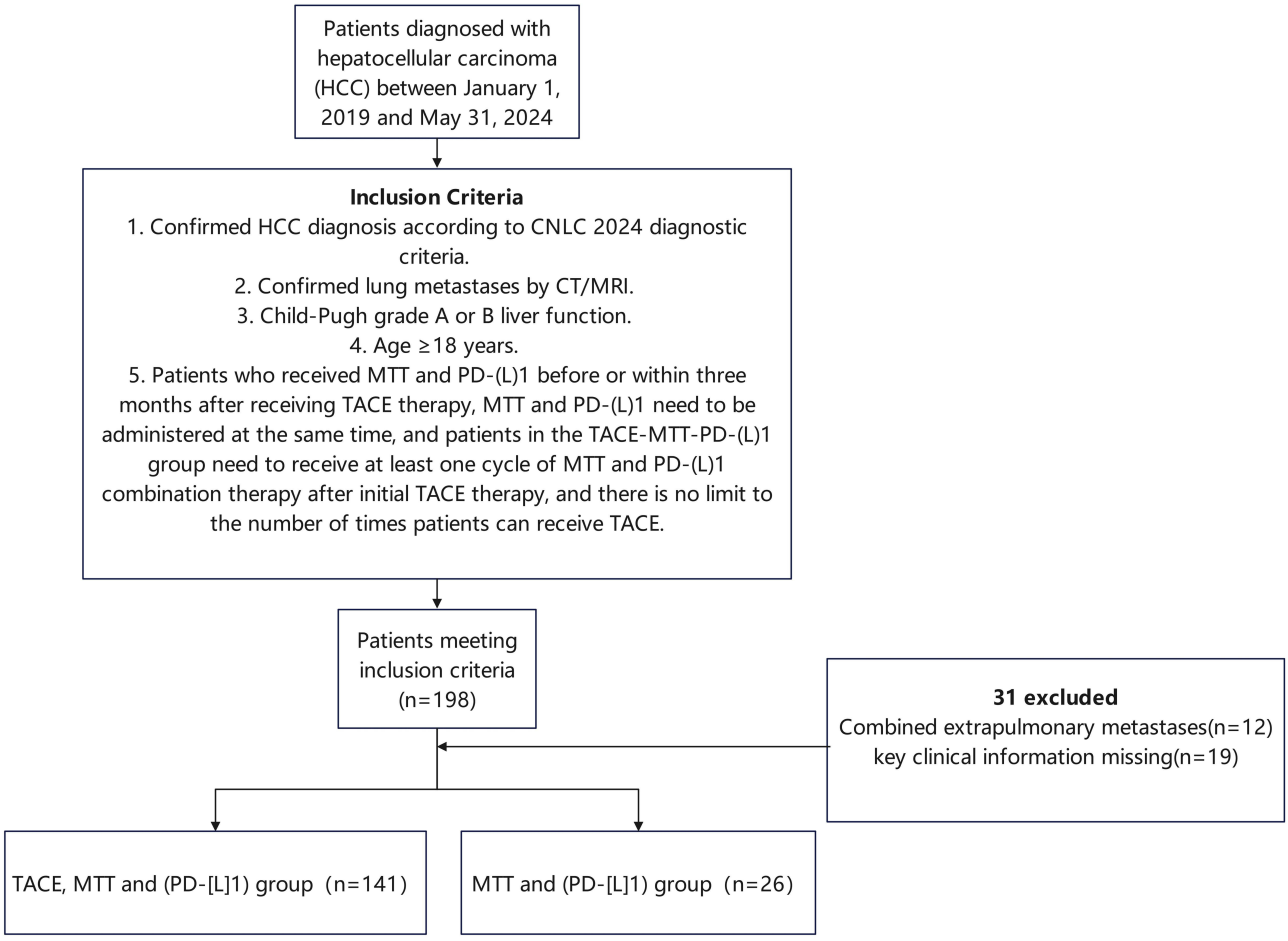

Figure 1 Patient Inclusion and Exclusion Flowchart.

Ethical Statement

This study was approved by the Clinical Trial Ethics Committee of the Affiliated Hospital of Southwest Medical University (Ethical Review Number: KY2024249) and conducted in strict accordance with the ethical standards outlined in the Declaration of Helsinki. Given the retrospective nature of this study, which involves no direct patient intervention and utilizes fully anonymized data, the Ethics Committee waived the requirement for obtaining patient consent. We rigorously adhere to data confidentiality principles to ensure the protection of patient privacy. All patient data were anonymized and used exclusively for scientific research purposes, with no identifiable information disclosed.

Patient Data Collection

This study meticulously collected personal information from the enrolled patients, including gender, age at the start of treatment, and the presence of high-risk factors for HCC, such as hepatitis B and C. Additionally, the history of chronic diseases, including hypertension and diabetes, was recorded, along with lifestyle factors such as smoking and alcohol consumption.

Upon patient admission, a comprehensive series of laboratory tests was conducted, including but not limited to alpha-fetoprotein (AFP), alanine aminotransferase (ALT), total bilirubin, albumin, platelet count, hemoglobin, and white blood cell count.

We also gathered detailed information about the tumors through imaging studies, including tumor size, number, specific location, presence of portal vein tumor thrombus, and the distribution of lung metastases (size, number, and location of lung

metastases). Subsequently, we performed a graded assessment of liver function based on the results of imaging studies and laboratory tests. All laboratory data were obtained within one week prior to the initiation of the first treatment.

Treatment

The treatment strategy is decided by a multidisciplinary team, and the treatment to be performed is decided based on the physician's judgment, financial burden, and patient consent. TACE was performed by experienced interventional physicians in accordance with clinical guidelines. Treatment options included conventional TACE (C-TACE) and drug-eluting bead TACE (DEB-TACE), chosen based on patient preference. During the procedure, physicians utilized the Seldinger technique to insert a catheter into the femoral artery. Under digital subtraction angiography (DSA) guidance, they advanced the catheter into the hepatic artery for angiography to assess the tumor condition.

Subsequently, based on the patient's condition, a mixed emulsion of chemotherapy agents and embolic agents, such as doxorubicin, fluorouracil, and platinum-based drugs, was infused through the hepatic artery, with dosages adjusted according to various factors. To optimize the embolization effect, a combination of iodized oil and gelatin sponge or microspheres was commonly used for cross-embolization.

In this study, tyrosine kinase inhibitors (TKI) such as Sorafenib and Lenvatinib were key therapeutic agents. Sorafenib was administered orally at a dose of 400 mg twice daily. The oral dosage of Lenvatinib was weight-dependent: 8 mg once daily for patients weighing less than 60 kg, and 12 mg once daily for those weighing 60 kg or more. Additionally, PD-1 inhibitors such as Camrelizumab and Sintilimab were used, administered as a 200 mg intravenous infusion diluted in saline every three weeks.

Physicians adjusted dosages based on liver function, overall condition, and drug tolerance. Treatment could be paused if necessary. Upon improvement of symptoms, therapy could be resumed or switched to alternative MTT and (PD-[L]1).

Follow-Up

After the initiation of treatment, we continuously monitored the survival status and survival time of patients through telephone follow-ups and the hospital's imaging system. All relevant clinical data were meticulously organized and analyzed. The follow-up period extended until May 31, 2024, or until the patient passed away, at which point the follow-up was automatically terminated.

Follow-ups were conducted by trained resident physicians and professionals with higher qualifications. For patients lost to follow-up, multiple attempts were made to contact them via phone or email. If contact could not be established, they were marked as lost to follow-up for statistical purposes. This approach effectively ensured the comprehensive and detailed collection of clinical research data, providing robust support for this study.

Outcomes

OS is the primary endpoint of this study, defined as the time interval from the initiation of treatment to death from any cause, censoring, or the end of follow-up (May 31, 2024).

Secondary endpoint of the study include PFS, ORR, and various adverse reactions recorded during the follow-up period. In this study, two independent radiologists with more than five years of experience in imaging diagnosis evaluated tumor response according to mRECIST criteria,[13–15] and the treatment response was divided into complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). PFS is defined as the time from the start of treatment to first tumor progression, death from any cause, censoring, or the end of follow-up, as assessed according to mRECIST criteria. ORR is defined as the sum of CR and PR.

Statistical Analysis

Statistical methods were employed using IBM SPSS Statistics version 25 and R software version 4.4.1 to evaluate the study data. Quantitative data are presented as median ± interquartile range, while qualitative data are presented as frequencies and percentages.

Stabilized inverse probability of treatment weighting (sIPTW) was utilized to reduce bias. Chi-square tests were conducted to compare differences in data characteristics between the two groups. The Log rank test was used to compare

OS and PFS between the groups, generating Kaplan-Meier curves. The Cox proportional hazards model was employed to estimate hazard ratios (HR) and 95% confidence intervals (CI), and forest plots were generated for visual representation.

All comparisons were two-tailed, with a p-value of <0.05 considered statistically significant.

Results

Patient Characteristics

A total of 167 patients were included in this study, among whom 141 patients received TACE, MTT and (PD-[L]1), and 26 patients received MTT and (PD-[L]1). The median age was 55 years (IQR [49, 64]), with 145 patients (86.8%) being male. Additionally, 137 patients (82.0%) were HBV related, and 85 patients (50.9%) had a maximum tumor diameter greater than 10 cm.

Regarding the number of liver tumors: 104 patients (62.3%) had a solitary tumor, while 63 patients (37.7%) had multiple tumors. All patients had Child-Pugh grades of A or B.

In terms of lung metastases, 16 patients (9.6%) had tumors in one lung, while 151 patients (90.4%) had tumors in both lungs. The distribution of the maximum diameter of lung tumors was as follows: 61 patients (36.5%) had tumors with a diameter of 0.8 cm or less, while 106 patients (63.5%) had tumors with a diameter greater than 0.8 cm.

Characteristics as hospital, age, Child-Pugh grade, ALBI, Multiple, AFP, PVTT, HBV, liver diameter range, Cirrhosis, ascites, HGB, PLT, TBIL are not balanced before applying sIPTW. After applying sIPTW, the baseline characteristics were well balanced (Table 1).

Table 1 Comparison of General Information Between the TACE, MTT and (PD-[L]1) Group and the MTT and (PD-[L]1) Group

		Before sIPTW					After sIPTW			
	Level	**Overall**	**MTT and (PD-[L]1)**	**TACE, MTT and (PD-[L]1)**	**p**	**SMD**	**MTT and (PD-[L]1)**	**TACE, MTT and (PD-[L]1)**	**p**	**SMD**
n		167	26	141			19.4	140.1		
Hospital (%)	SWMU	55(32.9%)	15(57.7%)	40(28.4%)	0.007	0.62	5.9(30.2%)	44.8(32.0%)	0.885	0.038
	WCH	112(67.1%)	11(42.3%)	101(71.6%)			13.6(69.8%)	95.3(68.0%)		
Age (%)	<60	112(67.1%)	21(80.8%)	91(64.5%)	0.164	0.37	13.6(70.3%)	94.1(67.1%)	0.956	0.012
	≥60	55(32.9%)	5(19.2%)	50(35.5%)			5.8(29.7%)	46.0(32.9%)		
Gender (%)	F	22(13.2%)	3(11.5%)	19(13.5%)	0.788	0.609	1.3(6.6%)	18.3(13.1%)	0.148	0.467
	M	145(86.8%)	23(88.5%)	122(86.5%)			18.2(93.4%)	121.8(86.9%)		
Child-Pugh grade (%)	A	43(25.7%)	9(34.6%)	34(24.1%)	0.378	0.589	4.1(21.1%)	35.0(25.0%)	0.709	0.092
	B	124(74.3%)	17(65.4%)	107(75.9%)			15.3(78.9%)	105.1(75.0%)		
ALBI (%)	1	93(55.7%)	9(34.6%)	84(59.6%)	0.027	0.609	13.7(70.4%)	80.1(57.2%)	0.724	0.084
	2	70(41.9%)	17(65.4%)	53(37.6%)			5.8(29.6%)	56.6(40.4%)		
	3	4(2.4%)	0(0.0%)	4(2.8%)			0.0(0.0%)	3.4(2.4%)		
Multiple (%)	Single	104(62.3%)	10(38.5%)	94(66.7%)	0.012	0.589	9.6(49.2%)	88.0(62.8%)	0.744	0.077
	Multiple	63(37.7%)	16(61.5%)	47(33.3%)			9.9(50.8%)	52.1(37.2%)		
ALT (%)	<40U/L	80(47.9%)	12(46.2%)	68(48.2%)	0.846	0.042	10.7(55.3%)	66.5(47.5%)	0.632	0.157
	≥40U/L	87(52.1%)	14(53.8%)	73(51.8%)			8.7(44.7%)	73.6(52.5%)		
AFP (%)	<400ng/mL	81(48.5%)	10(38.5%)	71(50.4%)	0.367	0.241	13.1(67.5%)	69.7(49.7%)	0.648	0.101
	≥400ng/mL	86(51.5%)	16(61.5%)	70(49.6%)			6.3(32.5%)	70.5(50.3%)		
PVTT (%)	Absent	104(62.3%)	13(50.0%)	91(64.5%)	0.236	0.297	13.1(67.2%)	87.9(62.8%)	0.979	0.084
	Present	63(37.7%)	13(50.0%)	50(35.5%)			6.4(32.8%)	52.2(37.2%)		
HBV (%)	Absent	30(18.0%)	7(26.9%)	23(16.3%)	0.309	0.26	2.7(14.1%)	26.2(18.7%)	0.576	0.124
	Present	137(82.0%)	19(73.1%)	118(83.7%)			16.7(85.9%)	114.0(81.3%)		
Liver diameter range (%)	<3cm	8(4.8%)	2(7.7%)	6(4.3%)	0.694	0.247	1.0(5.2%)	7.4(5.3%)	0.266	0.262
	<5cm	19(11.4%)	4(15.4%)	15(10.6%)			1.8(9.2%)	15.4(11.0%)		
	<10cm	55(32.9%)	9(34.6%)	46(32.6%)			5.8(30.0%)	47.0(33.5%)		
	≥10cm	85(50.9%)	11(42.3%)	74(52.5%)			10.8(55.6%)	70.3(50.2%)		

(*Continued*)

Table 1 (Continued).

		Before sIPTW					After sIPTW			
	Level	**Overall**	**MTT and (PD-[L]1)**	**TACE, MTT and (PD-[L]1)**	**p**	**SMD**	**MTT and (PD-[L]1)**	**TACE, MTT and (PD-[L]1)**	**p**	**SMD**
Cirrhosis (%)	Absent	85(50.9%)	17(65.4%)	68(48.2%)	0.163	0.352	12.6(65.0%)	72.1(51.5%)	0.464	0.278
	Present	82(49.1%)	9(34.6%)	73(51.8%)			6.8(35.0%)	68.0(48.5%)		
Portal hypertension (%)	Absent	102(61.1%)	15(57.7%)	87(61.7%)	0.868	0.082	8.3(42.7%)	85.1(60.8%)	0.35	0.25
	Present	65(38.9%)	11(42.3%)	54(38.3%)			11.1(57.3%)	55.0(39.2%)		
Ascites (%)	Absent	79(47.3%)	18(69.2%)	61(43.3%)	0.026	0.542	15.4(79.4%)	65.5(46.8%)	0.458	0.16
	Present	88(52.7%)	8(30.8%)	80(56.7%)			4.0(20.6%)	74.6(53.2%)		
Diabetes (%)	Absent	145(86.8%)	22(84.6%)	123(87.2%)	0.962	0.075	16.6(85.4%)	122.1(87.1%)	0.979	0.006
	Present	22(13.2%)	4(15.4%)	18(12.8%)			2.8(14.6%)	18.1(12.9%)		
Hypertension (%)	Absent	132(79.0%)	20(76.9%)	112(79.4%)	0.979	0.061	12.8(66.1%)	111.1(79.3%)	0.669	0.103
	Present	35(21.0%)	6(23.1%)	29(20.6%)			6.6(33.9%)	29.0(20.7%)		
HCV (%)	Absent	163(97.6%)	25(96.2%)	138(97.9%)	0.598	0.101	17.9(92.3%)	136.2(97.2%)	0.501	0.141
	Present	4(2.4%)	1(3.8%)	3(2.1%)			1.5(7.7%)	3.9(2.8%)		
Smoke (%)	Absent	94(56.3%)	15(57.7%)	79(56.0%)	0.875	0.034	6.8(34.8%)	78.9(56.3%)	0.487	0.164
	Present	73(43.7%)	11(42.3%)	62(44.0%)			12.7(65.2%)	61.2(43.7%)		
Drink (%)	Absent	95(56.9%)	15(57.7%)	80(56.7%)	0.928	0.019	9.5(48.9%)	80.6(57.5%)	0.956	0.013
	Present	72(43.1%)	11(42.3%)	61(43.3%)			9.9(51.1%)	59.5(42.5%)		
WBC (%)	<4*10^9/L	19(11.4%)	3(11.5%)	16(11.3%)	0.978	0.006	1.5(8.0%)	16.2(11.5%)	0.787	0.057
	≥4*10^9/L	148(88.6%)	23(88.5%)	125(88.7%)			17.9(92.0%)	123.9(88.5%)		
HGB (%)	<120g/L	47(28.1%)	11(42.3%)	36(25.5%)	0.131	0.36	3.6(18.7%)	36.6(26.1%)	0.436	0.178
	≥120g/L	120(71.9%)	15(57.7%)	105(74.5%)			15.8(81.3%)	103.5(73.9%)		
PLT (%)	>100*10^11	20(12.0%)	2(7.7%)	18(12.8%)	0.687	0.168	1.1(5.8%)	16.9(12.1%)	0.729	0.091
	≥100*10^11	147(88.0%)	24(92.3%)	123(87.2%)			18.3(94.2%)	123.2(87.9%)		
ALB (%)	<35g/L	14(8.4%)	2(7.7%)	12(8.5%)	0.982	0.03	0.6(3.2%)	11.1(8.0%)	0.923	0.023
	≥35g/L	153(91.6%)	24(92.3%)	129(91.5%)			18.8(96.8%)	129.0(92.0%)		
TBIL (%)	<34umol/L	150(89.8%)	22(84.6%)	128(90.8%)	0.547	0.189	18.2(93.9%)	127.4(90.9%)	0.773	0.058
	≥34umol/L	17(10.2%)	4(15.4%)	13(9.2%)			1.2(6.1%)	12.7(9.1%)		
Lung.site (%)	Unilateral	16(9.6%)	3(11.5%)	13(9.2%)	0.712	0.076	1.3(6.9%)	12.8(9.1%)	0.776	0.066
	Bilateral	151(90.4%)	23(88.5%)	128(90.8%)			18.1(93.1%)	127.3(90.9%)		
Lung.diameter (%)	<0.8cm	61(36.5%)	10(38.5%)	51(36.2%)	0.824	0.047	10.8(55.5%)	50.4(36.0%)	0.501	0.161
	≥0.8cm	106(63.5%)	16(61.5%)	90(63.8%)			8.6(44.5%)	89.7(64.0%)		

Abbreviations: ALBI, albumin-bilirubin; lung.site, Distribution of pulmonary metastases; SMD, standardized mean difference.

Survival Comparison Between Two Groups

The median follow-up time was 28.0 months for the TACE, MTT and (PD-[L]1) group and 29.0 months for the MTT and (PD-[L]1) group, respectively. The survival curves for both groups are shown in Figure 2.

The TACE, MTT and (PD-[L]1) group had a median OS of 15 months and a median PFS of 8 months, while patients receiving MTT and (PD-[L]1) had a median OS of only 4.5 months and a median PFS of 4 months. There were significant differences in OS (p=0.023) and PFS (p=0.038).

After applying sIPTW, the TACE, MTT and (PD-[L]1) group were significantly better than those of the MTT and (PD-[L]1) group, with a median OS of 15 months versus 8 months and a median PFS of 8 months versus 5 months. The differences in OS (p=0.023) and PFS (p=0.038) remained statistically significant.

According to mRECIST criteria, the ORR for liver lesions was 42.6% in the TACE, MTT and (PD-[L]1) group and 46.2% in the MTT and (PD-[L]1) group. For lung lesions, the ORR was 26.2% in the TACE, MTT and (PD-[L]1) group and 19.2% in the MTT and (PD-[L]1) group. None of the results were statistically significant (p=0.73 and p=0.449).

Cox Regression Analysis Results

Univariate and multivariate Cox regression analyses were performed on the clinical characteristics of all patients included in the study, and a forest plot was generated (Figure 3).

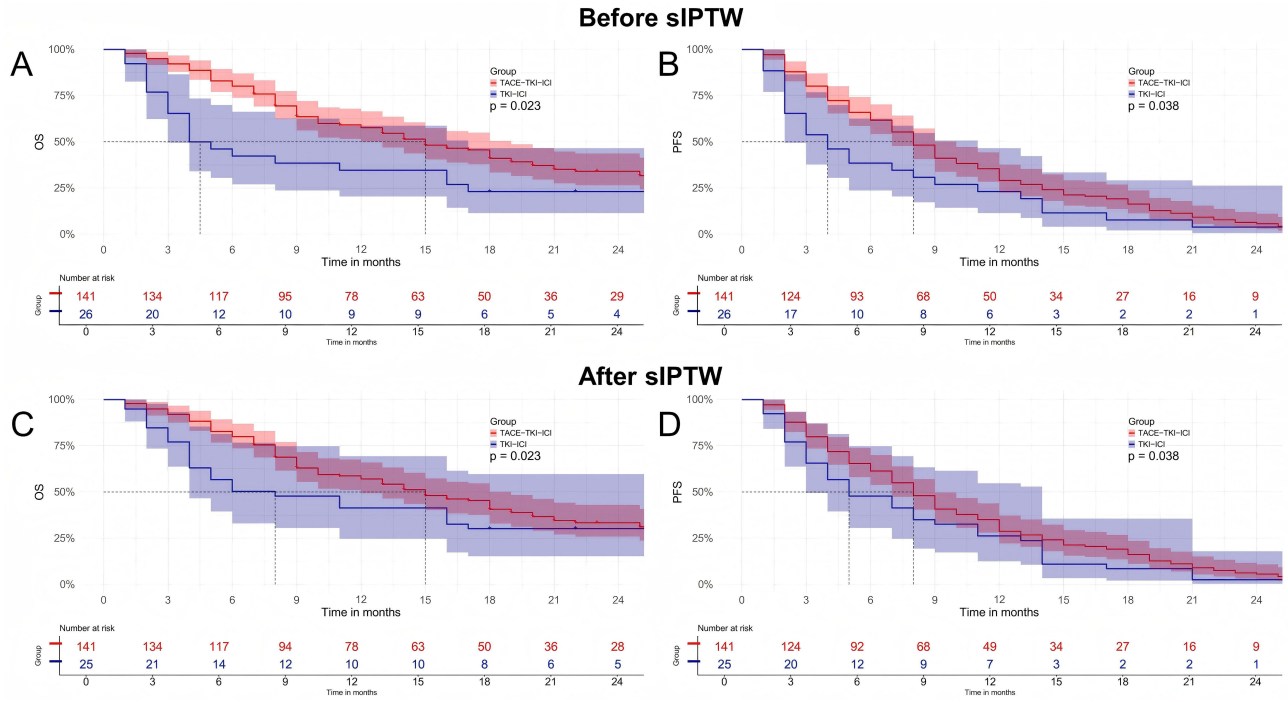

Figure 2 Kaplan–Meier curves of (**A**) OS, (**B**) PFS assessed by mRECIST before sIPTW and (**C**) OS, (**D**)PFS assessed by mRECIST after sIPTW.

Univariate and multivariate Cox regression analyses have indicated that the addition of TACE as a supplement to targeted and immunotherapy is an independent protective factor for patient survival. In contrast, higher white blood cell (WBC) counts, the presence of ascites, higher ALBI scores, and the bilateral distribution of lung metastases have been identified as risk factors for survival.

Adverse Reactions

During continuous follow-up of all patients, both groups experienced varying degrees of treatment-related adverse reactions. The reported adverse reactions included abdominal pain, fever, nausea and vomiting, rash and liver function abnormalities. In this study, a total of 78 patients (46.7%) reported adverse reactions, with 66 patients (46.8%) in the TACE, MTT and (PD-[L]1) group and 12 patients (46.2%) in the MTT and (PD-[L]1) group. The incidence of skin rash was higher in the MTT and (PD-[L]1) group, while there was no significant difference in the incidence of the other adverse effects (Table 2).

Discussion

This study reveals that for liver cancer with lung metastases, TACE combined with MTT and (PD-[L]1) significantly improves OS and PFS. The median OS increased from 4.5 to 15 months, and median PFS extended from 4 to 8 months. After applying sIPTW to eliminate confounding factors, median OS changed from 8 to 15 months, and PFS from 5 to 8 months. HCC with lung metastases shows variable responses to systemic therapy. The ORR of liver lesions was 42.6% versus 46.2% in the doublet group (P=0.73), and 26.2% versus 19.2% in lung lesions (P=0.449). These findings suggest the survival benefit may stem from synergistic effects of local and systemic therapies, rather than tumor shrinkage alone.

MTT and (PD-[L]1) combined treatment is the preferred first-line treatment for liver cancer. Previous clinical studies have primarily compared different targeted drugs, MTT and (PD-[L]1) combined treatment versus standalone interventions, and MTT and (PD-[L]1) alone. However, it remains unclear whether MTT and (PD-[L]1) combined with intervention treatment is superior to MTT and (PD-[L]1) alone, particularly for liver cancer patients with lung metastasis. Through real-world retrospective analysis, this study uniquely discovered that combined intervention treatment can extend median survival time by 7 months and median progression-free survival time by 3 months. These findings

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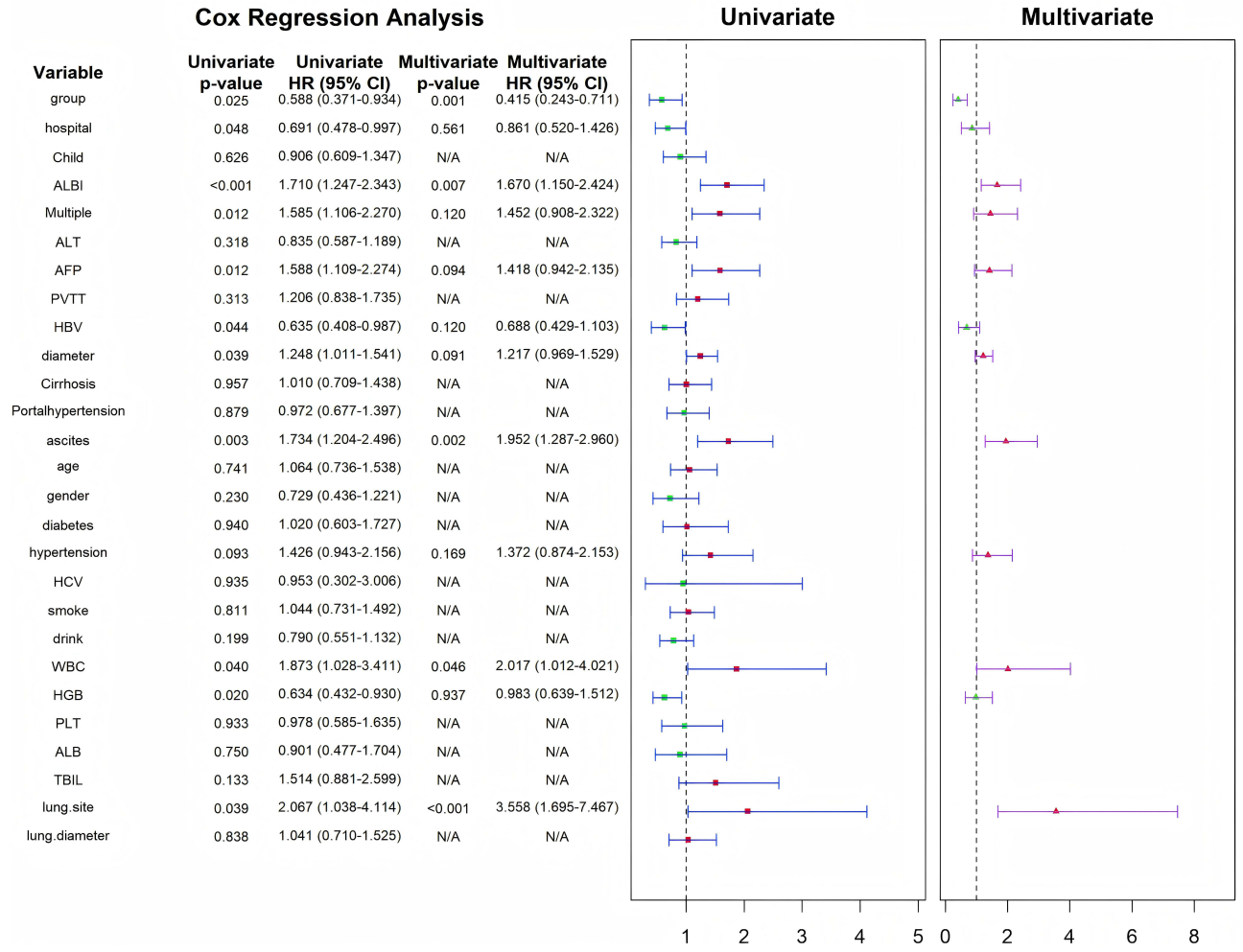

Figure 3 Results of Univariate COX regression analysis and multivariate COX analysis.

significantly improve treatment effectiveness for liver cancer with concomitant lung metastasis, potentially providing new insights and clinical practice references.

This treatment also has a favorable safety profile, with the most common adverse effects including abdominal pain, fever, nausea and vomiting, rash, and elevated aminotransferases. Rash is a common side effect of MTT and (PD-[L]1) drugs (especially epidermal growth factor receptor inhibitors and multikinase inhibitors) and may interfere with skin cell growth and repair.[16] In this study, the incidence of rash was higher in the MTT and (PD-[L]1) group while the incidence of other adverse reactions did not differ significantly, which may be presumed to be due to the application of symptomatic medications after TACE or the Patients cannot distinguish whether symptoms are due to treatment, as well as the insufficient sample size. In addition, patients' pain thresholds may be elevated as the number of TACE

Table 2 Number of Adverse Reactions During Follow-up in Both Groups of Patients

Adverse Reaction	Total Patients (n=141)	TACE, MTT and (PD-[L]1) (n=141)	MTT and (PD-[L]1) (n=26)	p
Abdominal Pain (%)	78(46.7%)	66 (46.8%)	12(46.2%)	0.951
Fever (%)	14(8.3%)	11(7.8%)	3(11.5%)	0.528
Nausea and Vomiting (%)	40(23.9%)	33 (23.4%)	7 (26.9%)	0.699
Rash (%)	32(19.1%)	21 (14.9%)	11(42.3%)	0.001
Liver Function Abnormalities (%)	87(52.1%)	73(51.8%)	14 (53.8%)	0.042

treatments increases.[17] These results are consistent with earlier reports on the safety and tolerability of combination therapy for unresectable HCC.[18]

A previous retrospective study evaluated TACE, lenvatinib, and PD-1 inhibitors for unresectable HCC, reporting PFS of 11.4–13.3 months and OS of 23.6–24.0 months.[19] A multicenter analysis by Jin ZCet al showed significant improvement in median OS (22.6 vs 15.9 months) and PFS (9.9 vs 7.4 months) for TACE-ICI-VEGF group.[20] The EMERALD-1 Phase III trial demonstrated that MTT and PD-(L)1 with TACE improved PFS compared to TACE alone (27.9 vs 15.0 months).[21] These survival times exceed our study's results, potentially due to the higher proportion (25.0%-54.5%) of BCLC stage B patients in prior studies, whose prognosis is relatively better than the BCLC stage C patients in our research.

TACE demonstrates promising efficacy in advanced HCC by inducing tumor necrosis, releasing antigens, and enhancing CD8+ T cell immune response.[5,22] The hypoxic environment may upregulate angiogenic factors and increase sensitivity to targeted drugs. Triple therapy combining TACE, targeted therapy, and PD-(L)1 inhibitors can remodel the immune microenvironment, inhibit angiogenesis, and restore anti-tumor activity.[23] This multi-target strategy compensates for local limitations of TACE and distant metastasis management, reduces drug resistance, and improves patient survival. However, challenges persist: potential treatment-related toxicity, the need for individualized screening, and the requirement for long-term efficacy validation through prospective studies. These limitations guide future research and underscore the importance of a critical, cautious approach in clinical applications.

In this study, patients with lung metastases from liver cancer received more than two distinct tyrosine kinase inhibitors (TKIs) such as sorafenib and lenvatinib. Although recent studies suggested comparable survival rates between lenvatinib and sorafenib,[24,25] the inconsistencies in treatment outcomes warrant further investigation. As a retrospective study, the research encountered inherent methodological challenges: a restricted sample size and treatment regimens determined by physician and patient preferences, which inevitably introduced selection bias. The study exclusively enrolled Chinese patients, predominantly infected with hepatitis B virus, potentially limiting its broader applicability. As a two-center investigation, the limited number of patients meeting molecular targeted therapy and immune checkpoint inhibitor criteria resulted in uneven sample sizes, potentially weakening statistical power despite employing standardized inverse probability of treatment weighting. These constraints underscore the critical need for prospective, multicenter studies targeting diverse etiologies and populations to validate and expand upon these preliminary findings, ultimately improving personalized treatment strategies for liver cancer patients with lung metastases.

Conclusion

In this study, we observed that TACE, MTT and (PD-[L]1) provides a better prognosis for patients with liver cancer accompanied by lung metastases compared to MTT and (PD-[L]1). Furthermore, there were no significant differences in adverse reactions between the two treatment modalities. These findings may offer valuable insights for future research on treatment strategies for patients with liver cancer and lung metastases. TACE, MTT and (PD-[L]1) is expected to emerge as a new clinical first-line treatment option for this patient population.

Abbreviations

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; MTT, molecular targeted treatments; PD-[L]1, programmed death-(ligand)1 inhibitors; BCLC, Barcelona Clinic Liver Cancer; SIPTW, Stable Inverse Probability of Treatment Weighting; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Data Sharing Statement

Data for this study can be reasonably obtained by contacting the corresponding authors, Xiaoli Yang (Email: 344920646@qq.com).

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Disclosure

The authors report no conflicts of interest in this work.

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