Journal of Hepatocellular Carcinoma Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Efficacy and Safety of Transcatheter Arterial Chemoembolization Combined with Lenvatinib Plus Anti-PD-1 Inhibitors for Hepatocellular Carcinoma Patients with Extrahepatic Metastases: A Multicenter Retrospective Study

De-Yi Liu[1,*], Yi-Nan Li[1,*], Jia-Yi Wu[1,2], Zhen-Xin Zeng[1], Yang-Kai Fu[1], Han Li[1], Xiang-Ye Ou[1], Zhi-Bo Zhang[3], Shuang-Jia Wang[4], Jun-Yi Wu[1,2], Mao-Lin Yan[1,2]

[1]Shengli Clinical Medical College of Fujian Medical University, Fuzhou, Fujian Province, People's Republic of China; [2]Department of Hepatobiliary Pancreatic Surgery, Fujian Provincial Hospital, Fuzhou, Fujian Province, People's Republic of China; [3]Department of Hepatopancreatobiliary Surgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian Province, People's Republic of China; [4]Department of Hepato-Biliary-Pancreatic and Vascular Surgery, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jun-Yi Wu; Mao-Lin Yan, The Shengli Clinical Medical College of Fujian Medical University, Department of Hepatobiliary Pancreatic Surgery, Fujian Provincial Hospital, Dongjie Road 134, Fuzhou, Fujian Province, 350001, People's Republic of China, Tel +86 591-88217130; +86 591-88217140, Fax +86 591-87557768, Email 1248087863@qq.com; yanmaolin74@163.com

Purpose: The prognosis of hepatocellular carcinoma (HCC) with extrahepatic metastases (EM) is poor. The efficacy and safety of transcatheter arterial chemoembolization combined with lenvatinib plus anti-programmed cell death 1 inhibitors (triple therapy) for HCC with EM remains unclear. In this study, we aimed to determine the efficacy and safety of triple therapy in HCC patients with EM.

Patients and Methods: This study retrospectively reviewed HCC patients with EM who received triple therapy and analyzed their survival rate using the Kaplan–Meier method. Univariate prognostic analysis of each data point was performed using the Log rank test, and multivariate prognostic analysis was performed using the Cox proportional risk regression model.

Results: Among 60 HCC patients with EM who underwent triple therapy, the most common sites of metastasis were as follows (in descending order): the lungs (n=27), lymph nodes (n=22), and bones (n=10). After triple therapy, the median progression-free survival and median overall survival were 6 and 18.63 months, respectively. The 6-month, 1-year, and 2-year cumulative survival rates were 87.7%, 68.6%, and 26.8%, respectively. In the multivariate analysis, neutrophil-to-lymphocyte ratio (NLR) ≥4 and alpha-fetoprotein (AFP) level ≥400 ng/mL were independently associated with overall survival.

Conclusion: Our findings revealed that triple therapy is an effective, well-tolerated regimen for HCC patients with EM. AFP level and NLR are prognostic risk factors for triple therapy in this patient population.

Keywords: hepatocellular carcinoma, transcatheter arterial chemoembolization, lenvatinib, alpha-fetoprotein, neutrophil-to-lymphocyte ratio

Introduction

Hepatocellular carcinoma (HCC) is an aggressive malignancy and the second leading cause of cancer-related mortality globally.[1] Surgical resection is the most effective treatment for patients with HCC and offers the possibility of cure and long-term survival.[2,3] However, most patients are diagnosed in advanced stages and often miss the opportunity for surgical intervention, resulting in an unsatisfactory survival.[1,3] Based on accumulated data, 10–37%[4–8] of patients with

Received: 1 June 2024
Accepted: 31 October 2024
Published: 25 November 2024

unresectable HCC present with extrahepatic metastases (EM). With the increased rates of disease screening and improvements in imaging techniques, the detection of HCC with EM has improved.

HCC with EM has a negative prognostic impact, resulting in unsatisfactory long-term survival. In HCC patients with EM, the median overall survival (mOS) ranges between 4.9 and 10.3 months.[4,6–12] In recent years, the success of several clinical studies on systemic therapy for patients with advanced HCC has resulted in improved survival prognosis. He et al[13] found that FOLFOX chemotherapy combined with lenvatinib and toripalimab could elicit promising antitumor activity and manageable toxicity in HCC patients with EM. The median progression-free survival (mPFS) was 9.73 months, the mOS was 14.63 months, and the objective response rate (ORR) was 43.3%. According to Sun et al,[14] combined FOLFOX4 with all-trans retinoic acid showed favorable antitumor activity and safety in HCC patients with EM, with an mPFS reaching 7.1 months, mOS of 16.2 months, and ORR of 24.5%. Kudo et al[15] found that in patients with advanced HCC, the overall survival rate of lenvatinib was non-inferior to that of sorafenib in untreated advanced HCC, with an mPFS of 7.3 months and mOS of 11.5 months in the subgroup with macroscopic portal vein invasion, extrahepatic spread, or both. Furthermore, several clinical studies[16–20] have assessed potential systemic therapies in patients with EM. However, data disclosure for subgroup analysis of EM remains limited, reducing the potential for guiding systemic therapy.

Several retrospective studies[7,21,22] have found that in HCC patients with EM, the cause of death in most patients was due to liver failure owing to further deterioration of the primary intrahepatic lesion rather than due to metastatic lesions, thereby suggesting the need to treat the primary intrahepatic lesion more aggressively. Yoo et al[21] found that in HCC patients with EM, Transcatheter arterial chemoembolization (TACE) offered a greater survival benefit than conservative treatment. Furthermore, the authors found that sorafenib combined with TACE may provide an independent survival benefit in such patients. However, its current efficacy remains unsatisfactory, and the prognosis of HCC with EM needs to be further improved.

According to Guan et al,[23] hepatic arterial infusion chemotherapy can improve the efficacy of lenvatinib and anti-programmed cell death 1 (PD-1) inhibitors therapy in HCC patients with EM, with an mPFS reaching 8.0 months, mOS of 27.0 months. Additionally, TACE combined with lenvatinib and PD-1 inhibitors can prolong the survival of patients with unresectable HCC and induce deeper remission.[24–26] However, the therapeutic potential of triple therapy in HCC patients with EM remains unclear. Accordingly, the objective of the current study was to evaluate the efficacy and safety of triple therapy in HCC patients with EM.

Materials and Methods

Patients

In total, 60 patients with a diagnosis of HCC with EM from three high-volume institutions in China (Fujian Provincial Hospital, First Affiliated Hospital of Fujian Medical University, and First Affiliated Hospital of Xiamen University) were included. Inclusion criteria were as follows: 1) patients with a primary diagnosis of HCC with EM who underwent triple therapy as first-line therapy; 2) aged 18–75 years; 3) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 or 1; 4) Child-Pugh class A or B; and 5) at least one measurable lesion according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[27] Exclusion criteria were as follows: 1) previous radical resection, radio-frequency, radiation, or other forms of antitumor treatment; 2) a history of other primary malignancies; 3) severe medical comorbidities (eg, severe heart disease, severe kidney disease, or severe pulmonary disease); and 4) incomplete data.

The diagnosis of HCC was based on the typical imaging features or liver biopsy pathology (when necessary). EM was diagnosed using computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, positron emission tomography-computed tomography (PET-CT), and biopsy of metastatic lesions. Baseline data, medical history, laboratory results, radiological results, and histological results were retrospectively collected from all patients.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Fujian Provincial Hospital (No: K2024-09-111). Informed consent was obtained from all patients for their data to be used for research purposes.

Treatment Procedure

The targeted drugs included oral lenvatinib (8 mg for body weight <60 kg or 12 mg for body weight ≥60 kg once daily). Immunotherapeutic drugs included intravenous carelizumab (200 mg once every 3 weeks), sintilimab (200 mg once every 3 weeks), tislelizumab (200 mg once every 3 weeks), toripalimab (240 mg once every 3 weeks), pembrolizumab (15 mg/kg once every 3 weeks), and penpulimab (200 mg once every 3 weeks). TACE was performed under sterile conditions via the right femoral artery using the Seldinger technique. After identifying the tumor-feeding arteries, the radiologist mixed iodized oil and pirarubicin and slowly injected the solution through a microcatheter into the tumor-feeding artery. Gelatin sponge particles were then injected until complete stasis of the tumor arterial blood flow was achieved. The decision to proceed with or repeat TACE depended on the recommendations of the multidisciplinary team. Treatment with lenvatinib and anti-PD-1 inhibitors was suspended for three days before and after TACE. All patients with hepatitis B virus (HBV) infection received oral antiviral treatment (entecavir or tenofovir).

Patients with resectable HCC were identified based on the following criteria: 1) R0 resection with sufficient preservation of residual liver function and volume was achievable; 2) ECOG-PS score of 0–1; 3) Child-Pugh class A; 4) EM lesions has achieved radiological complete responseand can be removed intact during surgery and could be removed intact during surgery; 5) no contraindications to salvage hepatectomy.

The multidisciplinary team was consulted to decide the course of second-line therapy when disease progression was detected.

Efficacy and Safety Assessments

According to the mRECIST criteria,[27] tumor response was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The ORR was calculated by adding the CR and PR rates, whereas the disease control rate (DCR) was obtained by adding the CR, PR, and SD rates. Treatment-related adverse events (TRAEs) were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[28]

Follow-Up

All HCC patients with EM who received triple therapy were followed up every 4–8 weeks to collect survival data, physical examination results, radiological data (chest enhanced CT, abdominal enhanced CT, and/or MRI), alpha-fetoprotein (AFP) level, and laboratory data. Disease progression was defined as an increase in the intrahepatic tumor burden or the appearance of new arterial-enhancing lesions documented in radiological reports. The primary endpoint of this study was overall survival (OS), and the secondary endpoints were progression-free survival (PFS) and TRAEs. OS was defined as the period from treatment initiation to either death or the latest follow-up. PFS was defined as the period from treatment initiation to the first radiologically confirmed progression, death, or latest follow-up. All patients were followed up until death or the end of December 2023.

Statistical Analysis

Continuous data are expressed as mean (standard deviation) or median (range), as appropriate. Categorical data are expressed as numbers (percentages) and compared using the chi-square test or Fisher's exact test. PFS and OS were plotted using the Kaplan–Meier method for survival curves and compared using the Log rank test. Univariate analysis was performed to determine the risk factors for PFS and OS, and the variables that were significant in the univariate analyses were introduced into Cox proportional risk regression models for multivariate analysis to identify independent risk factors that affect prognosis. All P-values were two-tailed, and values <0.05 indicated that the difference was statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

From July 2019 to January 2023, 60 patients diagnosed with HCC and EM who received triple therapy at three high-volume institutions in China were enrolled in this study. According to Table 1, the median patient age was 57 years (range: 26–76 years), and the study population included 47 males and 13 females. HBV infection was observed in 54 (90.0%) patients. Regarding the hepatic functional reserve, 49 patients (81.7%) were Child-Pugh grade A and 11 (18.3%) were Child-Pugh grade B. Regarding tumor markers, 39 (65.0%) patients had AFP levels of > 400 ng/mL. Regarding tumor burden, 47 (78.3%) patients had multiple intrahepatic tumors; 33 (55.0%) patients had tumors with a maximum diameter >10 cm; and 33 (55.0%) patients had concomitant macrovascular invasion.

Metastatic Sites

In this study, 27 patients (45.0%) presented with lung metastasis, which was the most common site of metastasis. The other major metastatic sites were lymph nodes in 22 patients (36.7%), bones in 10 patients (16.7%), and adrenal glands in 6 (10.0%). Diaphragm metastases were detected in 2 patients (3.3%), and metastases in the brain, pancreas, mesentery, gallbladder, peritoneum, and abdominal wall were detected in 1 patient each. EM was detected in two or more organs in 10 patients (15.5%) (Table 2).

Triple Therapy

All patients received the triple therapy as first-line treatment. The median number of TACE treatment cycles was 2 times (range, 1–8 times), the median duration of lenvatinib treatment was 12.1 months (range, 0.9–32.0 months). The median number of cycles of PD-1 inhibitors received was 10 cycles (range, 1–21 cycles).

Tumor Response Assessment

We assessed the degree of tumor response in the intrahepatic lesions of patients receiving triple therapy. CR was achieved in 3 (5%) patients, PR in 30 (50%) patients, SD in 18 (30%) patients, and PD in 9 (15%) patients. The ORR was 55%, and the DCR was 85% (Table 3).

Table 1 Characteristics of Metastatic HCC

Characteristic	n = 60
Age (median, range)	57 (26–76)
(<65/≥65)	41/19
Sex (male/female)	47/13
ECOG PS (0/1)	44/16
Child-Pugh grade (A/B)	49/11
HBsAg (positive/negative)	54/6
Pre-treatment Tbil, μmol/L (<34/≥34)	57/3
Pre-treatment ALB, g/L (<35/≥35)	17/43
Pre-treatment ALT, U/L (<40/≥40)	33/27
Pre-treatment AST, U/L (<40/≥40)	19/41
WBC, /L (<6.0*10^9/≥6.0*10^9)	23/37
NLR (<4/≥4)	41/19
Pre-treatment AFP, ng/mL (<400/≥400)	21/39
Tumor number (solitary/multiple)	13/47
Maximum tumor size, cm (<10/≥10)	27/33
Macrovascular invasion (positive/negative)	33/27
Anti-PD-1 Inhibitors (carelizumab/sintilimab/tislelizumab/toripalimab/pembrolizumab/penpulimab)	35/11/6/4/2/2

Abbreviations: HCC, Hepatocellular carcinoma; ECOG-PS, Eastern Cooperative Oncology Group performance status; HBsAg, hepatitis B surface antigen; Tbil, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell, NLR, neutrophil-to-lymphocyte ratio; AFP, alpha fetoprotein.

Table 2 Site of Extrahepatic Metastases in 60 Metastatic HCC

Sites	Patients (n=60), n (%)
Lung	27 (45.0)
Lymph node	22 (36.7)
Bone	10 (16.7)
Adrenal gland	6 (10.0)
Diaphragm	2 (3.3)
Brain	1 (1.7)
Pancreas	1 (1.7)
Mesentery	1 (1.7)
Gallbladder	1 (1.7)
Peritoneum	1 (1.7)
Abdominal wall	1 (1.7)
Metastasis to multiples sites	10 (15.5)

Table 3 Best Intrahepatic Tumor Response According to the mRECIST

Best Response, n (%)	
Complete response	3 (5)
Partial response	30 (50)
Stable disease	18 (30)
Progressive disease	9 (15)
Objective response rate, n (%)	33 (55)
Disease control rate, n (%)	51 (85)

Prognosis of HCC with EM

Figure 1 presents the Kaplan–Meier curves for all patients considering the follow-up data cut-off (December 2023). The mPFS was 6.0 months (range: 0.5–34 months), and the mOS was 18.63 months (range: 1.0–34 months), with a 6-month survival rate of 87.7%, a 1-year survival rate of 68.6%, and a 2-year survival rate of 26.8%. Survival data did not differ between patients with metastases at different sites (overall comparison P = 0.747).

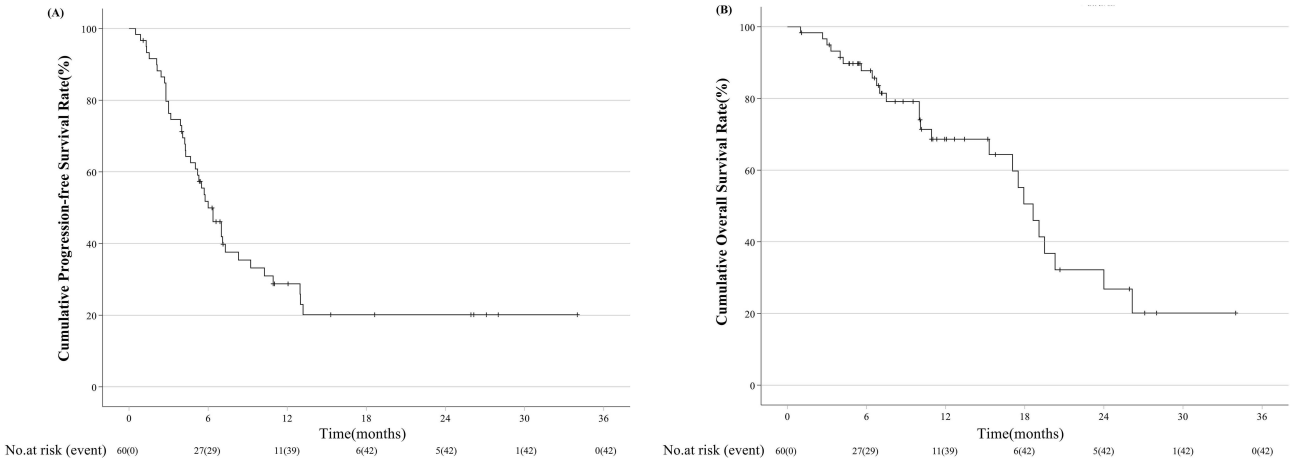

Figure 1 Kaplan-Meier curves of PFS and OS in HCC with EM. (**A**) PFS of HCC with EM. (**B**) OS of HCC with EM.
Abbreviations: PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma; EM, extrahepatic metastases.

Risk Factor Analysis of HCC with EM

The univariate analysis revealed that sex (female, P = 0.002), baseline AFP level (≥400 ng/mL, P = 0.006), and maximum tumor diameter (≥10 cm, P = 0.034) were significant risk factors that could negatively impact PFS. Furthermore, multivariate analysis confirmed that sex (female, P = 0.019, hazard ratio [HR] = 2.439, 95% confidence interval [CI] = 1.156-5.155) and baseline AFP level (≥400 ng/mL, P = 0.014, HR = 2.523, 95% CI = 1.203–5.291) were independent risk factors for PFS (Table 4).

For OS, the univariate analysis showed that neutrophil to lymphocyte ratio (NLR) (≥4, P = 0.013), AFP level (≥400 ng/mL, P = 0.039), and macrovascular invasion (positive, P = 0.023) were significant risk factors that could adversely impact OS. The multivariate analysis confirmed that NLR (≥4, P = 0.003, HR = 3.773, 95% CI = 1.569–9.074) and AFP level (≥400 ng/mL, P = 0.046, HR = 2.889, 95% CI = 1.021–8.180) were independent risk factors for OS (Table 5).

Salvage Hepatectomy

Of the 60 HCC patients with EM, 11 patients met the resectability criteria after triple therapy, and 7 underwent salvage hepatectomy, all of whom had localized lymph node metastases of HCC. The postoperative pathological results revealed a major pathological response (MPR) in three patients. Patients who underwent salvage surgery after reaching the resection criteria did not show a statistically significant difference in PFS and OS when compared with those in the non-surgery group (P = 0.360 and 0.382, respectively) (Figure 2).

Table 4 Univariate and Multivariate Analysis of Prognostic Factors for PFS

PFS						
Variables	**Univariate Analysis**			**Multivariate Analysis**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Sex (female)	3.151	1.533-6.478	0.002	2.439	1.156-5.155	0.019
Age (≥65), years	0.856	0.444–1.652	0.643			
ECOG-PS (1)	1.126	0.798–1.589	0.500			
Child-Pugh class (B/C)	0.852	0.356–2.038	0.719			
HBsAg (positive)	0.787	0.309–2.006	0.617			
Tbil (≥34), μmol/L	1.007	0.242–4.188	0.992			
ALB (≥35), g/L	0.802	0.409–1.573	0.521			
ALT (≥40), IU/L	0.825	0.444–1.532	0.542			
AST (≥40), IU/L	1.189	0.623–2.268	0.600			
WBC (≥6.0*10^9),/L	1.125	0.602–2.102	0.712			
NLR (≥4)	1.730	0.914–3.275	0.092			
Pre-treatment AFP (≥400), ng/mL	2.630	1.321–5.233	0.006	2.523	1.203–5.291	0.014
Tumor number (single)	0.856	0.409–1.792	0.679			
Maximum tumor size (≥10), cm	1.984	1.053–3.740	0.034	1.241	0.622–2.477	0.540
Macrovascular invasion (positive)	1.586	0.854–2.946	0.144			
Salvage Hepatectomy (yes)	1.609	0.572–4.523	0.367			
Site of extrahepatic metastasis						
Lungs (yes)	0.987	0.536–1.820	0.967			
Lymph nodes (yes)	0.599	0.317–1.132	0.115			
Bones (yes)	1.814	0.888–3.705	0.102			
Metastasis to multiples sites (yes)	0.750	0.332–1.697	0.490			

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; HBsAg, hepatitis B surface antigen; Tbil, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell, NLR, neutrophil-to-lymphocyte ratio; AFP, alpha fetoprotein.

Table 5 Univariate and Multivariate Analysis of Prognostic Factors for OS

OS						
Variables	**Univariate Analysis**			**Multivariate Analysis**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Sex (female)	2.119	0.753-5.960	0.155			
Age (≥65), years	1.058	0.454–2.462	0.896			
ECOG-PS (1)	1.090	0.406–2.924	0.864			
Child-Pugh class (B/C)	1.003	0.222–4.531	0.997			
HBsAg (positive)	0.795	0.271–2.335	0.677			
Tbil (≥34), μmol/L	1.698	0.222–12.989	0.610			
ALB (≥35), g/L	0.854	0.355–2.052	0.724			
ALT (≥40), IU/L	0.849	0.378–1.907	0.692			
AST (≥40), IU/L	1.628	0.675–3.930	0.278			
WBC (≥6.0*10^9),/L	1.112	0.477–2.592	0.806			
NLR (≥4)	2.819	1.242–6.399	0.013	3.773	1.569–9.074	0.003
Pre-treatment AFP (≥400), ng/mL	2.821	1.055–7.544	0.039	2.889	1.021–8.180	0.046
Tumor number (single)	0.993	0.391–2.525	0.989			
Maximum tumor size (≥10), cm	1.960	0.864–4.450	0.107			
Macrovascular invasion (positive)	2.688	1.149–6.292	0.023	2.388	0.981–5.812	0.055
Salvage Hepatectomy (yes)	1.887	0.443–8.035	0.390			
Site of extrahepatic metastasis						
Lungs (yes)	1.258	0.567–2.792	0.572			
Lymph nodes (yes)	0.863	0.387–1.926	0.720			
Bones (yes)	1.705	0.623–4.667	0.299			
Metastasis to multiples sites (yes)	0.857	0.249–2.950	0.807			

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; HBsAg, hepatitis B surface antigen; Tbil, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell, NLR, neutrophil-to-lymphocyte ratio; AFP, alpha fetoprotein.

Safety

All TRAEs that were monitored or followed are shown in Table 6. Of the 60 patients who received triple therapy, 49 (81.6%) experienced TRAEs. The most common symptoms were abnormal liver function (58.3%), fatigue (41.6%), and weight loss (30.0%). Seven patients (11.6%) experienced grade 3/4 TRAEs, and no treatment-related deaths occurred during the follow-up period.

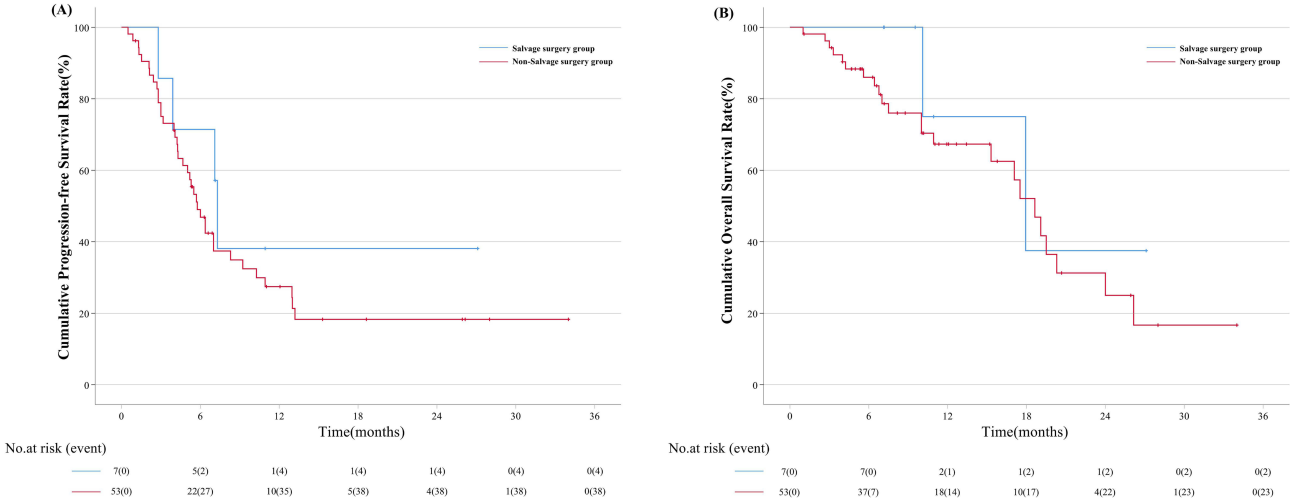

Figure 2 Kaplan-Meier curves of PFS and OS for HCC with EM who underwent salvage or non-salvage surgery. (**A**) PFS of HCC with EM. (**B**) OS of HCC with EM.
Abbreviations: PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma; EM, extrahepatic metastases.

Table 6 Treatment-Related Adverse Events Occurred in ≥10% of Total Patients

Adverse Events	Any Grade, n (%)	Grade 3/4, n (%)
Total	49(81.6)	7(11.6)
Abnormal liver function	35(58.3)	2(3.3)
Fatigue	25(41.6)	
Weight loss	18(30.0)	
Diarrhea	15(25.0)	
Decreased hemoglobin	15(25.0)	
Decreased appetite	12(20.0)	
Hand-foot syndrome	11(18.3)	
Hypertension	10(16.7)	1(1.7)
Rash	10(16.7)	1(1.7)
Hypothyroidism	8(13.3)	
Abdominal pain	8(13.3)	1(1.7)
Thrombocytopenia	7(11.7)	1(1.7)
Proteinuria	6(10)	1(1.7)

Discussion

In our study of 60 HCC patients with EM undergoing triple therapy, the common EM sites were lung, lymph nodes, bone, and adrenal gland, aligning with previous studies.[7,8,21,29] After treatment, the median PFS was 6.0 months, and the OS rates at 6 months, 1 year, and 2 years were 87.7%, 68.6%, and 26.8%, with a median OS of 18.63 months. During follow-up, 81.6% of patients had treatment-related adverse events (TRAEs), with 11.6% being grade 3/4; all were manageable with no occurrence of treatment-related deaths.

The clinical prognosis of HCC patients with EM is extremely poor, with only a few clinical studies exploring optimal treatments. In recent years, with the rapid progress in local therapy combined with tyrosine kinase inhibitors plus anti-PD -1 inhibitors therapy, improvements in long-term survival have been attained for patients with intermediate and advanced HCC; however, there are few reports on the application of this therapy in HCC patients with EM. To the best of our knowledge, this study is the first to investigate the prognosis of HCC with EM under triple therapy, achieving the longest OS reported to date (mOS, 18.63 months). After triple therapy, 11 (11.7%) patients met the resection criteria, of whom 7 with localized lymph node metastases underwent salvage hepatectomy, and the postoperative pathology showed a MPR in 3 patients.

In this study, the multivariate analysis revealed that sex and AFP were significant determinants of progression, and NLR and AFP were significant determinants of survival after the initial diagnosis of EM. AFP is a tumor biomarker for HCC and is associated with increased cell proliferation, angiogenesis, and cellular resistance to tumor necrosis factor-associated apoptosis. Higher AFP levels have also been associated with a more aggressive HCC phenotype, and numerous studies have reported that high AFP levels are a marker of tumor progression and poor prognosis.[30–33] Consistently, the present study found that high AFP levels substantially impacted the prognosis of HCC patients with EM after triple therapy.

Notably, we found that high NLR was an independent predictor of survival in HCC with EM. Various markers of systemic inflammatory response have been explored for their roles in cancer prognosis, and the NLR is one of the simplest markers of inflammation and has been associated with poor prognosis in various types of cancer.[34] The precise link between high NLR and poor prognosis has not been fully elucidated, and several studies have confirmed that NLR promotes tumor progression and metastasis through multiple pathways. As a possible explanation, high neutrophil levels may lead to HCC with a growth advantage by increasing pro-angiogenic factors, and relative lymphopenia leads to a weaker lymphocyte-mediated immune response to tumors, thereby resulting in increased EM and decreased survival in patients with HCC.[34,35] Thus, a high NLR is strongly associated with poor prognosis in HCC patients with EM receiving triple therapy.

Macrovascular invasion is a well-known predictor of poor survival in patients with HCC, and patients with coexisting macrovascular invasion and EM tend to have larger tumor burdens, more severe cirrhosis, and poorer performance statuses. However, in the current study, macrovascular invasion was not identified as a risk factor. In our previous study,[36] we reported that in patients with VP4 grade portal vein thrombus, TACE and lenvatinib plus anti-PD-1 inhibitors could be an effective conversion strategy for unresectable HCC with Vp4, given the presence of deeper tumor response rates and improved prognosis in these patients. Accordingly, triple therapy can be effective in treating HCC with macrovascular invasion, which may explain why macrovascular invasion does not affect prognosis. Although the prognosis of patients with both EM and macrovascular invasion is unfavorable, triple therapy may be an effective treatment option.

It is worth noting that of these 60 patients, 7 underwent salvage hepatectomy. In all 7 patients, metastatic sites were localized lymph node metastases, and lymph node dissection was performed simultaneously during the course of salvage hepatectomy. Kobayashi et al[37] retrospectively analyzed the data of 18 patients who underwent hepatectomy and metastatic lymph node dissection, concluding that elective lymph node dissection may provide a survival benefit, especially in patients with only a single lymph node metastasis. However, only a few patients met the criteria for surgical treatment owing to poor hepatic functional reserve and intrahepatic tumor staging. In the current study, triple therapy enabled some patients with HCC and lymph node metastases to undergo salvage hepatectomy. Although our prognostic univariate analysis revealed that subsequent treatment with salvage hepatectomy did not significantly improve the PFS and OS of the patients, we believe that this is a bias, which can be attributed to the small number of patients who underwent salvage hepatectomy after triple therapy, and that the efficacy of salvage surgery needs to be further explored.

This study had some limitations. First, this was a retrospective analysis with a small sample size and limited follow-up time. Thus, further long-term randomized controlled trials are required to confirm our findings. However, to our knowledge, this is the first study to analyze HCC with EM treated with triple therapy. Second, our study did not have a control group; however, we had a better long-term prognosis than reported previously. Third, the choice and duration of anti-PD-1 inhibitors were inconsistent in our study. Although there is no evidence in the literature to suggest that different anti-PD-1 inhibitors exert distinct effects, this could impact patient prognosis. Fourth, most patients in this study had HBV-related HCC, and our findings may warrant judicious application in HCC patients with EM of other etiologies.

Conclusions

In conclusion, our study showed that HCC patients with EM treated with triple therapy had promising survival outcomes. AFP level and NLR are prognostic risk factors for triple therapy in these patients.

Abbreviation

AFP, alpha-fetoprotein; CR, complete response; CT, computed tomography; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EM, extrahepatic metastases; HCC, hepatocellular carcinoma; mPFS, median progression-free survival; MPR, major pathological response; mOS, median overall survival; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; NLR, neutrophil-to-lymphocyte ratio; ORR, objective response rate; PET-CT, positron emission tomography-computed tomography; PD-1, programmed cell death 1; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transcatheter arterial chemoembolization; TRAEs, treatment-related adverse events.

Data Sharing Statement

The data supporting the findings of this study are available within the article.

Acknowledgments

We thank all the staff of the participating hospitals for their efforts, as well as all of the patients for their participation. Mao-lin Yan and Jun-yi Wu should be considered joint corresponding author.

Funding

This study was funded by the Medical Innovation Project of Health and Family Planning Commission of Fujian Province (Grant number: 2022CXA002); the Fujian Provincial Department of Finance (Grant number: 2023GGA006); the Fujian Provincial Health Technology Project (Grant number: 2023CXA005) and the Natural Science Foundation of Fujian Province (Grant number: 2022J011021).

Disclosure

All authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424. doi:10.3322/caac.21492
2. Roayaie S, Jibara G, Tabrizian P, et al. The role of hepatic resection in the treatment of hepatocellular cancer. *Hepatology*. 2015;62(2):440–451. doi:10.1002/hep.27745
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
4. Natsuizaka M, Omura T, Akaike T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol*. 2005;20(11):1781–1787. doi:10.1111/j.1440-1746.2005.03919.x
5. Hsu CY, Liu PH, Ho SY, et al. Metastasis in patients with hepatocellular carcinoma: prevalence, determinants, prognostic impact and ability to improve the Barcelona clinic liver cancer system. *Liver Int*. 2018;38(10):1803–1811. doi:10.1111/liv.13748
6. Xia F, Wu L, Lau WY, et al. Positive lymph node metastasis has a marked impact on the long-term survival of patients with hepatocellular carcinoma with extrahepatic metastasis. *PLoS One*. 2014;9(4):e95889. doi:10.1371/journal.pone.0095889
7. Uka K, Aikata H, Takaki S, et al. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol*. 2007;13(3):414–420. doi:10.3748/wjg.v13.i3.414
8. Uchino K, Tateishi R, Shiina S, et al. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. *Cancer*. 2011;117(19):4475–4483. doi:10.1002/cncr.25960
9. Aino H, Sumie S, Niizeki T, et al. Clinical characteristics and prognostic factors for advanced hepatocellular carcinoma with extrahepatic metastasis. *Mol Clin Oncol*. 2014;2(3):393–398. doi:10.3892/mco.2014.259
10. Nakano M, Tanaka M, Kuromatsu R, et al.; Kurume Liver Cancer Study Group of Japan. Sorafenib for the treatment of advanced hepatocellular carcinoma with extrahepatic metastasis: a prospective multicenter cohort study. *Cancer Med*. 2015;4(12):1836–1843. doi:10.1002/cam4.548
11. Chan KM, Yu MC, Wu TJ, et al. Efficacy of surgical resection in management of isolated extrahepatic metastases of hepatocellular carcinoma. *World J Gastroenterol*. 2009;15(43):5481–5488. doi:10.3748/wjg.15.5481
12. Aino H, Sumie S, Niizeki T, et al. The systemic inflammatory response as a prognostic factor for advanced hepatocellular carcinoma with extrahepatic metastasis. *Mol Clin Oncol*. 2016;5(1):83–88. doi:10.3892/mco.2016.879
13. He M, Huang Y, Du Z, et al. Lenvatinib, toripalimab plus FOLFOX chemotherapy in hepatocellular carcinoma patients with extrahepatic metastasis: a biomolecular exploratory, phase II trial (LTSC). *Clin Cancer Res*. 2023;29(24):5104–5115. doi:10.1158/1078-0432.CCR-23-0060
14. Sun J, Mao F, Liu C, et al. Combined FOLFOX4 with all-trans retinoic acid versus FOLFOX4 with placebo in treatment of advanced hepatocellular carcinoma with extrahepatic metastasis: a randomized, double-blind comparative study. *Signal Transduct Target Ther*. 2023;8(1):368. doi:10.1038/s41392-023-01604-3
15. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1
16. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
17. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–390. doi:10.1056/NEJMoa0708857
18. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56–66. doi:10.1016/S0140-6736(16)32453-9
19. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282–296. doi:10.1016/S1470-2045(18)30937-9
20. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54–63. doi:10.1056/NEJMoa1717002
21. Yoo DJ, Kim KM, Jin YJ, et al. Clinical outcome of 251 patients with extrahepatic metastasis at initial diagnosis of hepatocellular carcinoma: does transarterial chemoembolization improve survival in these patients? *J Gastroenterol Hepatol*. 2011;26(1):145–154. doi:10.1111/j.1440-1746.2010.06341.x
22. Lee JI, Kim JK, Kim DY, et al. Prognosis of hepatocellular carcinoma patients with extrahepatic metastasis and the controllability of intrahepatic lesions. *Clin Exp Metastasis*. 2014;31(4):475–482. doi:10.1007/s10585-014-9641-x
23. Guan R, Zhang N, Deng M, et al. Patients with hepatocellular carcinoma extrahepatic metastases can benefit from hepatic arterial infusion chemotherapy combined with lenvatinib plus programmed death-1 inhibitors. *Int J Surg*. 2024. doi:10.1097/JS9.0000000000001378
24. Wu JY, Wu JY, Li YN, et al. Lenvatinib combined with anti-PD-1 antibodies plus transcatheter arterial chemoembolization for neoadjuvant treatment of resectable hepatocellular carcinoma with high risk of recurrence: a multicenter retrospective study. *Front Oncol*. 2022;12:985380. doi:10.3389/fonc.2022.985380

25. Wu JY, Zhang ZB, Zhou JY, et al. Outcomes of salvage surgery for initially unresectable hepatocellular carcinoma converted by transcatheter arterial chemoembolization combined with lenvatinib plus anti-PD-1 antibodies: a multicenter retrospective study. *Liv Cancer*. 2022;12(3):229–237. doi:10.1159/000528356
26. Wu JY, Yin ZY, Bai YN, et al. Lenvatinib combined with anti-PD-1 antibodies plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: a multicenter retrospective study. *J Hepatocell Carcinoma*. 2021;8:1233–1240. doi:10.2147/JHC.S332420
27. Llovet JM, Lencioni R. mRECIST for HCC: performance and novel refinements. *J Hepatol*. 2020;72(2):288–306. doi:10.1016/j.jhep.2019.09.026
28. US Department of Health and Human Services. Common terminology criteria for adverse events version 5.0; Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed November 06, 2024.
29. Wu W, He X, Andayani D, et al. Pattern of distant extrahepatic metastases in primary liver cancer: a SEER based study. *J Cancer*. 2017;8(12):2312–2318. doi:10.7150/jca.19056
30. Chan MY, She WH, Dai WC, et al. Prognostic value of preoperative alpha-fetoprotein (AFP) level in patients receiving curative hepatectomy- an analysis of 1182 patients in Hong Kong. *Transl Gastroenterol Hepatol*. 2019;4:52. doi:10.21037/tgh.2019.06.07
31. Takayasu K, Arii S, Ikai I, et al.; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology*. 2006;131(2):461–469. doi:10.1053/j.gastro.2006.05.021
32. Tangkijvanich P, Anukulkarnkusol N, Suwangool P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol*. 2000;31(4):302–308. doi:10.1097/00004836-200012000-00007
33. Nakazawa T, Hidaka H, Takada J, et al. Early increase in α-fetoprotein for predicting unfavorable clinical outcomes in patients with advanced hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol*. 2013;25(6):683–689. doi:10.1097/MEG.0b013e32835d913b
34. Xiao WK, Chen D, Li SQ, Fu SJ, Peng BG, Liang LJ. Prognostic significance of neutrophil-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. *BMC Cancer*. 2014;14(1):117. doi:10.1186/1471-2407-14-117
35. Gong Y, Koh DR. Neutrophils promote inflammatory angiogenesis via release of preformed VEGF in an in vivo corneal model. *Cell Tissue Res*. 2010;339(2):437–448. doi:10.1007/s00441-009-0908-5
36. Li SQ, Wu JY, Wu JY, et al. Transarterial chemoembolization plus lenvatinib and PD-1 inhibitors for hepatocellular carcinoma with main trunk portal vein tumor thrombus: a multicenter retrospective study. *J Hepatocell Carcinoma*. 2023;10:1799–1811. doi:10.2147/JHC.S428980
37. Kobayashi S, Takahashi S, Kato Y, et al. Surgical treatment of lymph node metastases from hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci*. 2011;18(4):559–566. doi:10.1007/s00534-011-0372-y