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ORIGINAL RESEARCH

Sintilimab Plus Lenvatinib with or Without Radiotherapy for Advanced Hepatocellular Carcinoma with Pulmonary Metastasis

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Background: Hepatocellular carcinoma (HCC) with pulmonary metastasis (PM) significantly worsens prognosis, and current treatment options remain limited.

Methods: A retrospective study was conducted on HCC patients treated with sintilimab combined with lenvatinib at three hospitals in China between 2020 and 2021. Progression-free survival (PFS), overall survival (OS), and tumor response based on RECIST 1.1 were compared. Treatment safety was assessed by analyzing treatment-related adverse events (TRAEs).

Results: Among 144 patients, 105 received sintilimab combined with lenvatinib (S+L), while 39 were treated with radiotherapy combined with sintilimab and lenvatinib (RT+S+L). The RT+S+L group showed superior outcomes in OS (25 months vs 16 months, HR = 0.58, 95% CI = 0.35–0.94, P=0.025) and PFS (14 months vs 6 months, HR = 0.61, 95% CI = 0.40–0.94, P=0.022) compared to the S+L group. Similarly, the RT+S+L group exhibited significantly higher objective response rate (ORR) and disease control rate (DCR) compared to the S+L group (61.5% vs 27.6%, P<0.001; 94.9% vs 76.2%, P=0.011). The most common grade 3/4 TRAEs in the RT+S+L group were hypertension, decreased platelet count, elevated total bilirubin, and proteinuria.

Conclusion: Radiotherapy combined with sintilimab and lenvatinib is an effective strategy for treating HCC with pulmonary metastasis. These findings highlight the critical role of radiotherapy in the management of HCC.

Keywords: hepatocellular carcinoma, pulmonary metastasis, radiotherapy, targeted therapy, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common tumor globally and the third leading cause of cancer-related deaths.[1] Due to the subtle early symptoms of HCC, many patients are diagnosed at an advanced stage, with major vascular invasion or extrahepatic metastasis (EHM).[2] The presence of EHM presents a formidable challenge to the survival of HCC patients, with an expected median survival time of only 6 to 10 months.[3] The lungs are the most common site of HCC metastasis, accounting for 51% of all EHMs.[4,5] A large-scale population study revealed that the 1-year overall survival rate for patients diagnosed with HCC with pulmonary metastasis (PM) is merely 12.8%.[6] Therefore, improving the prognosis for these patients is an urgent issue.

For an extended period, sorafenib or lenvatinib has constituted the standard first-line treatment for patients with advanced HCC.[7–10] However, these therapies have consistently failed to meet the prevailing demands for better prognostic outcomes in advanced HCC. In recent years, systemic treatments for HCC have made significant strides, particularly with the combination of anti-angiogenic drugs and immune checkpoint inhibitors (ICIs), which have demonstrated remarkable efficacy.[11,12] The most notable example is the IMbrave150 trial. The latest results reveal that

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the median overall survival (OS) and progression-free survival (PFS) for HCC patients were 19.2 months and 6.9 months, respectively, both superior to sorafenib.[13–15] Additionally, positive results were observed with camrelizumab plus rivoceranib and sintilimab plus a bevacizumab biosimilar (IBI305) compared to sorafenib monotherapy.[16,17] Consequently, the combination of anti-angiogenic drugs and ICIs has become the standard first-line therapy for advanced HCC.

The evolution of systemic therapy has inspired new approaches, particularly the potential synergy between systemic and local treatments, becoming a focal point of interest.[18] Local treatments such as radiofrequency ablation, transcatheter arterial chemoembolization, and radiotherapy induce tumor necrosis and apoptosis, which release cancer antigens and initiate the cancer-immunity cycle.[18] This integrated approach of modulating the cancer-immune cycle is crucial for achieving sustained immunotherapeutic effects in most cancer patients.[19] Interestingly, radiotherapy can trigger a rare phenomenon known as the abscopal effect, where treating one tumor site leads to the regression of distant, untreated metastatic cancer.[20,21] Increasing evidence suggests that combining radiotherapy with immunotherapy enhances the likelihood of the abscopal effect.[22] Therefore, we hypothesize that combining radiotherapy with sintilimab plus lenvatinib may offer a promising treatment option for HCC patients with PM.

To validate our hypothesis, we conducted this retrospective study aiming to compare the efficacy and safety of sintilimab plus lenvatinib with or without radiotherapy.

Methods

Patient Population

A retrospective study was conducted on patients with HCC with PM from 2020 to 2021 at Eastern Hepatobiliary Surgery Hospital, Nantong Haimen People's Hospital, and The First people's Hospital of Yancheng. Inclusion criteria were: (1) HCC with PM confirmed by preoperative enhanced CT/MRI; (2) age over 18 years; (3) treatment with sintilimab combined with lenvatinib; (4) good general condition and liver function classified as Child-Pugh A or B. Exclusion criteria included: (1) contraindications to sintilimab or lenvatinib; (2) receiving treatments other than radiotherapy; (3) history of other anti-cancer treatments; (4) history of other cancers; (5) incomplete clinical data.

This study adhered to the ethical standards of the Declaration of Helsinki and received approval from the institutional ethics committees of each participating center. Due to strict confidentiality of patient information and the retrospective nature of the study, informed consent was waived by the ethics committees.

Treatment

The treatment plan for each patient was developed by a multidisciplinary team—including liver surgeons, medical oncologists, radiologists, and radiation oncologists—while respecting the patient's preferences. For patients receiving radiotherapy combined with sintilimab plus lenvatinib, the default radiotherapy regimen was intensity-modulated radio-therapy (IMRT), with radiation doses as previously described.[23] The primary gross tumor volume (GTV) was delineated on the planning CT scan, referencing pretreatment multiphasic contrast MRI through an image fusion approach. The clinical target volume included the primary GTV with a 0.5-cm margin in all directions, without an additional margin. To account for respiratory liver motion and setup errors in 4-dimensional CT, the planning target volume (PTV) was defined by expanding the clinical target volume by 0.5 cm in the anterior-posterior and left-right directions and by 1.0 cm in the cranial-caudal direction.[24] A minimal number of radiation fields, typically 7 to 9, and optimal radiation beam angles were selected during IMRT planning to minimize the dose and volume of irradiated normal liver tissue. The mean dose to the normal liver (total liver volume minus GTV) was restricted to ≤23 Gy, with the dose-volume histogram for the normal liver maintained within tolerance limits: liver volume receiving ≥5 Gy (V5) was <86%; V10, <68%; V15, <59%; V20, <49%; V25, <35%; V30, <28%; V35, <25%; and V40, <20%. The maximum allowable point dose for the stomach and duodenum was set to <54 Gy, for the colon <55 Gy, and for the spinal cord <40 Gy. The kidney volume receiving ≥20 Gy (V20) was limited to <50%. The planned target area of HCC received a daily dose of 200 cGy over a 28-day radiotherapy cycle, with a planned total dose of 52–56 Gy. Sintilimab plus lenvatinib was initiated at least three days after the completion of the first dose of radiotherapy.

Sintilimab was administered intravenously at a dose of 200 mg every three weeks. In the event of low-grade infusion reactions, the infusion rate was slowed or paused; treatment was resumed once symptoms resolved, with close monitoring. Lenvatinib was taken orally once daily, dosed by body weight at 12 mg (for patients ≥60 kg) or 8 mg (for patients <60 kg). In the case of lenvatinib-related toxicity, the dose was reduced to alleviate symptoms (to 8 mg or 4 mg daily, or 4 mg every other day). Treatment continued until the attending physician determined, based on imaging results, biochemical parameters, and the patient's clinical status, that unacceptable toxicity or loss of clinical benefit had occurred.

Outcomes and Follow-Up

All patients were followed up in the outpatient clinic every three months. During each follow-up visit, routine physical examinations, laboratory blood tests, and enhanced CT/MRI scans were performed. The primary outcome of this study was PFS, defined as the time from the start of treatment to tumor progression, death from any cause, or the most recent follow-up. Tumor progression was assessed based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1),[25] including progression of treated lesions and the appearance of new intrahepatic or extrahepatic lesions. Secondary endpoints included OS, objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events (TRAEs). OS was defined as the time from the start of treatment to death from any cause or the date of the most recent follow-up.

Data on TRAEs were collected from clinical follow-up records or medical records. The assessment of TRAEs was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If multiple instances of the same type of toxicity occurred, the highest grade in each specific category was recorded for each patient.

Statistical Analysis

All clinical data were analyzed using IBM SPSS Statistics 23 or R 4.0 software (http://www.r-project.org/). The comparison of continuous variables was performed using Student's *t*-test, and the comparison of categorical variables was performed using the chi-square test or Fisher's exact probability test. Survival curves were calculated using the Kaplan-Meier method and compared using the Log rank test. Hazard ratios (HR) were calculated using the Cox regression model. Univariate Cox regression analysis was used to evaluate the significance of variables in the entire cohort. All variables associated with PFS/OS ($p<0.1$) were included in the multivariate Cox regression analysis. $P < 0.05$ was considered to indicate a significant difference.

To mitigate potential confounders, we utilized propensity score matching (PSM), a statistical technique designed to balance covariates between treatment groups, thereby attributing observed differences in outcomes more directly to the treatments rather than confounding factors. Propensity scores were calculated using logistic regression, incorporating all baseline demographic and clinical characteristics. We employed 1:1 greedy nearest neighbor matching with a 0.2 caliper, utilizing the R package "MatchIt". The method calculated a distance between units from each group, assigning each unit a control unit as a match in sequence. This "greedy" approach did not optimize an overall criterion; each match was made without considering subsequent pairings.

Results

Patients

As shown in Figure 1, a total of 144 patients meeting the inclusion and exclusion criteria were included in this study, comprising 105 patients who received only sintilimab and lenvatinib treatment (S+L), and 39 patients who received radiotherapy combined with sintilimab and lenvatinib treatment (RT+S+L). After PSM, each group included 38 patients. The baseline characteristics of the two groups are detailed in Table 1, showing no significant differences between the groups.

The median follow-up time for the RT+S+L group was 20 months (range 4–44 months), and for the S+L group, it was 16 months (range 3–44 months). Throughout the entire cohort, a total of 96 patients died during the follow-up period, with 21 from the RT+S+L group and 75 from the S+L group.
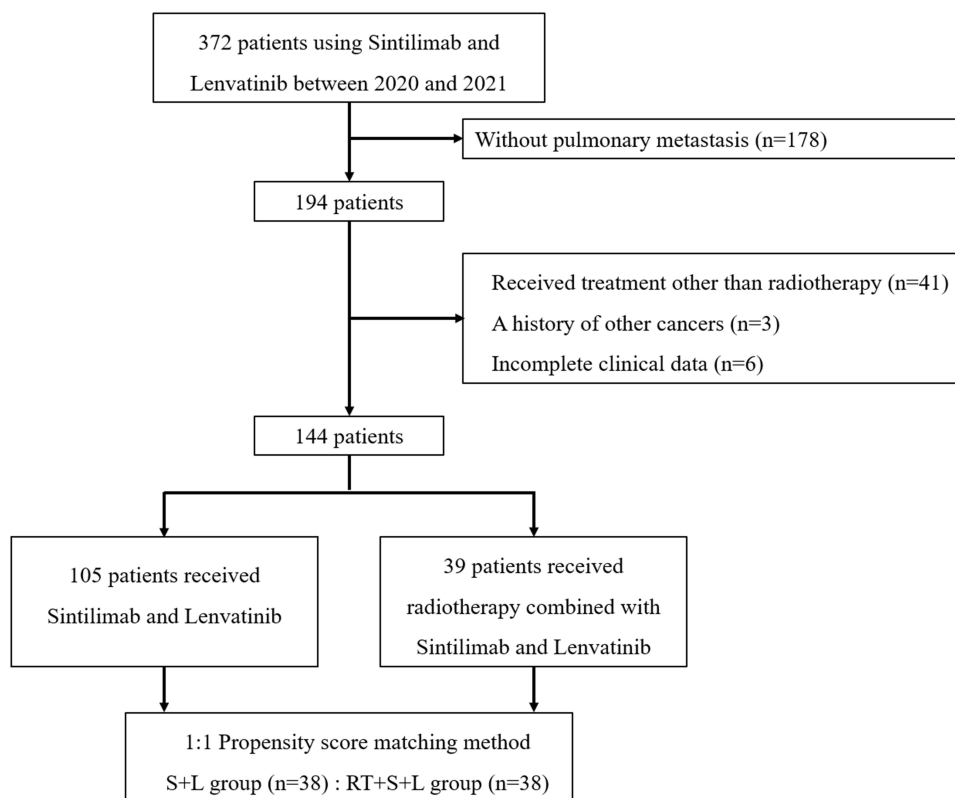
Figure 1 Flow diagram for the present study.

Efficacy

Table 2 summarizes the best tumor responses of patients assessed according to RECIST version 1.1. Before PSM, the ORR for the RT+S+L group was 61.5%, significantly higher than the 27.6% in the S+L group (P<0.001). The DCR in the RT+S+L group was 94.9%, also significantly higher than the 76.2% in the S+L group (P=0.011). After PSM, the ORR and DCR in the RT+S+L group remained higher than in the S+L group. The ORR was 60.5% in the RT+S+L group compared to 21.1% in the S+L group (P = 0.003), and the DCR was 94.7% versus 68.4%, respectively (P = 0.003).

Table 1 Baseline Covariates Before and After Matching

Variables	Level	Before Matching			After Matching		
		S+L (n=105)	RT+S+L (n=39)	SMD	S+L (n=38)	RT+S+L (n=38)	SMD
Age (%)	≤ 60	72 (68.6)	28 (71.8)	0.072	29 (76.3)	27 (71.1)	−0.117
	> 60	33 (31.4)	11 (28.2)	−0.072	9 (23.7)	11 (28.9)	0.117
Sex (%)	Female	18 (17.1)	7 (17.9)	0.021	10 (26.3)	7 (18.4)	−0.206
	Male	87 (82.9)	32 (82.1)	−0.021	28 (73.7)	31 (81.6)	0.206
Albumin (%)	≤ 35	23 (21.9)	5 (12.8)	−0.272	6 (15.8)	5 (13.2)	−0.079
	> 35	82 (78.1)	34 (87.2)	0.272	32 (84.2)	33 (86.8)	0.079
HBsAg (%)	Negative	32 (30.5)	11 (28.2)	−0.050	13 (34.2)	11 (28.9)	−0.117
	Positive	73 (69.5)	28 (71.8)	0.050	25 (65.8)	27 (71.1)	0.117
AFP.ng.mL (%)	≤ 400	49 (46.7)	13 (33.3)	−0.283	11 (28.9)	13 (34.2)	0.112
	> 400	56 (53.3)	26 (66.7)	0.283	27 (71.1)	25 (65.8)	−0.112
Alanine aminotransferase (%)	≤ 44	81 (77.1)	30 (76.9)	−0.005	29 (76.3)	30 (78.9)	0.062
	> 44	24 (22.9)	9 (23.1)	0.005	9 (23.7)	8 (21.1)	−0.062

(*Continued*)

Table 1 (Continued).

Variables	Level	Before Matching			After Matching		
		S+L (n=105)	RT+S+L (n=39)	SMD	S+L (n=38)	RT+S+L (n=38)	SMD
Total bilirubin (%)	≤ 17.1	57 (54.3)	21 (53.8)	−0.009	24 (63.2)	21 (55.3)	−0.158
	> 17.1	48 (45.7)	18 (46.2)	0.009	14 (36.8)	17 (44.7)	0.158
Platelet (%)	≤ 100	13 (12.4)	4 (10.3)	−0.070	4 (10.5)	4 (10.5)	0.000
	> 100	92 (87.6)	35 (89.7)	0.070	34 (89.5)	34 (89.5)	0.000
Tumor number (%)	Multiple	54 (51.4)	16 (41.0)	−0.211	14 (36.8)	16 (42.1)	0.107
	Single	51 (48.6)	23 (59.0)	0.211	24 (63.2)	22 (57.9)	−0.107
Maximum tumor diameter (%)	≤ 5	45 (42.9)	22 (56.4)	0.273	22 (57.9)	21 (55.3)	−0.053
	> 5	60 (57.1)	17 (43.6)	−0.273	16 (42.1)	17 (44.7)	0.053
Number of lung metastatic lesions (%)	1	36 (34.3)	8 (20.5)	−0.341	5 (13.2)	8 (21.1)	0.196
	2	9 (8.6)	5 (12.8)	0.127	7 (18.4)	5 (13.2)	−0.157
	3	4 (3.8)	2 (5.1)	0.060	1 (2.6)	2 (5.3)	0.119
	>3	56 (53.3)	24 (61.5)	0.169	25 (65.8)	23 (60.5)	−0.108
PVTT (%)	With	43 (41.0)	16 (41.0)	0.001	17 (44.7)	16 (42.1)	−0.054
	Without	62 (59.0)	23 (59.0)	−0.001	21 (55.3)	22 (57.9)	0.054
Child-Pugh classification (%)	A5	54 (51.4)	25 (64.1)	0.264	21 (55.3)	24 (63.2)	0.165
	A6	41 (39.0)	12 (30.8)	−0.179	14 (36.8)	12 (31.6)	−0.114
	B7	10 (9.5)	2 (5.1)	−0.199	3 (7.9)	2 (5.3)	−0.119
ECOG performance status score (%)	0	83 (79.0)	24 (61.5)	−0.360	26 (68.4)	24 (63.2)	−0.108
	1	22 (21.0)	15 (38.5)	0.360	12 (31.6)	14 (36.8)	0.108
Other extrahepatic spread (%)	Bone	11 (10.5)	4 (10.3)	−0.007	5 (13.2)	4 (10.5)	−0.087
	Lymph node	18 (17.1)	8 (20.5)	0.083	8 (21.1)	7 (18.4)	−0.065
	None	76 (72.4)	27 (69.2)	−0.068	25 (65.8)	27 (71.1)	0.114

Abbreviations: RT+S+L, radiotherapy combine with sintilimab plus lenvatinib; S+L, sintilimab plus lenvatinib; SMD, Standardized Mean Difference; HBsAg, hepatitis B surface antigen; AFP, alpha fetoprotein; ECOG, Eastern Cooperative Oncology Group; PVTT, portal vein tumor thrombus.

Table 2 Best Tumor Response According to RECIST v1.1

	Before Matching			After Matching		
	RT+S+L (n=39)	S+L (n=105)	P value	RT+S+L (n=38)	S+L (n=38)	P value
Radiation target						
CR	1 (2.6%)	2 (1.9%)		1 (2.6%)	1 (2.6%)	
PR	23 (59.0%)	27 (25.7%)		22 (57.9%)	7 (18.4%)	
SD	13 (33.3%)	51 (48.6%)		13 (34.2%)	16 (42.1%)	
PD	2 (5.1%)	25 (23.8%)		2 (5.3%)	12 (34.2%)	
Non-radiation target						
CR	1 (2.6%)	2 (1.9%)		1 (2.6%)	1 (2.6%)	
PR	13 (33.3%)	24 (22.9%)		12 (31.6%)	6 (15.8%)	
SD	20 (51.3%)	60 (57.1%)		20 (52.6%)	23 (60.5%)	
PD	2 (5.1%)	12 (11.4%)		2 (5.3%)	5 (13.2%)	
NE	3 (7.7%)	7 (6.7%)		3 (7.9%)	3 (7.9%)	
ORR	24 (61.5%)	29 (27.6%)	<0.001	23 (60.5%)	8 (21.1%)	0.003
DCR	37 (94.9%)	80 (76.2%)	0.011	36 (94.7%)	26 (68.4%)	0.003

Abbreviations: RT+S+L, radiotherapy combine with sintilimab plus lenvatinib; S+L, sintilimab plus lenvatinib; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, Not Evaluable; ORR, objective response rate; DCR, disease control rate.

Before PSM, the median PFS for the RT+S+L group was 14 months (95% CI = 11–22) compared to 6 months (95% CI = 5–9) for the S+L group, with RT+S+L significantly prolonging PFS (Figure 2A, HR = 0.61, 95% CI = 0.40–0.94, P=0.022). Univariate Cox regression results indicated that, besides treatment grouping, the number of tumors and the number of lung metastatic lesions were also potential factors affecting PFS. After adjusting for these factors, RT+S+L still significantly extended PFS (Supplementary Table 1, HR = 0. 49, 95% CI = 0.31–0.78, P=0.002). The median OS for the RT+S+L group was 25 months (95% CI = 19-not reached) compared to 16 months (95% CI = 14–24) for the S+L group, with RT+S+L significantly prolonging OS (Figure 2B, HR = 0.58, 95% CI = 0.35–0.94, P=0.025). Univariate Cox regression results showed that, besides treatment grouping, the number of tumors and portal vein tumor thrombus were also potential factors affecting OS. After adjusting for these factors, RT+S+L still significantly extended OS (Supplementary Table 2, HR = 0.53, 95% CI = 0.32–0.87, P=0.013).

After PSM, the median PFS for the RT+S+L group was 25 months (95% CI = 19–20) compared to 15.9 months (95% CI = 4–7) for the S+L group, with RT+S+L significantly prolonging PFS (Figure 2C, HR = 0.37, 95% CI = 0.22–0.62, P < 0.0001). The median OS for the RT+S+L group was 25 months (95% CI = 19-not reached) compared to 15.9 months (95% CI = 8–21.5) for the S+L group, with RT+S+L significantly prolonging OS (Figure 2D, HR = 0.44, 95% CI = 0.25–0.77, P=0.025).

Treatment on Progression

Throughout the cohort, 117 patients experienced progression during follow-up, including 30 from the RT+S+L group and 87 from the S+L group, with progression details summarized in Supplementary Table 3.
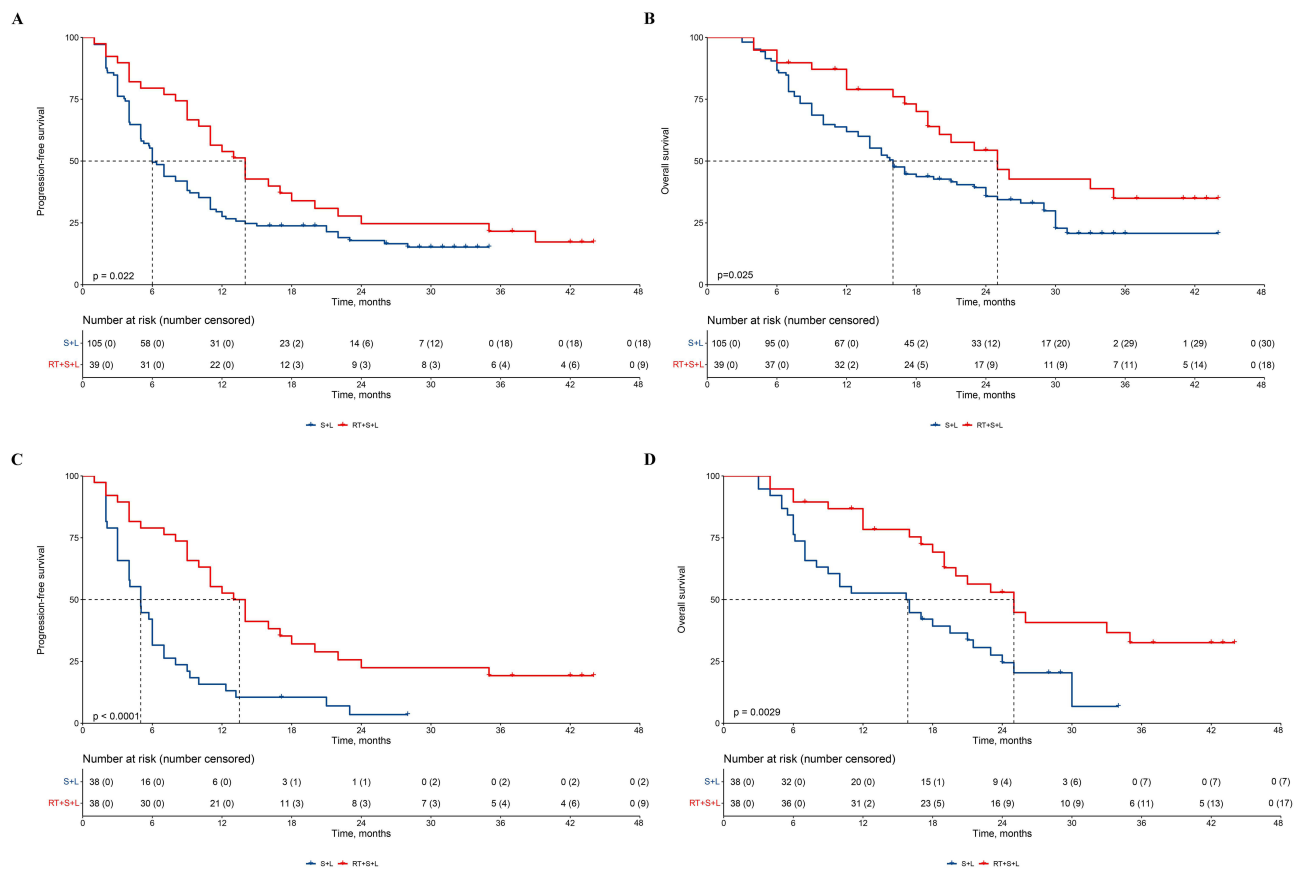

Figure 2 Kaplan–Meier-estimated PFS and OS curves in HCC patients with PM receiving different therapies. (**A**) PFS before PSM; (**B**) OS before PSM; (**C**)PFS after PSM; (**D**) OS after PSM.
Abbreviations: PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma; PM, pulmonary metastases; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; S+L, sintilimab combined with lenvatinib; RT+S+L, radiotherapy combined with sintilimab and lenvatinib.

Table 3 Treatment Emergent Adverse Events

Adverse Events	RT+S+L (n = 39)		S+L (n = 105)	
	Grade 1/2.n (%)	Grade 3/4. n (%)	Grade 1/2.n (%)	Grade 3/4. n (%)
Any treatment-emergent adverse event	21 (53.8%)	17 (43.6%)	51 (48.6%)	42 (40.0%)
Elevated TB	15 (38.5%)	4 (10.3%)	31 (29.5%)	8 (7.6%)
Fatigue	15 (38.5%)	1 (2.6%)	35 (33.3%)	1 (1.0%)
Elevated AST	14 (35.9%)	3 (7.7%)	29 (27.6%)	7 (6.7%)
Proteinuria	14 (35.9%)	4 (10.3%)	28 (26.7%)	9 (8.6%)
Decreased PLT	13 (33.3%)	5 (12.8%)	28 (26.7%)	10 (9.5%)
Elevated ALT	12 (30.8%)	2 (5.1%)	27 (25.7%)	7 (6.7%)
Hypertension	9 (23.1%)	7 (17.9%)	24 (22.9%)	16 (15.2%)
Pyrexia	9 (23.1%)	1 (2.6%)	20 (19.0%)	4 (3.8%)
Hypoalbuminaemia	8 (20.5%)	1 (2.6%)	17 (16.2%)	2 (1.9%)
Bleeding (gingiva)	7 (17.9%)	0 (0.0%)	16 (15.2%)	0 (0.0%)
Diarrhea	5 (12.8%)	1 (2.6%)	14 (13.3%)	2 (1.9%)
Anaemia	5 (12.8%)	3 (7.7%)	14 (13.3%)	5 (4.8%)
Hypothyroidism	4 (10.3%)	0 (0.0%)	13 (12.4%)	0 (0.0%)
Gastrointestinal hemorrhage	3 (7.7%)	1 (2.6%)	7 (6.7%)	1 (1.0%)
Hand-foot skin reaction	3 (7.7%)	1 (2.6%)	7 (6.7%)	1 (1.0%)
Elevated creatinine	3 (7.7%)	1 (2.6%)	7 (6.7%)	0 (0.0%)
Rash	3 (7.7%)	0 (0.0%)	6 (5.7%)	0 (0.0%)

Abbreviations: RT+S+L, radiotherapy combine with sintilimab plus lenvatinib; S+L, sintilimab plus lenvatinib; PLT, platelet; AST, aspartate transaminase; ALT, alanine aminotransferase; TB, total bilirubin.

Supplementary Table 4 summarizes the treatment on progression. In the RT+S+L group, among the patients with progression, 10 received regorafenib, 7 received apatinib, 6 received atezolizumab plus bevacizumab, 5 received donafenib, and 2 received supportive care. In the S+L group, among the patients with progression, 31 received regorafenib, 16 received apatinib, 23 received atezolizumab plus bevacizumab, 12 received donafenib, 4 received supportive care, and 1 refused further treatment.

Safety

Table 3 details the TRAEs for both groups, with no treatment-related deaths (Grade 5 adverse events) reported. The incidence of Grade 3/4 adverse events was 43.6% in the RT+S+L group, with the most common being hypertension, decreased PLT, elevated TB, and proteinuria. In the S+L group, the incidence of Grade 3/4 adverse events was 40.0%, with the most common being hypertension, decreased PLT, and proteinuria.

Discussion

This study compares the efficacy and safety of sintilimab plus lenvatinib with or without radiotherapy in patients with advanced HCC with PM. The results indicate that RT+S+L significantly prolongs PFS and OS compared to S+L. Additionally, the combination therapy exhibited higher ORR and DCR. No unexpected TRAEs were observed with the addition of radiotherapy, confirming its acceptable safety profile. In summary, we consider RT+S+L as a potential treatment option for patients with advanced HCC with PM.

In current clinical practice, PD-1/PD-L1 inhibitors combined with anti-VEGF agents have been widely recognized as first-line treatments for advanced HCC.[11,14,16,17] However, the ORR for this combination is below 30%, necessitating further research for improvement. Data on radiotherapy in HCC, especially in conjunction with systemic treatments, are encouraging. Mechanistically, RT enhances immune cell activation and infiltration into tumors. Conversely, radiotherapy induces the expression of immune checkpoint molecules and VEGF, which, when targeted by specific drugs, further amplify the effects of radiotherapy.[26] A recent prospective single-arm clinical trial demonstrated an ORR of 58.7% for sintilimab plus bevacizumab combined with radiotherapy in patients with advanced HCC.[27]

IMRT is an advanced high-precision radiotherapy technique that uses computer-controlled linear accelerators to deliver precise radiation doses to malignant tumors or specific areas within the tumor.[28] This technique allows the radiation dose to conform more precisely to the tumor's three-dimensional shape, minimizing exposure to surrounding normal structures. IMRT is utilized in various malignancies, including prostate cancer, head and neck cancers, gastro-intestinal cancers, gynecologic cancers, and brain tumors.[29–31] In each case, IMRT has proven effective by improving tumor control and reducing treatment-related morbidity. A prospective observational study found that IMRT combined with atezolizumab and bevacizumab achieved an impressive ORR of 76.6% in patients with advanced HCC. These findings underscore the critical role of IMRT in enhancing tumor control.

However, the aforementioned studies were single-arm with historical controls, making it difficult to draw definitive conclusions. A limited retrospective propensity score-matched study indicated that combining PD-1 inhibitors with anti-angiogenic therapy and radiotherapy was more effective than PD-1 inhibitors with anti-angiogenic therapy, with no significant difference in treatment-related adverse events between the two groups.[32] This aligns with our study's results, where the RT+S+L group had an ORR of 61.5%, higher than the S+L group's 27.6%. The S+L group's ORR was similar to the IMBRAVE 150 and ORIENT-32 trials,[15,17] further validating our findings' robustness. Notably, the ORR rate of the non-radiotherapy target in the RT+S+L group was 34.2%, higher than the 18.4% in the S+L group, potentially due to the induction of an abscopal response. As previously explained, when tumors are exposed to radiation, cellular stress or damage within the tumor might lead to the release of neoantigens or tumor-specific antigens in the context of necrotic and apoptotic tumor cells. In this case, the addition of immunotherapy to RT enhances this effect. The RT+S+L group had a PFS of 14 months, comparable to Zhu et al's report on sintilimab plus bevacizumab with radiotherapy,[27] and longer than Wang et al's results, possibly due to the latter's inclusion of more advanced patients with main trunk tumor thrombus.[23] Compared to the S+L group's 6 months, the addition of radiotherapy significantly prolonged PFS, indicating that radiotherapy combined with systemic treatment benefits not only liver-confined HCC but also patients with PM, though caution is needed in interpreting results from this retrospective study. This suggests that future clinical trials in HCC treatment should consider incorporating radiotherapy as an effective option.

One reason for the limited adoption of radiotherapy in HCC is potential liver damage. In terms of safety, no unexpected toxicity was observed in the RT+S+L group. The incidence of Grade 3/4 adverse events was 43.6% in the RT+S+L group, with the most common being hypertension, decreased platelet count, elevated total bilirubin, and proteinuria. These adverse events were mostly manageable, with no treatment-related deaths reported.

Our study has limitations. First, being retrospective, it is inherently susceptible to selection and confounding biases. Additionally, although our regular follow-up interval was three months, actual patient follow-up times may have varied, potentially affecting PFS measurement accuracy. Furthermore, the relatively small sample size may reduce statistical power, necessitating future prospective studies to further verify the efficacy of combination therapy.

In conclusion, this study suggests that RT+S+L combination therapy may offer enhanced efficacy compared to S+L in managing HCC patients with lung metastases, with manageable safety concerns. These findings contribute to the growing body of evidence supporting comprehensive treatment strategies in advanced hepatocellular carcinoma, though further studies are warranted to confirm these results.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author (Dr. Jie Shi, docshijie@aliyun.com) on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki and the Eastern Hepatobiliary Surgery Hospital (EHBH) Clinical Research Ethics Committee approved this retrospective study. The requirement for informed consent was waived due to the retrospective nature of the study, and no personal information was disclosed.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Authors declare no Conflict of Interests for this article.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Xie DY, Ren ZG, Zhou J, Fan J, Gao Q. 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary Surg Nutr*. 2020;9(4):452–463. doi:10.21037/hbsn-20-480
3. Kanda M, Tateishi R, Yoshida H, et al. Extrahepatic metastasis of hepatocellular carcinoma: incidence and risk factors. *Liver Int*. 2008;28 (9):1256–1263. doi:10.1111/j.1478-3231.2008.01864.x
4. 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
5. Katyal S, Oliver JH 3rd, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. *Radiology*. 2000;216 (3):698–703. doi:10.1148/radiology.216.3.r00se24698
6. Wu C, Ren X, Zhang Q. Incidence, risk factors, and prognosis in patients with primary hepatocellular carcinoma and lung metastasis: a population-based study. *Cancer Manag Res*. 2019;11:2759–2768. doi:10.2147/CMAR.S192896
7. Jeong SW, Jang JY, Shim KY, et al. Practical effect of sorafenib monotherapy on advanced hepatocellular carcinoma and portal vein tumor thrombosis. *Gut Liver*. 2013;7(6):696–703. doi:10.5009/gnl.2013.7.6.696
8. Qi X, Guo X. Sorafenib for the treatment of hepatocellular carcinoma with portal vein tumour thrombosis: a systematic review of comparative studies. *Prz Gastroenterol*. 2015;10(3):142–147. doi:10.5114/pg.2015.52470
9. Nakazawa T, Hidaka H, Shibuya A, et al. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. *BMC Gastroenterol*. 2014;14(1):84. doi:10.1186/1471-230X-14-84
10. 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
11. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76 (3):681–693. doi:10.1016/j.jhep.2021.11.018
12. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922–1965. doi:10.1097/HEP.0000000000000466
13. 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
14. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(7):991–1001. doi:10.1016/S1470-2045(21)00151-0
15. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862–873. doi:10.1016/j.jhep.2021.11.030
16. Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. *Lancet*. 2023;402(10408):1133–1146. doi:10.1016/S0140-6736(23)00961-3
17. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, Phase 2-3 study. *Lancet Oncol*. 2021;22(7):977–990. doi:10.1016/S1470-2045(21)00252-7
18. Llovet JM, De Baere T, Kulik L, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2021;18(5):293–313. doi:10.1038/s41575-020-00395-0
19. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39(1):1–10. doi:10.1016/j.immuni.2013.07.012
20. Craig DJ, Nanavaty NS, Devanaboyina M, et al. The abscopal effect of radiation therapy. *Future Oncol*. 2021;17(13):1683–1694. doi:10.2217/fon-2020-0994
21. Chen AC, Butler EB, Lo SS, Teh BS. Radiotherapy and the abscopal effect: insight from the past, present, and future. *J Radiat Oncol*. 2015;4 (4):321–330. doi:10.1007/s13566-015-0223-6
22. Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, Formenti SC, Demaria S. Immunological mechanisms responsible for radiation-induced abscopal effect. *Trends Immunol*. 2018;39(8):644–655. doi:10.1016/j.it.2018.06.001
23. Wang K, Xiang YJ, Yu HM, et al. Intensity-modulated radiotherapy combined with systemic atezolizumab and bevacizumab in treatment of hepatocellular carcinoma with extrahepatic portal vein tumor thrombus: a preliminary multicenter single-arm prospective study. *Front Immunol*. 2023;14:1107542. doi:10.3389/fimmu.2023.1107542
24. Zhao YT, Liu ZK, Wu QW, et al. Observation of different tumor motion magnitude within liver and estimate of internal motion margins in postoperative patients with hepatocellular carcinoma. *Cancer Manag Res*. 2017;9:839–848. doi:10.2147/CMAR.S147185

25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi:10.1016/j.ejca.2008.10.026

26. Lee YH, Tai D, Yip C, Choo SP, Chew V. Combinational immunotherapy for hepatocellular carcinoma: radiotherapy, immune checkpoint blockade and beyond. *Front Immunol*. 2020;11:568759. doi:10.3389/fimmu.2020.568759

27. Zhu M, Liu Z, Chen S, et al.Sintilimab plus bevacizumab combined with radiotherapy as first-line treatment for hepatocellular carcinoma with portal vein tumor thrombus: a multicenter, single-arm, phase 2 study. *Hepatology*. 2024;2024:10-–1097

28. Teh BS, Woo SY, Butler EB. Intensity modulated radiation therapy (IMRT): a new promising technology in radiation oncology. *Oncologist*. 1999;4 (6):433–442.

29. Bortfeld T. IMRT: a review and preview. *Phys Med Biol*. 2006;51(13):R363–379. doi:10.1088/0031-9155/51/13/R21

30. Hatano K, Tohyama N, Kodama T, Okabe N, Sakai M, Konoeda K. Current status of intensity-modulated radiation therapy for prostate cancer: history, clinical results and future directions. *Int J Urol*. 2019;26(8):775–784. doi:10.1111/iju.14011

31. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gérard JP. Past, present, and future of radiotherapy for the benefit of patients. *Nat Rev Clin Oncol*. 2013;10(1):52–60. doi:10.1038/nrclinonc.2012.203

32. Su K, Guo L, Ma W, et al. PD-1 inhibitors plus anti-angiogenic therapy with or without intensity-modulated radiotherapy for advanced hepatocellular carcinoma: a propensity score matching study. *Front Immunol*. 2022;13:972503. doi:10.3389/fimmu.2022.972503