Liver Research 9 (2025) 29–35

Contents lists available at ScienceDirect

Liver Research

journal homepage: http://www.keaipublishing.com/en/journals/liver-research

Original Article

Prognostic comparison between pulmonary metastasectomy and combination immunotherapy with targeted molecular therapies for advanced hepatocellular carcinoma with pulmonary metastasis: A propensity score matching analysis

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ARTICLE INFO

Article history:
Received 10 November 2023
Received in revised form
24 January 2025
Accepted 26 January 2025

Keywords:
Hepatocellular carcinoma (HCC)
Pulmonary metastasis (PM)
Pulmonary metastasectomy
Immunotherapy
Targeted therapy

ABSTRACT

Background and aims: Advanced hepatocellular carcinoma (HCC) with pulmonary metastasis (PM) has a poor prognosis, and optimal treatment strategies remain controversial. This study aimed to compare the long-term outcomes of patients with advanced HCC with PM who were treated with resection of pulmonary metastases versus those treated with targeted therapies combined with immunotherapy.

Methods: A retrospective analysis was conducted on the medical records of HCC patients with PM who underwent either pulmonary metastasectomy or immunotherapy combined with targeted therapies at the Eastern Hepatobiliary Surgery Hospital, Changhai Hospital of Shanghai, Fujian Provincial Hospital, and West China Hospital of Sichuan University from September 2013 to October 2022. One-to-one propensity score matching (PSM) was employed to control the influence of potential confounders, and the survival outcomes were compared.

Results: A total of 119 HCC patients with PM were included in this study. The overall survival (OS) of patients who underwent pulmonary metastasectomy was significantly longer than that of patients who received immunotherapy targeted combinations (OS: 1-year, 80.0% *vs.* 59.3%; 2-year, 31.7% *vs.* 20.3%; 3-year, 20.0% *vs.* 0; $P < 0.001$). After PSM, the long-term prognosis of the pulmonary metastasectomy group remained significantly better than that of the immunotherapy combination group (OS: 1-year, 87.0% *vs.* 69.6%; 2-year, 34.8% *vs.* 30.4%; 3-year, 21.7% *vs.* 0; $P = 0.005$). Multivariate analysis revealed that treatment allocation (hazard ratio (HR) = 2.177, 95% confidence interval (CI) = 1.068–4.439) and hepatic tumor T stage (HR = 2.342, 95% CI = 1.209–4.538) were independent risk factors for OS.

Conclusions: Pulmonary metastasectomy was associated with improved survival compared to immunotherapy combined with targeted therapies and may represent an optimal treatment option for highly selected HCC patients with resectable PM.

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Peer review under the responsibility of Editorial Office of Liver Research.
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https://doi.org/10.1016/j.livres.2025.01.006

1. Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death globally.[1] More than 70% of HCC patients are at an advanced stage when diagnosed because of the lack of symptoms, and resultantly, HCC historically has only a 10%–18% 5-year survival rate.[2,3] Extrahepatic metastasis (EHM), a main feature of advanced HCC, is found in 14.3%–82.4% of autopsy cases with the lungs being the most common metastatic site accounting for 77.8% of all extrahepatic metastases.[4–7] This poor prognosis of advanced HCC with pulmonary metastasis (PM) has led to the development of different strategies currently used in clinical trials.

Multitargeted tyrosine kinase inhibitors (TKIs), such as sorafenib and lenvatinib in first-line therapy, were first approved in advanced HCC patients including HCC with PM based on positive results of phase III trials.[8,9] However, the efficacy of TKIs alone is insufficient, as they have only been shown to prolong overall survival (OS) by approximately 3 months. More recently, immune checkpoint inhibitors (ICIs) have been evaluated in advanced HCC patients including HCC with PM with an objective response rate (ORR) of only 15% in phase II and III trials so far.[10] Immunotherapy combinations, including TKIs, have been developed to improve prognosis and subsequently increased the ORR to approximately 30%.[11–14] Pulmonary metastasectomy has long been an important therapeutic method for HCC patients with resectable pulmonary lesions.[15,16] The median OS of HCC patients with PM who undergo pulmonary metastasectomy ranges from 10.7 to 77.0 months.[17] Direct comparisons between these two treatments have yet to be published.

This study aimed to compare the efficacy of immunotherapy combined with targeted therapies to that of pulmonary metastasectomy in HCC patients with resectable PM and further explored risk factors that may be found to independently predict OS. Because we were concerned that significant differences in baseline data between the two groups may confound the final results, propensity score matching (PSM) was used to eliminate possible biases and improve the reliability of our conclusions.

2. Patients and methods

2.1. Ethical approval

This study was conducted in compliance with the Declaration of Helsinki. Ethical approval for this study was obtained from the Ethics Committee of Eastern Hepatobiliary Surgery Hospital (Ethical approval No. EHBHKY2023-K029-Y001). Written informed consent was obtained from each participant recruited from the four participating hospitals.

2.2. Patients

HCC patients with PM treated at the Eastern Hepatobiliary Surgery Hospital (Shanghai, China), Changhai Hospital of Shanghai (Shanghai, China), Fujian Provincial Hospital (Fuzhou, China), and West China Hospital of Sichuan University (Chengdu, China) from September 2013 to October 2022 were included in this study. The inclusion criteria were as follows: (1) patients diagnosed with HCC based on histopathological findings or from a noninvasive assessment according to the American Association for the Study of Liver Diseases criteria for patients with confirmed cirrhosis; (2) resectable PM; (3) pulmonary function test clearance for lung resection; (4) liver functional status of Child-Pugh A; (5) controlled state of primary HCC; (6) and no other EHM. The exclusion criteria were as follows: patients without sufficient follow-up data, patients who received off-protocol medications, and patients who were noncompliant (Fig. 1).

2.3. Treatment

All patients in the immunotherapy combination group received intravenous administration of ICIs and TKIs, including atezolizumab (1200 mg) plus bevacizumab (15 mg/kg of body weight) (F. Hoffmann-La Roche Ltd, Basel, Switzerland) every 3 weeks, sintilimab (200 mg) plus bevacizumab biosimilar (IBI305, 15 mg/kg) (Innovent Ltd, Suzhou, China) every 3 weeks, camrelizumab (200 mg) every 2 weeks plus apatinib (250 mg) (Hengrui Pharmaceuticals Co., Ltd, Lianyungang, China) per day, and tislelizumab (200 mg) (BeiGene, Beijing, China) every 3 weeks plus lenvatinib (Misato Plant of Eisai Co., Ltd, Japan) ($\leq$60 kg, 8 mg; >60 kg, 12 mg) per day, according to the standard usage reported to be effective in patients with advanced HCC.[11–14] Treatment was discontinued with evidence of disease progression or unacceptable toxicity.

All patients in the surgical group were treated with the standardized wedge resection, segmentectomy, or lobectomy as mandated by tumor size, number, and location. Video-assisted thoracic surgery was the preferred technique whenever possible. Intraoperative and postoperative management met or exceeded all current standards.

2.4. Evaluation and follow-up

Pre-treatment examinations included imaging examinations (abdominal ultrasonography, contrast-enhanced magnetic resonance imaging (MRI; General Electric Company, MA, United States), and/or computed tomography (CT; General Electric Company, MA, USA), and noncontrast CT of the chest), and laboratory examinations (routine blood tests, liver and renal function tests, hepatitis B and C serology, hepatitis B virus (HBV) DNA load, and serum alpha-fetoprotein (AFP) level). The baseline examinations for the immunotherapy combination group only included thyroid, pituitary and adrenal gland function examination, serum cardiac markers, and B-type natriuretic peptide.

All patients were evaluated every 6–8 weeks. Each follow-up visit included a routine history of present illness and physical examination, laboratory blood tests, and enhanced abdominal CT/MRI and noncontrast chest CT.

OS was the endpoint of this study. OS was measured from the date of pulmonary metastasectomy (surgery group) or from the first dosage of immunotherapy and TKIs (immunotherapy combination group) to the date of patient death or the date of the last follow-up. Recurrence-free survival (RFS) was defined as the interval between the date of pulmonary metastasectomy and the date of tumor recurrence. Progression-free survival (PFS) was defined as the interval between the date of start of immunotherapy and TKIs and the date of tumor progression.

2.5. Statistical analysis

Continuous variables were expressed as medians (range), and categorical data were analyzed using Fisher's exact test. Kaplan–Meier analysis was used to illustrate OS. Factors that were significantly ($P < 0.05$) associated with survival in the univariate analysis and the imbalanced factors between the groups were entered into a Cox proportional hazards model to test for significant effects while adjusting for multiple factors simultaneously. Efficacy was also assessed in patient subgroups based on baseline demographics and disease characteristics. For all tests, a two-tailed P-value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software, version 21.0 (SPSS

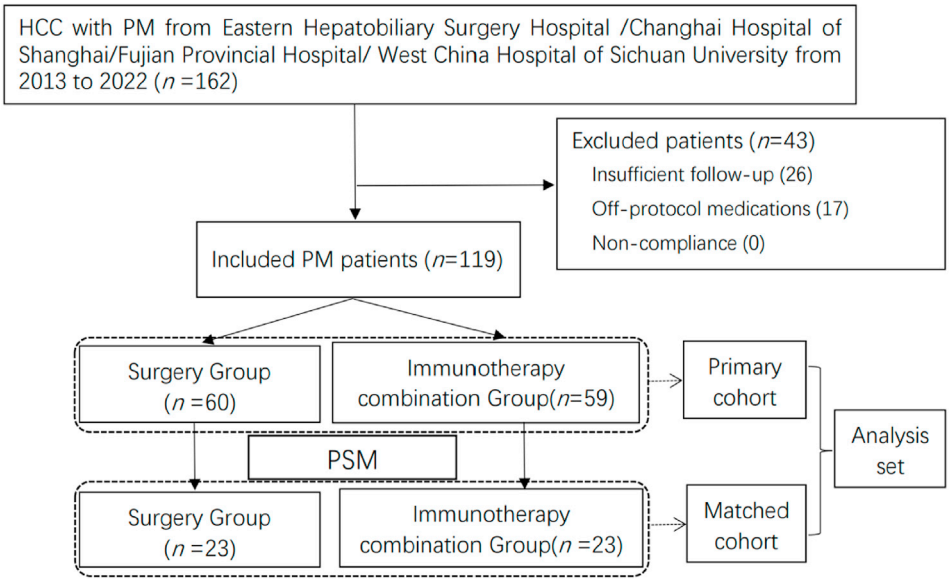

Fig. 1. Flowchart to select eligible HCC patients with PM for the study. Abbreviations: HCC, hepatocellular carcinoma; PM, pulmonary metastasis; PSM, propensity score matching.

Inc., Chicago, IL, USA). PSM was performed to decrease the confounding effects and balance the baseline characteristics of the two groups. PSM was conducted via the MatchIt package of the R program, version 3.4.3 (R Development Team, Vienna, Austria).

3. Results

3.1. Patient characteristics

From September 2013 to October 2022, a total of 119 HCC patients with PM were included in this study comprised of 96 men and 23 women. All enrolled patients completed the study. The median age of the patients was 55 years (range, 23–78 years). All patients had Child-Pugh A liver function and an Eastern Cooperative Oncology Group performance status of 2 or less. Fifty-nine patients were included in the immunotherapy combination group and 60 patients in the surgery group (Fig. 1). The median duration of follow-up was 26 months. Baseline characteristics of all patients are summarized in Table 1. The surgery group had a lower AFP level ($P < 0.001$), a lower hepatic tumor T stage ($P < 0.001$), and a smaller PM number ($P < 0.001$) compared with the combination immunotherapy group. After PSM, there were 23 patients in each group, and all clinicopathological characteristics were balanced between the two groups (all $P > 0.05$, Table 1).

3.2. Survival analysis before and after PSM

As shown in Fig. 2, the OS of the patients in the surgery group was significantly longer compared to the patients in the immunotherapy combination group (OS: 1-year, 80.0% *vs.* 59.3%; 2-year, 31.7% *vs.* 20.3%; 3-year, 20.0% *vs.* 0; $P < 0.001$; Fig. 2A). After PSM, the long-term prognosis of the surgery group was further confirmed as being significantly better than that of the immunotherapy combination group. (OS: 1-year, 87.0% *vs.* 69.6%; 2-year, 34.8% *vs.* 30.4%; 3-year, 21.7% *vs.* 0; $P = 0.005$; Fig. 2B). The ORR was 37.3%, and the median OS was 24 months in the immunotherapy combination group; however, due to the limited study duration, the surgery group did not reach the median OS.

Pulmonary metastasectomy provided a clinical benefit in all preplanned subgroup analyses, despite some patients having characteristics associated with poor prognosis, including older age (≥50 years), greater AFP level, HBV infection, greater hepatic tumor T stage, and a greater number of pulmonary metastases (Fig. 3).

The 1-, 2-, and 3-year RFS rates of the surgery group were 65.0%, 25.0%, and 16.7%, respectively. After PSM, the 1-, 2-, and 3-year RFS rates were 69.6%, 26.1%, and 13.0%, respectively. The 1-, 2-, and 3-year PFS of the immunotherapy combination group was 35.6%, 8.5%, and 0, respectively. After PSM, the 1-, 2-, and 3-year PFS rates were 39.1%, 4.3%, and 0, respectively.

3.3. Risk factors associated with OS for all the patients

Before PSM, treatment allocation (HR = 2.845, 95% CI = 2.524–5.311), AFP level (HR = 1.837, 95% CI = 1.006–3.352), and hepatic tumor T stage (HR = 3.053, 95% CI = 1.627–5.728) were potential risk factors for OS (Table 2). Only treatment allocation (HR = 2.177, 95% CI = 1.068–4.439) and hepatic tumor T stage (HR = 2.342, 95% CI = 1.209–4.538) were independent risk factors for OS (Table 2) as determined by multivariate analysis, which considers the effects of all variables.

After PSM, treatment allocation (HR = 4.441, 95% CI = 1.413–13.955) and hepatic tumor T stage (HR = 3.086, 95% CI = 1.087–8.763) were confirmed as independent risk factors for OS (Table 2).

3.4. Adverse events

The median operation time for pulmonary metastasectomy was 130 mins with an average blood loss of approximately 220 mL. One patient died of massive intraoperative hemorrhage. Two patients suffered from postoperative pulmonary infections which both successfully resolved within 2 weeks. In the immunotherapy combination group, hypertension, hand-foot skin reaction, diarrhea, leukocytopenia, nausea with or without vomiting, and alanine aminotransferase elevation were the most common toxicities, but these were mostly National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade 1 to 2. Only one patient

Table 1
The clinicopathological features of all patients before and after PSM.

Variables	Before PSM			After PSM		
	Immunotherapy combination group ($n = 59$)	Surgery group ($n = 60$)	*P*-value	Immunotherapy combination group ($n = 23$)	Surgery group ($n = 23$)	*P*-value
Age (years)			0.214			0.326
≥50	37 (62.7)	44 (73.3)		15 (65.2)	18 (78.3)	
<50	22 (37.3)	16 (26.7)		8 (34.8)	5 (21.7)	
Gender			0.514			1.000
Men	49 (83.1)	47 (78.3)		19 (82.6)	19 (82.6)	
Women	10 (16.9)	13 (21.7)		4 (17.4)	4 (17.4)	
HBsAg			0.153			0.381
Negative	7 (11.9)	13 (21.7)		2 (8.7)	4 (17.4)	
Positive	52 (88.1)	47 (78.3)		21 (91.3)	19 (82.6)	
AFP (ng/mL)			**<0.001**			1.000
≥20	45 (76.3)	19 (31.7)		10 (43.5)	10 (43.5)	
<20	14 (23.7)	41 (68.3)		13 (56.5)	13 (56.5)	
ALT, U/L			0.272			0.710
≥40	18 (30.5)	13 (21.7)		5 (21.7)	4 (17.4)	
<40	41 (69.5)	47 (78.3)		18 (78.3)	19 (82.6)	
TBIL (μmol/L)			0.944			0.753
≥17.1	22 (37.3)	22 (36.7)		7 (30.4)	8 (34.8)	
<17.1	37 (62.7)	38 (63.3)		16 (69.6)	15 (65.2)	
PLT ($\times 10^9$/L)			0.636			1.000
≥100	51 (86.4)	50 (83.3)		19 (82.6)	19 (82.6)	
<100	8 (13.6)	10 (16.7)		4 (17.4)	4 (17.4)	
WBC ($\times 10^9$/L)			0.153			0.265
≥4	52 (88.1)	47 (78.3)		20 (87.0)	17 (73.9)	
<4	7 (11.9)	13 (21.7)		3 (13.0)	6 (26.1)	
Hepatic tumor			**<0.001**			0.326
T stage						
0/I	33 (55.9)	54 (90.0)		15 (65.2)	18 (78.3)	
II	26 (44.1)	6 (10.0)		8 (34.8)	5 (21.7)	
PM number			**<0.001**			1.000
Singe	20 (33.9)	42 (70.0)		13 (56.5)	13 (56.5)	
Multiple	39 (66.1)	18 (30.0)		10 (43.5)	10 (43.5)	

The data are expressed as *N* (%).
Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; PLT, platelet; PM, pulmonary metastasis; TBIL, total bilirubin; WBC, white blood cell.

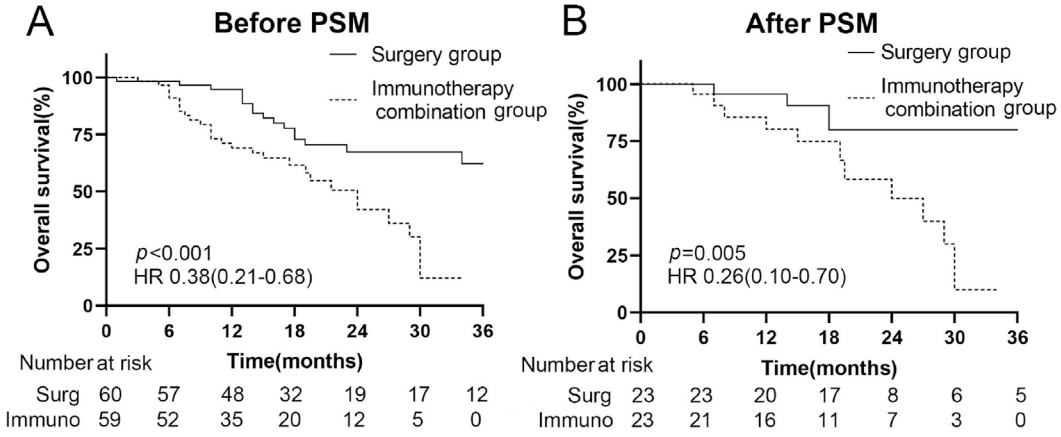

Fig. 2. Comparing OS between two groups before and after PSM. Kaplan-Meier survival curves comparing OS among HCC patients with PM who underwent surgery or immunotherapy combinations before (**A**) and after PSM (**B**). Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; Immuno, immunotherapy combinations; OS, overall survival; PM, pulmonary metastasis; PSM, propensity score matching; Surg, surgery group.

developed diarrhea of CTCAE grade 3. No gastrointestinal bleeding occurred. All patients suffering from leukocytopenia or alanine aminotransferase elevation recovered after completion of immunotherapy combination therapy.

4. Discussion

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, HCC patients with PM are classified as stage C, and systemic

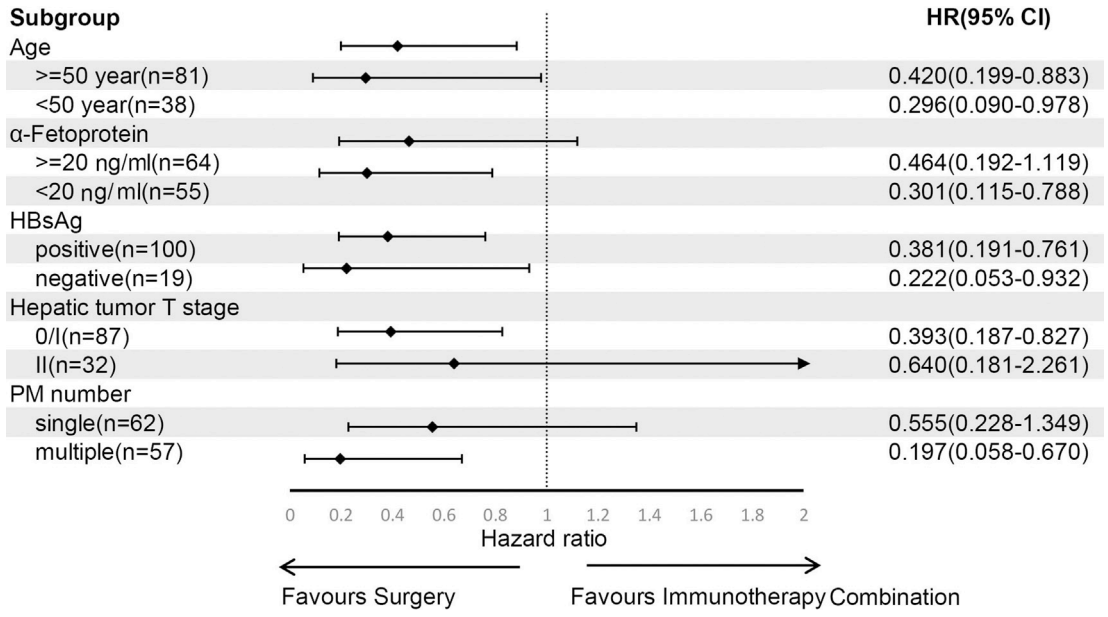

Fig. 3. Subgroup analyses. Abbreviations: CI, confidence interval; HBsAg, hepatitis B surface antigen; HR, hazard ratio; PM, pulmonary metastasis.

Table 2
Prognostic factors for overall survival before and after PSM.

Clinical variables	Before PSM				After PSM			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Treatment allocation, immuno	2.845 (2.524–5.311)	**0.001**	2.177 (1.068–4.439)	**0.032**	4.317 (1.386–13.449)	**0.012**	4.441 (1.413–13.955)	**0.011**
Age, ≥50 years	0.818 (0.446–1.503)	0.518			0.997 (0.338–2.946)	0.996		
Gender, men	0.956 (0.474–1.927)	0.899			1.290 (0.293–5.684)	0.737		
HBsAg, positive	0.890 (0.415–1.912)	0.766			1.042 (0.231–4.702)	0.957		
AFP, ≥20 ng/mL	1.837 (1.006–3.352)	**0.048**	1.219 (0.624–2.382)	0.561	0.641 (0.233–1.764)	0.389		
ALT, ≥40 U/L	0.759 (0.392–1.470)	0.414			0.618 (0.176–1.162)	0.451		
TBIL, ≥17.1 μmol/L	1.015 (0.546–1.885)	0.963			1.287 (0.464–3.569)	0.628		
PLT, ≥100 × 10^9/L	0.976 (0.413–2.307)	0.956			0.620 (0.175–2.197)	0.459		
WBC, ≥4 × 10^9/L	1.473 (0.581–3.736)	0.415			0.839 (0.237–2.974)	0.786		
Hepatic tumor T stage, II	3.053 (1.627–5.728)	**<0.001**	2.342 (1.209–4.538)	**0.012**	2.939 (1.065–8.113)	**0.037**	3.086 (1.087–8.763)	**0.034**
PM number, multiple	1.483 (0.829–2.653)	0.184			0.611 (0.219–1.703)	0.611		

The data are expressed as *N* (%).
Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; HBsAg, hepatitis B surface antigen; HR, hazard ratio; Immuno, immunotherapy combination; PLT, platelet; PM, pulmonary metastasis; PSM, propensity score matching; TBIL, total bilirubin; WBC, white blood cell.

therapy is the recommended first-line treatment strategy. However, it has been reported that HCC patients with PM cannot benefit from sorafenib due to the high drug resistance rate.[18,19] A retrospective study reported that apatinib had only slight therapeutic effects on advanced HCC with PM.[20] Further validation studies are needed for the administration of TKIs alone in HCC patients with PM. As knowledge regarding the mechanisms of tumor immune escape expands, it has been discovered that the inhibition of immune checkpoints could minimize immune exhaustion, reduce Treg activity, and lead to the reactivation of the anticancer immune response.[21–24] ICIs for various cancers with favorable results have also been recently developed. There have been multiple single-agent studies with cytotoxic T-lymphocyte-associated protein 4/programmed cell death protein 1 /programmed death-ligand 1 inhibitors, including tremelimumab,[25] nivolumab,[26] pembrolizumab,[27] durvalumab,[13] and tislelizumab,[28] all yielding similar ORRs of 15%–20% for advanced HCC patients. However, single ICIs did not initially meet their endpoints in phase III trials. In addition to finding predictable biomarkers, combining ICIs with other agents may become another way to improve efficacy.

To the best of our knowledge, this may be the first study to compare the therapeutic efficacy of immunotherapy combined with TKIs with pulmonary metastasectomy for advanced HCC patients with PM. The results showed that receiving pulmonary metastasectomy provided a better long-term prognosis than immunotherapy combined with TKIs for advanced HCC patients with resectable PM. This provides more options for the treatment of this subgroup of HCC patients. Recent studies have demonstrated that combining ICIs with TKIs is a successful strategy in improving OS and resetting the standard of care for advanced HCC patients.[11–14] The IMbrave150 study was an open-label global phase III study evaluating the combination of atezolizumab and bevacizumab versus sorafenib in patients with unresectable HCC, and the recently updated results revealed that the median OS was

19.2 months (95% CI = 17.0–23.7) with atezolizumab plus bevacizumab and 13.4 months (95% CI = 11.4–16.9) with sorafenib (HR = 0.66; 95% CI = 0.52–0.85; descriptive $P < 0.001$).[29] Sintilimab and BI305 have resulted in comparable results.[12] Atezolizumab with bevacizumab and sintilimab with IBI305 are now positioned as first-line therapies for patients with advanced HCC in China. Multiple ongoing clinical trials, and several commonly used combination strategies, such as cabozantinib plus atezolizumab and camrelizumab plus apatinib,[14,30] have already achieved their primary endpoints. All patients in our immunotherapy combination group were treated with the effective combination strategies mentioned above, the ORR was 37.3%, and the median OS was 24 months.

Pulmonary metastases are a known independent risk factor for the prognosis of advanced HCC patients, and effective control of PM significantly improves OS.[18,31,32] Surgical removal of the PM in patients with resectable pulmonary lesions is believed to be the option leading to the best OS.[15,16] It has been reported that the median OS of HCC patients with PM who undergo pulmonary metastasectomy ranges from 10.7 to 77.0 months.[17] These findings are consistent with the results of this study, affirming that treatment allocation and hepatic tumor T stage are independent risk factors affecting OS. In our study, the 3-year survival rate after pulmonary metastasectomy was 20.0%. Successful control of hepatic tumors contributes to the prolongation of the OS of HCC patients with PM, which indicates that local control of hepatic tumors is imperative whether undergoing pulmonary metastasectomy or systemic combination immunotherapy.

Confounding variables in observational studies are often difficult to completely control; however, PSM balances confounding factors among comparison groups through matching technology which improves the accuracy and reliability of our research results. After PSM, the long-term prognosis of the surgery group was confirmed to be significantly better than that of the immunotherapy combination group ($P = 0.005$).

We must acknowledge that our study had limitations. First, the therapeutic drugs used in the immunotherapy combination group were inconsistent. Second, the follow-up period was not long enough for an evaluation of OS. Third, this is a retrospective study, and the sample size was small. A well-designed, multi-institutional, prospective study is warranted to both confirm our findings and further investigate successful options for the treatment of advanced HCC with PM.

5. Conclusions

Pulmonary metastasectomy provided longer survival than immunotherapy combined with TKIs and has the potential to become the optimal treatment for highly selected HCC patients with resectable PM.

Authors' contributions

Juxian Sun, Chang Liu, and Xiandong Tao contributed equally to this paper and should be considered co-first authors. **Juxian Sun:** Writing – original draft, Methodology, Data curation, Conceptualization. **Chang Liu:** Writing – original draft, Methodology, Data curation. **Xiandong Tao:** Writing – review & editing, Methodology, Investigation, Data curation. **Yu Yang:** Writing – review & editing, Methodology, Data curation. **Hai Jin:** Writing – review & editing, Data curation. **Shuqun Cheng:** Writing – review & editing, Methodology, Funding acquisition. **Huazheng Shi:** Writing – review & editing, Supervision, Methodology, Data curation. **Maolin Yan:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Jie Shi:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. All authors approved the final version of the manuscript for publication.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. Research data are not shared, owing to the privacy or ethical restrictions.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work is supported by the School-level project of Naval Medical University (No. 2022MS038); National Natural Science Foundation of China (No.82073293); National Key R&D Program of China (No.2022YFC2503700).

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