Comparing the efficacy of immune checkpoint inhibitors with and without microwave ablation in advanced hepatocellular carcinoma in real-world clinical practice: A retrospective cohort study

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Abstract. Immune checkpoint inhibitors (ICIs) are widely used in the treatment of hepatocellular carcinoma (HCC). Microwave ablation (MWA), a form of thermal ablation, may elicit systemic immune responses and could potentially augment the clinical activity of ICIs, particularly in advanced disease. The present study retrospectively assessed 52 eligible patients with limited progression or oligometastatic disease treated between January 2022 and January 2024 with either ICIs alone or ICIs plus MWA. A total of 21 patients received the combination regimen (predominantly programmed cell death protein 1 inhibitors), and 31 received ICI monotherapy. The recorded baseline characteristics did not suggest notable between-group imbalances; however, key tumor burden descriptors were incompletely captured, and residual confounding cannot be excluded. The objective response rate (ORR) and disease control rate (DCR) were 9.7 and 51.6% with ICIs alone, respectively, vs. 28.6 and 81.0% with ICIs plus MWA. The DCR was higher in the combination group (P=0.031), whereas the between-group difference in ORR was not statistically significant (P=0.133) compared with the monotherapy group. Median overall survival (OS) was 11.0 months with monotherapy and 16.8 months with combination therapy (log-rank P=0.008). In the multivariable Cox analysis, the combination therapy was associated with improved OS (adjusted HR=0.176; 95% CI, 0.048-0.642; Wald P=0.008); however, given the small sample size and limited number of OS events, this adjusted HR may be imprecise and sensitive to model specification and should be interpreted as exploratory. The median progression-free survival (PFS) was 4.0 vs. 9.0 months (log-rank P<0.001), consistent with the multivariable model (adjusted HR=0.270; 95% CI, 0.122-0.595; Wald P=0.001). There was not a clear unexpected safety pattern observed, but safety comparisons were descriptive only and underpowered. In the present retrospective cohort of selected patients with advanced HCC and limited progression/oligometastatic disease, ICIs plus MWA was associated with longer PFS and OS compared with ICIs alone. The interpretation is limited by the small sample size, potential residual confounding and model instability. The direction of benefit was consistent across Kaplan-Meier and Cox analyses, although the adjusted OS effect estimate may be imprecise. The present study was registered on ClinicalTrials.gov on 03 September 2024 (trial no. NCT06581497).

Introduction

Although systemic therapy has improved outcomes in advanced hepatocellular carcinoma (HCC), which accounts for the vast majority of primary liver cancers and remains among the leading causes of cancer-related death worldwide, durable disease control remains limited for many patients, likely due to underlying cirrhosis/liver dysfunction and tumor heterogeneity with an immunosuppressive microenvironment that promotes primary or acquired resistance (1). Thermal ablation (TA) techniques, such as radiofrequency ablation (RFA) and microwave ablation (MWA), are widely accepted for treating HCC, especially for small liver cancers (2-5), and offer a feasible alternative for patients with advanced HCC (1,2,5). MWA has been increasingly adopted due to its practical advantages, including shorter ablation times and larger ablation zones, with local control and overall survival (OS) broadly comparable to RFA (6). MWA has also been reported to induce abscopal effects, with untreated lesions showing regression (7,8). However, similar to other local treatments, recurrence and metastasis after MWA treatment remain notable concerns for patients with HCC.

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Immunotherapy can enhance antitumor immune responses, restore immune recognition of tumor cells and provide durable clinical benefit in a subset of patients with HCC, particularly those who achieve an objective response or sustained disease stabilization with immune checkpoint blockade (1,9,10). It can induce long-lasting antitumor effects through immune memory, achieving durable tumor control (9). Previous research suggests that destruction of HCC lesions can induce or enhance systemic antitumor immune responses (11-13). This response arises from the tumor-associated antigens (TAAs) processed and presented by antigen-presenting cells, followed by the amplification or stimulation of antitumor T cell responses (13,14). After TA, specific T cell reactions can be triggered, leading to an increase in the proportion of circulating activated T cells and natural killer cells, as well as the production of tumor-specific antibodies (15,16). Accordingly, combining MWA with immunotherapy may enhance clinical activity by reducing tumor burden while potentially augmenting antitumor immunity.

Previous studies have shown that MWA can enhance the body's immune response against tumors by releasing more TAAs, particularly 3-8 days after treatment (15,17-19). As ablation-associated immune modulation may be transient (18), combination strategies pairing MWA with immunotherapy have been explored with the aim of improving tumor control and clinical outcomes compared with MWA alone. Prior translational and early clinical studies have suggested that local ablation may augment antitumor immunity and provide a rationale for combination strategies with immunotherapy (11,20). This approach has attracted increasing interest in HCC, due to its potential to enhance both local and systemic immune responses (21).

Although prior studies have suggested potential synergy between thermal ablation and immunotherapy in advanced HCC, optimal management remains uncertain for patients who develop limited progression or oligometastatic disease during systemic therapy and remain technically eligible for local ablation (11,20). Importantly, this clinical scenario differs from prior reports that primarily evaluated ablation as an upfront local therapy or in broader advanced-stage populations without explicitly focusing on limited progression/oligometastatic disease during systemic treatment (2-5,20). In routine practice, these patients represent a distinct clinical subset whom clinicians often consider treating with local cytoreduction of a small number of escaping lesions while continuing immunotherapy, with the intent to prolong systemic disease control. However, real-world evidence specifically evaluating MWA as a targeted salvage local intervention (rather than upfront debulking) in this context remains limited. Therefore, a retrospective cohort study was conducted to assess the efficacy and safety of ICIs plus CT-guided MWA applied to ≤2 technically feasible lesions vs. ICIs alone in advanced HCC patients presenting with limited progression/oligometastatic disease.

Materials and methods

Participants. The present study screened consecutive patients with advanced HCC treated at the Cancer Center of the Second People's Hospital of Neijiang (Neijiang, China) between January 2022 and January 2024. Eligible patients were those who, after prior locoregional and/or systemic therapies, developed limited progression/oligometastatic disease that was considered technically amenable to CT-guided ablation and then received ICIs with or without MWA. In the present study, limited progression/oligometastatic disease was defined as the appearance or growth of ≤3 intrahepatic and/or extrahepatic lesions, with the largest lesion ≤5.0 cm, and no radiographic evidence of macrovascular invasion [(including portal vein tumor thrombus (PVTT)] at the time of treatment decision. According to the China Liver Cancer (CNLC) staging system, included patients were stage IIa, IIb or IIIb (generally corresponding to Barcelona Clinic Liver Cancer stage B/C) (5). Prior treatments commonly included transarterial chemoembolization and hepatic arterial infusion chemotherapy. Baseline demographic, laboratory and available imaging variables were extracted from medical records. The overall cohort comprised 52 patients, including 46 males (88.5%) and 6 females (11.5%), with a median age of 58.5 years (range, 47-71 years). Screening confirmed that none of the 52 patients had radiographic macrovascular invasion at the time of treatment decision. Eligibility also required a largest lesion ≤5.0 cm. While eligibility (largest lesion ≤5.0 cm and site-level assessment) was verified by clinicians during the initial screening of radiology reports and clinical notes to ensure protocol compliance, the exact continuous numerical measurements for all lesions and standardized categorical coding for each specific extrahepatic site were not consistently recorded as structured variables in the retrospective database (52/52 patients for each variable). Consequently, these granular descriptors were not available for formal quantitative comparison between groups. The present study was approved by the Ethics Committee of the Second People's Hospital of Neijiang (approval no. 2026RP-0106-03). The committee approved retrospective use of de-identified clinical data collected during routine care and waived the requirement for a study-specific informed consent form. The present study is registered with ClinicalTrials.gov (trial no. NCT06581497).

Eligibility criteria. Patients were included using the following eligibility criteria: i) Had advanced HCC (CNLC IIa-IIIb); ii) developed limited progression/oligometastatic disease defined as the appearance or growth of ≤3 intrahepatic and/or extrahepatic lesions with the largest lesion ≤5.0 cm; iii) had no radiographic macrovascular invasion, including PVTT, at the time of treatment decision; and iv) received PD-1-based ICIs with or without CT-guided MWA as salvage local therapy. Patients were excluded if they had diffuse progression beyond the oligometastatic definition, uncontrolled comorbidities or contraindications to ablation/immunotherapy per institutional practice, or insufficient follow-up to assess outcomes.

Anti-programmed cell death protein 1 (PD-1) therapy and ablation combination procedures. In the present retrospective study, the ICIs used were PD-1 inhibitors, including pembrolizumab (22), camrelizumab (23), toripalimab (24), tislelizumab (25) and sintilimab (26). ICI dosing and administration followed the manufacturers' prescribing information. Evaluation of treatment responses was conducted every 6-8 weeks using the modified Response Evaluation Criteria in

Solid Tumors (mRECIST) (27). According to mRECIST, complete response (CR) is defined as the disappearance of any intratumoral arterial enhancement in all target lesions; partial response (PR) is characterized by a ≥30% reduction in the sum of diameters of viable (enhancing) target lesions from baseline; and progressive disease (PD) is identified by an increase of ≥20% from baseline. MWA was performed under CT guidance within 10-14 days following the baseline imaging assessment to ensure feasibility. Subsequent immunotherapy was administered or resumed within 3-7 days after ablation. The ablation procedure was intended to achieve complete ablation of the target lesions (up to two lesions selected based on technical feasibility), whether intrahepatic or extrahepatic, in a single session. If up to three lesions met the oligometastatic definition, MWA was prioritized for the dominant/progressing lesions considered most technically feasible, and the remaining lesions continued to be managed with ongoing systemic therapy and/or other clinically indicated locoregional approaches per the discretion of the treating physician.

Safety and efficacy. Adverse events (AEs) were monitored throughout immunotherapy and up to 90 days after the last administered dose and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) (28). Continuous safety evaluations were conducted. If a patient experienced Grade ≥3 AEs or intolerable Grade 2 treatment-related AEs, treatment interruption and supportive management were implemented according to institutional practice and the prescribing information of the ICIs. Treatment was resumed once AEs improved to Grade 1-2 when clinically appropriate; permanent discontinuation was considered in cases of severe toxicity or substantial clinical disease progression. In the combination group, switching to an alternative ICI agent was permitted at the discretion of the treating physician. Procedure-related complications of ablation were assessed during the immediate post-procedure period (0-24 h) and the post-procedural period (1-30 days). Tumor response was evaluated by imaging using mRECIST. Disease control rate (DCR) was defined as the proportion of patients achieving CR, PR or stable disease (SD) as their best overall response according to mRECIST. The waterfall plot was based on mRECIST target-lesion response assessments recorded for routine efficacy evaluation, rather than on uniformly extractable baseline whole disease tumor burden descriptors; therefore, these target lesion measurements cannot substitute for standardized baseline maximum lesion diameter or metastatic site coding.

Collection of data and study objectives. The follow-up process included regular phone calls or outpatient visits. All patients underwent postoperative imaging and a comprehensive evaluation within 1 month after treatment. Follow-up visits occurred every 3 weeks, during which blood tests [a-fetoprotein (AFP), total bilirubin and alanine aminotransferase] were performed. Contrast-enhanced CT or magnetic resonance imaging (MRI) scans were conducted every 3 months.

Statistical analysis. The statistical analysis was performed using IBM SPSS Statistics (version 26.0; IBM Corp.). As this was a retrospective, single-center study with strict eligibility criteria (limited progression/oligometastatic disease amenable to ablation), the cohort size (n=52) reflected the number of consecutive eligible patients treated during the study period rather than an a priori sample-size calculation. The analysis should be regarded as exploratory and hypothesis-generating. Effect sizes [hazard ratios (HRs) with 95% CIs] are reported alongside P-values; findings should be interpreted cautiously due to the limited sample size and number of outcome events.

Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were considered; however, they were not implemented because the small cohort size, limited number of events and incomplete availability of key baseline tumor-burden variables which could yield unstable matches or extreme weights. The sample size is comparable to other single-center real-world retrospective cohorts evaluating locoregional therapy combined with immunotherapy in advanced HCC, which commonly include several dozen patients (16,17).

Categorical variables are presented as frequencies and percentages. Group comparisons were performed using Pearson's χ^2 test or Fisher's exact test, as appropriate based on the expected frequencies [for example Pearson's χ^2 test for DCR and Fisher's exact test for objective response rate (ORR) and other variables with small cell counts]. Continuous variables were compared using the Mann-Whitney U test. OS and progression-free survival (PFS) were estimated using the Kaplan-Meier method and compared using the log-rank test. Median OS and PFS with 95% CIs were calculated using the Brookmeyer-Crowley method. HRs and 95% CIs were estimated using univariable and multivariable Cox proportional hazards models to identify independent prognostic factors. A two-sided $P<0.05$ was considered to indicate a statistically significant difference. No adjustment was applied for multiple comparisons; P-values are therefore reported for descriptive inference. As the cohort size and event counts were small, multivariable Cox estimates may be unstable and should be interpreted as exploratory. The adjusted models were therefore interpreted alongside the Kaplan-Meier curves and univariable Cox results.

Results

Patient demographic and baseline clinical characteristics. From January 2022 to January 2024, a total of 52 eligible patients meeting the inclusion and exclusion criteria were enrolled in the present study. Among them, 31 patients underwent ICI monotherapy, while 21 patients received a combination therapy involving MWA and ICIs (Fig. 1). The recorded baseline characteristics were broadly similar between groups (Table I). The majority of the study population was male (88.5%), and hepatitis B virus (HBV) infection was identified as the primary cause of HCC in 88.5% of the cases. Importantly, all patients testing positive for HBV surface antigen received antiviral treatment, utilizing either entecavir or tenofovir.

Treatment efficacy

Short-term therapeutic efficacy. Among the 31 patients receiving ICIs, 1 (3.2%) achieved CR, 2 (6.5%) achieved PR, 13 (41.9%) had SD, 13 (41.9%) had PD and 2 (6.5%) were not

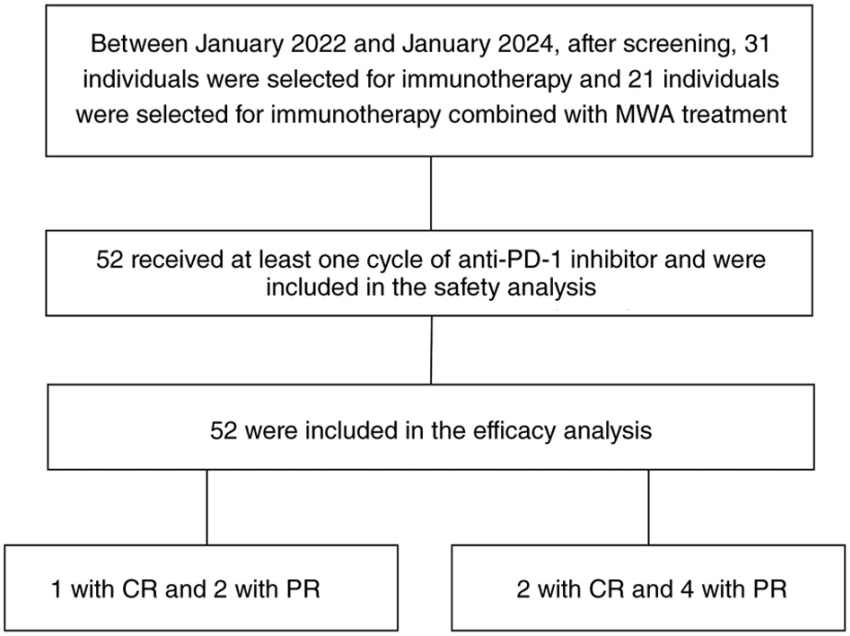

Figure 1. Patient selection flow. MWA, microwave ablation; PD-1, programmed cell death protein 1; CR, complete response; PR, partial response.

assessable. By contrast, among the 21 patients treated with MWA plus ICIs, 2 (9.5%) achieved CR, 4 (19.0%) achieved PR, 11 (52.4%) had SD, 3 (14.3%) had PD and 1 (4.8%) was not assessable (Table II). The ORR was 28.6% (6/21) in the combination group vs. 9.7% (3/31) with ICIs alone, and the DCRs were 81.0% (17/21) vs. 51.6% (16/31), respectively. Based on the distribution of expected frequencies, the improvement in DCR reached statistical significance (P=0.031; Pearson's χ^2 test). ORR was higher in the combination group but was not statistically significant (P=0.133; Fisher's exact test). A total of 3 patients had non-assessable responses due to atypical post-treatment imaging findings and/or insufficient imaging data that precluded classification as CR, PR, SD or PD according to mRECIST; these cases were recorded as 'not assessable' in Table II. Fig. 2 shows that a greater proportion of patients in the MWA plus ICI group experienced tumor shrinkage of the target lesions and fewer patients had marked target-lesion growth compared with the ICI-alone group, consistent with the higher DCR observed in the combination cohort. Fig. 3 further demonstrates that responses and disease stabilization were generally more durable in the MWA plus ICI group, whereas earlier progression events were more frequent with ICI monotherapy. Figs. 4-6 provide representative longitudinal imaging examples from the combination group, illustrating complete ablation of the treated lesions with loss of arterial enhancement on follow-up CT/MRI, accompanied by decreasing target-lesion size over time and corresponding declines in serum AFP in responding patients.

Long-term efficacy. The data cutoff was June 2025; median OS for the overall cohort was 15.1 months and median PFS was 6.0 months (Fig. 7A and B). Compared with the ICI monotherapy group, the MWA plus ICIs group achieved a longer median OS (11.0 vs. 16.8 months; log-rank P=0.008; Fig. 7C). The median PFS was also longer in the combination group (4.0 vs. 9.0 months; log-rank P<0.001; Fig. 7D). HRs with 95% CIs were estimated using Cox proportional hazards models and are provided in Tables III and IV; due to the small number of events, the adjusted OS HR should be interpreted together with the Kaplan-Meier curves and the more conservative univariable estimate.

In patients with AFP ≥400 ng/ml, median OS (9.0 vs. 17.0 months; log-rank P=0.042; Fig. 8A) and median PFS (2.5 vs. 8.0 months; log-rank P<0.001; Fig. 8B) were longer in the MWA plus ICIs group. In the subgroup with AFP <400 ng/ml, no statistically significant differences in OS or PFS were observed between groups (Fig. 8C and D).

Analysis of prognostic factors. The Cox univariate analysis revealed that OS and PFS were influenced by factors such as MWA combined with ICIs treatment and AFP concentration. Elevated AFP concentration was identified as a risk factor associated with decreased OS (P=0.047) and PFS (P=0.013). Conversely, receipt of MWA plus ICIs was associated with improved OS (HR=0.585; 95% CI, 0.155-0.992; P=0.046) and PFS (HR=0.386; 95% CI, 0.198-0.753; P=0.005) in univariable Cox models. These associations remained significant in multivariable Cox models adjusting for available covariates for both OS (HR=0.176; 95% CI, 0.048-0.642; Wald P=0.008) and PFS (HR=0.270; 95% CI, 0.122-0.595; Wald P=0.001) (Tables III and IV). The adjusted OS HR was notably smaller than the univariable estimate and may reflect an unstable model in this small dataset. The OS trend is therefore more informative than the exact adjusted OS point estimate. Notably, the adjusted HR for AFP in the OS model (HR=5.912; 95% CI, 1.669-20.941) showed a wide confidence interval, suggesting potential sparse-data bias or model overfitting due to the small number of events; therefore, this covariate estimate should be interpreted with caution.

Safety profile. Safety analyses were descriptive only. The present study did not observe a clear unexpected safety pattern, but it was underpowered for formal between-group

Table I. Patient baseline demographic and clinical characteristics.

Variables	ICIs (n=31)	MWA + ICIs (n=21)	P-value
Median age, years (range)	59 (48-71)	58 (47-69)	0.555
Age category, years[a]			
<65	21 (67.7)	15 (71.4)	
≥65	10 (32.3)	6 (28.6)	
Sex			0.380
Male	26 (83.9)	20 (95.2)	
Female	5 (16.1)	1 (4.8)	
ECOG performance status			0.282
0	13 (41.9)	12 (57.1)	
1	18 (58.1)	9 (42.9)	
Hepatitis B surface antigen			0.672
Negative	3 (9.7)	3 (14.3)	
Positive	28 (90.3)	18 (85.7)	
Hepatitis C virus antibody			0.672
Negative	28 (90.3)	18 (85.7)	
Positive	3 (9.7)	3 (14.3)	
AFP			0.327
<400 ng/ml	13 (41.9)	6 (28.6)	
≥400 ng/ml	18 (58.1)	15 (71.4)	
CNLC stage			0.895
IIa	5 (16.1)	3 (14.3)	
IIb	12 (38.7)	7 (33.3)	
IIIb	14 (45.2)	11 (52.4)	
Total bilirubin			0.943
≤20 μmol/l	13 (41.9)	9 (42.9)	
>20 μmol/l	18 (58.1)	12 (57.1)	
Alanine aminotransferase			0.236
<50 U/l	17 (54.8)	8 (38.1)	
≥50 U/l	14 (45.2)	13 (61.9)	
Number of active tumors			0.822
1	23 (74.2)	15 (71.4)	
2-3	8 (25.8)	6 (28.6)	

Data are presented as n (%). P-values were calculated using the Pearson's χ^2 test or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables. For 2x2 categorical variables, Fisher's exact test was used when any expected cell count was <5; otherwise Pearson's χ^2 test was used. [a]Age as a categorical variable (<65/≥65) is presented as a descriptive distribution without a separate P-value. ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; CNLC, China Liver Cancer; MWA, microwave ablation; ICIs, immune checkpoint inhibitors.

comparisons (Table V). Any-grade hepatic laboratory abnormalities were common in both groups. Numerically, some laboratory abnormalities were more frequent in the combination cohort (such as Grade 3-4 transaminitis was 33.3 vs. 0.0%), which is consistent with the transient acute liver injury expected following thermal ablation, but between-group comparisons were underpowered and should be interpreted descriptively. Treatment-emergent AEs were defined as events occurring during ICI therapy and up to 90 days after the last dose; procedure-related events following MWA were additionally assessed within 0-24 h and 1-30 days post-procedure. The final AE tabulation applied the same prespecified safety window uniformly across both cohorts to minimize misclassification. Between-group comparisons were descriptive and used Fisher's exact test because of small cell counts, without adjustment for multiple comparisons. Transaminitis and hyperbilirubinemia were the most common AEs in both groups. The high incidence of any-grade hyperbilirubinemia in the combination cohort (85.7%) may, at least in part, reflect transient post-ablation liver injury rather than prolonged systemic drug toxicity. In the combination cohort, Grade 3-4 transaminitis was observed in 7 patients (33.3%)

Table II. Short-term efficacy.

Response	ICIs (n=31)	ICIs + MWA (n=21)	P-value
CR	1 (3.2)	2 (9.5)	-
PR	2 (6.5)	4 (19.0)	-
SD	13 (41.9)	11 (52.4)	-
PD	13 (41.9)	3 (14.3)	-
Not assessable	2 (6.5)	1 (4.8)	-
ORR[a], %	9.7	28.6	0.133
DCR[b], %	51.6	81.0	0.031

ORR and DCR were calculated on an intention-to-treat basis, counting 'not assessable' as non-responders; sensitivity analyses excluding not-assessable cases yielded similar trends. [a]P-values for ORR and individual response categories (CR, PR, SD, PD) were calculated using Fisher's exact test due to small, expected cell counts; [b]P-values for DCR were calculated using Pearson's χ^2 test. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; MWA, microwave ablation; ICIs, immune checkpoint inhibitors.

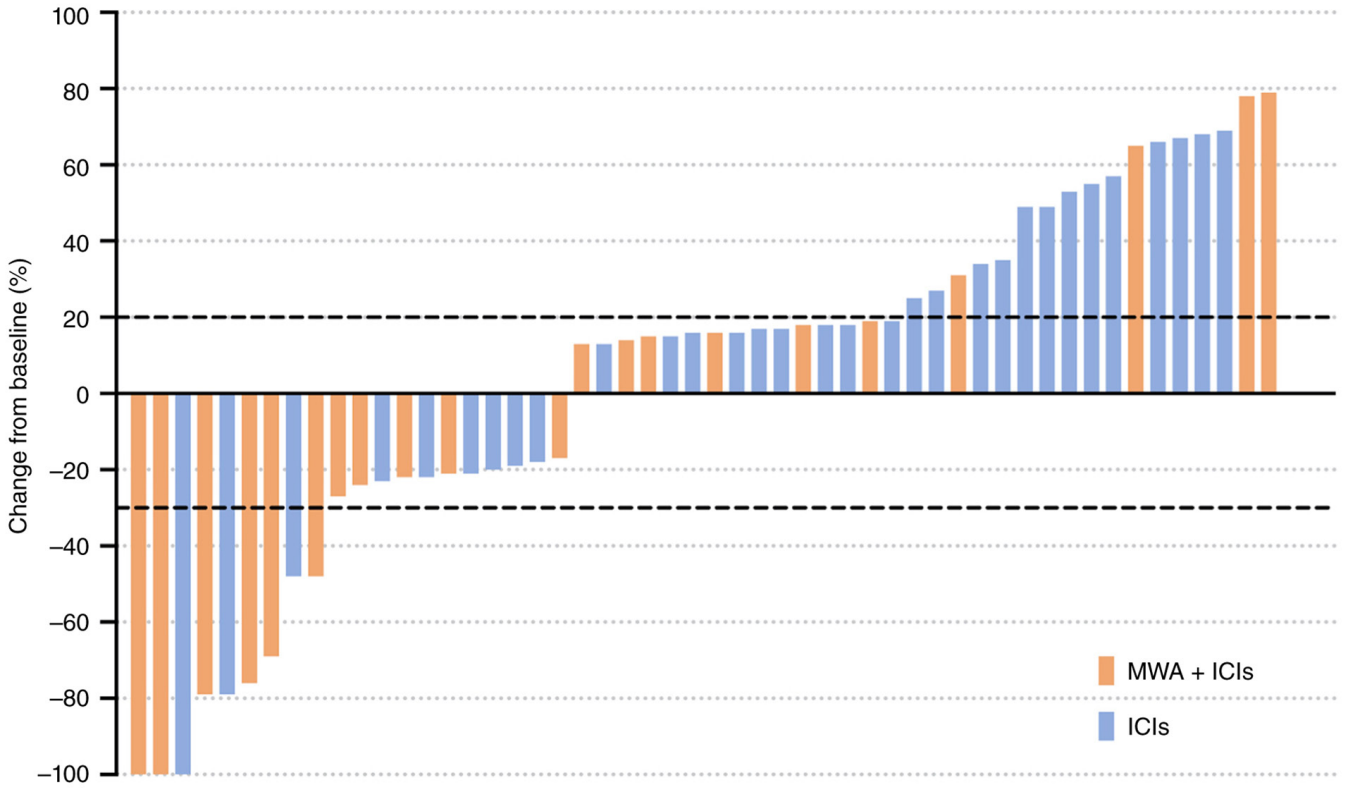

Figure 2. Waterfall plot of target lesion size. Percentage change in target lesion size compared with baseline in 52 patients. The percentage change was calculated from modified Response Evaluation Criteria in Solid Tumors target-lesion measurements used for routine response assessment and does not represent standardized baseline whole-disease tumor burden variables (such as structured maximum lesion diameter or metastatic site coding). MWA, microwave ablation; ICIs, immune checkpoint inhibitors.

and Grade 3-4 hyperbilirubinemia in 5 patients (23.8%). In the ICIs alone cohort, Grade 3-4 transaminitis was not observed, although Grade 3-4 hyperbilirubinemia occurred in 3 patients (9.7%).

Regarding the categorization of AEs, while all events were monitored, immune-related AEs (irAEs) were not prospectively tracked as a distinct, strictly defined category separate from other treatment-emergent or procedure-related AEs in the present retrospective dataset. These events were managed with temporary ICI interruption when indicated, hepatoprotective therapy and corticosteroids when an immune-related mechanism was clinically suspected, and they generally improved to Grade 1-2 without permanent organ dysfunction. Treatment discontinuation due to toxicity occurred in 3/21 patients (14.3%) in the combination group and 5/31 patients (16.1%) in the monotherapy group, whereas discontinuation due to disease progression occurred in 11/21 (52.4%) and 19/31 (61.3%) patients, respectively.

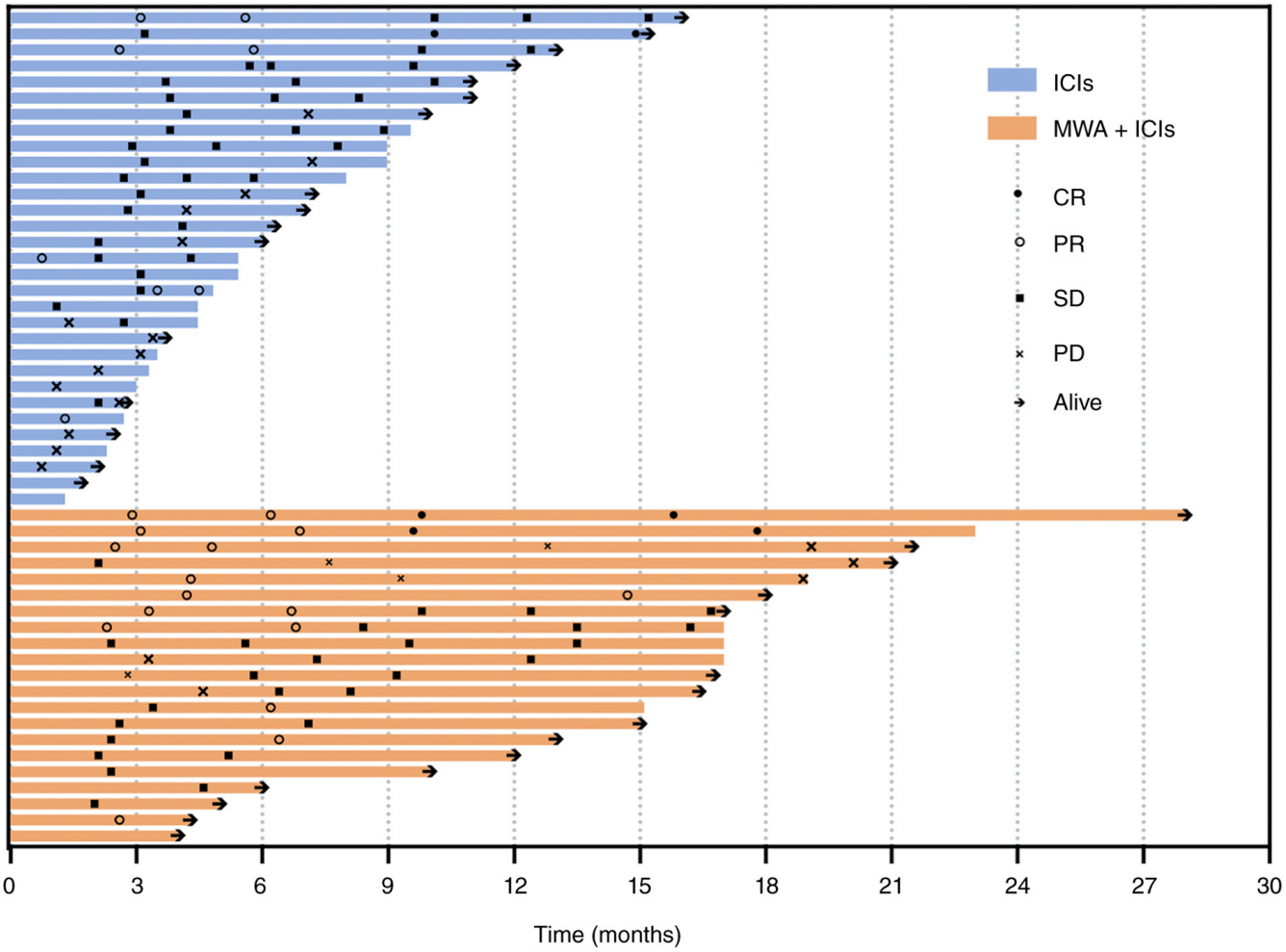

Figure 3. Swimmer plot of response duration and current status for the 52 patients. MWA, microwave ablation; ICIs, immune checkpoint inhibitors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

With respect to MWA-related local reactions, events were primarily consistent with post-ablation syndrome (such as transient fever and localized pain) and resolved within a few days with conservative symptomatic care. No major procedure-related complications (severe hemorrhage, bile duct injury, liver abscess or treatment-related mortality) occurred in the combination cohort.

Discussion

MWA is widely used as a locoregional treatment for HCC and is recommended as a first-line option for local therapy in the 2022 Chinese Society of Clinical Oncology guidelines (29). The high temperatures generated during MWA lead to coagulation and necrosis of HCC tissue, reducing tumor burden and disrupting the immunosuppressive environment of the tumor. This process exposes TAAs, promotes the synthesis of heat shock proteins and effectively activates antitumor immune responses (14,21). Despite its potential, the efficacy of MWA may be limited by high postoperative recurrence and metastasis rates.

Immunosuppression serves a key role in cancer recurrence and metastasis (30-34). Immunotherapy aims to boost the body's immune system to TAAs and induce tumor cell death. When combined with other treatments, immunotherapy can reduce the risk of both local and distant recurrence. However, tumor-induced immune suppression often weakens the effectiveness of immunotherapy. MWA helps to overcome this by eliminating tumor cells and releasing antigens from apoptotic and necrotic tissue. Evidence from animal models and clinical studies suggests that MWA induces immunogenic tumor cell death, releasing tumor-associated antigens and damage-associated molecular patterns (such as high mobility group box 1/ATP/heat-shock proteins) that promote dendritic-cell activation and antigen cross-presentation, thereby priming cytotoxic $CD8^+$ T cell responses via type I interferon-linked pathways (including cyclic GMP-AMP synthase-stimulator of interferon genes), while also modulating the tumor microenvironment and checkpoint signaling (such as programmed death ligand 1 upregulation), providing a rationale for combination with ICIs (1,11,14). However, this response tends to be short-lived, and the post-MWA window may be the optimal time to enhance antitumor immunity.

Accordingly, combining MWA with immunotherapy has been proposed as a potentially effective treatment strategy (8,15,20,21). However, while earlier proof-of-concept and retrospective reports have established the rationale for this combination, data specifically focusing on its use as a

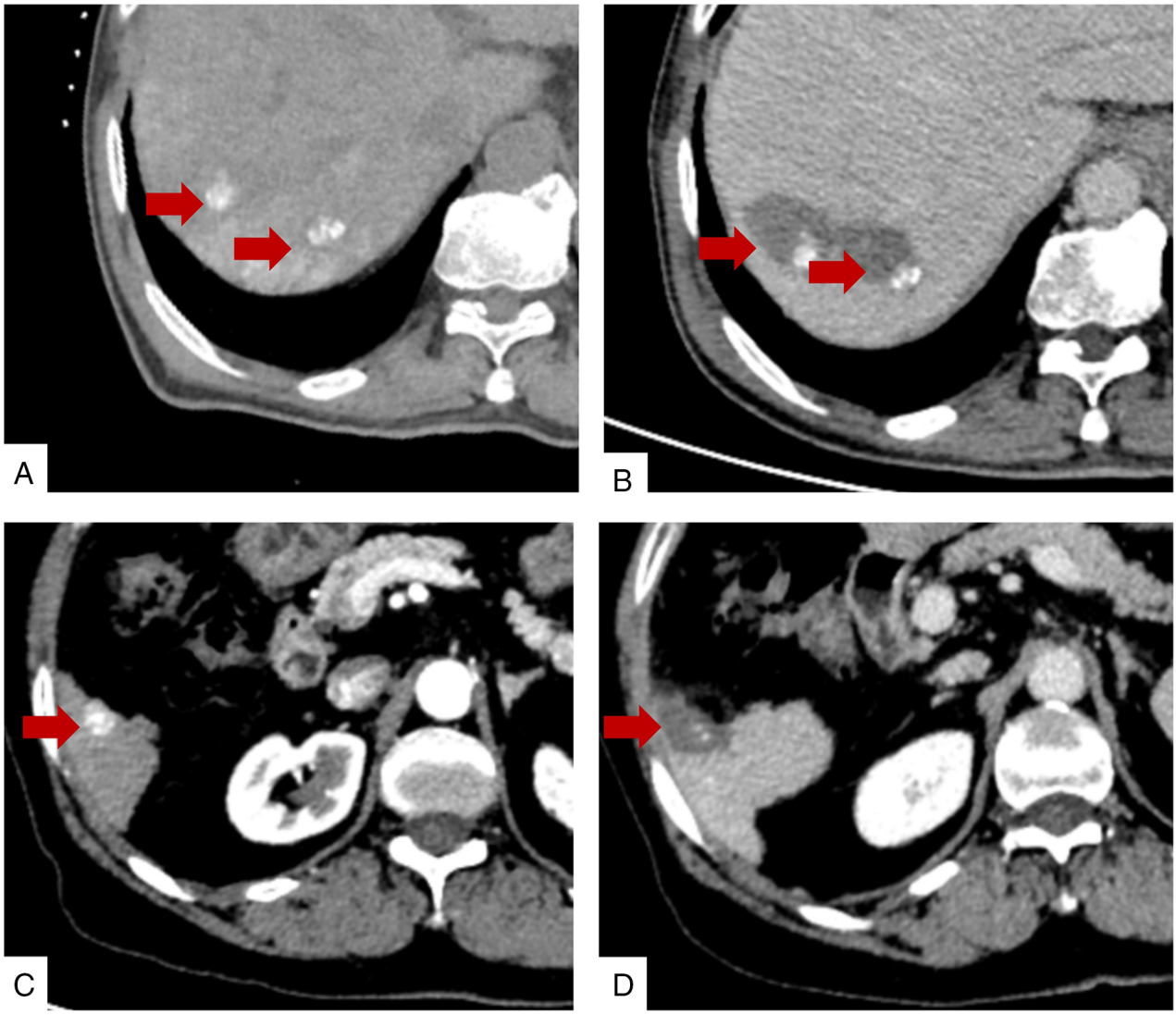

Figure 4. Comparison of imaging before and after combined treatment for patients. (A) CT scan of a 49-year-old male patient revealed tumor recurrence following transcatheter arterial embolization. (B) At 1 month after undergoing microwave ablation, a follow-up CT scan showed no enhancement in the tumor area. (C) A 69-year-old female patient, who had undergone liver resection, was found to have a right intrahepatic metastatic nodule measuring 1.1 cm in diameter on an enhanced CT scan 3 months post-surgery. (D) At 2 months after microwave ablation, a re-examination CT scan showed no enhancement in the tumor area.

rescue therapy for patients with limited progression remain relatively scarce. The present study builds on prior reports by evaluating this clinical scenario in a real-world setting. In the selected retrospective cohort, MWA as a targeted intervention for limited progression was associated with longer mPFS (9.0 vs. 4.0 months) and mOS (16.8 vs. 11.0 months) than ICI monotherapy. The direction of association was consistent in the Kaplan-Meier analyses and in both univariable and multivariable Cox models, but the adjusted OS effect size should be interpreted cautiously in view of model instability.

The outcomes of the present study should not be directly compared with external trials because of differences in patient selection, line of therapy and study design. For instance, in the KEYNOTE-224 trial evaluating second-line pembrolizumab monotherapy, the ORR was 17%, with an mPFS of 4.9 months and an mOS of 12.9 months (22). The present ICIs monotherapy group demonstrated comparable baseline outcomes (ORR of 9.7%, mPFS of 4.0 months and mOS of 11.0 months). By contrast, the present combination cohort achieved a significantly improved DCR of 81.0% and a numerically higher ORR of 28.6%, alongside extended mPFS (9.0 months) and mOS (16.8 months). The between-group difference in ORR did not reach significance, which may reflect limited power in this small cohort. These findings are broadly consistent with prior retrospective reports of ablation-immunotherapy combinations, which have reported median PFS values in the range of 5-8 months (17,20). The observed survival differences may reflect, at least in part, a combination of local cytoreduction by MWA and immunologic effects related to tumor-associated antigen release, which could potentially augment systemic ICI activity. In the univariable Cox analysis, the OS HR was 0.585, whereas in the multivariable model the adjusted HR shifted further away from the null (HR=1.0) to 0.176, suggesting a stronger apparent association after covariate adjustment; however, due to the small sample size and limited number of events, this shift may reflect model sensitivity/instability and should be interpreted cautiously. In

Table III. Univariate and multivariate analysis of overall survival in patients with advanced hepatocellular carcinoma.

	Univariate analysis		Multivariate analysis	
Variables	HR	P-value	HR	P-value
Age (per year)	1.040 (0.994-1.089)	0.090	1.025 (0.972-1.082)	0.363
Sex (male/female)	1.091 (0.324-3.669)	0.888	0.772 (0.185-3.225)	0.723
ECOG performance status (0/1)	1.777 (0.755-4.18)	0.188	1.592 (0.544-4.658)	0.395
Hepatitis B surface antigen	0.778 (0.231-2.615)	0.685	0.435 (0.101-1.871)	0.263
AFP (<400/≥400 ng/ml)	2.558 (1.011-6.467)	0.047	5.912 (1.669-20.941)	0.006
CNLC stage				
IIb	1.396 (0.608-3.207)	0.432	0.903 (0.214-3.799)	0.889
IIIb	0.728 (0.314-1.688)	0.459	1.604 (0.38-6.761)	0.520
Total bilirubin	1.447 (0.633-3.31)	0.381	2.154 (0.783-5.924)	0.137
Alanine aminotransferase	0.928 (0.406-2.122)	0.860	1.093 (0.411-2.908)	0.858
Number of active tumors	1.044 (0.411-2.651)	0.928	1.046 (0.315-3.477)	0.942
Treatment (MWA + ICIs vs. ICIs)	0.585 (0.155-0.992)	0.046	0.176 (0.048-0.642)	0.008

MWA, microwave ablation; ICIs, immune checkpoint inhibitors; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; CNLC, China Liver Cancer; HR, hazard ratio.

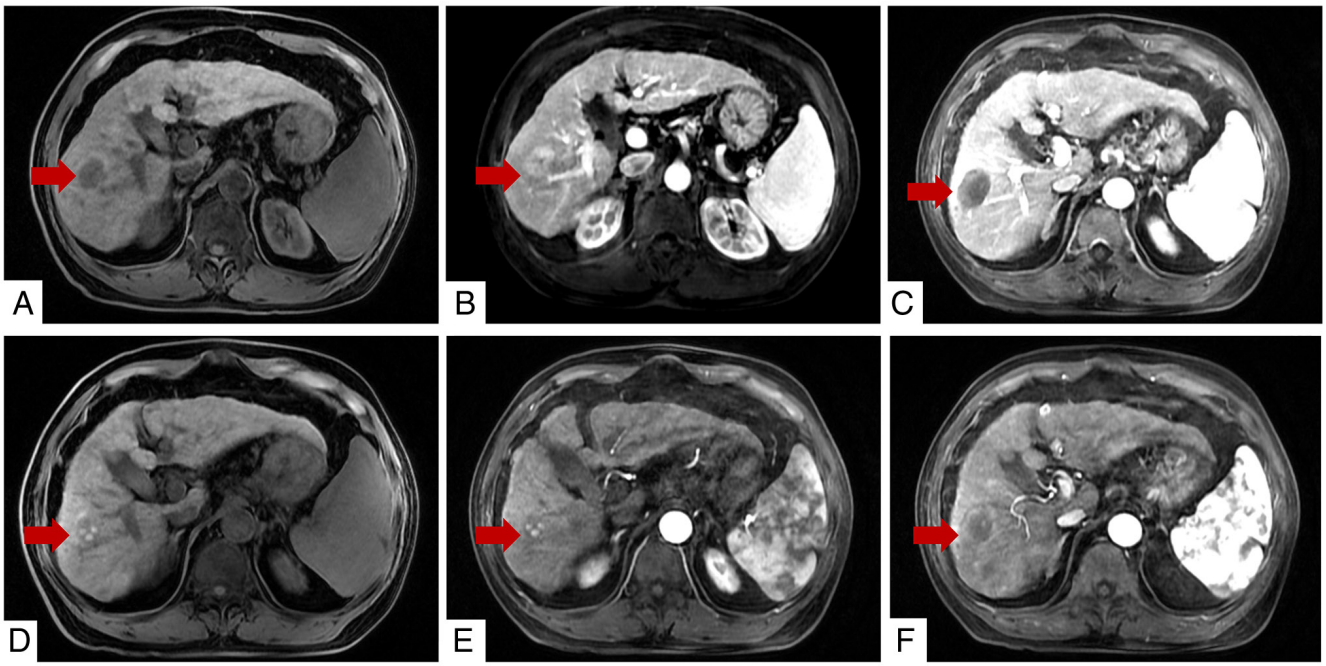

Figure 5. Comparison of pre- and post-treatment MRI of a patient undergoing combination therapy. (A) Baseline T1-weighted image shows a new lesion in the right lobe of the liver. (B) Baseline arterial-phase contrast-enhanced MRI shows typical arterial hyperenhancement of the lesion. (C) Baseline portal venous-phase image shows washout. (D) At 1 month after microwave ablation combined with immunotherapy, follow-up T1-weighted image shows the treated lesion/ablation zone. (E) Follow-up arterial-phase image shows no notable enhancement. (F) Follow-up portal venous-phase image also shows no notable enhancement.

addition, log-rank and Cox tests are based on different statistics and may yield different P-values, particularly in small cohorts with limited events. This discrepancy, together with the wide confidence interval, suggests possible sparse-data bias or overfitting in the small-event setting. Therefore, interpretation should emphasize the consistent direction of association across Kaplan-Meier and Cox analyses rather than the point estimate of the adjusted OS HR. For PFS, receipt of MWA plus ICIs was also associated with improved outcome after adjustment after adjusting for available covariates, such as baseline AFP levels. The present study was not powered to establish comparable safety between groups, and the AE findings should be interpreted descriptively.

The present study is limited by its retrospective design and potential selection bias. Patients selected for MWA necessarily had anatomically feasible lesions, which may have been

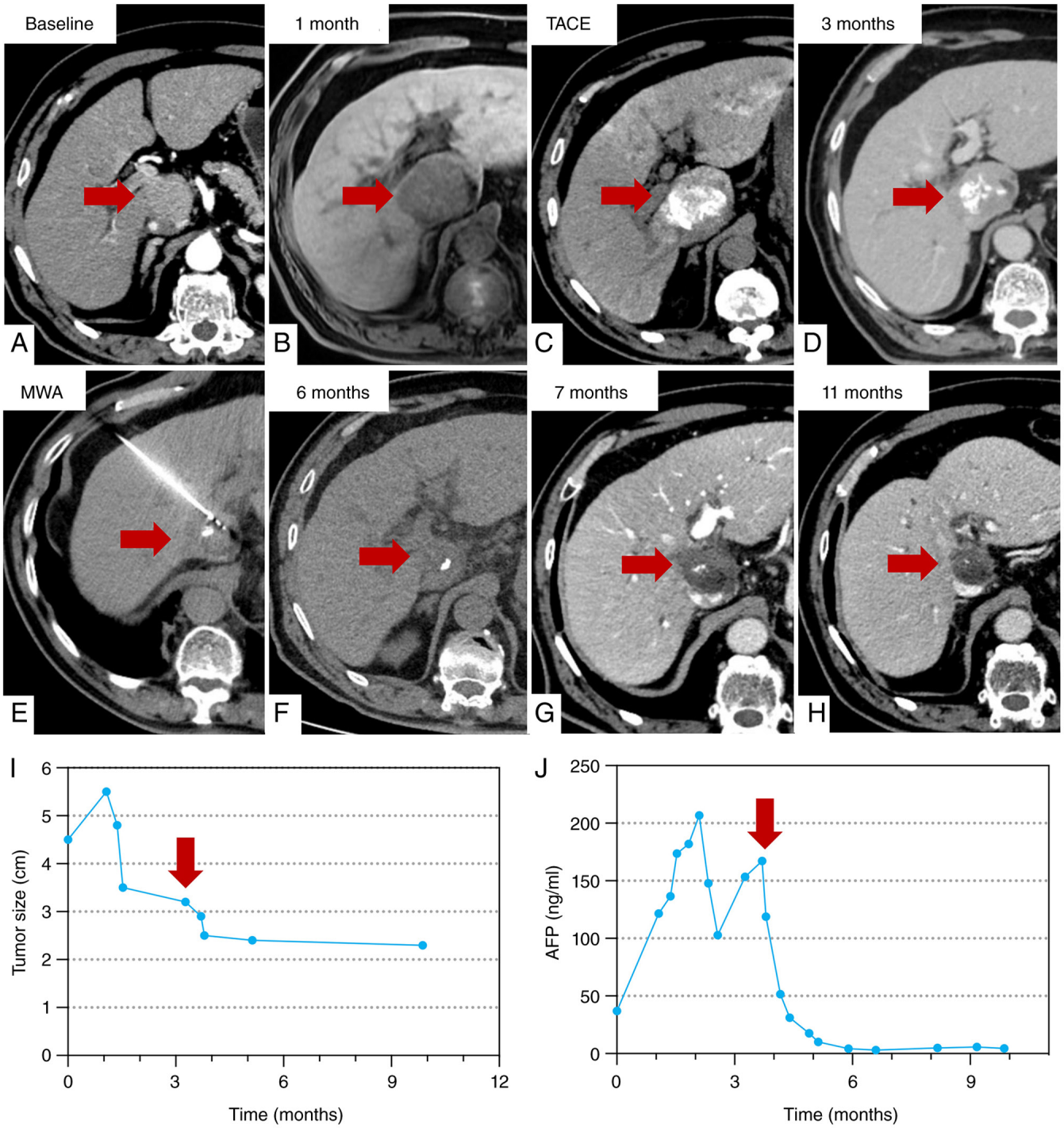

Figure 6. Imaging examination of patients who responded to combination therapy. (A) At initial diagnosis (November 2022), a mass was identified in the caudate lobe of the liver. (B) On re-examination (January 2023), the mass had increased in size. (C) CT scan after transarterial chemoembolization (TACE) showing lipiodol deposition within the tumor. (D) The intrahepatic lesion recurred 2 months after first-line treatment. (E) The patient subsequently underwent MWA. (F) Follow-up CT scan at 6 months showing the post-ablation zone. (G) Follow-up CT scan at 7 months demonstrating continued stable disease. (H) An enhanced CT scan revealed a reduction in tumor size from 4.5 cm at baseline to 2.2 cm after MWA treatment. (I) The dynamic changes in lesion size before and after MWA are shown. (J) The dynamic curve of serum AFP concentration before and after MWA is illustrated. The red arrow in diagram I and J indicates the time point of ablation. MWA, microwave ablation; AFP, α-fetoprotein; TACE, transarterial chemoembolization.

associated with a more favorable baseline disease profile than that of patients treated with ICIs alone. Screening confirmed that none of the 52 patients had radiographic macrovascular invasion at the time of treatment decision, and eligibility required a largest lesion ≤5.0 cm. While eligibility (largest lesion ≤5.0 cm and site-level assessment) was verified by clinicians during the initial screening of radiology reports and clinical notes to ensure protocol compliance, the exact continuous numerical measurements for all lesions and standardized categorical coding for each specific extrahepatic site were not consistently recorded as structured variables in the retrospective database (52/52 patients for each variable).

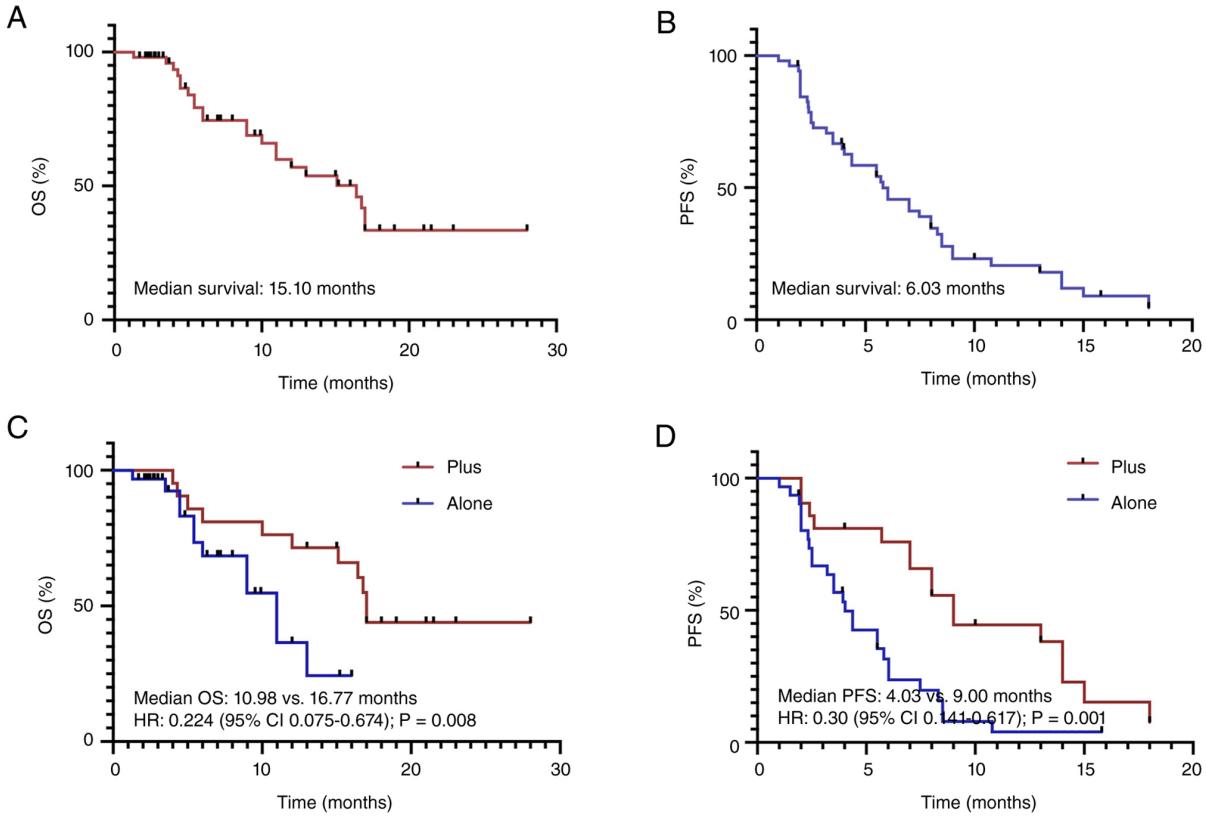

Figure 7. Kaplan-Meier curves of OS and PFS for the two groups. (A) The OS of the entire population. (B) The PFS of the entire population. (C) OS of two groups of patients. (D) PFS of two groups of patients. The red line represents the MWA combined with ICI treatment group, and the blue line represents the ICI monotherapy group. Plus, ICIs in collaboration with MWA; alone, ICIs; OS, overall survival; PFS, progression-free survival; MWA, microwave ablation; ICIs, immune checkpoint inhibitors.

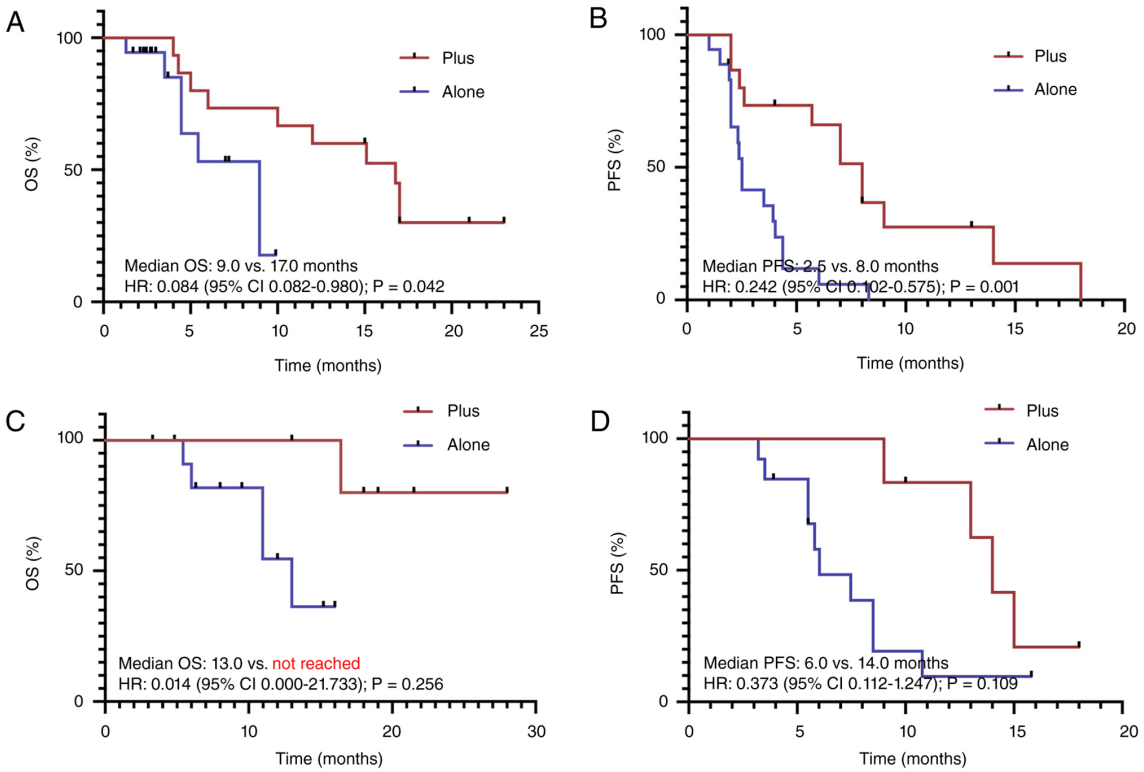

Figure 8. Kaplan-Meier curves of OS and PFS in the AFP subgroups. (A) OS in patients with AFP ≥400 ng/ml. (B) PFS in patients with AFP ≥400 ng/ml. (C) OS in patients with AFP <400 ng/ml. (D) PFS in patients with AFP <400 ng/ml. The red line represents the MWA plus ICIs group, and the blue line represents the ICIs monotherapy group. Plus, ICIs in collaboration with MWA; alone, ICIs; OS, overall survival; PFS, progression-free survival; MWA, microwave ablation; ICIs, immune checkpoint inhibitors; AFP, α-fetoprotein.

Table IV. Univariate and multivariate analysis of PFS in patients with advanced HCC.

	Univariate analysis		Multivariate analysis	
Variables	HR	P-value	HR	P-value
Age (per year)	1.000 (0.971-1.03)	0.997	1.010(0.976-1.045)	0.578
Sex (male/female)	0.691 (0.289-1.656)	0.408	0.398 (0.134-1.184)	0.098
ECOG performance status (0/1)	1.060 (0.573-1.96)	0.853	0.779 (0.36-1.685)	0.527
Hepatitis B surface antigen	0.943 (0.368-2.416)	0.903	0.510 (0.169-1.543)	0.233
AFP(<400/≥400 ng/ml)	2.276 (1.188-4.361)	0.013	4.327 (1.853-10.106)	0.001
CNLC stage				
IIb	1.082 (0.582-2.013)	0.802	0.803 (0.274-2.357)	0.690
IIIb	0.843 (0.453-1.569)	0.589	1.368 (0.504-3.713)	0.539
Total bilirubin	1.023 (0.557-1.878)	0.943	0.891 (0.45-1.763)	0.740
Alanine aminotransferase	1.068 (0.585-1.949)	0.831	0.790 (0.389-1.605)	0.515
Number of active tumors	1.266 (0.619-2.59)	0.519	1.512 (0.588-3.887)	0.391
Treatment (MWA + ICIs vs. ICIs)	0.386 (0.198-0.753)	0.005	0.270 (0.122-0.595)	0.001

MWA, microwave ablation; ICIs, immune checkpoint inhibitors; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; CNLC, China Liver Cancer; HR, hazard ratio.

Table V. Comparison of complications between the two groups.

	Grade 3-4			Any grade[a]		
AEs	ICIs + MWA (n=21)	ICIs (n=31)	P-value	ICIs + MWA (n=21)	ICIs (n=31)	P-value
Fatigue	0	0	-	0	2 (6.5)	0.509
Transaminitis	7 (33.3)	0	0.001	7 (33.3)	11 (35.5)	>0.999
Fever	0	0	-	4 (19.0)	2 (6.5)	0.207
Diarrhea	0	0	-	8 (38.1)	13 (41.9)	>0.999
Pneumonitis	0	0	-	4 (19.0)	2 (6.5)	0.207
Hyperbilirubinemia	5 (23.8)	3 (9.7)	0.244	18 (85.7)	20 (64.5)	0.118
Hypothyroidism	0	0	-	0	2 (6.5)	0.509
Pruritus	0	0	-	2 (9.5)	11 (35.5)	0.050
Rash	0	0	-	2 (9.5)	11 (35.5)	0.050
Hyperthyroidism	0	0	-	0	1 (3.2)	>0.999
Hypoalbuminemia	0	0	-	13 (61.9)	11 (35.5)	0.090
Nausea	0	0	-	0	1 (3.2)	>0.999

Data are presented as n (%). AEs were graded according to CTCAE v5.0. Between-group comparisons were performed using two-sided Fisher's exact tests. [a]Any grade AEs include Grades 1-4. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MWA, microwave ablation; ICI, immune checkpoint inhibitor.

Consequently, these granular descriptors were not available for formal quantitative comparison between groups, so residual confounding in tumor burden cannot be excluded. Due to the small cohort size and limited number of events, multivariable Cox estimates, particularly for OS, may be unstable and should be interpreted as exploratory and alongside the Kaplan-Meier curves and univariable Cox results. The present study did not use propensity-based methods (PSM/IPTW) because the key baseline tumor-burden variables needed for a credible propensity model were not available, and the small sample could yield unstable matches or extreme weights.

In the present small retrospective real-world cohort, MWA plus immunotherapy was feasible and was associated with improved OS and PFS compared with ICI monotherapy in selected patients with advanced HCC and limited progression. These observations are exploratory, and the adjusted OS estimate should be interpreted cautiously due to the small dataset; confirmation in larger prospective studies is required.

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Availability of data and materials

The data generated in the present study are not publicly available due to institutional and privacy restrictions but may be requested from the corresponding author.

Authors' contributions

CW and YL conceived and designed the study. CW, SC, LD, TZ, FH, YW, OJ and YL collected the clinical data from electronic medical records, organized and structured the variables into a standardized database for statistical analysis, and verified the accuracy of the records. CW, OJ and YL performed the statistical analysis and generated the figures and tables. CW and YL drafted the manuscript, and all authors critically revised the manuscript for important intellectual content. OJ and YL supervised the study. CW and YL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present retrospective protocol was reviewed and approved by the Ethics Committee of the Second People's Hospital of Neijiang (approval no. 2026RP-0106-03) in accordance with the Declaration of Helsinki. The approval specifically authorized the retrospective analysis of de-identified clinical data from the 2022-2024 patient cohort and was obtained prior to data extraction and statistical analysis. Under the hospital's routine admission process, patients provided generic written consent for the research use of de-identified clinical data. As the present study was a retrospective analysis of existing records, the requirement for study-specific informed consent was waived by the ethics committee. The present study is registered with ClinicalTrials.gov (trial no. NCT06581497).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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