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ORIGINAL RESEARCH

Trans-Arterial Chemoembolization Combined with Microwave Ablation versus Microwave Ablation Alone for 3–5 cm Hepatocellular Carcinoma: A Multicenter Retrospective Study

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Objective: To compare safety and efficacy of transarterial chemoembolization (TACE) combined with microwave ablation (MWA) (TACE+MWA) versus only MWA treating hepatocellular carcinoma (HCC) 3–5 cm.

Methods: A retrospective analysis was conducted on data collected from 202 HCC patients who attended four hospitals between January 2014 and December 2017. Diagnosis of all lesions was based on histopathology and radiology. In total, 202 patients with HCC 3–5 cm were included in this retrospective cohort study. These patients were classified into TACE+MWA and MWA groups based on the treatment. Patients were followed up with contrast enhanced CT or MRI. Images were evaluated and compared for treatment response and Adverse Events (AEs). Observe the occurrence of overall survival (OS), progression free survival (PFS) and AEs after the patient's treatment. Survival analysis was performed using Kaplan-Meier method. Multivariate Cox proportional hazards regression analysis was performed to explore the relevant factors influencing the prognosis of patients.

Results: A total of 202 patients (median age, 58 years; 178 male) were included, with 102 in the TACE+MWA group and 100 in the MWA group. Baseline characteristics were well balanced between the two groups. Complete response (CR) was achieved by 78.4% of patients who received combined therapy compared with 76% with only MWA. The median PFS was 49.2 months (95% CI: 45.4–53.0) in the TACE+MWA group and 46.3 months (95% CI: 42.1–50.5) in the MWA group, with no significant difference (P=0.530). The median OS was significantly longer in the TACE+MWA group compared with the MWA group (81.7 months [95% CI: 78.2–85.3] vs. 72.3 months [95% CI: 68.9–75.7], P=0.013). The objective response rates (ORR) were comparable between the two groups (100.0% vs. 100.0%, P=1.000). The incidence of AEs was similar between the two groups, with no significant differences in major or minor complications. No treatment-related deaths were observed.

Conclusion: TACE combined with MWA was associated with improved OS compared with MWA alone in patients with 3–5 cm HCC, while maintaining a comparable safety profile. These findings suggest that combination therapy may be a promising treatment strategy, although further prospective studies are needed to confirm these results.

Keywords: microwave ablation, transarterial chemoembolization, safety, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most common malignant tumor and the second leading cause of cancer-related mortality in China, posing a significant threat to public health. Due to its insidious early symptoms, only

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20% to 30% of patients are eligible for curative treatments such as liver transplantation or surgical resection.[1] HCC, which frequently arises from chronic liver diseases, represents the predominant histological subtype of primary liver cancer and exhibits marked biological and clinical heterogeneity.[2] The selection of therapeutic strategies for HCC patients in influenced by multiple factors, including clinical manifestations, underlying cirrhosis severity, and tumor burden, given the intrinsic heterogeneity of this malignancy.[3]

The management of HCC is characterized by multidisciplinary collaboration and the integration of various therapeutic modalities. Common treatment options include hepatic resection, liver transplantation, ablation therapy, and traditional Chinese medicine (TCM)-based treatment. Each modality has distinct advantages and limitations, with overlapping indications in clinical practice.[4,5] However, for patients ineligible for or declining surgical intervention, TACE emerges as the principal therapeutic modality.[6] According to the Barcelona Clinic Liver Cancer (BCLC) staging system and current clinical practice guidelines, including those from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), treatment strategies for HCC are stage dependent. TACE is recommended as the standard of care for patients with intermediate-stage (BCLC stage B) disease, whereas ablative therapies such as microwave ablation (MWA) are considered curative options for early-stage tumors.[4] However, TACE monotherapy has limitations in achieving durable tumor control and long-term survival.[7] Residual tumor tissue following TACE may promote tumor angiogenesis through the upregulation of vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs), thereby contributing to tumor progression and recurrence.[8]

With the rapid advancement of image guided technologies, thermal ablation has emerged as a minimally invasive curative treatment for HCC and is now widely adopted in clinical practice. This technique offers several distinct advantages, including broad applicability, non-invasiveness, minimal trauma, and rapid recovery, thereby providing potentially curative options for HCC patients who are ineligible for surgical resection.[9] Ablative therapy has been established as achieving comparable therapeutic efficacy to surgical resection in the management of early-stage HCC, with reduced functional impairment.[10] Patients demonstrating absence of vascular/biliary invasion, adjacent airway involvement, or distant metastasis, coupled with preserved hepatic function (Child-Pugh class A/B), are candidates for achieving curative-intent treatment outcomes in HCC management.[11,12] Currently available ablative modalities primarily include radiofrequency ablation (RFA), MWA, percutaneous ethanol injection (PEI), and cryoablation. In this study, MWA was selected as the interventional approach.

Thermal ablation is widely regarded as definitive therapy for early-stage HCC, but its efficacy decreases in tumors greater than 3 cm. Extensive clinical studies have supported improved outcomes provided through combining transarterial embolic therapy with ablation in the treatment of larger tumors.[13] MWA has emerged as an advanced thermal ablation technique with several advantages over RFA. Compared with RFA, MWA can achieve higher intratumoral temperatures, resulting in more rapid and efficient tumor necrosis. In addition, MWA is capable of producing larger and more uniform ablation zones, which is particularly advantageous for tumors larger than 3 cm. Furthermore, MWA is less susceptible to the heat-sink effect caused by adjacent blood flow, thereby improving treatment efficacy for tumors located near major vessels. It also allows for shorter procedure times and fewer needle insertions, enhancing procedural efficiency and expanding its clinical applicability.[14]

In combined TACE and MWA therapy, TACE induces tumor necrosis and size reduction through arterial blood supply occlusion, thereby creating optimal conditions for subsequent precise MWA application. Thermal sink effect is significantly attenuated following occlusion of tumor-feeding arteries. MWA effectively complements TACE by targeting residual tumor regions with incomplete embolization, thereby enhancing tumor eradication rates.[15] This multimodal approach achieves a synergistic therapeutic effect through spatial cooperation between locoregional embolization and thermal ablation.[16] The combination of TACE with local ablative therapies has emerged as a widely adopted strategy to optimize therapeutic efficacy in HCC management. Combination therapy of TACE and ablation has been demonstrated to yield superior clinical outcomes compared to monotherapy, particularly in HCC measuring less than 7 cm in diameter. For larger tumors, TACE can be used to downstage the tumor prior to ablation.[17] Multiple prospective studies indicate that TACE combined with ablation achieves favorable results in HCC treatment.[16,18]

Although previous studies have demonstrated that combining TACE with ablative therapies can improve clinical outcomes in HCC, most of these studies have focused on RFA or have included heterogeneous tumor sizes. Evidence specifically evaluating the efficacy of TACE combined with MWA compared with MWA alone, particularly in patients with tumors measuring 3–5 cm, remains limited. Given that tumor size significantly influences treatment response and prognosis, it is important to clarify whether the addition of TACE provides incremental benefit over MWA alone in this subgroup. Therefore, this study aimed to compare the efficacy and safety of TACE combined with MWA versus MWA alone in patients with 3–5 cm HCC.

Materials and Methods

Patients

A total of 274 patients from four tertiary hospitals in China between January 2014 and December 2017 were retrospectively screened. Patients were followed up until December 2024. As this was a retrospective study, no formal sample size calculation was performed, and all eligible patients who met the inclusion criteria during the study period were consecutively included. This study was approved by the institutional review board of our hospital, as well as the ethics committees of the other three centers, and was conducted in accordance with the Declaration of Helsinki (1975). Treatment allocation was not randomized. The choice of treatment strategy was determined based on a combination of clinical factors, including tumor size, number, and location, liver function status, performance status, as well as physician experience and patient preference. Patients who did not meet the inclusion criteria were excluded from the study.

The main inclusion criteria were (a) all patients with an initial diagnosis of 3–5 cm HCC by histopathology or radiology. (b) age of 18 to 80 tears. (c) patients with a life expectancy >3 months who are unable to tolerate or unwilling to undergo resection or liver transplantation. (d) no vascular invasion or extrahepatic metastasis. (e) Eastern Cooperative Oncology Group performance status of 0–1. (f) preserved liver function reflected by a Child-Pugh grade A or B.

The main exclusion criteria were (a) patients who had previously undergone liver transplantation, ablation, surgical resection, or related therapies. (b) patients with a life expectancy <3 months. (d) tumors measuring <3 cm or >5 cm in diameter, accompanied by vascular invasion and/or extrahepatic metastasis. (e) Child-Pugh grade C.

Treatment Strategies

All the operations of the participating center are completed by experienced interventional radiologists and ultrasound doctors and follow the basic consistent treatment principles and institutional procedures. However, given that this study adopts retrospective multi-center design, there may be slight differences in operational technology and perioperative management.

TACE+MWA Group

TACE procedure: Under local anesthesia, femoral artery puncture was performed using the Seldinger technique, followed by the insertion of a 5F catheter into the celiac trunk artery, superior mesenteric artery, and splenic artery for angiography.[19] After selective catheterization of the tumor feeding artery with a microcatheter, 10 mL of lipiodol (Laboratoire Guerbet, France) emulsion thoroughly mixed with 20–40 mg doxorubicin or epirubicin was injected into the tumor vasculature. Following by embolization with 350–560 um polyvinyl alcohol (PVA) particles (manufactured by Hangzhou Alicon Medical) or gelatin sponge particles, until complete disappearance of tumor staining was achieved. All cTACE procedures were performed by interventional radiologists with a minimum of 10 year's experience. Postoperative supportive care routinely included hepatoprotective agents, antiemetics, and analgesic as needed.

MWA procedure: All MWA procedures were performed by experienced. Standardized procedural principles were applied across centers, including pre-procedural imaging evaluation, treatment planning, and post-procedural assessment. In this study, MWA procedures were categorized into three groups based on imaging guidance modalities, Dyna CT-guided MWA, CT-guided MWA and ultrasound-guided MWA.

TACE was performed 5–7 days before the procedure. MWA treatment was conducted on the same DSA machine with Dyna CT. After intravenous or general anesthesia, the patient's position was adjusted according to the tumor location, and Dyna CT images were acquired. The acquired images were uploaded to the workstation to generate reconstructed 3D

volumetric images, as well as axial, sagittal, and coronal plane images. Based on these images, the puncture plan was formulated. Under Dyna CT guidance, the tumor was punctured following the iGuide 3D puncture positioning technique. The tumor ablation strategy was as follows: the sequence prioritized deep before superficial regions. For lesions adjacent to the gallbladder, intestines, or blood vessels, the microwave needle was advanced along a trajectory parallel to the long axis of the adjacent organ whenever feasible. The output power and ablation duration were adjusted according to tumor size, typically ranging from 40 to 70 W, with the ablation zone extending at least 0.5 cm beyond the tumor margin. The needle tract was cauterized by gradually withdrawing the ablation antenna while applying thermal energy to minimize the risk of bleeding and tumor seeding along the puncture tract. For tumors measuring 3–5 cm in diameter, 2–4 ablation sessions were performed based on the tumor morphology. These procedures were conducted following generally consistent technical protocols across centers to ensure treatment uniformity.

MWA Alone Group

The monotherapy group underwent precision ablation therapy under real-time ultrasound guidance. During the puncture procedure, color Doppler ultrasound was utilized to confirm whether the MWA electrode needle (ECO Microwave System Co, Nanjing, China) traversed or was adjacent to major bile ducts or blood vessels. The tumor ablation strategy was identical to that described previously. Following ablation completion, manual compression was applied to the puncture site for 10 minutes. When clinically indicated, postprocedural ultrasound examination was performed to assess for potential complications such as hemorrhage or biliary leakage.

Outcomes and Follow-Up

The primary outcome was overall survival (OS), defined as the interval from the date of random assignment to death or to the last follow-up. The secondary outcomes were progression free survival (PFS) and safety. PFS was defined as the time interval from treatment initiation either disease progression or death from any cause. Postoperative imaging and biochemical parameters were systematically evaluated to assess the extent of tumor necrosis and detect any newly developed lesions, with radiographic response quantified according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Complete Response (CR) define as complete disappearance of arterial-phase enhancement in all target lesions on contrast-enhanced abdominal CT and/or MRI. Partial Response (PR) define as ≥30% reduction in the sum of diameters of arterial-enhancing portions of target lesions compared to baseline. Stable Disease (SD) define as neither sufficient shrinkage to meet PR criteria nor sufficient growth to reach PD threshold. Progressive Disease (PD) define as ≥20% increase in the sum of diameters of enhancing target lesions and/or development of new measurable lesions. AEs were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

The R (version 3.6.3) and SPSS 22.0 statistical packages were used for data analyses in this study. Categorical variables were represented as numbers and percentages. Continuous data were expressed as mean ± standard deviation. The differences among treatment groups were analyzed using the Student's *t*-test and analysis of variance test for numerical variables and the chi-squared test for qualitative data. PFS and OS were estimated via Kaplan–Meier analysis, and the curves were compared via the Log rank test. Hazard ratios (HRs) with 95% CIs were calculated using the Cox proportional hazards model. Subgroup analyses were conducted based on baseline variables. Cox regression analysis was conducted to identify independent variables related to OS and PFS. A two-sided P value <0.05 was considered to indicate a statistically significant difference.

Results

Patients

Between January 2014 and December 2017, 274 patients were screened, and 202 patients were ultimately included in the study (Figure 1). The follow-up data were censored as of December 2024, with a median follow up time of 89.0 months (95% CI: 78.8–99.2). The TACE +MWA group comprised 102 cases, and the MWA group included 100 cases. Both groups exhibited well-balanced baseline characteristics, with no statistically significant differences observed (all P>0.05, Table 1).

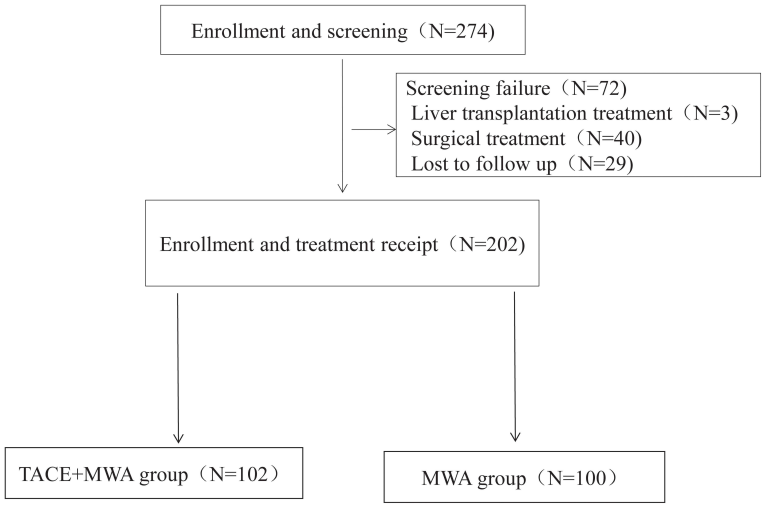

Figure 1 Enrollment process of the study population. Hospital 1, The First Affiliated Hospital of Zhengzhou University; hospital 2, The Third Affiliated Hospital of Sun Yat-sen University; hospital 3, Huaihe Hospital of Henan University; hospital 4, Dengzhou People's Hospital.

Different treatment modalities were chosen for each participant according to the progression of their lesions. After disease progression, some participants received new systemic treatment regimens, and the rest underwent local treatments. In the TACE+MWA group, 37 patients received MWA combined with targeted therapy and immunotherapy, 13 patients

Table 1 Patient Characteristics

	TACE+MWA Group (n=102)	MWA Group (n=100)	*P*
Gender	102	100	
Male	93	85	0.177
Female	9	15	
Age, median, years	58.11±8.89	57.30±10.20	0.565
ECOG score			0.690
0	38	40	
1	64	60	
Tumor number			0.323
1	69	74	
2	33	26	
Maximum tumor diameter (cm, mean±SD) (%)	3.92±0.51	3.82±0.64	0.188
Etiology			0.629
HBV infection	74	70	
HCV infection	6	5	
Alcoholic hepatitis	2	3	
Others	20	22	
AFP (ng/mL)			0.549
≤400 ng/mL	43	38	
>400 ng/mL	59	62	
Comorbidities			
Hypertension	12	10	0.689
Diabetes mellitus	8	5	0.419
Heart disease	4	5	0.712
BCLC stage			0.586
A	70	65	
B	32	35	

(*Continued*)

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Table 1 (Continued).

	TACE+MWA Group (n=102)	MWA Group (n=100)	*P*
CNLC stage			0.310
IA	30	36	
IB	39	38	
IIA	33	26	
ALBI score			0.367
1	83	85	
2	19	15	
High risk location			0.727
Yes	15	13	
No	87	87	

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer Staging; ALBI, Albumin-Bilirubin Score.

underwent surgical intervention, 52 patients were treated with combined TACE and MWA therapy. In the MWA group, 50 patients received MWA combined with targeted therapy, 17 patients underwent surgical intervention, 33 patients continued to receive MWA monotherapy.

Comparison of PFS and OS Between the TACE+MWA Group and MWA Group

Patients in the TACE+MWA group had a similar median PFS 49.2 (95% CI: 45.4–53.0) compare with that in the MWA group 46.3 (95% CI: 42.1–50.5) months (*P*=0.530) (Figure 2A). The median OS of the TACE+MWA group 81.7 (95% CI: 78.2–85.3) months was longer than the MWA group 72.3 (95% CI: 68.9–75.7) months (*P*=0.013) (Figure 2B).

A cox proportional hazards regression model was employed to assess the association between patients' baseline clinical characteristics and PFS, with the corresponding results presented in Table 2. Multivariate Cox regression analysis, performed after identifying significant variables in univariate analysis, revealed that tumor number (HR, 1.44; 95% CI: 1.05–1.96; *P*=0.022), BCLC stage (HR, 1.38; 95% CI: 1.03–1.86; *P*=0.032), and tumor high risk location (HR, 1.76; 95% CI: 1.17–2.65; *P*=0.007) were independently associated with PFS, High risk location defined as a minimum distance of less than 10 mm from the heart/great vessels, diaphragm, gastrointestinal tract, and gallbladder, as determined by preoperative CT or MRI imaging.[20]

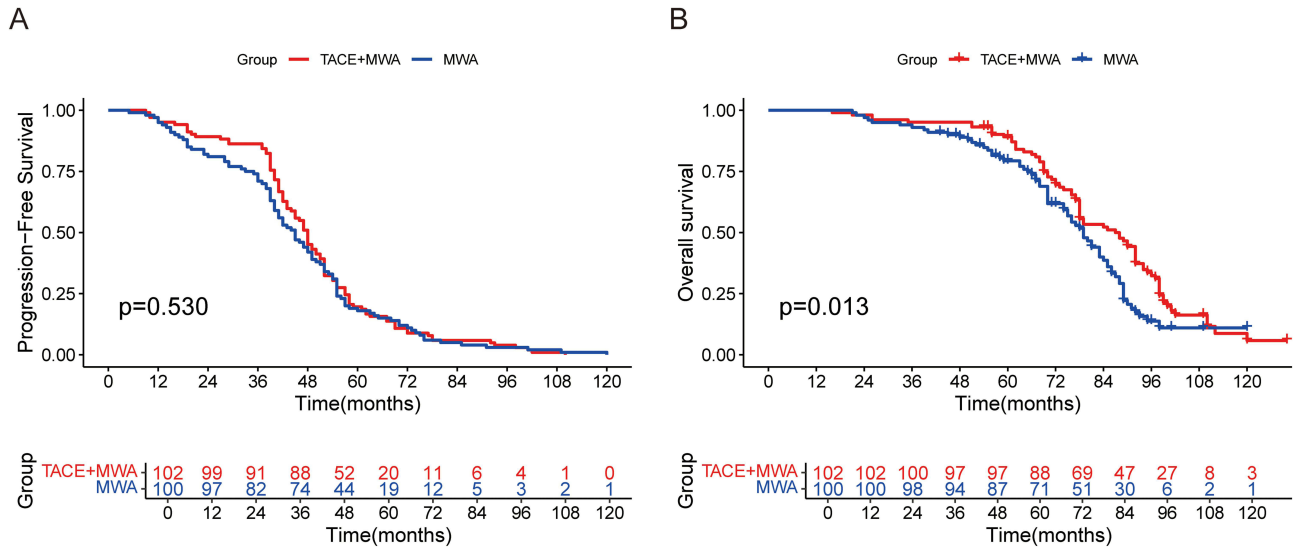

Figure 2 (**A**) Kaplan–Meier plots of median Progression-Free Survival (PFS). (**B**) Kaplan–Meier plots of median Overall Survival (OS).

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Table 2 Univariable and Multivariable Analyses of PFS in Intention-to-Treat Population

Characteristic	Univariable Analyses		Multivariable Analyses	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≤60 vs. >60, years)	1.07 (0.81–1.42)	0.612	1.64 (0.92–2.95)	0.095
Sex (Male vs. Female)	1.32 (0.86–2.03)	0.213	1.52(0.98–2.38)	0.065
ECOG score (0 vs. 1)	1.08(0.81–1.44)	0.591	0.74 (0.51–1.07)	0.114
Tumor number. (1 vs. 2)	1.44(1.05–1.96)	0.022	0.97 (0.58–1.61)	0.893
BCLC stage (A vs. B)	1.38(1.03–1.86)	0.032	1.67 (1.10–2.54)	0.017
AFP (≤400 vs. >400, ng/mL)	0.98 (0.74–1.31)	0.911	1.62 (0.90–2.95)	0.114
High risk Location (Yes vs. No)	1.76 (1.17–2.65)	0.007	2.09 (1.19–3.68)	0.011

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein.

Table 3 Univariable and Multivariable Analyses of OS in Intention-to-Treat Population

Characteristic	Univariable Analyses		Multivariable Analyses	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≤60 vs. >60, years)	0.98 (0.71–1.35)	0.891	1.20 (0.56–2.57)	0.641
Sex (Male vs. Female)	1.37 (0.80–2.35)	0.246	1.51 (0.87–2.61)	0.140
ECOG score (0 vs. 1)	1.26 (0.91–1.75)	0.161	0.96 (0.63–1.47)	0.853
Tumor number. (1 vs. 2)	1.83 (1.27–2.65)	0.001	1.21 (0.65–2.34)	0.553
BCLC stage (A vs. B)	1.34 (0.94–1.91)	0.108	1.18 (0.71–1.97)	0.532
AFP (≤400 vs. >400, ng/mL)	1.02(0.74–1.42)	0.894	1.26(0.58–2.75)	0.566
High risk Location (Yes vs. No)	2.99 (1.79–5.00)	0.001	2.67 (1.31–5.44)	0.007

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein.;

The association between patients' baseline clinical characteristics and OS was assessed using Cox proportional hazards regression models. Univariate analysis identified variables with significant effects, which were subsequently included in the multivariate analysis. As shown in Table 3. Multivariate analysis of variables showing significant differences in univariate analysis revealed that tumor number (HR, 1.83; 95% CI: 1.27–2.65; P=0.001) and tumor high risk location (HR, 2.99; 95% CI: 1.79–5.00; P=0.001) were independent prognostic factors for OS.

Treatment Response

The best treatment responses after initial therapy in the TACE+MWA combination group versus MWA alone group are summarized in Table 4. Tumor response was assessed according to mRECIST criteria. In the TACE+MWA combination

Table 4 Best Tumor Response Based on mRECIST After the First Treatment Between the Two Groups

	TACE+MWA Group (n=102)	MWA Group (n=100)	*P*
Best overall response			0.662
CR	80 (78.4)	76 (76.0)	
PR	22 (21.6)	24 (24.0)	
SD	0	0	
PD	0	0	
ORR (CR+PR)	102(100.0)	100(100.0)	1
DCR (CR+PR+SD)	102(100.0)	100(100.0)	1

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 5 Treatment-Related Adverse Events

Adverse Event	TACE+MWA (n=102) No. (%)		MWA (n=100) No. (%)		
	All Grade	Grade≥3	All Grade	Grade≥3	*P*
Fever	20(19.6)	4(3.9)	17(17.0)	2(2.0)	0.615
Abdominal pain	35(34.3)	2(1.9)	29(29.0)	3(3.0)	0.376
Fatigue	40((39.2)	0	32(32.0)	0	0.238
Vomiting and nausea	15((14.7)	0	12(12.0)	0	0.559
Myelosuppression	3(2.9)	0	0	0	0.083
Pleural effusion	2(1.9)	1(0.9)	7(7.0)	2(2.0)	0.079
Pneumothorax	2(1.9)	0	6(6.0)	1(1.0)	0.137
Bile lake	3(1.9)	0	2(1.0)	0	0.665
Liver abscess	3(2.9)	2(1.9)	7(7.0)	3(3.0)	0.178
Bile injury	2(1.9)	0	2(2.0)	0	0.984
Liver hemorrhage	0	0	3(3.0)	0	0.077
Ascites	3(2.9)	0	3(3.0)	0	0.980

therapy group, 80 patients achieved CR and 22 patients showed PR. While in the MWA alone group, 76 patients achieved CR, and 24 patients achieved PR. No statistically significant difference was observed between the two groups ($P>0.05$).

Comparison of AEs Between the TACE+MWA Group and the MWA Group

There were no treatment related deaths in either group. Postembolization syndrome consisting of fever, pain, vomiting and nausea was common in TACE+MWA group. Liver abscess was found in 3 patients in the TACE+MWA group and 7 patients in the MWA group. These cases were treated with percutaneous drainage and anti-inflammatory treatment. There were no significant differences between the two groups in terms of major and minor complications ($P>0.05$) (Table 5).

Discussion

The study by Mohamed M. A. Zaitoun et al[21] demonstrated that for patients with 3–5 cm HCC, the combination of cTACE and MWA is safe, well-tolerated, and more effective than either TACE or MWA alone. Ablation monotherapy has been established as an effective treatment modality for HCC patients with tumor diameters <3 cm.[22,23] Jia et al[22] demonstrated that ablation and surgical resection exhibit equivalent efficacy for patients with a single tumor <3 cm and well preserved liver function as assessed by the Child-Pugh score. Kang et al[23] demonstrated there were no significant differences in therapeutic outcomes between the ablation and the surgical resection groups, including 5-tears cumulative intrahepatic distant recurrence (47.0% vs 40.2%, respectively; $P=0.240$) and disease-free survival rates (48.9% vs 54.4%, respectively; $P=0.201$). However, there are currently no relevant guidelines recommending the use of TACE+MWA for tumors smaller than 3 cm. For patients with larger tumor diameters, the combination of TACE and ablation therapy is commonly employed, and this approach has been demonstrated to exhibit favorable efficacy and safety profiles.[24,25] A prospective randomized trial demonstrated that for HCC patients with tumors smaller than 7 cm, TACE+RFA is superior to RFA alone in improving survival rates.[26]

MWA demonstrates superior clinical advantages compared to RFA, including higher ablation efficiency, shorter procedure duration, and reduced susceptibility to the heat sink effect.[27,28] Furthermore, MWA is unaffected by metallic implants, thereby expanding its applicability to patients with vascular stents or pacemakers.[29] MWA as a method for performing thermal ablation of HCC, has the capacity to achieve larger and faster ablations than RFA through maintaining guarded and consistently higher intertumoral temperatures.[30] Compared with RFA, MWA can reduce the number of needle insertions, shorten procedure duration, and exhibit broader clinical applicability.[10] Notably, MWA demonstrates superior efficacy in ablating HCC located in high-risk anatomical regions, particularly those adjacent to major blood vessels or the gallbladder.[27]

Previous reports have confirmed that ablation with TACE could achieve better clinical outcomes in patient with HCC. A prospective study shows that the TACE+ MWA group exhibited a 5-years OS of 52%, a 7-years OS of 36.4%,

a 5-years RFS of 41.4%, and a 7-years RFS of 34.5%.[31] In another retrospective study with a large solitary or multinodular HCC, where some patients opted for TACE+MWA, the median time to progression (TTP) and OS were 12.5 months and 26.6 months.[30] Liang et al[12] showed MWA achieves comparable OS to laparoscopic liver resection, after propensity score matching, the 1-year, 3-year, and 5-year OS rates were 97.4%, 82.7%, and 68.0% in the MWA group and 97.0%, 82.0%, and 63.3% in the laparoscopic liver resection. Furthermore, for patients with 2–3 lesions distributed across distinct hepatic segments or tumors located in deep-seated or centrally positioned liver regions, either ablation monotherapy or combined surgical resection with ablation may be considered as viable therapeutic strategies.[12]

In the present study, median OS and PFS were 79.9 and 49.2 months in case administered TACE+MWA, respectively. These results suggest improvement compared with the 74.0 and 46.3 months achieved with MWA alone. The combination therapy of TACE+MWA did not significantly prolong PFS compared to MWA alone. This could be attributed to the fact that PFS is primarily driven by pre-existing, radiologically occult micrometastases, which are beyond the reach of local therapeutic modalities, whether MWA or TACE+MWA, leading to similar risks of long-term recurrence in both patient groups. The combined application of TACE and MWA demonstrates synergistic therapeutic advantages. Better local tumor control and OS were achieved with TACE+MWA combination therapy versus TACE monotherapy in patients with BCLC stage A HCCs.[32] TACE not only induces tumor ischemia by occluding tumor feeding arteries through embolization but also enables targeted delivery of chemotherapeutic agents directly to the tumor site, thereby significantly enhancing treatment efficacy.[26] Furthermore, the intraprocedural application of lipiodol in TACE exhibits dual clinical utilities. First, emulsions of lipiodol and doxorubicin/epirubicin creating a local drug depot which significantly prolongs the intratumoral retention of chemotherapeutic agents after it embolized tumor feeding arteries. Second, high destiny lipiodol deposition enables real-time intraprocedural visualization of tumor boundaries through imaging guidance, providing critical visual navigation for precise demarcation of ablation zones.[33] The synergistic utilization of lipiodol in this sequential therapeutic strategy not only potentiates the biological efficacy of TACE but also elevates the precision of MWA, culminating in a harmonized enhancement of overall treatment outcomes.[34]

Previous studies have confirmed that for surgically unresectable solitary or multifocal tumors measuring 3–7 cm in diameter classified as China Liver Cancer (CNLC) stage Ib or IIa, combination therapy with TACE and ablation demonstrates superior efficacy compared to ablation monotherapy.[26,35] The study by Yan et al demonstrated that HCC patients initially classified as advanced stage, who were downstaged to BCLC stage A through TACE, achieved long term outcomes comparable to those of patients with de novo BCLC stage A HCC when treated with MWA.[17]

Two clinically established approaches for combining TACE with ablation exist: one is sequential therapy, TACE is performed first, followed by ablation within 1-week to 1-month post-TACE; the other is synchronous ablation, ablation is administered concurrently with the TACE procedure under integrated imaging guidance. In this study, the TACE combined with MWA group underwent MWA treatment one week after the TACE procedure, which reduced the risk of postoperative complications, decreased the likelihood of postoperative liver failure, and enhanced the precision of tumor ablation.

In previous studies, although TACE combined with RFA achieved tumor vascular embolization to ensure therapeutic temperatures in the ablation zone, residual tumor tissue near major blood vessels failed to reach the required treatment temperature due to the "heat sink effect", leading to tumor recurrence.[36]

During MWA alone procedure, artificial ascites is frequently employed to facilitate surgical manipulation.[37] However, this technique presents notable limitations. Prolonged procedural duration increases operator workload, while subdiaphragmatic tissues exhibit limited tolerance to ablation-induced thermal stimuli, predisposing patients to postoperative complications.[38] Moreover, the inability to establish effective artificial ascites due to peritoneal adhesions or anatomical limitations in a subset of patients may compromise procedural efficacy and lead to incomplete ablation. Additionally, the preparation of artificial ascites requires supplementary procedural steps, extending surgical time and amplifying perioperative anesthesia hazards. Considering these constraints, the selective application of artificial ascites was implemented in this study for ablating lesions adjacent to high-risk anatomical zones-including the diaphragmatic dome, hepatic capsule, gallbladder, and hollow viscera to optimize safety and precision. The TACE+MWA group included 9 cases, and the MWA alone group included 17 cases.

In this study, fewer patients in the TACE combined with MWA group received artificial ascites. Firstly, the dual guidance of DSA and Dyna CT, combined with the clear visualization of lipiodol under X-ray, enable precise needle

placement and avoided puncture related bleeding. Secondly, the TACE procedure, by embolizing the tumor vasculature, significantly reduced the risk of tumor hemorrhage during both the initial puncture and subsequent needle repositioning. Furthermore, the combined therapy group exhibited significantly lower incidences of adverse reactions, including pneumothorax, pleural effusion, and liver abscess, compared to the MWA alone group. This reduction is likely attributable to two factors, rapid and precise needle placement reduced the risk of pleural effusion and hemorrhage, and the prior TACE procedure allowed for the use of lowered ablation power during MWA. This reduction in power mitigated the risk of reactive pleural effusion, liver abscess formation associated with excessive thermal energy.

In our study, compared with MWA alone, the combination therapy of TACE followed by MWA demonstrated no additional hemorrhagic. Moreover, the preoperative TACE provided precise tumor localization, thus significantly reducing the requirement for artificial hydrothorax or ascites assistance during subsequent MWA procedures in the combination therapy group.

This study has several inherent limitations. First, due to its retrospective design, potential selection bias cannot be completely avoided. Although baseline characteristics between the two groups were well balanced, unmeasured confounding factors may still exist. In addition, the relatively limited sample size precluded the implementation of matching procedures, which may have further contributed to bias. Second, as a multi-center study, treatments in the MWA group and TACE+MWA group were performed by different clinical teams across four institutions, which may have introduced operator-related heterogeneity and potential technical bias. Variations in surgical techniques and operator experience across centers could have introduced additional confounding factors in intergroup comparisons. However, the multi-center design may also enhance the external validity and generalizability of our findings. Third, during the study period (2014–2017), systemic therapies such as targeted therapy and immunotherapy were not routinely available in clinical practice. Therefore, post-progression treatments mainly consisted of repeat locoregional therapies or surgical interventions. These subsequent treatments may have influenced overall survival outcomes to some extent and should be considered when interpreting the results. To address these limitations, future studies should prioritize prospective, large-scale randomized controlled trials, as well as standardized multi-institutional protocols with rigorous operator training and quality control measures, to further validate our findings.

In conclusion, compared with MWA alone, TACE combined with MWA was associated with improved survival outcomes in patients with 3–5 cm HCC, with a favorable safety profile. However, given the retrospective nature of this study, these findings should be interpreted with caution. Prospective, large-scale randomized controlled trials are warranted to further validate these results.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Approval No. 2023-KY-0736-002). The study received approval from the ethics committee of each center. The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study, which involved the analysis of anonymized clinical data and posed no additional risk to the participants. All patient data were handled in accordance with institutional and national guidelines to ensure confidentiality and privacy. The study was conducted in compliance with the Declaration of Helsinki.

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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

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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