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ORIGINAL ARTICLE

Combination transarterial chemoembolization and microwave ablation vs. microwave ablation monotherapy for hepatocellular carcinomas greater than 3 cm: a comparative study

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PURPOSE

To evaluate the efficacy of combination therapy using transarterial chemoembolization with microwave ablation (MWA) therapy vs. MWA monotherapy for hepatocellular carcinomas (HCCs) >3 cm in size.

METHODS

This two-arm retrospective observational study included patients with HCCs >3 cm who underwent either combination therapy (29 patients) or MWA monotherapy (35 patients) between 2014 and 2020. The treatment outcomes related to primary treatment efficacy, local tumor progression (LTP), tumor control rate, and overall survival were compared between each cohort.

RESULTS

The technical success and primary efficacy were 96.56% and 100.00% in the combination therapy cohort, and 91.42% and 100.00% in the MWA cohort, respectively, over a mean follow-up period of 27.6 months. The 1- and 3-year rates of LTP-free survival were 78.57% and 69.56% in the combination therapy cohort, vs. 72.45% and 35.44% in the MWA cohort, respectively ($P = 0.001$). The overall progression-free survival was longer in the combination therapy cohort compared with the MWA cohort (median: 56.0 vs. 13.0 months; $P = 0.017$). With the incorporation of additional locoregional therapy, the overall survival rates were not significantly different, with 1- and 3-year overall survival rates of 100.00% and 88.71% in the combination therapy cohort and rates of 90.15% and 82.76% in the MWA cohort, respectively ($P = 0.235$).

CONCLUSION

The combination therapy provided significantly longer upfront LTP-free survival in HCCs >3 cm when compared with the MWA treatment alone, albeit with similar local tumor control and overall survival rates when accounting for additional locoregional therapies.

KEYWORDS

Combination therapy, hepatocellular carcinoma, liver, transarterial chemoembolization, tumor ablation, combined therapy, comparative study

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Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer worldwide and continues to rise in incidence in the United States due to non-alcoholic steatohepatitis.[1] The Barcelona Clinic Liver Cancer (BCLC) staging system provides a framework for addressing the treatment of HCC based on liver function, tumor burden, macrovascular invasion, extrahepatic spread, and performance status.[2] For very early and early-stage HCC, surgery and thermal ablation are utilized with curative intent. Thermal ablation techniques have improved over the past 20 years to become the standard of care for

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the treatment of unresectable HCCs <3 cm in diameter, with efficacy and survival rates approaching that of surgical resection at centers of excellence.[3]

Microwave ablation (MWA) has supplanted traditional radiofrequency ablation (RFA) as the preferred thermal ablation modality for HCC due to its ability to create larger and more homogeneous ablation zones with less heat-sink effects compared with RFA.[4] These heating advantages have led to its rapid adoption for HCC treatments, especially for HCC lesions >3 cm in diameter. The use of the latest generation MWA devices, including high-powered gas-cooled MWA devices, while the integration of multiple antennas simultaneously enables the safe and effective treatment of HCCs of up to 5 cm in diameter, with a treatment efficacy approaching that achieved with smaller HCCs.[5]

There has also been interest in exploiting the dual synergy between transarterial chemoembolization (TACE) therapy in conjunction with MWA to treat large tumors more effectively. First, TACE decreases the arterial blood flow to HCC lesions, mitigating the heat-sink effects and amplifying the heating capabilities of MWA, leading to larger ablation zones.[6] Second, TACE also delivers cytotoxic drugs to segmental or subsegmental regions of the tumor-bearing liver, thereby treating imaging-occult, microscopic satellite HCCs that are associated with larger HCC lesions.[7] These dual synergies (combination therapy) of TACE and MWA have led to overall improved primary efficacy and progression-free survival in larger tumor cases when compared with monotherapy TACE.[8] However, this treatment strategy requires two interventional procedures to be delivered upfront instead of one.

Main points

- The combination transarterial chemoembolization–microwave ablation (MWA) therapy provided significantly longer overall progression-free survival compared with MWA monotherapy alone (56 vs. 13 months, P = 0.017) in hepatocellular carcinomas >3 cm.
- The local tumor control rates, which incorporated additional locoregional therapies based on a strict follow-up protocol, were not significantly different between the treatment cohorts. However, the combination therapy still required, on average, significantly more interventional sessions to achieve the equivalent local tumor control.
- The overall survival rates were not significantly different between the combination therapy and MWA monotherapy cohorts.

While combination therapy and MWA monotherapy have both demonstrated efficacy in treating large solitary tumors, there have been limited studies comparing the two treatment strategies.[9-11] The present study aimed to evaluate the efficacy of TACE–MWA combination therapy vs. MWA monotherapy in patients with HCCs >3 cm in size.

Methods

This two-arm retrospective observational study was approved by the Ronald Reagan UCLA Medical Center Institutional Review Board, and the need for patient consent was waived (UCLA IRB, IRB#19-001363; approved 9/6/2019). The study comprised patients with HCC lesions >3 cm with Childs–Pugh A/B liver function who underwent MWA or combination therapy between 2014 and 2020 at a single, high-volume tertiary medical center. All patients with vascular invasion or portal vein thrombosis, inadequate follow-up imaging, or prior treatment (including liver transplant) were excluded (Figure 1). The HCC was confirmed using multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) criteria and was stratified according to the Liver Reporting and Data System classification method within 90 days of treatment. The patients were presented to a multidisciplinary board with recommendations for locoregional therapy for curative intent or a bridge to transplant.

Combination transarterial chemoembolization–microwave ablation procedure

The TACE procedures were performed by two board-certified interventional radiologists (J.P.M., F.H.) with 3–12 years of experience in intra-arterial therapies. The procedures were performed under moderate sedation in an angiography suite with cone-beam CT capabilities. Arterial access was obtained via ultrasound-guided femoral or radial arterial puncture. Visceral and hepatic angiography was performed, with most treatments delivered superselectively. Once an appropriate catheter position was obtained, TACE was performed. Drug-eluting beads (DEBs) were utilized in 19 (65.52%) of the cases, with a mean dose of 58.67 ± 23.34 mg of doxorubicin incubated on either 100–300 µm low-compression beads (LC Bead™, Boston Scientific, USA) (n = 12) or 75 µm oncozene beads (Varian Medical Systems, USA) (n = 5), or a combination of 75 µm oncozene with 300–500 µm LC beads (n = 2), and administered under fluoroscopic guidance until stasis in the tumor-bearing branches was achieved. Depending on user preference, in some cases, additional bland embolic material, such as Gelfoam® (n = 3) or 100–300 µm embospheres (Merit Medical Systems, USA) (n = 5) were administered after DEBs were delivered.

Conventional TACE was performed in 10 (34.48%) cases, using a mean dose of 30.80 ± 15.25 doxorubicin mixed with lipiodol (Guerbet, LLC, USA) in a 1:2 ratio, and was administered under fluoroscopic guidance until stasis in the tumor-bearing branches was achieved. Additional bland embolization was administered in some cases, which included gelfoam (n = 3), 100–300 µm embospheres (n = 1), and 40–120 µm embospheres (n = 1). Within 4 weeks (14 ± 7 days) after the TACE procedure, MWA was performed using the protocol described above.

Microwave ablation procedure

Percutaneous MWA in an outpatient setting was performed by one of four interventional radiologists (D.S.K.L, S.R.R., J.P.M, F.H.) with 3–27 years of experience with liver tumor ablation using combined ultrasound and CT guidance. All patients underwent monitored or general anesthesia, administered by an anesthesiologist. For all included cases, a 2.45 GHz MWA device (Neuwave Medical, USA) was used. The number of antennas, ablation stations, and the ablation power and time were determined by the attending physician with the goal of a 5 mm minimum ablation margin (Table 1). Hydrodissection was utilized for subcapsular tumor locations when needed to minimize the risk to adjacent sensitive organs such as the diaphragm or bowel.

Assessment of treatment response

The standard imaging protocol included contrast-enhanced CT at the conclusion of the procedure, or same-day MRI prior to discharge. In some cases, post-ablation MRI was performed in an outpatient capacity in the days following the ablation. Surveillance imaging was performed at 1, 3, 6, 9, and 12 months after ablation and every 3–6 months thereafter. The definitions of treatment response were based on the Society of Interventional Radiology (SIR) Standardization of Terminology and Reporting.[12] Technical success was defined as complete tumor coverage by the ablation zone on the first post-ablation multiphasic contrast-enhanced CT or MRI. An ablation treatment course was defined as all ablation sessions performed per nodule based on surveillance imaging for up to 3 months. Primary technique efficacy was

Table 1. Patient and tumor characteristics

Characteristics	MWA (n = 35)	TACE + MWA (n = 29)	*P* value
Age (year)	67.26 ± 8.86	65.13 ± 9.19	0.443
Male sex, %	29 (82.86)	23 (79.31)	0.717
BMI (kg/m^3)	27.35 ± 6.67	27.83 ± 5.74	0.586
ECOG performance status, %			0.624
0	19 (54.28)	20 (68.97)	
1	12 (34.29)	8 (27.59)	
2	3 (8.57)	1 (3.45)	
3	1 (2.86)	0 (0.00)	
Child–Pugh class, %			0.835
A	27 (77.14)	23 (79.31)	
B	8 (22.86)	6 (20/69)	
Etiology of liver disease, %			
HBV	13 (37.14)	2 (6.90)	0.005
HCV	11 (31.43)	17 (58.62)	0.029
Alcohol	2 (5.71)	4 (13.79)	0.397
NASH	3 (8.57)	2 (6.90)	1.000
PSC	0 (0.00)	1 (3.45)	0.453
HCV/Alcohol	4 (11.43)	2 (6.90)	0.681
HCV/NASH	2 (5.71)	0 (0.00)	0.497
Other	0 (0.00)	1 (3.45)	0.453
Multifocal, %	10 (28.57)	6 (20.69)	0.469
AFP (ng/mL)	13.60 (4.55–50.25)	11.70 (4.60–159.88)	0.852
Tumor size (cm)	3.69 ± 0.62	4.18 ± 0.85	0.009
Tumor lobe, %			0.717
Left	6 (17.14)	6 (20.69)	
Right	29 (82.86)	23 (79.31)	
Well-circumscribed margin, %	23 (65.71)	19 (65.52)	0.987
Subcapsular location, %	29 (82.86)	19 (65.52)	0.111
Peribiliary location, %	4 (11.43)	10 (34.48)	0.026
Perivascular location, %	10 (28.57)	18 (62.07)	0.007
Organ at risk, %			
Heart	0 (0.00)	3 (10.34)	0.088
Esophagus	1 (2.86)	0 (0.00)	1.000
Stomach	1 (2.86)	1 (3.45)	1.000
Diaphragm	13 (37.14)	8 (27.59)	0.418
Gallbladder/bile duct	0 (0.00)	1 (3.45)	0.453
Colon	4 (11.43)	1 (3.45)	0.366
Adrenal/kidney	2 (5.71)	2 (6.90)	1.000
Varix	0 (0.00)	1 (3.45)	0.453

Demographic and baseline clinical characteristics of the study groups. Continuous variables with normal distribution were expressed as mean ± standard deviation; those with non-normal distributions were expressed as median (interquartile range). BMI, body mass index; HBV, hepatitis B; HCV, hepatitis C; ECOG, Eastern Cooperative Oncology Group; MWA, microwave ablation; NASH, non-alcoholic steatohepatitis; TACE, transarterial chemoembolization; PSC, primary sclerosing cholangitis; AFP: alpha fetal protein.

defined as no evidence of residual tumor at the ablation site at the conclusion of the initial ablation treatment course. Local tumor progression (LTP) could be re-treated with ablative therapy for continued local tumor control and the patient would still be considered locally disease-free.[5] Adverse events were determined according to the clinical symptoms, imaging results, and laboratory evaluations after treatment and stratified according to SIR standard classification.[13]

The median follow-up period was 14 months [interquartile range (IQR): 9.50–19.25 months] in the combination therapy cohort and 18 months (IQR: 11.50–29.50 months) in the MWA cohort. The primary endpoints of this study were overall survival and primary technique efficacy. The secondary endpoints included local tumor control rate and safety.

Statistical analysis

The follow-up period ended at the time of death, liver transplantation, or the final clinical follow-up evaluation. The differences among the treatment groups were analyzed using a t-test for normally distributed variables (confirmed by a Kolmogorov–Smirnov test) or a Mann–Whitney U test for non-normally distributed continuous variables. Fisher's exact test or the Fisher–Freeman–Halton exact test, as well as Pearson's chi-squared test, were performed for all categorical variables. The descriptive statistics were described as mean ± standard deviation for normally distributed numeric variables and as median (IQR) for non-normally distributed numeric variables. The descriptive term, n (%), was used for all categorical variables. Kaplan–Meier analysis using the Fleming–Harrington test was utilized to identify differences in survival times.[14] The Fleming–Harrington test was selected rather than the traditional log-rank test since the survival curves overlapped on the later follow-up studies, and our intention was to highlight the longer-term effects of the interventions.[15,16] The follow-up time for the Kaplan–Meier curves was reported as mean ± standard error of the mean, as well as the median when available. For the LTP analysis, the patients were censored at the time of death, liver transplant, or loss to follow-up. Fisher's exact test was used to compare the local tumor control rates and primary technique efficacy. A *P* value of <0.050 was considered statistically significant. The entire statistical analysis was performed using GraphPad Prism v.9 (GraphPad Software Inc.) and Stata Statistical Software v.15 (StataCorp LLC).

Results

Baseline patient characteristics

The overall study group comprised 29 patients (23 men, 6 women) in the combination therapy group and 35 (29 men, 6 women) in the MWA group. The tumor diameter in the combination and MWA cohorts was 4.18 ± 0.85 and 3.69 ± 0.62 cm (*P* = 0.009),

Table 2. Ablation parameters

Parameter	MWA (n = 35)	TACE+MWA (n = 29)	*P* value
MWA			
No. ablation positions	1.00 (1.00–2.00)	2.00 (1.00–2.00)	0.307
No. probes	2.14 ± 0.47	2.05 ± 0.52	0.303
Duration (min)	11.57 ± 6.10	11.75 ± 5.74	0.867
Energy (W)	70.06 ± 11.87	68.06 ± 8.93	0.541
Technical success, %	32 (91.43)	28 (96.55)	0.620

Ablation parameters in the monotherapy microwave ablation and combination therapy group. Continuous variables with normal distribution were expressed as mean ± standard deviation; those with non-normal distributions were expressed as median (interquartile range). Technical success for MWA was defined as complete tumor coverage by ablation zone on the first follow-up imaging performed within 1 month after ablation. MWA, microwave ablation; TACE, transarterial chemoembolization.

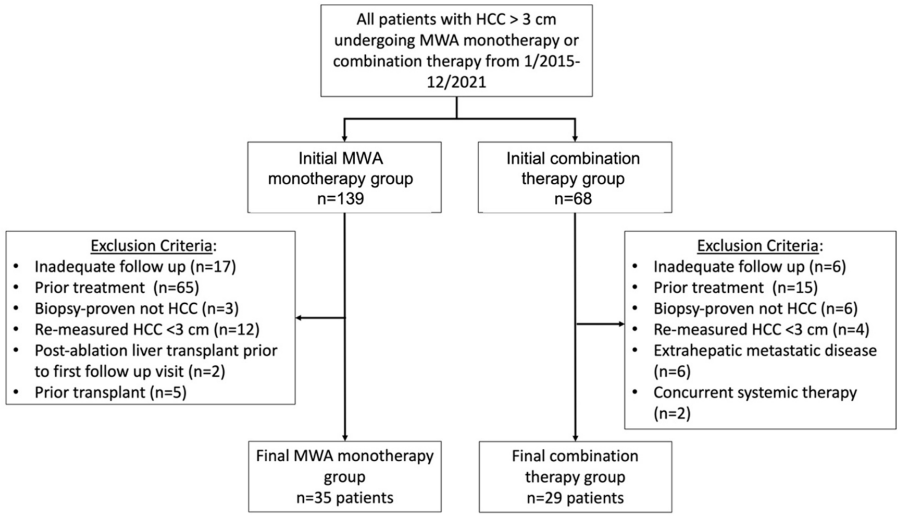

Figure 1. Comparative flow chart showing the participant selection and exclusion criteria. MWA, microwave ablation; HCC, hepatocellular carcinoma.

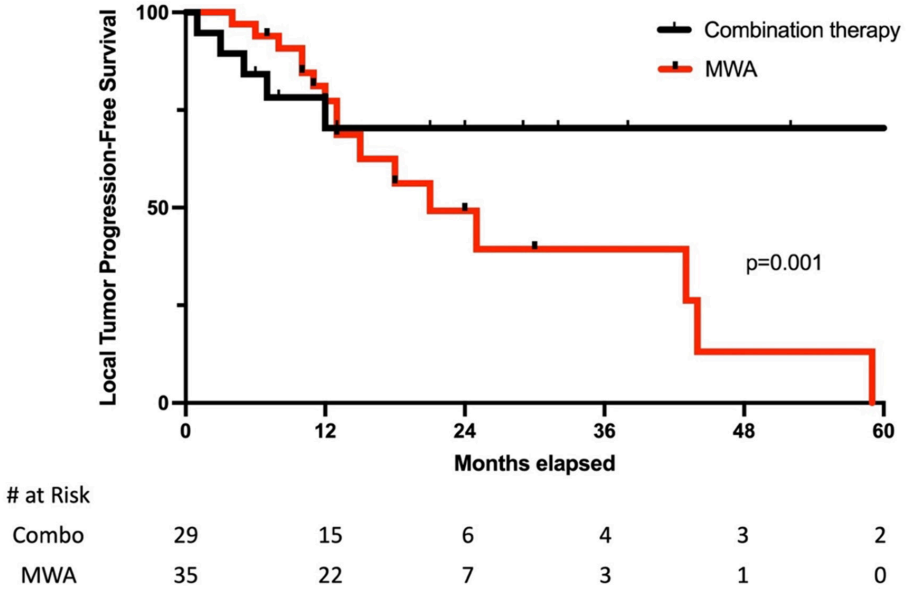

Figure 2. Local tumor progression (LTP)-free survival in the patient groups over 5 years. Significantly longer LTP-free survival was demonstrated (Fleming–Harrington test) in the combination therapy group compared with the microwave ablation-only group (*P* = 0.001). MWA, microwave ablation.

respectively, with a higher proportion of HCC lesions in the combination cohort being perivascular (62.07% vs. 28.57%; *P* = 0.007) in location. There were significantly more patients with hepatitis C in the combination therapy group (58.62% vs. 31.43%; *P* = 0.029), while there were significantly more patients with hepatitis B in the MWA group (37.14% vs. 6.90%, *P* = 0.005). The patient demographics, underlying causes of HCC, and tumor characteristics are presented in Table 1.

Technical success and primary technique efficacy rate

In the 29-patient combination therapy cohort, one patient (3.45%) presented with imaging-based residual disease within 3 months post-therapy, resulting in a technical success rate of (28) 96.55%. After retreatment with MWA, there were no additional patients with residual diseases at the 3 month time point, resulting in a primary technical efficacy rate of (29) 100.00%.

In the 35-patient MWA therapy cohort, three patients (8.57%) presented with an imaging-based residual disease following ablation within 3 months, resulting in a technical success rate of (32) 91.43%. After successful retreatment with MWA, there was no demonstrable residual disease at the 3-month time point, resulting in a primary technique efficacy of (35) 100.00%. Ablation parameters in each cohort are shown in Table 2.

Local tumor progression and local tumor control rate

The overall rate of LTP was significantly lower in the combination therapy cohort (8%, 27.59%) compared with the MWA therapy cohort (19%, 54.29%) (*P* = 0.031). The 1- and 3-year LTP-free survival rates were 78.57% and 69.56% in the combination therapy cohort and 72.45% and 35.44% in the MWA therapy cohort. Compared with the MWA cohort, the combination therapy cohort had significantly longer LTP-free survival times according to Kaplan–Meier analysis [47.75 ± 5.44 (median not reached) vs. 22.82 ± 3.13 months (median: 13.00 months); *P* = 0.001] (Figure 2). In the combination therapy cohort, the LTP in six tumors was successfully re-treated via MWA, leading to a local tumor control rate of (27) 93.10%. The other two patients were treated palliatively with systemic therapies. In the MWA cohort, the LTP in 15 tumors was successfully re-treated via additional MWA, yielding a local tumor control rate of (31) 88.57%. Overall, there was

no significant difference in the combination cohort compared with the MWA cohort in terms of local tumor control rate [58.02 ± 5.98 (median not reached) vs. 62.33 ± 5.98 months (median: 72.00 months); $P = 0.377$] (Figure 3). The remaining patients were not retreated due to medical comorbidities or were treated palliatively with TACE, radioembolization, or systemic therapies. A summary of the follow-up time, rate of tumor progression, rate of transplant, and additional therapies are presented in Table 3.

Extra-segmental progression and overall progression-free survival

The rate of extra-segmental progression over the study period was significantly lower in the combination therapy cohort than in the MWA therapy cohort (8%, 27.58% vs. 20%, 57.14%; $P = 0.018$). There was also a smaller rate for extrahepatic metastasis in the combination therapy group (2%, 6.90% vs. 6%, 17.14%; $P = 0.275$), albeit not significantly so. The 1- and 3-year rates of total tumor progression-free survival were 68.28% and 51.21% for the combination therapy cohort and 68.57% and 11.15% for the MWA therapy cohort. The overall progression-free survival was observably longer in the combination therapy cohort than in the MWA cohort [33.35 ± 5.57 (median: 56.00 months) vs. 14.11 ± 1.65 months (median: 13.00 months)] according to the Kaplan–Meier analysis ($P = 0.017$) (Figure 4).

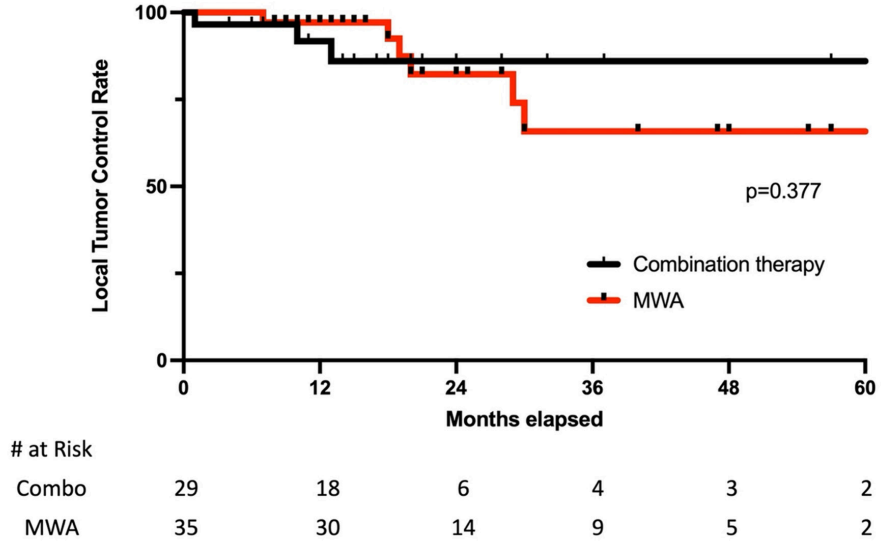

Figure 3. Local tumor control rate in the patient groups, which included additional locoregional therapy, over 5 years. There was an equivalent local tumor control rate (Fleming–Harrington test) in the combination therapy group compared with the MWA-only group ($P = 0.377$). MWA, microwave ablation.

Table 3. Follow-up and disease progression

	MWA (n = 35)	TACE+MWA (n = 29)	*P* value
Follow-up time (months)	14 (9.50–19.25)	18 (11.50–29.50)	0.295
Disease progression, %			
Local recurrence	19 (54.43)	8 (27.59)	0.031
Extra-segmental progression	20 (57.14)	8 (27.59)	0.018
Extrahepatic metastases	6 (17.14)	2 (6.90)	0.275
Transplant, %	6 (17.14)	6 (20.69)	0.717
Death, %	4 (11.43)	3 (10.34)	1.000
Additional locoregional therapies to achieve local control, %			
MWA	16 (45.71)	6 (20.69)	0.036
TACE	5 (14.29)	0 (0.00)	0.058
Y-90	3 (8.57)	0 (0.00)	0.243
Systemic therapy, %	3(8.57)	3 (10.34)	1.000
Total number of locoregional therapies per patient to achieve local control	1.00 (1.00–2.00)	2.00 (2.00–2.50)	<0.001

Clinical follow-up from monotherapy microwave ablation and combination therapy group. Continuous variables with non-normal distributions were expressed as median (interquartile range). Additional locoregional therapies include those performed as part of the initial course of ablation therapy. The total number of locoregional therapies includes every interventional procedure over the lifetime of the patient's treatment for HCC. MWA, microwave ablation; TACE, transarterial chemoembolization; Y-90, Yttrium-90.

Overall survival and transplant rates

Within the follow-up period, three patients in the combination therapy group and four in the MWA therapy cohort died. Six of the seven patients died from HCC progression, and one patient in the MWA cohort died from renal failure. The 1- and 3-year overall survival rates were 100.00% and 88.71% in the combination therapy cohort, and 90.15% and 82.76% in the MWA therapy cohort, with an overall survival of 58.24 ± 4.15 months (median not reached) and 61.21 ± 5.02 months (median not reached), respectively ($P = 0.235$) (Figure 5).

Total number of treatment sessions

Overall, additional locoregional therapies were performed more frequently for the MWA monotherapy patients compared with the combination therapy group to achieve the aforementioned local tumor control and overall survival rates (Table 3). However, considering that the combination therapy comprised two interventional procedures upfront, the median number of procedures per patient over the lifetime of the patient's treatment was 1.00 (1.00–2.00) in the monotherapy group and 2.00 (2.00–2.50) in the combination therapy group ($P < 0.001$).

Adverse events

There was one severe adverse event (AE) in the combination therapy cohort, which was an unexpected elevation in serum bilirubin due to biliary stricture following the ablation procedure. This stricture required the placement of an external biliary drain for decompression, which was subsequently converted to an internal–external biliary drain.[17] There were also two moderate AEs among the patients in the combination therapy cohort, including one patient who developed hepatic encephalopathy requiring the initiation of lactulose and another who had slight asymptomatic intracapsular bleeding during placement of the microwave antenna, which was resolved with subsequent thermal coagulation using the MWA probe. To minimize the risk of infection, the hematoma was aspirated with an 8 French pigtail

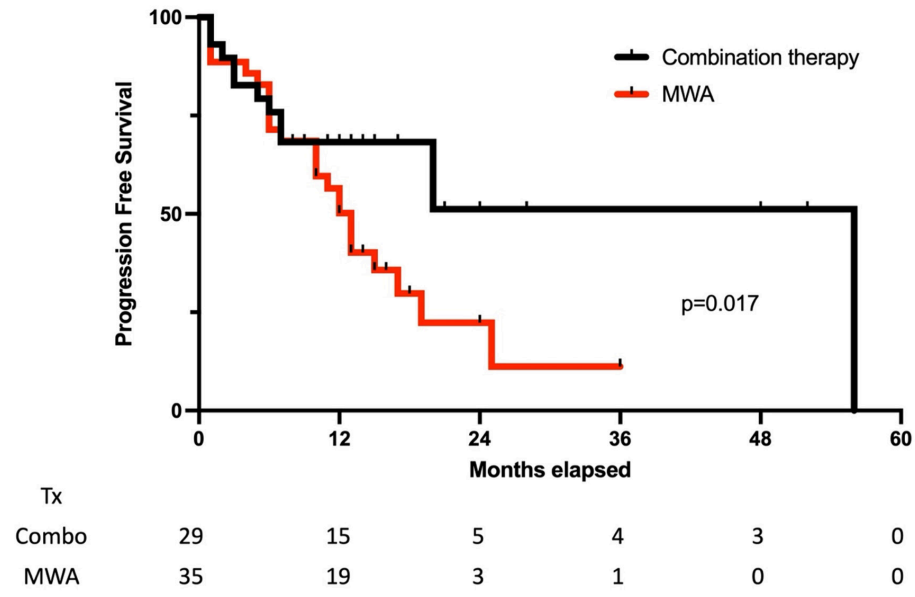

Figure 4. Overall progression-free survival in the patient groups over 5 years. The Fleming–Harrington test indicated longer overall progression-free survival in the combination therapy group compared with the MWA-only group ($P = 0.017$). MWA, microwave ablation.

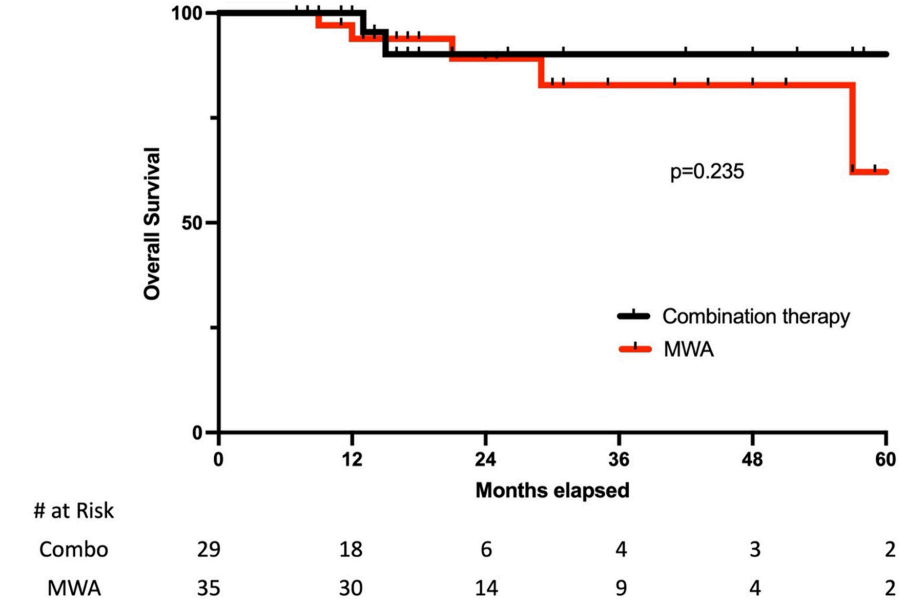

Figure 5. Overall survival over 5 years. The Fleming–Harrington test indicated an equivalent survival rate in the combination therapy group compared with the MWA-only group ($P = 0.235$). MWA, microwave ablation.

drain and the drain was removed at the end of the treatment without further sequelae. There were two mild AEs in the MWA cohort, both of which were asymptomatic hepatic dysfunction based on abnormal laboratory values. Both patients were followed closely, and their hepatic dysfunction was resolved without any further therapy. The rate of fever was (12) 41.38% and (3) 8.57% ($P = 0.003$) in the combination and MWA therapy cohorts, respectively, but without significant differences in the rates of post-procedural abdominal pain, chest pain, nausea/vomiting, fatigue, or confusion (Table 4).

Discussion

This study demonstrated that combination therapy is associated with significantly longer initial LTP-free and total progression-free survival rates compared with MWA therapy alone for HCC lesions >3 cm, while the overall survival rates at 5 years and the progression to liver transplantation rates were similar. The local tumor control rates, which incorporated additional locoregional therapies, based on a strict follow-up protocol, were not significantly different between the treatment cohorts. However, on average, the combination therapy required significantly more interventional sessions to achieve the equivalent local tumor control rate.

The efficacy of combination therapy compared with ablation monotherapy remains under active investigation. While prior studies have focused more on comparing combination therapy with RFA, more recent research evaluated the utility of MWA, with most outcomes supporting combination therapy over MWA alone. Recently, a randomized controlled three-arm trial compared the efficacy of MWA with TACE and combination therapy for HCCs of 3–5 cm in size. The trial results indicated that combination therapy achieved a complete response in 86.5% of the patients, while monotherapy using TACE achieved a complete response in 54.8% and MWA in 56.5%. The recurrence rate after 1 year was significantly lower in the combination group (22.5%) compared with the MWA-only (51.1%) and TACE-only (60.7%) groups. There was also a significantly higher rate of median survival in the combination group than in the TACE and MWA groups (24 months vs. 19 and 21 months, respectively).[9] Another single-center retrospective study looked at propensity-matched BCLC stage B patients with HCC who had undergone either combination therapy or TACE monotherapy for tumors <7 cm.[10] In the above study, the combination therapy significantly improved progression-free survival and overall survival compared with TACE only, with the former returning a tumor control rate of 74.0% and 47.8% at 6 months and 1 year and the latter returning rates of 55.5% and 37.3%. The median survival time of the combination therapy cohort was 18.5 months compared with 14.8 months in the TACE monotherapy cohort. Similarly, in a study of 3–5-cm HCCs, Smolock et al.[18] reported that TACE–MWA combination therapy was associated with a lower rate of LTP compared with TACE monotherapy (34.8% vs. 62.5%) and longer median progression-free survival (22.3 vs. 4.2 months). Conversely, a recent retrospective study with propensity matching did not report any therapeutic superiority in combination vs. MWA therapy for 150 patients in BCLC stage B with a mean tumor diameter >6 cm.[11] However, a sub-cohort analysis of the above study found that tumor number and size were independent risk factors for long-term outcomes, with better LTP and survival rates indicated for combination therapy in tumors >7 cm.

The improved efficacy of combination therapy may be related to the dual syner-

Table 4. Post-procedural complications

	MWA (n = 35)	TACE + MWA (n = 29)	*P* value
Procedural site pain, %	1 (2.86)	2 (6.90)	0.586
Chest pain, %	1 (2.86)	0 (0.00)	1.000
Shortness of breath, %	1 (2.86)	3 (10.34)	0.321
Fever, %	3 (8.57)	12 (41.38)	0.002
Nausea/vomiting, %	0 (0.00)	3 (10.34)	0.088
Confusion, %	4 (11.43)	5 (17.24)	0.720
Fatigue, %	0 (0.00)	1 (3.45)	0.453
Lower extremity edema, %	1 (2.86)	0 (0.00)	1.000
Acute kidney injury, %	0 (0.00)	1 (3.45)	0.453
Urinary retention, %	0 (0.00)	1 (3.45)	0.453

Post-procedural complications from the microwave ablation (MWA) and combination therapy group [transarterial chemoembolization (TACE) + MWA].

gistic effect of TACE and MWA. In this study, TACE preceded MWA by an average of 14 days. The TACE procedure is known to have an embolic effect on the tumor microvasculature of HCCs, decreasing the blood flow to minimize the heat-sink effect and resulting in larger, more homogeneous ablation zones.[19-21] However, if too much time elapses after embolization, as a growing body of literature suggests, the region may become hypoxic, potentially imparting pro-tumorigenic pathways.[22] Thus, the amount of time that elapses between TACE and ablation is important for maximizing the therapeutic response, although there is only limited evidence supporting an optimal timepoint.[23] The intra-arterial nature of TACE also allows therapeutic agents to be delivered to an entire liver segment or sub-segment, potentially treating imaging-occult satellite lesions surrounding an index tumor that may be located outside of the tumor capsule.[7] While the primary technical efficacy rate of MWA monotherapy may be compromised by the presence of nearby satellite lesions, combination therapy with prior TACE could effectively treat microscopic diseases, maximize MWA efficacy, and minimize the risk of incomplete treatment.

There are aspects of this study that may limit the comparisons and generalizability to a broader patient population. First, the MWA cohort had a smaller mean tumor size than the combination therapy cohort. Larger tumors may be more resistant to locoregional therapy and are generally associated with higher rates of tumor progression and poorer overall survival rates. Second, there was a heterogenous institutional protocol for embolization, with most patients receiving DEB–TACE, but a non-negligible number of patients receiving conventional TACE. Furthermore, there were significantly higher proportions of patients with hepatitis B in the MWA-only group and hepatitis C in the combination therapy group, which may have confounded the study endpoints. The baseline patient population in each study cohort was otherwise well-matched; however, the restrictive tumor size and liver function criteria led to a small study population that made it difficult to perform further sub-group analysis.

In conclusion, this study confirms that combination therapy can achieve significantly higher initial upfront local tumor control rates compared with MWA therapy alone for HCCs >3 cm without increased rates of adverse events. While the combination therapy cohort had a larger mean tumor size compared with the MWA cohort, the combination therapy patients required, on average, a higher number of total procedures due to the upfront performance of two separate interventions. The overall survival and major complication rates were comparable between the two groups when a strict follow-up protocol and additional necessary treatments were incorporated into the overall treatment strategy. A prospective trial is warranted for providing better evidence and an understanding of how to stratify patients into combination vs. MWA therapy for intermediate-to-large-size HCCs.

Conflict of interest disclosure

J.P.M., D.S.K.L., S.S.R. has received speaker fees from Neuwave Medical Inc. D.S.K.L and S.S.R. has received speaker fees from Covidien.

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