Abdominal Radiology

Published online: 15 February 2018

Abdom Radiol (2018) 43:2497–2504
https://doi.org/10.1007/s00261-018-1464-9

Combination transarterial chemoembolization and microwave ablation improves local tumor control for 3- to 5-cm hepatocellular carcinoma when compared with transarterial chemoembolization alone

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Abstract

Purpose: To compare transarterial chemoembolization (TACE) monotherapy to combination TACE and microwave ablation (MWA) for local control of 3- to 5-cm hepatocellular carcinoma (HCC).
Methods: Patients with HCC between 3 and 5 cm treated with TACE monotherapy or combination TACE + MWA at a single institution between 2007 and 2016 were retrospectively reviewed. Twenty-four HCCs (median diameter 3.8 cm) in 16 patients (13 males; median age 64 years) were treated using TACE monotherapy. Combination TACE + MWA was used to treat 23 HCCs (median diameter 4.2 cm) in 22 patients (18 males; median age 61 years). Microwave ablation was performed at a target time of two weeks following TACE. Individual tumors were followed by serial contrast-enhanced CT or MR. Response to treatment was evaluated on a tumor-by-tumor basis using mRECIST criteria with the primary outcome being local tumor progression (LTP). Data were analyzed using Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Time to LTP was estimated with the Kaplan–Meier method.
Results: Relative to TACE monotherapy, TACE + MWA provided a trend toward both a lower rate of LTP (34.8% vs. 62.5%, $p = 0.11$) and a higher complete response rate (65.2% vs. 37.5%; $p = 0.12$). Time to LTP (22.3 months vs. 4.2 months; $p = 0.001$) was significantly longer in the TACE + MWA group compared to TACE monotherapy.
Conclusions: Combination therapy with TACE and microwave ablation improves local control and increases time to LTP for 3–5 cm HCC.

Hepatocellular carcinoma (HCC) is a devastating complication of chronic liver disease with an estimated 746,000 deaths per year worldwide [1]. The only definitive treatment for both HCC and cirrhosis is liver transplantation, but long wait times in some regions and a relatively fixed number of donor organs negatively impact access to liver transplantation [2]. Percutaneous

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locoregional therapies, such as thermal tumor ablation and transarterial chemoembolization (TACE), are established treatment options for patients with HCC and are increasingly being utilized, particularly as bridging therapy for patients on the transplant wait list [3–5].

The Barcelona Clinic Liver Cancer (BCLC) guidelines have been adopted by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) as consensus recommendations for treatment of HCC stratified by stage and performance status [6]. The most recent iteration of BCLC guidelines recommends treatment of very early and early-stage HCC with curative intent using either resection, ablation, or transplantation. For intermediate stage and multifocal tumors, TACE is recommended. However, other factors, including tumor location, tumor size, and imaging appearance, complicate this simple stratification of tumor treatment presented in the BCLC guidelines. Large or infiltrative tumors and tumors bridging two or more Couinaud-Bismuth segments of the liver are associated with lower rates of complete response with monotherapies [7]. Therefore, there has been growing interest in alternative treatment strategies, including combination therapy with TACE and thermal ablation.

Previous studies of combination intra-arterial and ablative therapies suggest that treatment of HCC with both TACE and radiofrequency (RF) ablation may be superior to monotherapy with either modality [8, 9]. Specifically, combined TACE + RFA has been associated with improved disease-free and overall survival when treating intermediate (3–5 cm) and large (> 5 cm) tumors [8, 9]. Most reports of thermal ablation for treating HCC have focused on RFA because clinical RF systems have been available longer. However, there is growing interest in microwave ablation (MWA) for the treatment of HCC as it has been shown to create larger and hotter ablation zones in less time when compared with RFA [10]. There are reports, predominantly from Asia, combining TACE and microwave ablation for the treatment of HCC [11–14]. However, these studies either focused on the treatment of small (< 3 cm) HCC or included patients with a wide range of tumor diameters. To our knowledge, no reports have addressed treatment of intermediate-sized HCC with TACE + MWA, particularly in Western populations. Therefore, the purpose of this study was to compare TACE monotherapy with TACE + MWA combination therapy for local control of HCC ranging from 3 to 5 cm.

Methods

Patient selection

Institutional review board approval was granted for this retrospective review of a clinical database, and a waiver of informed consent was granted. Interventional oncology treatments between 2007 and 2016 were reviewed, and all cases of HCC measuring 3–5 cm were included in the study if treatment was undertaken either by (1) conventional TACE alone or (2) combination conventional TACE and microwave ablation. HCCs were confirmed using imaging criteria and classified according to the Organ Procurement and Transplantation Network (OPTN) classification system. Multifocal disease was defined as having at least two distinct HCCs (OPTN Class 5 tumors). Prior to undergoing locoregional therapies, all patients were reviewed at a multidisciplinary tumor board that included hepatologists, oncologists, radiation oncologists, diagnostic and interventional radiologists, and transplant and hepatobiliary surgeons and assigned a treatment plan. Patients underwent intra-arterial and/or ablative therapies based on the recommendation of the tumor board. Briefly, tumors were deemed appropriate for combination therapy if larger than 3 cm and either not well visualized by CT or US or in areas associated with higher recurrence rates (e.g., watershed regions). Tumors that had been previously treated by other approaches, including radiation therapy, were excluded from analysis. Likewise, only tumors in treatment-naïve hepatic parenchyma were included in the study. Additionally, patients treated with TACE using drug-eluting beads were excluded from the study because conventional TACE was used for combined TACE + MWA treatments.

Patient demographics

Table 1 lists patient and tumor characteristics. Twenty-four tumors were treated in 16 patients (13 males; median age 64 years) between 2007 and 2016 by conventional TACE alone. Of the TACE monotherapy treatments, eleven patients had multifocal disease with at least one tumor within the selected size criteria of 3–5 cm, accounting for 16 of the 24 tumors (67%). Some tumors in patients with multifocal disease were not evaluated because those tumors did not meet the size inclusion criteria of 3–5 cm.

Combination therapy with TACE and MWA was performed on 23 tumors in 22 patients (18 male; median age 61 years) between 2011 and 2016. Of the TACE + MWA treatments, two patients had multifocal disease with at least one tumor within the selected size criteria of 3–5 cm, accounting for three of the 23 tumors (13%). Again, some tumors in patients with multifocal disease were not evaluated because those tumors did not meet the size inclusion criteria of 3–5 cm.

Tumor diameter was not significantly different between groups (median 4.2 cm in the TACE + MWA group vs. 3.75 cm in the TACE group, $p = 0.51$). The range of tumor sizes in both groups was 3–5 cm. Patients undergoing TACE monotherapy had a higher rate of multifocal disease (67% vs. 13.0%, $p < 0.001$). No sig-

Table 1. Patient and tumor characteristics

Factor	TACE ($N = 24$)	TACE + MWA ($N = 23$)	p value
Number of patients	16	22	
Median age (range)	64 (43–76)	61 (44–85)	0.86
Sex			0.72
M	13 (81%)	18 (82%)	
F	3 (19%)	4 (18%)	
Primary and secondary etiology			0.086
HCV	8 (33%)	14 (61%)	
ETOH	2	2	
ETOH	9 (38%)	4 (17%)	
HCV	0	1	
HBV	1	0	
NASH	1 (4%)	4 (17%)	
ETOH	0	0	
Cryptogenic	4 (17%)	1 (4%)	
HBV	1 (4%)	0 (0%)	
Hemochromatosis	1 (4%)	0 (0%)	
Multifocal			< 0.001
No	8 (33%)	20 (87%)	
Yes	16 (67%)	3 (13%)	
Median MELD (range)	6 (1–14)	7 (1–15)	0.44
Child–Pugh			0.3
A	14 (58%)	14 (61%)	
B	7 (29%)	9 (39%)	
C	3 (12%)	0 (0%)	
Median AFP (range)	23.5 (3.3–117.8)	11.85 (3.8–3139)	0.51
Median tumor size (range), cm	3.75 (3–5)	4.2 (3–5)	0.51
Vascular invasion			0.49
No	24 (100%)	22 (96%)	
Yes	0 (0%)	1 (4%)	
PV thrombosis			0.99
No	23 (96%)	23 (100%)	
Yes	1 (4%)	0 (0%)	
BCLC			< 0.001
A	0 (0%)	10 (43%)	
B	11 (46%)	9 (39%)	
C	11 (46%)	4 (17%)	
D	2 (8%)	0 (0%)	

$N = 7$ AFP; etiology comparison based on primary etiolgy group

nificant differences were seen between the two groups with regard to etiology of cirrhosis, MELD score, Child–Pugh score, or pre-treatment AFP. Patients treated with TACE monotherapy did demonstrate a higher rate of more advanced BCLC stage disease compared to the TACE + MWA group.

TACE technique

Transarterial chemoembolization procedures were performed by one of six board-certified interventional radiologists experienced in performing liver-directed intra-arterial therapies, including TACE. The procedures were performed under conscious sedation in a hybrid angiography—CT suite (ACT table/Smart Gantry option LS for GE LightSpeed 16; GE Medical Systems, Waukesha, WI) or angiography suite with cone-beam CT capabilities (Artis Zeego; Siemens Healthineers, Erlangen, Germany). Arterial access was obtained via an ultrasound-guided common femoral or radial arterial puncture. Visceral and hepatic angiography was performed. Attempts were made to be as selective as possible, with most treatments rendered from a segmental or subsegmental location. Once appropriate catheter position was confirmed, conventional TACE (30 mg doxorubicin, 20 mg mitomycin C, 0.1 g cisplatin [before it became unavailable] mixed with Lipiodol (Guerbet, LLC, Bloomington, IN) in a 1:1 ratio) was administered under fluoroscopic guidance to near stasis of antegrade flow. This was followed by bland embolic material to achieve substasis (100–300 μm and/or 300–500 μm Embosphere Microspheres, Merit Medical Systems, Inc., South Jordan, UT) at the discretion of the physician operator. Post-procedure non-contrast CT was obtained within 24 h to document Lipiodol deposition in the targeted tumor.

Ablation technique

Percutaneous microwave ablations were performed by one of five board-certified radiologists experienced in performing thermal tumor ablation using a high-powered, gas-cooled microwave ablation system (Certus 140, NeuWave Medical, Inc., Madison, WI). Ablations were

conducted with the patient under general anesthesia in an imaging suite. Using sterile technique, one to three 17-gauge microwave antennas were placed percutaneously under real-time sonography (Logiq E9, GE Medical Systems). Specific power and time settings were determined by the physician operator based on tumor size and intra-procedural sonography, but generally, tumors are ablated for 5–10 min at 65 W. When multiple antennas were used, they were powered simultaneously. Mean power was 64 W, and mean ablation time was 6.6 min using 1–3 antennas. Arterial and portal venous phase contrast-enhanced CT (LightSpeed Ultra, GE Medical Systems) was performed using 100–150 mL IV contrast (Omnipaque 300, GE Healthcare, Waukesha, WI) immediately following the procedure to document the ablation zone, assess the need for immediate retreatment of residual untreated tumor, and evaluate for immediate complications. Microwave ablations were performed at a target time of 2 weeks (median 15 days, range 0–31 days) following TACE to allow for improved targeting of the Lipiodol-stained tumor and patient recovery from any post-embolization syndrome.

Follow-up

Electronic medical records were reviewed for pre- and post-treatment laboratory values and treatment-related complications. Imaging follow-up was performed with contrast-enhanced MRI or CT at intervals of 1, 3, 6, 9, 12, 18, and 24 months with a 6-month interval follow-up thereafter. All post-procedure and follow-up images were reviewed for consensus between a senior radiology resident and a board-certified interventional radiology faculty member with 7 years of experience in oncologic imaging and interventions. Images were evaluated for incomplete treatment, local tumor progression, and complications. Complications were recorded and classified according to the Society of Interventional Radiology guidelines [15].

Evaluation of tumor response

Baseline tumor size was measured on the most recent pre-procedure contrast-enhanced CT or MRI in the longest axial diameter. Local tumor progression (LTP) was defined according to standard imaging criteria: new nodular enhancement along the ablation margin or growth of the ablation zone on follow-up imaging examinations [16]. In addition, tumor response was classified according to mRECIST criteria [17].

Time to progression

Time to LTP was defined as time from (first) treatment until LTP as determined by imaging. Tumors without LTP were censored at the latest imaging date. Tumors in patients undergoing liver transplantation were censored at the latest imaging date prior to transplantation.

Statistical analysis

Patient and tumor characteristics were summarized by treatment group. Differences by treatment group were analyzed using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. The endpoint of interest was LTP, which was analyzed using the Kaplan–Meier method. Time to LTP was compared by treatment group using the log-rank test. Statistical tests were two-sided, and the level of significance was set at 5% ($p < 0.05$). All statistical analysis was done in R 3.3.1 including the "survival" package.

Table 2. Follow-up and local tumor progression

Factor	TACE ($N = 24$)	TACE + MWA ($N = 23$)	p-value
Intra-procedure complications			0.11
No	24 (100%)	20 (87%)	
Yes	0 (0%)	3 (13%)	
Median pre-procedure bilirubin (range)	1 (0.4–3.7)	1.1 (0.3–2.6)	0.81
Median post-procedure bilirubin (range)	1.2 (0.3–3.5)	1.1 (0.3–2.9)	0.69
Median change[a] in bilirubin (range)	0 (− 0.6, 1.4)	− 0.1 (− 1.4, 0.2)	0.24
mRECIST (local)			
CR	9 (38%)	15 (65%)	
PR	9 (38%)	7 (30%)	
SD	5 (21%)	1 (4%)	
PD	1 (4%)	0 (0%)	
Transplant			0.04
No	24 (100%)	17 (74%)	
Yes	0 (0%)	4 (17%)	
Median imaging follow-up (range), mos.	9.4 (1.3–15.5)	7.4 (1.5–34.9)	0.55
Number of LTP	15	8	0.11
Median time to LTP (95% CI), mos.	4.2 (1.2–NR)	22.3 (16.3–NR)	0.001

$N = 11$ missing post-procedure bilirubin, $N = 2$ missing/not applicable transplant information
[a]Change = post-pre

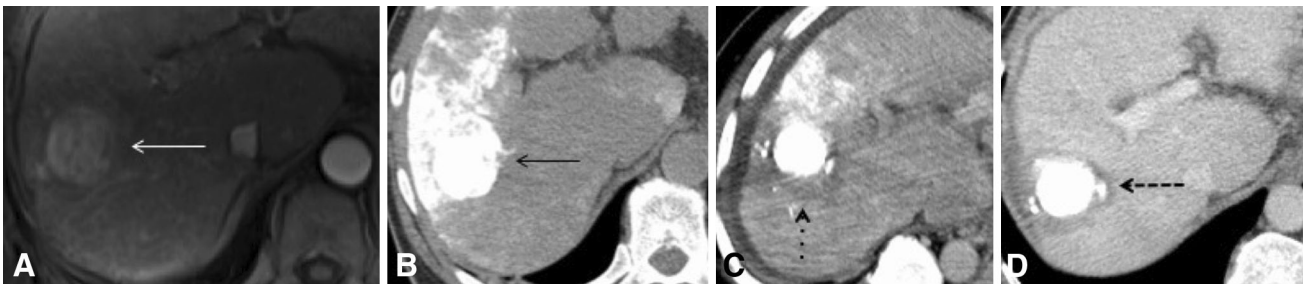

Fig. 1. **A** 62-year-old male with a 3.4-cm HCC (white arrow) treated with combination TACE + MWA therapy. **B** TACE was performed first, and immediate post-procedure CT demonstrated diffuse Lipiodol uptake in the tumor (black arrow). **C** Subsequently, MWA was performed with immediate post-ablation CT demonstrating adequate tumor ablation (dotted black arrow). **D** Surveillance imaging demonstrates no evidence of recurrent tumor after combination therapy consistent with CR (dashed black arrow).

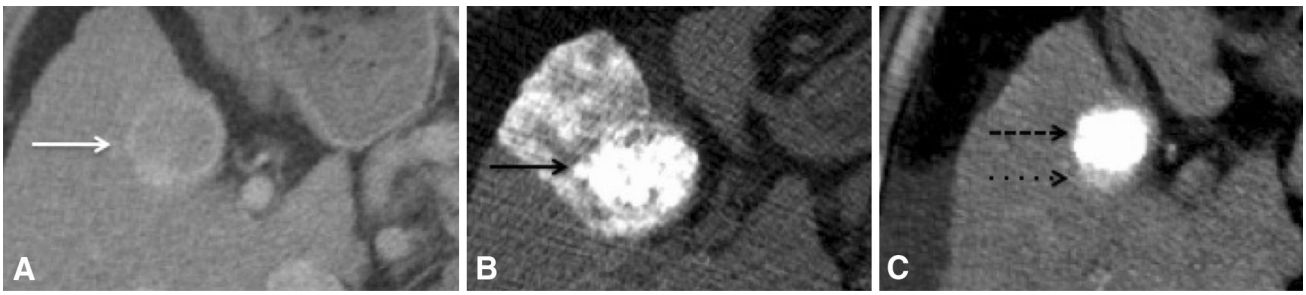

Fig. 2. **A** 62-year-old male with a 3.6-cm HCC (white arrow). The patient received monotherapy with TACE. **B** Immediate post-embolization CT demonstrates diffuse Lipiodol uptake by the tumor (black arrow), which was completely covered. **C** Follow-up CT performed 3 months post-treatment demonstrates peripheral enhancement (dotted black arrow) at the treated tumor site which has retained Lipiodol (dashed black arrow) consistent with LTP/PR.

Results

Tumor response

Technical success rate was 100%. Treatment follow-up data are summarized in Table 2. Imaging follow-up was similar in the two groups (median 9.4 months, range 1.3–15.5 months in the TACE group compared to 7.4 months, range 1.5–34.9 months in the TACE + MWA group). Representative images from each treatment group are provided in Figs. 1 and 2.

Tumors treated with TACE + MWA had a trend toward a lower rate of LTP compared to tumors treated with TACE alone (8/23 [34.8%] compared to 15/24 [62.5%], respectively, $p = 0.11$). There was a trend toward a higher rate of complete response (CR) with combination TACE + MWA (15/23; 65%) when compared to TACE monotherapy (9/24; 38%, $p = 0.12$). Four patients in the TACE + MWA therapy group went on to liver transplantation, while there were no transplanted patients in the TACE monotherapy group (Table 2).

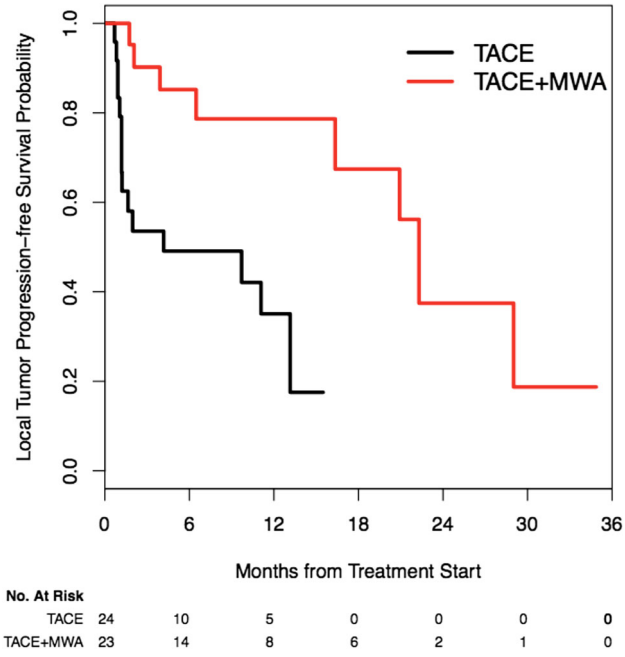

Fig. 3. Time to local tumor progression.

Time to LTP

Tumors treated with TACE + MWA demonstrated a longer time to LTP when compared to conventional TACE monotherapy (median 22.3 months vs. 4.2 months, respectively, $p = 0.001$; Fig. 3).

Complications

No major complications were observed in either treatment group. There was a trend toward a higher rate of minor complications in the TACE + MWA group (3 vs. 0, $p = 0.11$). Two of these were minor bleeds related to the ablation procedure, and one was a groin site bleed related to arterial access for the TACE procedure. The patient who experienced groin access bleeding was transfused 2 units of platelets, but no further intervention was otherwise required for any of the complications. Post-procedure bilirubin values and the change in bilirubin were not significantly different between groups, indicating that neither treatment group, and specifically the group that received two therapies, experienced a significant decline in hepatic function.

Discussion

The results of this study demonstrate that adding MWA to conventional TACE improves local tumor control of 3- to 5-cm HCC compared to conventional TACE alone. The TACE + MWA combination group had a significantly longer time to LTP. Additionally, the TACE + MWA group demonstrated a trend toward both a lower rate of LTP and an increased rate of complete response compared to tumors treated by TACE alone.

The mechanism for increased local tumor control seen in the combination group is likely multifactorial resulting from the complementary nature of the two different treatments. Specifically, intra-arterial therapies decrease blood flow, and thereby, decrease perfusion-mediated cooling, allowing for the creation of larger ablation zones [18]. TACE is also a regional technique and thus can treat satellite lesions surrounding the index tumor that are generally inconspicuous on conventional imaging, and which may be located up to 5 mm away from the tumor capsule. Satellite lesions can contribute to treatment failure with local thermal ablation techniques. An additional possible advantage of combination treatments is the substantial synergistic effect of applying thermal ablation to a chemotherapy-laden tumor [19]. Specifically, prior work has shown that chemotherapy agents may cause a heat-sensitizing effect and thermal injury may sensitize tumors to the chemotherapeutic agents [20].

At our institution, patients undergo MWA at a target time of 2 weeks after TACE. There is no current consensus on the order or timing of the treatments, and it is likely that the two treatments are synergistic regardless of the order. However, this sequence of events is based on a seminal animal experiment that demonstrated larger zones of necrosis when TACE was followed by ablation rather than the converse [21]. The rationale for a 2-week delay between treatments is to allow increased contrast between the Lipiodol-stained tumor and surrounding background liver tissue, which facilitates targeting of the tumor by CT and ultrasound, increases confidence that the ablation devices are appropriately placed, and improves the ability to visualize the ablation margins immediately post-procedure (Figs. 1 and 2). Additionally, a short waiting period between therapies allows patients to recover from any post-embolization symptoms that may develop.

The results of this study suggest that TACE + MWA combination therapy improves local tumor control for 3–5 cm HCCs, and thus, thermal ablation should be added to TACE when feasible. Achieving local control of 3–5 cm HCCs is particularly important given that these patients are often at the threshold for being transplantable and can be at risk of being removed from the transplant list if their tumors progress or fail to achieve an adequate treatment response. Therefore, outcomes data specific to tumors in this size range are particularly important for clinical practice and decision making.

Previous studies demonstrated improved overall and recurrence-free survival in patients treated with TACE + RFA compared to RFA alone, particularly when treating larger tumors [8, 22]. Microwave ablation was used as the thermal ablation modality for this study due to the high tissue temperatures, large ablation zones, rapid volumetric heating, and synchronous multiple antenna capability microwaves provide [10, 23, 24]. Currently, there is a relative paucity of data regarding the use of MWA in combination with intra-arterial therapies. Early studies demonstrated the feasibility of combining TACE and MWA, but were limited to small tumors (< 3 cm) [11, 12]. Xu et al. subsequently showed a survival advantage for combination TACE + MWA compared to TACE alone for the treatment of large HCC [25], and Ginsburg et al. demonstrated comparable survival for patients with HCC undergoing either TACE + MWA or TACE + RFA [14]. Our study compares favorably with CR rates reported by Ginsburg et al. for combination TACE + MW, which included a wide range of tumor sizes from 1.6 to 12.5 cm. Furthermore, our study had a higher complete response rate for 3-5 cm HCC treated by TACE + MWA than a recent study of larger tumors with a mean size of approximately 7 cm treated by TACE + MWA (65% vs. 45%) [13].

It is important that outcomes for combination therapies be reported for specific tumor size ranges given that treatment goals vary based on BCLC stage and tumor burden. To the best of the authors' knowledge, this is the

first study to compare TACE and TACE + MWA for HCC ranging from 3 to 5 cm, a size where local failures after monotherapy have historically been high and can dictate transplantation status. The favorable tumor response for the TACE + MWA group in this study may not translate to larger tumors, but can help guide treatment decisions for patient specifically with tumors in the 3–5 cm range.

This study analyzed treatment response on a tumor basis after selecting for an intermediate tumor size range. Therefore, local tumor response was the primary endpoint of our study. Comparison of overall survival was not performed in this retrospective study because of the inherent differences in the treatment groups introduced by generally following the accepted treatment guidelines for HCC. While no differences were seen between the groups with regard to Child–Pugh or MELD scores, there was a difference between the groups in terms of individual patient tumor burden and disease severity with the TACE monotherapy group having more patients with multifocal disease and in a higher BCLC stage.

The combination group had slightly more complications than the TACE monotherapy group. These were minor complications and were attributable to both MWA and TACE treatments. Thus, this finding may be due to chance, although certainly performing two procedures introduces additional risk with each procedure. There does not appear to be significant hepatocyte damage induced by performing more than one locoregional therapy, as there was no difference in post-treatment bilirubin values or change in bilirubin between groups.

Our study has several limitations. This was a retrospective study of patients previously stratified into treatment groups. The criteria for treatment allocation were not strict and were based on a multidisciplinary tumor board discussion of each patient, thereby leaving a possible treatment selection bias. The disease status and tumor burden for each patient were variable, and in this tumor-by-tumor analysis, the contribution of more than one tumor by a single patient cannot be accounted for. Furthermore, the treatment groups showed a difference in disease burden, with the TACE monotherapy group being more likely to have multifocal disease and advanced BCLC stage. These differences were the reason that the analysis was done on a lesion-by-lesion basis and the primary endpoint was LTP, not OS.

In conclusion, our findings demonstrate that combination conventional TACE and MWA therapy is a safe and effective treatment option for HCC with improved tumor response and local control of intermediate-sized tumors. TACE + MWA therapy resulted in a prolonged time to LTP compared to TACE monotherapy.

Compliance with ethical standards

Funding No funding was provided for this study.

Conflict of interest Christopher L. Brace: (1) consulting fees, NeuWave Medical, Inc., Madison, WI (2) shareholder and consulting fees, Symple Surgical, Inc., Menlo Park, CA. J. Louis Hinshaw: Consulting fees, NeuWave Medical, Inc., Madison, WI. Paul Laeseke: consulting fees, NeuWave Medical, Inc., Madison, WI. Fred T. Lee, Jr: (1) Board Member, Stockholder, and Grant recipient (pending) Histosonics, Inc., Ann Arbor, MI (2) Paid consultant, Ethicon, Inc., Somerville, NJ (3) Stockholder, Elucent, Inc., Minneapolis, MN (4) Patent holder and Royalties, Medtronic/Covidien, Inc., Boulder, CO (5) Stockholder, Zurex, Inc., HealthMyne, Inc., and Eximis Surgical, Inc. Meghan G. Lubner: (1) Grant recipient, Ethicon, Inc., Somerville, NJ (2) Grant recipient, Philips, Amsterdam, Netherlands. Shane A. Wells: consulting fees, NeuWave Medical, Inc., Madison, WI. Timothy J. Ziemlewicz: consulting fees, NeuWave Medical, Inc., Madison, WI.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study prior to undergoing procedures. This retrospective study was approved by our institutional review board, and the requirement for informed consent was waived.

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