Safety and effectiveness of multi-antenna microwave ablation-oriented combined therapy for large hepatocellular carcinoma

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Ther Adv Gastroenterol

2019, Vol. 12: 1–14

DOI: 10.1177/1756284819862966

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Abstract

Background: In patients with a large, unresectable hepatocellular carcinoma (HCC), the primary recommendation is for transarterial chemoembolization (TACE) but used alone TACE is not typically curative. Combinations of TACE followed in a delayed fashion by single-applicator thermal ablation have also been suboptimal. As an alternative, we investigated the combination of TACE followed within 1–3 days by multi-antenna microwave ablation (MWA) in patients with a large HCC, to determine the feasibility, safety, local control, and short-term survival rates of this approach.

Methods: We retrospectively studied 43 patients with a large HCC (mean diameter, 8.8 cm; SD, 2.8 cm) treated between July 2015 and July 2018, who underwent TACE followed within 3 days by multi-antenna simultaneous MWA. We measured the liver and renal function before and after treatment, recorded complications, used three-dimensional software and imaging to calculate tumor necrosis rates at 1 month after therapy, and calculated overall survival (OS) and progression-free survival (PFS) using the Kaplan–Meier method.

Results: Mean follow up was 12.2 (range, 3.5–35.6) months. All patients completed the treatment protocol. At 1 month after combined therapy, tumor necrosis was complete in 16 (37.2%), nearly complete in 19 (44.2%), and partial in 8 (18.6%) patients. The 1- and 2-year OS rates were 64.0% and 46.8%, respectively, with a median OS of 23.0 months; and the 1- and 2-year PFS rates were 19.9% and 4.4%, respectively, with a median PFS of 4.2 months. A transient change in liver function occurred 3 days after MWA but resolved within 1 month. Only two patients had major complications, which were treatable and resolved.

Conclusion: Multi-antenna MWA-oriented combined therapy is feasible and well tolerated, and it results in satisfactory initial local control and short-term survival in some but not all patients with a large HCC.

Keywords: HCC, local control, microwave ablation, minimally invasive therapy

Received: 20 December 2018; revised manuscript accepted: 14 June 2019.

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy, with incidence and mortality rates ranking sixth and fourth in the world, respectively.[1] More than half of patients with HCC in the world are in China, and most patients with HCC have developed a large (>5 cm) or massive (>10 cm) HCC by the time of diagnosis.[2] About 80% of patients have tumors that are unresectable, because of either severe hepatitis-related cirrhosis or tumor invasion of the intrahepatic vessels.[3] More recently, a variety of minimally invasive treatments have been used successfully in patients with a large, unresectable HCC.[4–6]

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Minimally invasive treatments for HCC include transarterial chemoembolization (TACE) and various forms of energy ablation. TACE, which causes tumor inactivation through the occlusion of blood flow and the slow release of chemotherapeutic drugs into tumors, is the standard treatment recommended by the Barcelona Clinic Liver Cancer (BCLC) guidelines for unresectable HCC with large diameters or multiple intrahepatic lesions.[7] However, because tumor neovascularization can rapidly restore tumor blood supply after TACE, TACE alone is not generally considered a potentially curative treatment for HCC.[8]

An alternative minimally invasive approach to treating HCC involves the use of thermal ablation, and this has been shown to be potentially curative for small (⩽3 cm) HCC.[9] However, conventional energy ablation techniques for treating HCC have typically used only a single antenna to deliver energy, resulting in relatively small ablation zones and increased risks of local tumor residual, intrahepatic recurrences, or distant metastases, particularly in intermediate-sized (⩽5 cm) HCC.[10] Investigators working with microwave ablation (MWA) techniques have compared the use of single and multiple antennas in animal liver models and have reported the ability to create substantially larger ablation zones with multiple antennas.[11,12] We have recently taken this approach a step further, by comparing sequential and simultaneous multi-antenna MWA techniques in *ex vivo* bovine liver models, and we found significantly larger ablation zones in livers treated with the simultaneous approach (unpublished data).

Another potential option for the treatment of large, unresectable HCC has been the use of combined therapy using both TACE and thermal ablation. For this approach, many clinicians have recommended that TACE be performed before ablation, in part because of concerns that if done first, ablation would cause damage to the arteries supplying the cancer, rendering subsequent TACE less effective.[13] In this TACE-oriented combined approach, TACE has typically been done with the goal of reducing tumor size, preferably ⩽3 cm, so that the resulting lesion would then be more amenable to adjuvant single-antenna ablation. However, a delay of several months between TACE and ablation is generally required to allow enough time for this level of tumor size reduction to occur.

We have recently treated patients with large, unresectable HCC using an alternative ablation-oriented combined approach. In this approach, we considered multi-antenna MWA to be the primary treatment method used to address the entire large tumor, and we used TACE in a pre-ablation fashion. We postulated that we could still use TACE initially to obstruct the tumor blood supply,[14,15] but that instead of a delay of several months, we could follow this within a few days using MWA with multiple antennas, and that both parts of this treatment could be completed during a single hospitalization.

We hypothesized that this ablation-oriented combination therapy, focused on simultaneous multi-antenna MWA done within days of TACE, would be clinically feasible without patients needing multiple hospitalizations, would be well tolerated, and would create ablation zones large enough to achieve local control in most patients. With that in mind, the objective of this study was to review the records of patients at our institution who had undergone what we call 'multi-antenna MWA-oriented combined therapy', in order to determine the clinical feasibility, efficiency, and tolerability of this approach, and to assess the initial local HCC control and short-term survival rates of our patients with large, unresectable HCC who have been treated with this technique.

Patients and methods

Patient selection

The treatment methods in this retrospective study were part of routine clinical patient care at our institution and were approved by the Ethics Committee of Sun Yat-sen University Cancer Center, China (B2019-051-01). The written informed consent was waived due to the retrospective nature of this study.

Patient characteristics

The study involved 43 consecutive patients with large HCC diagnosed by imaging, serum alpha-fetoprotein (AFP) level, or pathological examination, who fitted the inclusion criteria, between July 2015 and July 2018.

Patients were included who had the following: (1) maximum HCC tumor diameter >5 cm and <15 cm; (2) fewer than three intrahepatic

metastases; (3) a Child–Pugh score (used to assess the prognosis of chronic liver disease and cirrhosis) of 7 or lower; (4) prothrombin time (PT) not exceeding the upper limit of normal by 3 s or more; (5) serum creatinine level lower than 1.5-times the upper limit of normal; (6) no history of heart and lung disease; and (7) no previous treatment or TACE as the only previous treatment for HCC. Patients were excluded who had the following: (1) tumor thrombus in the main portal vein, bile duct, inferior vena cava, or hepatic vein; (2) extrahepatic metastasis; or (3) coagulation dysfunction.

Each patient included in the study received contrast-enhanced liver computed tomography (CT) or magnetic resonance imaging (MRI), blood tests, and tumor classification according to the BCLC staging system.

Treatment protocol

The patients received combined TACE with MWA as part of routine care at our institution and in accordance with national guidelines.[16] TACE was performed 1–3 days prior to MWA. During TACE, lobaplatin (30–50 mg) and pirarubicin (30–50 mg) were mixed with lipiodol (5–10 ml) and injected into the artery supplying the HCC. This was followed by embolization with Embosphere Microspheres (Merit Medical, South Jordan, UT, USA) until the arterial supply was completely occluded. Multi-antenna MWA was performed under CT guidance, using a microwave generator (2450 MHz, Vison-China Medical Devices R&D Center, Nanjing, China), which was coupled to coaxial microwave antennas measuring 14 G in diameter. The power output of ablation for each microwave antenna was set at 60 W. For each patient, the number of antennas, spacing of parallel antennas, and duration of ablation were determined based upon tumor diameter, with the goal of creating ablation zones large enough to completely cover the index tumor.

Starting in 2017, the Medi-GPS 3D Visualization System (HOKAI Medical Equipment Co., Ltd., Zhuhai, China) was used, with 3-mm-thick MRI slices or 1.25-mm-thick CT slices, to provide a three-dimensional (3D) reconstruction of tumors and adjacent tissues for ablation planning. It was also used for all patients to perform retrospective tumor necrosis rate calculations.

The number of antennas used depended upon rounded maximum tumor diameters: three antennas were used for tumors with diameters in the 5 cm to $<$7 cm range; four antennas were used for tumors with diameters in the 7 cm to $<$9 cm range; and five antennas were used for tumors with diameters $\geqslant$9 cm. For each MWA session, the sites of antenna placement were determined by the location of best access, the deeper portion of the tumor was treated initially, then the antennas were drawn back and the shallower portion of the tumor was treated. After treatment sessions, the antenna tracks were ablated to reduce the risk of bleeding or track seeding. Routine post-procedure management included hydration, antiemetics, and analgesia as needed.

Outcome measures

Local tumor responses and tumor necrosis rates. Local tumor response was measured using the modified Response Evaluation Criteria in Solid Tumor (mRECIST) for HCC, applied to MRI or CT images obtained 1 month after combined therapy. Using these criteria, we defined complete response (CR) as the disappearance of viable (enhancing) target lesions, and partial response (PR) as a 30% or more decrease in the sum of the diameters of target lesions.

The tumor necrosis rate was calculated using CT or MRI images obtained 1 month after ablation, along with 3D visualization software. The tumor necrosis rate was determined by dividing the estimated volume of residual tumor (if any) by the estimated volume of the original tumor. Based on the calculation, tumor necrosis was then classified as being either complete (100%), nearly complete (90–99%), partial (50–89%), or incomplete (less than 50%), according to the necrotic rate classification scheme proposed by Livraghi and colleagues.[17] All imaging studies were reviewed separately by two radiologists, and inter-observer disagreement was settled by mutual review and discussion.

Survival rates. Overall survival (OS) and progression-free survival (PFS) were calculated for each patient from the date of completion of the first session of ablation to the date of death or 30 July 2018, and to the date of local tumor progression or 30 July 2018, respectively. When a residual or recurrent tumor was detected, decisions about additional treatment were made according to the recurrence pattern, underlying liver function, and overall clinical condition of the patient.

Safety. The follow-up protocol included a routine physical examination, liver and renal function tests, alpha-fetoprotein (AFP) levels, and Child–Pugh classification, all performed within 3 days, and then 1 month and every 3 months after treatment. Adverse events and complications after therapy were identified and described according to both the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and the Society of Interventional Radiology Classification system for Complications by Outcome.[18–20]

Statistical methods

Quantitative data were expressed as means with standard deviation (SD) and compared using the Student's *t* test. Survival analysis was reported as OS and PFS rates, which were estimated using the Kaplan–Meier method. Patients were censored in the survival analysis if they were alive without recurrence at their last follow up or if they were lost to follow up. A p value <0.05 was considered statistically significant. SPSS statistical computer software (version 25.0, SPSS Inc., USA) was used for data analyses.

Results

Protocol feasibility

All 43 patients (100%) completed combined TACE and MWA therapy according to the treatment protocol (TACE followed within 1–3 days by MWA). The mean total ablation duration per patient was 27.1 (range, 8–53) min. The number of antennas used for MWA was two in 2 patients, three in 13 patients, four in 12 patients, and five in 16 patients.

Patient characteristics

The mean age of patients was 52.6 years (range, 32–73 years). Of the 43 patients, 28 (65.1%) were 60 years old or younger, 38 (88.4%) were male, and 37 (86.1%) were hepatitis B virus (HBV)-positive (Table 1). Among the 43 patients, the mean HCC tumor diameter was 8.8 (SD, 2.8; range, 5.4–14.8) cm, and 14 (32.6%) had tumors >10 cm in diameter. In addition, 17 (39.5%) patients were considered to be BCLC Stage A, while 18 (44.2%) were considered to be BCLC Stage B.

Table 1. Characteristics of 43 patients with large HCC who received ablation-oriented combined therapy[a] between July 2015 and July 2018.

Characteristics	**Patients**	
	N	**%**
Age[b], *years*		
>60	15	34.9
⩽60	28	65.1
Sex		
Male	38	88.4
Female	5	11.6
Hepatitis B surface antigen		
Positive	37	86.1
Negative	6	13.9
Child–Pugh Class[c]		
A	42	97.7
B	1	2.3

(Continued)

Table 1. (Continued)

Characteristics	Patients	
	N	**%**
BCLC stage[d]		
A	17	39.5
B	18	44.2
C	8	18.6
Tumor diameter[d], cm		
5.0–7.0	14	32.6
7.1–10	15	34.9
>10	14	32.6
Tumor location in liver		
Right lobe	40	93.0
Left lobe	2	4.7
Both lobes	1	2.3
Tumor thrombus		
Portal vein branches	6	13.9
Hepatic vein branches	2	4.7
None	35	81.4
AFP level, ng/l		
⩾400	22	51.2
<400	21	48.8
Previous TACE		
0	25	58.1
1	9	20.9
2	5	11.6
⩾3	4	9.3

[a]Ablation-oriented combined therapy involved TACE followed within 1–3 days by multi-antenna MWA.
[b]Mean age 52.6 (range, 32–73) years.
[b]Child–Pugh Class is a multi-organ assessment of patients with underlying cirrhosis: Class A, 5–6 points; B, 7–9 points, and C, 10–15 points.
[c]Barcelona Clinic Liver Cancer stage is a validated classification using variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms. Stages include 0, A, B, C, and D; Stage A (early stage) involves up to 3 nodules up to 3 cm, Stage B (intermediate stage) involves large, multiple tumors, and Stage C (advanced stage).
[d]Mean tumor diameter ± SD was 8.8 ± 2.8 cm (range, 5.4–14.8 cm).
AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; MWA, microwave ablation; SD, standard deviation; TACE, transarterial chemoembolization.

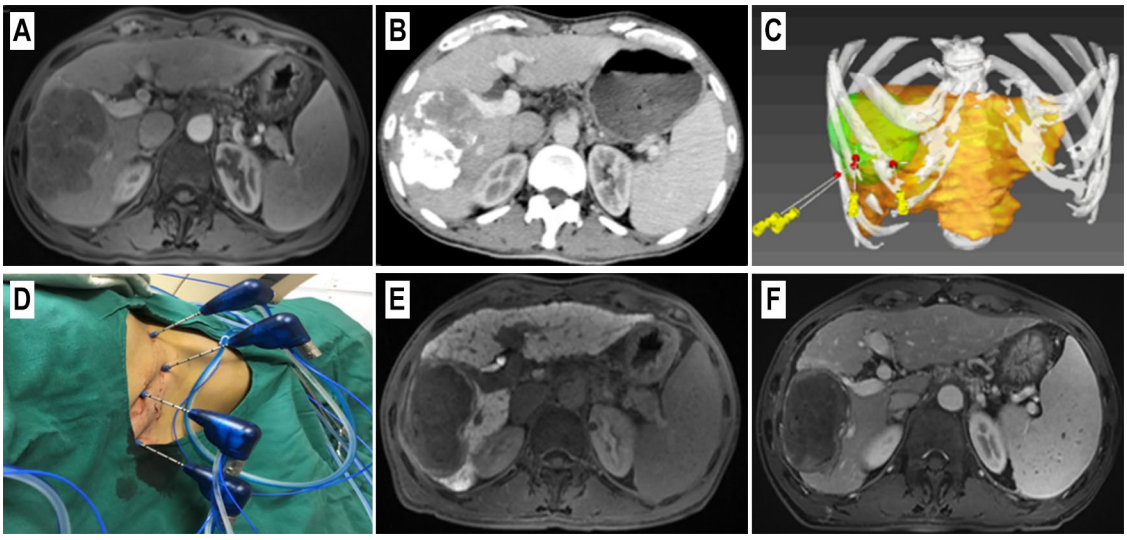

Figure 1. A 61-year-old male with a large HCC, treated with ablation-oriented combined therapy, resulting in complete tumor necrosis.
Ablation-oriented combined therapy involved TACE followed within 1–3 days by multi-antenna MWA. (a) Contrast-enhanced MRI reveals a 6.1 cm × 8.7 cm HCC in the right hepatic lobe, with enhancement (arrows) demonstrating viable tumor; (b) Contrast-enhanced CT after TACE shows tumor with heterogeneous deposition of lipiodol, and the portion without lipiodol deposition (so not addressed by TACE) was still enhanced in the arterial phase; (c) 3D image of planning for four-antenna MWA of large tumor shows reconstruction of tumor and adjacent tissue, which improves visualization and precision of design of ablation site; image includes liver (orange), large HCC (yellow), MWA antenna positioning (gray needles, yellow heads, red patient entry sites), and ablation zone (green); (d) MWA set-up with four antennas, using settings of 60 W power and 15 min duration for each antenna, two simultaneous cycles (deep and shallow), and total ablation duration 30 min; (e) Contrast-enhanced MRI in Primovist hepatobiliary phase, 3 months after ablation-oriented combined therapy, reveals complete tumor necrosis (arrow); (f) Contrast-enhanced MRI 6 months after combined therapy reveals reduced lesion size and a satisfactory nonviable fibrous capsule (arrow).
3D, three-dimensional; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; MWA, microwave ablation; TACE, transarterial chemoembolization.

Local response

When all 43 patients were evaluated with imaging 1 month after treatment, 10 (23.3%) patients had a CR and 33 (76.7%) patients had a PR, according to the mRECIST definitions. Alternatively, based on imaging and use of 3D visualization software to calculate tumor necrosis rates, 16 (37.2%) patients had complete tumor necrosis (Figure 1), 19 (44.2%) had nearly complete necrosis (Figure 2), and 8 (18.6%) had partial necrosis (Figure 3). The mean tumor necrosis rate in all 43 patients was 92.2%, and in no patient did combined therapy result in less than 50% necrosis. The proportion of patients with 90% or greater tumor necrosis was 81.4%.

Survival rates

As of July 30, 2018, the mean follow up was 12.2 (range, 3.5–35.6) months. At the end of follow up, 31 (72.1%) of the 43 patients remained alive, whereas 12 (27.9%) had died. The causes of death were HCC progression in 10 patients (intrahepatic recurrence in 7 patients and extrahepatic recurrence in 3 patients) and hepatic failure without tumor progression in the other 2 patients. The 1- and 2-year OS rates were 64.0% and 46.8%, respectively, with a median OS of 23.0 months (Figure 4). The 1- and 2-year PFS rates were 19.9% and 4.4%, respectively, with a median PFS of 4.2 months.

Treatment safety

When measured 3 days after therapy, mean blood urea nitrogen (BUN) and creatinine (CRE) levels remained within the normal range (Figure 5). However, mean total bilirubin (TBiL; $p = 0.001$) levels and PT ($p = 0.042$) increased significantly and mean albumin (ALB; $p = 0.035$) levels decreased significantly, but these values all

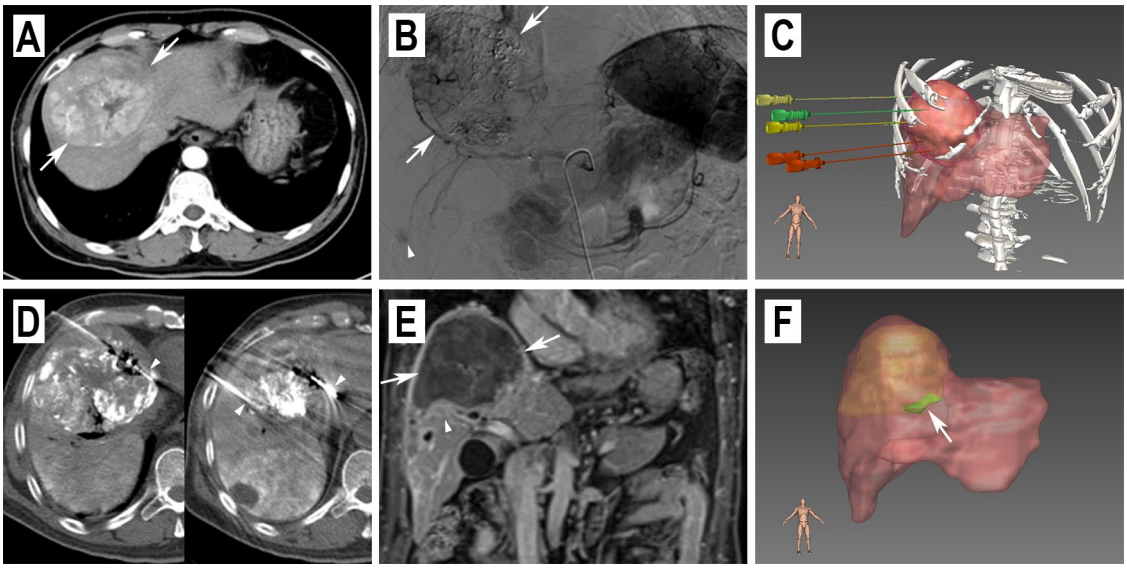

Figure 2. A 64-year-old male with a large HCC, treated with ablation-oriented combined therapy, resulting in nearly complete tumor necrosis.
Ablation-oriented combined therapy involved TACE followed within 1–3 days by multi-antenna MWA. (a) Contrast-enhanced CT reveals an 8.0 cm × 9.7 cm HCC in liver segment 4/8 (arrow); (b) Hepatic arterial angiography reveals tumor staining (blush) in the hepatic dome (arrows) and a small intrahepatic tumor focus (arrowhead); (c) 3D image of planning for five-antenna MWA of large tumor; (d) Intraoperative CT shows five-antenna MWA undertaken using settings of 60 W power and 12 min duration for each antenna, for two simultaneous cycles (deep and shallow), total ablation duration 24 min; (e) Coronal contrast-enhanced MRI 1 month after ablation-oriented combined therapy reveals small residual tumor nodule (arrowhead) adjacent to large necrotic tumor (arrows); (f) Using 3D reconstruction software, volume of residual tumor nodule (green with arrow) estimated at 4.73 cc, volume of original tumor estimated at 431.46 cc, so tumor necrosis rate was calculated as 98.9% and tumor necrosis was classified as nearly complete. (Another ablation procedure was conducted for the small residual tumor nodule.).
3D, three-dimensional; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; MWA, microwave ablation; TACE, transarterial chemoembolization.

returned to normal within 30 days. Because of the transient liver function abnormalities noted 3 days after therapy, 11 patients were downgraded from Child–Pugh Class A to Class B and 1 patient from Class B to Class C; however, all of these patients returned to their pretreatment Child–Pugh classes by 1 month after treatment.

Postoperative fever, pain, right pleural effusions (not needing treatment) were the most common adverse events after therapy (Table 2). With two exceptions, all adverse events and complications were CTCAE Grade 1 or 2 (asymptomatic or mild symptoms, clinical or diagnostic observations only, no or local/noninvasive intervention indicated), or Society of Interventional Radiology Classification Grade A or B (no or nominal therapy, no consequence). Of the exceptions, one patient developed a massive right pleural effusion, requiring chest tube drainage, and another patient developed a subcapsular liver hemorrhage, requiring laparoscopic intervention for hemostasis.

Treatment of residual and recurrent tumors

Among the 43 patients, 29 (67.4%) had either residual tumor or tumor recurrence outside the tumor bed discovered during the follow-up period. Of these 29 patients, 17 (58.6%) underwent repeated combined TACE and MWA, 4 (13.8%) underwent combined TACE and MWA along with sorafenib antineoplastic systemic therapy, 3 (10.3%) underwent MWA only, 3 (10.3%) received sorafenib only, and 2 (6.9%) underwent TACE only.

Discussion

To date, most investigators using combined therapy for HCC have concentrated their efforts on the

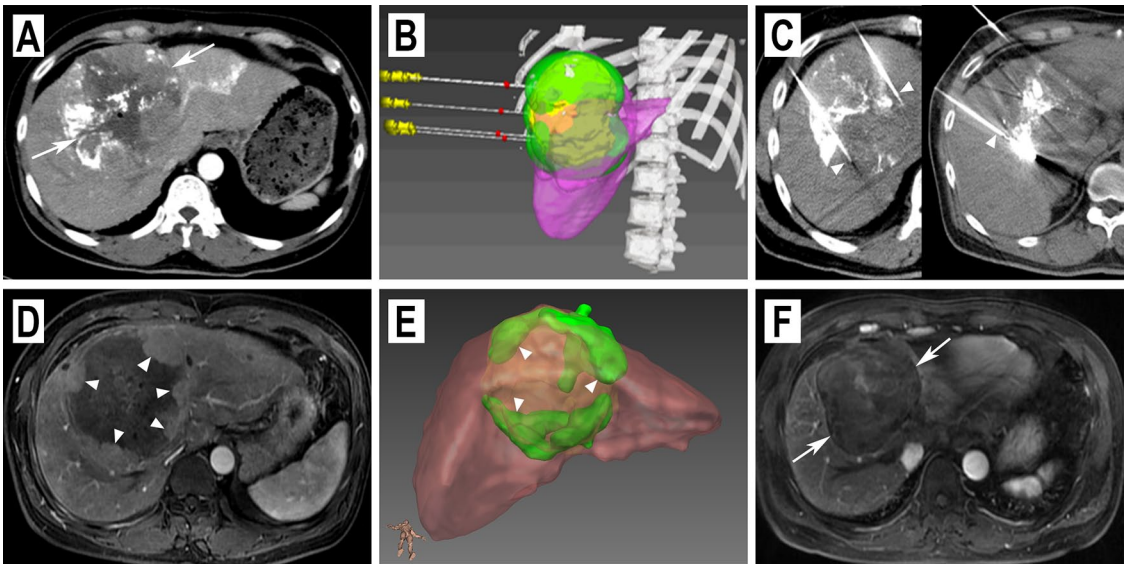

Figure 3. A 43-year-old male patient with large HCC, treated with ablation-oriented combined therapy, resulting in partial tumor necrosis.
Ablation-oriented combined therapy involved TACE followed within 1–3 days by multi-antenna MWA. (a) Contrast-enhanced CT reveals an 11.0 cm × 11.3 cm HCC in liver segment 4/8 (arrow); (b) 3D image of planning for five-antenna MWA of large tumor; image includes liver (purple), MWA antenna positioning (gray needles, yellow heads, red patient entry sites), and large HCC and ablation zone (green); (c) Intraoperative CT shows five-antenna MWA undertaken using settings of 60 W power and 15 min duration for each antenna, for two simultaneous cycles (deep and shallow), total ablation duration 30 min; (d) Contrast-enhanced MRI 1 month after ablation-oriented combined therapy shows multiple small residual tumors (arrowheads) located along outer margin of otherwise necrotic tumor, and within separate fibrous capsule; (e) Using 3D reconstruction software, volume of residual tumor (green with arrowheads) estimated at 175.82 cc, volume of original tumor estimated at 782.65 cc, so tumor necrosis rate was calculated as 77.5% and tumor necrosis was classified as partial; (f) Contrast-enhanced MRI 3 months after ablation-oriented combined therapy and 2 months after supplementary MWA, revealing a satisfactory nonviable fibrous capsule (arrows).
3D, three-dimensional; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; MWA, microwave ablation; TACE, transarterial chemoembolization.

TACE portion of the therapy, using ablation in a delayed fashion as a secondary or adjuvant component of the therapy. In contrast, in this study we focused our efforts on treating large HCC by employing TACE in a pre-ablation fashion, and then promptly (within 1–3 days) following it with MWA, which served as the primary component of therapy. Also, given the challenges of completely destroying large tumors with single-antenna ablation techniques, we endeavored in this study to leverage the power of multi-antenna MWA, to determine whether it would be feasible and tolerable to address entire tumors in a single ablation session performed soon after TACE. The results of this preliminary clinical study show that this multi-antenna microwave ablation-oriented combined therapy can be completed tolerably and in a single hospitalization, and that it can provide satisfactory outcomes for some patients with large HCC and few other options.

Combined therapy with TACE and ablation has been described as an option for treating HCC in several recent national guidelines, but mainly for patients with intermediate-sized (3–5 cm) or smaller, unresectable HCC.[21–23] Indeed, studies of combined therapy for small and intermediate-sized HCC have demonstrated good feasibility and tolerability, enhanced local control, low levels of tumor progression, and improved survival.[24,25] However, many of these studies have used radiofrequency ablation or only single-antenna MWA.

We are aware of only a limited number of studies similar to ours, in which large HCC have been

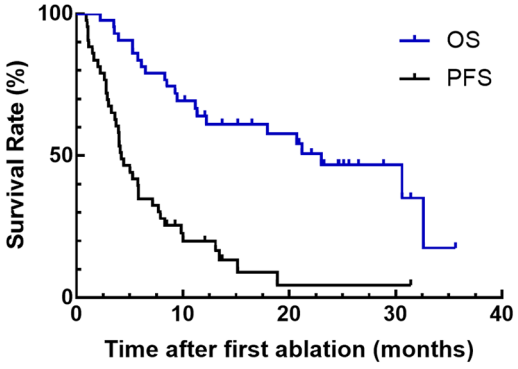

Figure 4. Kaplan–Meier OS and PFS rate curves of 43 patients with large HCC who underwent ablation-oriented combined therapy between July 2015 and July 2018.
Ablation-oriented combined therapy involved TACE followed within 1–3 days by multi-antenna MWA. Mean follow up of patients was 12.2 (range, 3.5–35.6) months. Cumulative OS probability estimates at 1 and 2 years were 64.0% and 46.8%, respectively, with a median OS of 23.0 months. Cumulative PFS probability estimates at 1 and 2 years were 19.9% and 4.4%, respectively, and median PFS was 4.2 months. On the plot, small vertical tick-marks indicate individual patients whose survival times were censored (because they were alive without recurrence at last follow up or were lost to follow up).
HCC, hepatocellular carcinoma; MWA, microwave ablation; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization.

treated with combined therapy using TACE and multi-antenna MWA. A 2018 report from Hu and colleagues demonstrated that combined therapy for large HCC in 84 patients using TACE and MWA during a single hospitalization was tolerable, feasible, and effective.[4] However, they used MWA in more of an adjuvant fashion, applying sequential overlapping focal MWA by inserting antennas only into areas exhibiting poor lipiodol deposition during TACE. Because of the central role played by TACE in their combined therapy, we would consider their approach to be more TACE-oriented. In contrast, in our ablation-oriented approach, we used simultaneous multi-antenna ablation with the goal of treating the entire tumor. Also, rather than employing a standardized protocol as we did, they used an individualized approach, which may be difficult to replicate from one patient to the next and by one medical provider to the next.

Also, they reported cumulative 1- and 2-year OS rates of 81% and 68%, respectively, which were higher than our 1- and 2-year OS rates of 64% and 47%, respectively.[4] However, the median tumor size in their study was 6.2 cm, whereas that in our study was 8.8 cm; it is possible that our lower OS rates were a reflection of the larger HCC being treated in our study. A variety of

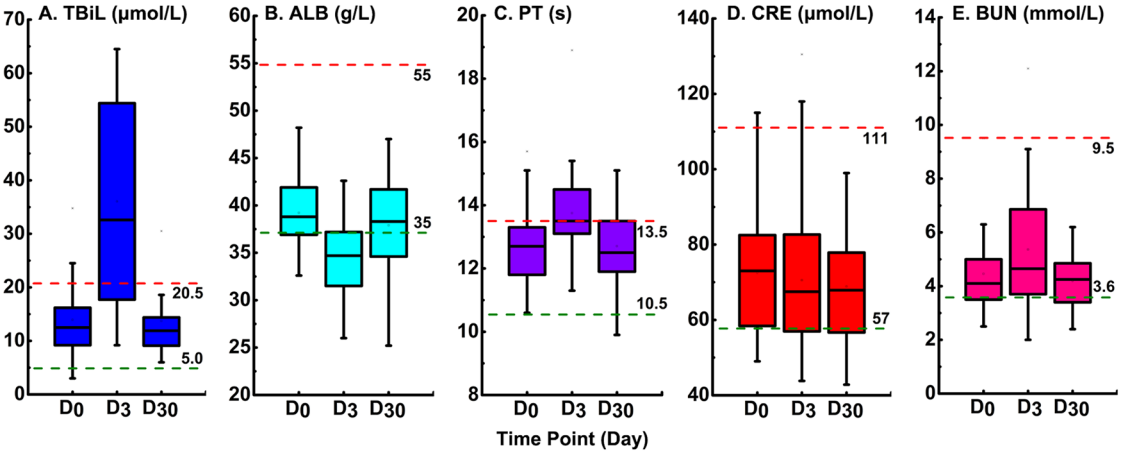

Figure 5. Hepatic and renal function test results before (D_0), 3 days after (D_3), and 30 days after (D_{30}) ablation-oriented combined therapy performed between July 2015 and July 2018 in 43 patients with large HCC.
Ablation-oriented combined therapy involved TACE followed within 1–3 days by multi-antenna MWA. Broken red line indicates upper limit of normal range, and broken green line indicates lower limit of normal range. (a) Mean TBiL increased significantly at D_3 and returned to normal at D_{30}; (b) Mean ALB decreased significantly at D_3 and returned to normal at D_{30}; (c) Mean PT increased significantly at D_3 and returned to normal at D_{30}; (d) Mean CRE remained normal at D_3 and D_{30}; (e) Mean BUN remained normal at D_3 and D_{30}.
ALB, albumin; BUN, blood urea nitrogen; CRE, creatinine; HCC, hepatocellular carcinoma; MWA, microwave ablation; PT, prothrombin time; TACE, transarterial chemoembolization; TBiL, total bilirubin

Table 2. Adverse events and complications after ablation-oriented combined therapy[a] performed on 43 patients with large HCC, between July 2015 and July 2018.

Categories	Grades		Patients, *N* (%)
	CTCAE v4.03[b]	SIR classification[c]	
Adverse events			
Fever, maximum 38°C, no treatment	1	A	13 (30.2)
Nausea or vomiting	2	A	12 (27.9)
Asymptomatic right pleural effusion	1	A	9 (20.9)
Mild pain, requiring nonopioid oral analgesic treatment	1	B	11 (25.6)
Moderate pain, requiring opioid oral analgesic treatment	2	B	20 (46.5)
Mild liver dysfunction, requiring conservative treatment	2	B	12 (25.6)
Total bilirubin elevation, transient	2	B	12 (25.6)
Hypoalbuminemia, transient	1	B	1 (2.3)
Minor complications			
Asymptomatic intrahepatic bile duct dilation	1	B	1 (2.3)
Asymptomatic perihepatic fluid	1	B	1 (2.3)
Major complications			
Massive right pleural effusion, requiring chest tube drainage[d]	2	C	1 (2.3)
Subcapsular liver hemorrhage, requiring laparoscopic hemostasis	4	D	1 (2.3)

[a]Ablation-oriented combined therapy involved TACE followed within 1–3 days by multi-antenna MWA.
[b]CTCAE, version 4.03, uses Grades 1 through 5 to refer to the severity of the adverse events, based on general guidelines: Grade 1 mild - asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2 moderate - minimal, local or noninvasive intervention indicated; Grade 3 severe - medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling; Grade 4 life-threatening - urgent intervention indicated; Grade 5 death - related to adverse event.[18]
[c]SIR classification system for Complications by Outcome describes minor complications (Grade A – no therapy, no consequence; Grade B – nominal therapy, no consequence) and major complications (Grade C – require therapy, minor hospitalization; Grade D – require major therapy, unplanned increase in level of care, prolonged hospitalization; Grade E – permanent adverse sequelae; Grade F – death).[20]
[d]Chest tube drainage was necessary for only 1 day.
CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; HCC, hepatocellular carcinoma; MWA, microwave ablation; SIR, Society of Interventional Radiology; TACE, transarterial chemoembolization.

others have also reported OS results for TACE alone, but these are difficult to compare to compare with ours, because of the different patient populations involved. However, a comparable study of 40 patients with a mean HCC size of 7 cm (range, 4–14 cm) involved treatment with repeated TACE alone every 2–3 months, and reported 1- and 2-year OS of 57% and 31%, respectively.[26] Comparing these results with ours lends support to the notion that there may be a survival benefit by adding MWA to TACE.

Unlike most studies involving combined therapy with MWA, we used up to five antennas for large

HCC in our study, and we activated these antennas simultaneously. This choice of this technique is important, because compared with sequential multi-antenna MWA, simultaneous multi-antenna MWA has the advantages of requiring shorter treatment durations and producing larger ablation zones.[27] In fact, at least two groups have achieved effective local tumor ablation and coagulation necrosis using three-antenna MWA alone on HCC with diameters up to 6 cm.[28,29] It has been postulated that simultaneous multi-antenna MWA may perform so well because of the creation of unusually high concentrations of heat deposition within the tumor, while the tumor pseudo-capsule may help retain that heat as it also forms a barrier that minimizes injury to the normal surrounding tissue, thus increasing safety.

Another unique aspect of our study was that we performed MWA within 3 days of TACE. We chose this approach for several reasons. We were interested in determining the feasibility of a combined treatment that could be accomplished in a single hospitalization, improving the clinical efficiency for patients. We also postulated that, although MWA works primarily by near-field heating, it may also rely on conductive heating at the margins of the ablation zone, which may be particularly susceptible to the 'heat sink' effect.[30] Thus, occluding all tumor-supplying arteries with TACE just prior to MWA would theoretically reduce the risk of the 'heat sink' effect during MWA, particularly in large HCC which are known to have a many, large, abnormal internal and peripheral blood vessels. This notion was supported by recent published work involving an *in vivo* nontumor-bearing bovine liver model, in which the addition of TACE just before MWA resulted in a 27% increase in the observed ablation zone diameters.[31] In addition, others have argued against a long interval between TACE and ablation, because of concerns that this delay may allow the formation of collateral blood supply, or that it may allow ischemia and hypoxia from TACE to cause an elevation of hypoxia-inducible factors, resulting in upregulation of vascular endothelial growth factor, and thus increasing the risk of intrahepatic recurrences or distant metastases.[13]

Historically, the majority of reports of combined therapy for HCC have described waiting anywhere from a week to a month between TACE and ablation.[13] In some cases, reported delays have been even longer, based on the time necessary for large tumors to shrink to the 3-cm size at which ablation has previously been most effective. In other cases, delays may have been based on concerns about the tumor lysis syndrome occurring after TACE for large HCC.[32,33] However, in a study of 2863 patients with HCC who underwent TACE over a 6-year period, only 1 (0.034%) patient experienced tumor lysis syndrome.[34] In our study, none of the patients demonstrated symptoms of tumor lysis syndrome or evidence of renal insufficiency. A theoretical benefit of the simultaneous multi-antenna ablation technique that we employed is that it likely creates extensive tumor necrosis, involving the rapid coagulation, denaturation, and deactivation of tissue and intracellular proteins. As a result, inflammatory factors, allergic factors, and other protein substances may remain in the cell, rather than entering the blood and causing tumor lysis syndrome.

In this study, we were able to show the feasibility of performing TACE and multi-antenna MWA in patients with large HCC, with completion of both procedures during a single hospitalization in all patients. We were also able to demonstrate the safety of this approach. Similar to what has been reported in other studies, we observed liver function test abnormalities in our group of patients when these were measured 3 days after treatment, all of which returned to normal levels when measured again 30 days after treatment.[35–37] Almost all adverse events were considered low-grade by the two classification systems we used. Of note, 10 (23.3%) patients in our study developed right pleural effusions after treatment, which may have been the result of thermal impact on the ipsilateral diaphragm and pleura. Of these, the effusions in nine patients were noted to resolve spontaneously within 1–3 months, whereas one patient required a temporary chest tube. The most serious complication was subcapsular liver hemorrhage that required laparoscopic intervention for hemostasis in one patient.

Finally, we were also able to show the successful use of imaging and 3D visualization software to calculate tumor necrosis rates. We were encouraged by the findings that 37% of patients had evidence of complete tumor necrosis, that the mean tumor necrosis rate in all 43 patients was 92.2%, and that 81% of these patients had 90% or greater tumor necrosis. In those patients with less than

complete tumor necrosis, we postulate that the fibrous capsules around nodules-within-nodules inside large HCC may block some of the heat conduction during ablation, creating a barrier to achieving complete ablation for the entire tumor. Another possibility, particularly in large HCC with an abundant blood supply, is that peripheral tumor neovascularity and collateral vessels may still be playing a role. Though ideally during pre-ablation TACE the vasculature is all occluded and during MWA the tumor is being ablated by near-field rather than peripheral conductive heating, there still could be some 'heat sink' effects in the periphery. This is supported by the fact that some of our patients with incomplete necrosis had primarily peripheral tumor residual (see Figure 3). Though some patients with incomplete necrosis can undergo repeat ablation-oriented combined therapy or MWA, additional research will be needed to determine how to improve the complete necrosis rate in these patients.

Limitations

The findings in this study should be interpreted with caution, given that this was a retrospective study, with a relatively small sample size, short-term follow up, and no control group. However, the primary purposes of the study were to demonstrate clinical feasibility, assess safety, measure tumor necrosis rates, and evaluate the degree of local control possible with ablation-oriented combined therapy, all of which were accomplished. We were only able to collect anecdotal information about subsequent treatments and results in these patients, which though interesting, could not be put into a suitable format for inclusion in this manuscript. Also, we were only able to obtain renal and liver function test results for the period after TACE and before MWA for 14 patients, which we determined was not robust enough to include in the manuscript. Finally, although the vast majority of our patients achieved tumor necrosis rates of at least 90%, just over a third achieved 100% tumor necrosis. In the future, it will be important to investigate whether technical modifications can be identified that increase the proportion of patients that achieve complete tumor necrosis.

Conclusions

Multi-antenna microwave ablation-oriented combined therapy is feasible and well tolerated and it results in satisfactory initial local tumor control and short-term survival for some but not all patients with large HCC. If these findings are confirmed in larger prospective, controlled studies, this technique could be considered a viable therapy alternative for patients with large, unresectable HCC.

Acknowledgments

Tian-qi Zhang and Zhi-mei Huang contributed equally to this work and are considered co-first authors. The following author contributions are acknowledged:

Study concept and design: Jin-hua Huang; acquisition of data: Tian-qi Zhang, Jing-xian Shen, Gui-qun Chen; analysis and interpretation of data: Tian-qi Zhang, Zhi-mei Huang, Lu-jun Shen.

drafting of manuscript: Tian-qi Zhang, Zhi-mei Huang; critical revision of manuscript for intellectual content: Jin-hua Huang, Min-shan Chen; statistical analysis: Tian-qi Zhang, Zhi-mei Huang; administrative, technical, or material support: Min-shan Chen, Yang-kui Gu, Wang Yao, Yan-yang Zhang; and study supervision: Jin-hua Huang, Min-shan Chen.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (No. 81771955), Guangzhou Science and Technology Program, key projects of collaborative innovation of health medicine (No. 201704020228), Guangzhou Science and Technology Program, China key projects of collaborative innovation of production, learning and research (No. 201704020134), and Sun Yat-sen University Clinical Trial 5010 Project (No. 2016002).

Conflict of interest statement

The authors declare that there is no conflict of interest.

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