Preliminary Outcome of Microwave Ablation of Hepatocellular Carcinoma: Breaking the 3-cm Barrier?

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ABSTRACT

Purpose: To evaluate preliminary outcomes after microwave ablation (MWA) of hepatocellular carcinoma (HCC) up to 5 cm and to determine the influence of tumor size.

Materials and Methods: Electronic records were searched for HCC and MWA. Between January 2011 and September 2014, 173 HCCs up to 5 cm were treated by MWA in 129 consecutive patients (89 men, 40 women; mean age, 66.9 y ± 9.5). Tumor characteristics related to local tumor progression and primary and secondary treatment efficacy were evaluated by univariate analysis. Outcomes were compared between tumors ≤ 3 cm and tumors > 3 cm.

Results: Technical success, primary efficacy, and secondary efficacy were 96.5%, 99.4%, and 94.2% at a mean follow-up period of 11.8 months ± 9.8 (range, 0.8–40.6 mo). Analysis of tumor characteristics showed no significant risk factor for local tumor progression, including subcapsular location ($P = .176$), tumor size ($P = .402$), and perivascular tumor location ($P = .323$). The 1-year and 2-year secondary or overall treatment efficacy rates for tumors measuring ≤ 3 cm were 91.2% and 82.1% and for tumors 3.1–5 cm were 92.3% and 83.9% ($P = .773$). The number of sessions to achieve secondary efficacy was higher in the larger tumor group (1.13 vs 1.06, $P = .005$). There were three major complications in 134 procedures (2.2%).

Conclusions: With use of current-generation MWA devices, percutaneous ablation of HCCs up to 5 cm can be achieved with high efficacy.

ABBREVIATIONS

HCC = hepatocellular carcinoma, LTP = local tumor progression, MWA = microwave ablation

Percutaneous radiofrequency (RF) ablation has become a standard treatment for hepatocellular carcinomas (HCCs) < 3 cm associated with underlying liver disease (1). Several studies reported RF ablation in this patient population to be comparable to liver resection in overall survival with fewer complications (2–5). RF ablation has also been shown to be more cost-effective than hepatic resection in HCCs < 3 cm (6). In contrast, RF ablation in tumors > 3 cm has not been as successful, and tumor size is considered one of the most important factors influencing outcome of RF ablation in general (7–9). In the Barcelona Clinic Liver Cancer guidelines for treatment of HCC, only tumor nodules up to 3 cm are considered candidates for RF ablation as first-line treatment. The decreased effectiveness of RF ablation in larger tumors is multifactorial,

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including increased likelihood of tumor abutting adjacent vessels or sensitive structures, resulting in more "heat-sink" effect and more challenging access to parts of the tumor. As tumor volume increases, the need for "sculpting" of the tumor by multiple applicators or reinsertions also renders the procedure more technically challenging.

Microwave ablation (MWA), although not new, has gained increasing popularity more recently as a method of thermal ablation. MWA has several theoretical advantages compared with RF ablation. For example, larger ablation zones can be produced faster as a result of hotter tissue temperatures achievable by microwaves. Simultaneous activation of multiple microwave applicators is not influenced by the electrical interference seen in RF ablation, allowing for synergistic tissue heating (10). Two randomized trials showed no significant difference in outcomes between RF ablation and MWA for HCC treatment (11,12). Liang et al (13) reported tumor size, tumor number, and Child-Pugh classification to be significant factors influencing survival of patients with HCC after MWA. However, these studies were conducted with earlier generation MWA systems. New MWA devices and antennas have been introduced, with more efficient energy delivery (10,14). The purpose of this study was to evaluate the effectiveness of current-generation MWA devices in the treatment of HCCs up to 5 cm by analyzing the preliminary outcomes, including local tumor progression (LTP) and control of tumor, using current-generation MWA devices in patients with HCCs up to 5 cm. We also sought to determine the influence of tumor size, especially tumors > 3 cm.

MATERIALS AND METHODS

The study was approved and need for patient consent was waived by the medical center institutional review board. Electronic records were searched for HCC and MWA. Between January 2011 and September 2014, 129 patients with 173 HCCs up to 5 cm were treated by MWA without additional assistive or combined procedures other than hydrodissection. Patients included 89 men and 40 women (age range, 39–89 y; mean age, 66.9 y ± 9.5). All patients had liver disease, including hepatitis B (n = 28), hepatitis C (n = 70), hepatitis C and alcoholic liver disease (n = 5), alcoholic liver disease (n = 6), coexistent hepatitis B and C (n = 2), nonalcoholic steatohepatitis (n = 7), cryptogenic cirrhosis (n = 9), hemochromatosis (n = 1), and autoimmune hepatitis (n = 1) (Table 1). The diagnosis of HCC was based on either pathology or imaging criteria (Liver Imaging Reporting and Data System 5, Organ Procurement and Transplantation Network 5, and American Association for the Study of Liver Diseases) (1,15,16).

Table 1. Patient Characteristics

Characteristic	No. Patients (n = 129)
Age (y)	66.9 ± 9.5 (range, 39–89)
Sex (male:female)	89:40
Etiology of liver disease	
Hepatitis B	28 (21.7%)
Hepatitis C	70 (54.2%)
Hepatitis B and C	2 (1.6%)
Hepatitis C and alcoholic hepatitis	5 (3.9%)
Alcoholic hepatitis	6 (4.6%)
Autoimmune hepatitis	1 (0.8%)
Hemochromatosis	1 (0.8%)
Nonalcoholic steatohepatitis	7 (5.4%)
Cryptogenic cirrhosis	9 (7.0%)
Child-Pugh classification	
A	92 (71.3%)
B	33 (25.6%)
C	4 (3.1%)

Note–Values are number (percent) unless otherwise indicated.

MWA Procedure

Percutaneous MWAs were performed by one of five abdominal interventional radiologists with 3–22 years of experience with hepatic tumor ablation (S.S.R., J.P.M., M.D., S.B., D.S.K.L). All patients underwent monitored or general anesthesia administered by an anesthesiologist. All cases were performed with combined ultrasound (iU22; Philips Healthcare, Bothell, Washington) and computed tomography (CT) guidance, which is standard protocol at our institution. Two systems were used for MWA at our institution, both operating at 2.45 GHz: the AMICA device, which supports a 16-gauge antenna (HS Medical, Boca Raton, Florida), and the Certus device, which supports up to three 17-gauge PR (short tip) or LK (long tip) antennas (NeuWave Medical, Madison, Wisconsin). Number of applicators, ablation stations, and power and time of each ablation were determined by the performing physician, with the aim of generating a sufficient ablation zone to encompass the visible mass and at least a 5-mm ablation margin. The Certus device was used to treat 139 tumors, and the AMICA device was used to treat 34 tumors. Multiple applicators or overlapping technique was used in tumors > 2.5 cm. In cases where multiple applicators were deemed to be necessary, the Certus device was used because the AMICA system supported only a single antenna. Feedback for completeness of ablation was provided primarily through visualization of the microbubble zone by real-time ultrasound or CT during active heating and on-table contrast-enhanced CT after ablation, with additional ablation performed if necessary. Tract ablation was performed in all patients.

In 65 ablation procedures, hydrodissection was performed for subcapsular tumor locations adjacent to sensitive organs, such as diaphragm, stomach, or bowel. The hydrodissection technique was described previously (17).

Assessment of Treatment Response

The imaging assessment protocol at our institution consisted of contrast-enhanced CT or magnetic resonance imaging performed before discharge; at 1, 3, 6, 9, and 12 months after ablation; and every 3–6 months thereafter. Definitions of treatment response used were based on the Society of Interventional Radiology (SIR) Standardization of Terminology and Reporting (18). Technical success was defined as complete tumor coverage by ablation zone on first follow-up imaging performed within 1 month after ablation. A treatment course was defined as all ablation sessions performed per nodule based on early imaging up to 3 months. Primary technique efficacy was achieved if there was no evidence of residual tumor at the ablation site by the last available imaging within 3 months, after which any imaging evidence of active tumor was considered LTP. LTP could be retreated by MWA or RF ablation for continued local tumor control and patients could still be rendered locally disease-free. Secondary or overall technique efficacy was defined as successful retreatment of index tumor after LTP. Complications were evaluated by clinical symptoms, imaging results, and serum examinations after treatment and were stratified according to SIR standard classification (19).

The mean follow-up period was 11.8 months ± 9.8 (range, 0.8–40.6 mo). The primary endpoints of the study were LTP and control of tumor growth. Secondary endpoints included liver transplantation and overall survival.

Risk Factors Analyzed

The tumor-related risk factors for LTP, including tumor size, number, and proximity to large blood vessels as well as critical structures that might be at risk for injury during an ablative procedure, were analyzed. Lesions were defined as perivascular if there was direct contact with vessels $\geq$ 3 mm in caliber. Lesions were considered subcapsular if located $<$ 10 mm from the liver capsule. Adjacent organs were considered high risk for injury if $<$ 10 mm from the tumor.

Statistical Analysis

Follow-up ended at the time of death, liver transplantation, or last clinical follow-up evaluation. Data were analyzed by using the χ^2 test to determine whether local recurrence rate was related to tumor size, tumor location, prior treatment before ablation, manufacturer of MWA system, and serum α-fetoprotein. Independent-sample t test was used to compare mean number of sessions to achieve complete ablation. Kaplan-Meier analysis was used to evaluate local tumor control rate. All statistical analyses were performed using IBM SPSS Statistics for Windows version 19.0 (IBM Corporation, Armonk, New York). A difference with $P < .05$ was considered to be significant.

RESULTS

Complications

There were three major complications in 134 treatment procedures (2.2%). These consisted of hemoperitoneum in one patient requiring blood transfusion and severe transaminitis requiring prolonged hospitalization in two patients. The two patients eventually recovered; both were in Child-Pugh classification B and had tumors $>$ 3 cm.

There were five minor complications (3.7%), including two clinically insignificant intrahepatic biliary strictures; one small biloma, which resolved spontaneously; and two vascular complications, one involving thrombosis of the anterior branch of the right portal vein and one involving focal nonocclusive thrombosis of the left main portal vein. The two thromboses did not require treatment. No incidence of tumor seeding was found.

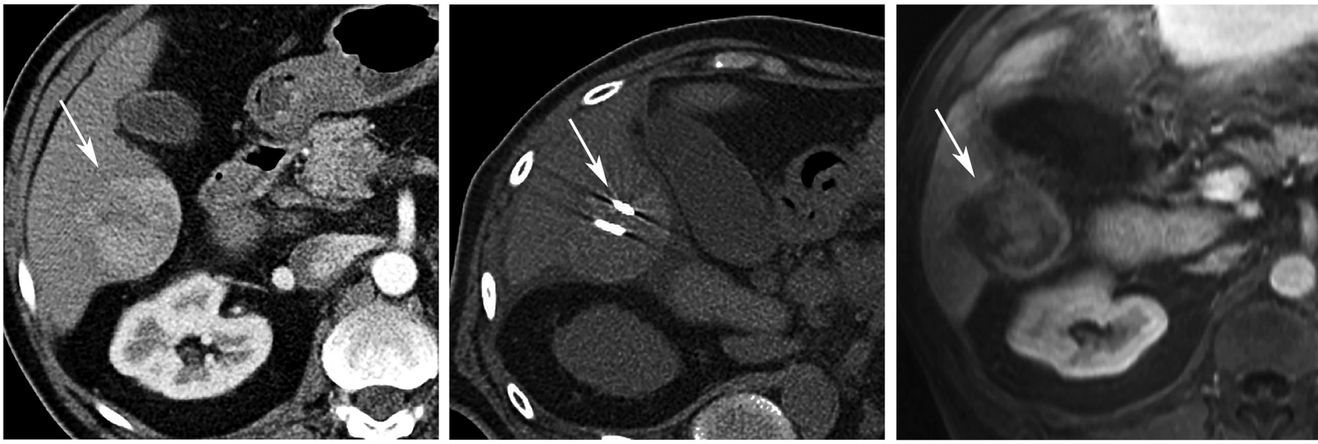
Technical Success and Primary Technique Efficacy Rate

Among the 173 HCC nodules treated by MWA, six showed residual disease based on imaging up to 1 month after ablation, and five had a second thermal ablation session to complete the treatment course within 3 months. One patient did not receive further locoregional treatment because of newly discovered portal vein invasion and extrahepatic metastasis. The technical success rate of the initial MWA session was 96.5%, and primary technique efficacy rate based on imaging criteria by completion of the treatment course at 3 months was 99.4% (172 of 173 tumors) (**Fig 1**).

Univariate analysis showed a significantly higher ratio of subcapsular tumor location, organ proximity, adjunctive hydrodissection, and failed previous treatments in the larger tumor group (3.1–5 cm) compared with the smaller tumor group (1–3 cm) (**Table 2**). Technical success rates and primary efficacy rates were not statistically significant between these two groups, although mean number of ablation sessions was higher for the larger versus smaller tumors (1.05 vs 1.02 sessions, $P = .006$)

LTP

LTP occurred in 20 of 173 tumors (11.6%). LTP in 10 tumors was successfully treated by additional thermal ablations (MWA in five and RF ablation in five) for a secondary technique efficacy rate of 94.2% (163 of 173 tumors) (**Fig 2**). One patient was successfully treated by additional transarterial chemoembolization. The remaining patients either were not treated further



a. b. c.

Figure 1. Hypervascular HCC in a 62-year-old man with nonalcoholic steatohepatitis. **(a)** Axial contrast-enhanced arterial phase CT image shows a large hypervascular mass (4.5 cm) at a subcapsular location of segment 6 of liver (arrow). **(b)** Axial noncontrast CT image during MWA shows two electrodes placed in the center of the tumor (arrow). **(c)** Gadolinium-enhanced T1-weighted magnetic resonance image obtained 1 month after MWA shows a heterogeneous high signal intensity area encompassing the previous hypervascular tumor without evidence of an arterial enhancing nodule , which represents complete tumor ablation (arrow).

Table 2. Univariate Analysis of Tumor Characteristics and Results between Tumor Size ≤ 3 cm and 3.1–5 cm

Variable	Tumor Size ≤ 3 cm	Tumor Size 3.1–5 cm	*P* Value
No. tumors	118	55	
Age (y)	66.0 ± 10.6	66.2 ± 8.6	.902
Sex			
Male	77 (65.3%)	39 (70.9%)	.461
Female	41 (34.7%)	16 (29.1%)	
Child-Pugh classification			
A	89 (75.4%)	38 (69.1%)	.469
B	25 (21.2%)	16 (29.1%)	
C	4 (3.4%)	1 (1.8%)	
Ablation device			
Certus	86 (72.9%)	53 (96.4%)	< .001
AMICA	32 (27.1%)	2 (3.6%)	
Subcapsular location	78 (66.1%)	47 (85.5%)	.008
Perivascular location	33 (28%)	18 (32.7%)	.522
Organ proximity	28 (23.7%)	27 (49.1%)	.001
Hydrodissection	33 (27.1%)	33 (60%)	< .001
Prior treatment	8 (6.8%)	14 (25.5%)	.001
Result			
Technical success	116 (98.3%)	51 (92.7%)	.062
Primary efficacy	118 (100%)	54 (98.2%)	.14
No. sessions*	1.02	1.05	.006
LTP	12 (10.2%)	8 (14.5%)	.402
Secondary efficacy	111 (94.1%)	51 (92.7%)	.737
No. sessions†	1.06	1.13	.005
Extrahepatic metastases‡	5/77 (6.5%)	6/52 (11.5%)	.314

Note–Values are number (percent) unless otherwise indicated.
LTP = local tumor progression.
*Number of sessions to achieve primary efficacy.
†Number of sessions to achieve secondary efficacy.
‡Extrahepatic metastases per patient.

because of medical comorbidities or were treated palliatively by transarterial chemoembolization or systemic therapies.

Univariate analysis of various tumor-related prognostic factors for LTP is shown in Table 3. No significant risk factors, including subcapsular location (P = .176), tumor

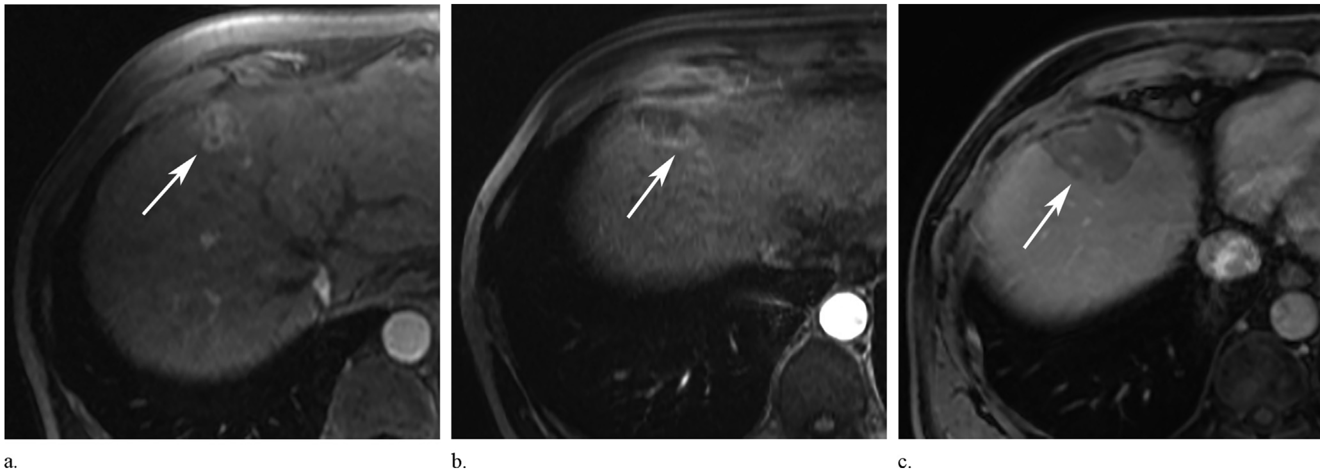


Figure 2. Hypervascular HCC in a 61-year-old man with chronic hepatitis C. **(a)** Gadolinium-enhanced T1-weighted magnetic resonance image shows a 2.7-cm nodule at hepatic dome (arrow). **(b)** Image obtained 8 months after MWA shows LTP at posterior edge of ablated zone (arrow). **(c)** Gadolinium-enhanced T1-weighted MR image shows new ablation zone completely encompassing the target tumor (arrow).

Table 3. Univariate Analysis of Prognostic Factors for LTP

Variable	No. Tumors	No. LTPs	*P* Value
Diameter of largest tumor			
0–3.0 cm	118	12 (10.2%)	.402
3.1–5.0 cm	55	8 (14.5%)	
Ablation device			
AMICA	34	1 (2.9%)	.08
Certus	139	19 (13.7%)	
Subcapsular location			
Present	125	17 (13.6%)	.176
Absent	48	3 (6.3%)	
Perivascular location			
Present	51	4 (7.8%)	.323
Absent	122	16 (13.1%)	
Organ proximity			
Present	55	8 (14.5%)	.402
Absent	118	12 (10.2%)	
Hydrodissection			
Performed	65	10 (15.4%)	.222
Not performed	108	10 (9.3%)	
Prior treatment			
None	151	17 (11.2%)	.744
Transarterial chemoembolization or RF ablation	22	3 (13.6%)	
Serum AFP level (μg/L) before ablation			
AFP $\leq$ 20	103	15 (14.6%)	.134
AFP $>$ 20	70	5 (7.1%)	

AFP = α-fetoprotein; LTP = local tumor progression.

size (P = .402), and perivascular tumor location (P = .402), were identified. Taking into account all ablations, including initial and repeated treatments, the 1-year and 2-year secondary or overall efficacy rates for tumors up to 3 cm were 91.2% and 82.1% and for tumors 3.1–5 cm were 92.3% and 83.9%, which were not significantly different (P = .773) (Fig 3). In achieving these results, more ablation sessions were required to retreat LTP in the larger tumor group compared with the smaller tumor group (mean 1.13 vs 1.06 sessions, P = .005).

New Disease Progression

New remote disease progression, including intrahepatic and extrahepatic disease, occurred in 47 patients. New

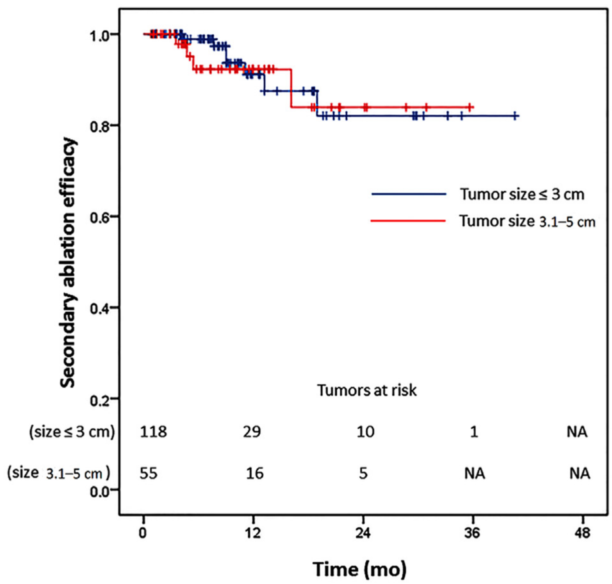


Figure 3. Graph shows overall or secondary efficacy rate of MWA of HCC. No significant difference was noted between tumor size up to 3 cm and 3.1–5 cm ($P = .773$, log-rank test).

intrahepatic tumors occurred in 41 of 129 patients (31.8%), and extrahepatic tumors occurred in 11 patients (8.5%), including bone, adrenal, lung, and intraabdominal lymph node metastases. Treatment for new intrahepatic tumors was as follows: additional tumor ablation (n = 20 patients), transarterial chemoembolization (n = 8 patients), combined ablation and transarterial chemoembolization (n = 1 patient), radioembolization (n = 2 patients), and systemic chemotherapy (n = 1 patient). The remaining patients did not receive additional treatment because of other concurrent medical comorbidities.

There were 12 patient deaths during the follow-up period. Of these, 3 patients died as a result of tumor progression. The 1-year and 2-year overall survival rates were 91.3% and 81.7%. Of 129 (13.9%) patients, 18 were bridged to liver transplantation. Mean time to liver transplantation was 11.6 months ± 9.5 (range, 1.4–29.5 mo).

DISCUSSION

Although surgical resection is the most effective curative approach for patients with resectable HCC, resection is contraindicated in most patients with HCC because of inadequate liver reserve, multifocal disease, anatomic limitations, or medical comorbidities. Therefore, tumor ablation has been developed as an alternative strategy. The first ablative modality was percutaneous ethanol injection therapy, which proved to be an effective curative treatment only for small HCC nodules (< 2 cm). After introduction of RF ablation, randomized controlled trials showed better local control of disease using RF ablation compared with percutaneous ethanol injection therapy (20). Therefore, RF ablation is currently considered to be a first-line treatment option in early-stage HCC (21). However, although RF ablation is more effective than percutaneous ethanol injection therapy, its effectiveness also declines with increasing tumor size, and current guidelines still limit RF ablation to tumors < 3 cm (22). With the introduction of current-generation MWA systems, which promised larger tumor ablation volumes in faster ablation times (23,24), the question remains whether this can translate into effective and complete ablations for tumors > 3 cm.

Overall LTP in this study was 11.5%, and local progression rates for tumors 1–3 cm and tumors 3.1–5 cm were 10.2% and 14.5%, respectively ($P = .402$). Similarly, as shown by Liu et al (25), comparing local recurrence rate between two size classifications showed no statistically significant difference. In a recent clinical study of MWA for tumors 3–4 cm, a 100% local control rate was achieved; however, the number of tumors was small (n = 16), and combination transarterial chemoembolization with MWA was used in 38% of treatments (26). In the present study, tumors up to 5 cm were also included, and all 3.1–5 cm tumors were treated with MWA alone, with a high 2-year local tumor control or secondary efficacy rate of 83.9%, which is nearly identical to rate for tumors up to 3 cm (82.1%). In addition, these results were achieved despite the higher ratio of challenging factors for tumor ablation in the larger versus smaller size group.

Tumor location has always been considered an important factor affecting success rate and affecting LTP. There has been debate in the literature regarding the effectiveness and complications of percutaneous tumor ablation in subcapsular tumors (27–29), which may have been in part due to differences in the definition of subcapsular tumor and differences in technique and study design. In our study, we defined the subcapsular tumor location as tumor located < 1 cm away from liver capsule. By this definition, subcapsular location is not a significant risk factor of LTP (13.6% vs 6.3%, $P = .176$), which is similar to the findings of Sartori et al (28) in the largest prospective study of effectiveness of ablation in subcapsular tumors.

In perivascular locations, RF ablation can be limited in achieving complete ablation because of the heat-sink effect (30). Owing to the theoretical advantage of MWA systems, which can heat faster with hotter tissue temperatures achieved, such heat-sink–related effects may be reduced, as was demonstrated in vivo (15). In a more recent study, MWA ablation zones were unaffected by changes in portal venous blood flow in a blood-perfused ex vivo bovine liver model, in contradistinction to RF ablation (31). However, Leung et al (32), in a clinical study using MWA, found perivascular location to be one of two significant independent predictors of local recurrence on multivariate analysis (the other one being tumor size). Nevertheless, our results show that MWA may be less susceptible to heat-sink effect from large vessels in contact with the tumor, given the lack of statistically significant difference of LTP ($P = .323$) between perivascular and nonperivascular tumors (7.8% vs 13.1%).

Major and minor complication rates in our study were 2.2% and 3.7%, respectively, similar to the largest report of complications of MWA (33). Two complications involving vascular thrombosis (1.2%) were seen in our study, which was similar to the rate of venous thrombosis after RF ablation reported by Kim et al (34). One case of thrombosis of the anterior branch of the right portal vein occurred despite tumor location and ablation site being in segment 6 of the liver. Portal vein thrombosis outside the ablation zone by heat has been reported in the porcine model as a rare complication (35). In our two cases of thrombosis, the complications were not clinically significant.

Limitations of this study include its retrospective design and loss of some patients during follow-up. Because this was a nonrandomized study, the absence of comparison with alternative thermal ablation techniques is another limitation. Both MWA systems used in this study were 2,450-MHz systems, limiting the applicability of the data to 915-MHz systems. Long-term outcomes would also require longer follow-up times. However, this study was intended to be a pilot report on the early experience of MWA of HCC using the latest microwave systems.

In conclusion, in this clinical study, early indications of percutaneous ablation of HCC using current-generation MWA devices are promising. We found low complication and high tumor control rates, not only for small tumors but also for intermediate-size tumors between 3 cm and 5 cm.

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CME TEST QUESTIONS: MAY 2016

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The CME questions in this issue are derived from the article "Preliminary Outcome of Microwave Ablation of Hepatocellular Carcinoma: Breaking the 3-cm Barrier?" by Thamtorawat et al.

In this article, the authors report the outcomes following microwave ablation (MWA) of hepatocellular carcinoma (HCC) measuring up to 5 cm.

1. Based on the results reported in this study, what percentage of HCCs, including those up to 5 cm, achieved complete response with a single session of MWA?
   a. 70%
   b. 80%
   c. 90%
   d. >95%

2. While comparing larger HCCs (3.1–5 cm) to smaller HCCs (1–3 cm), which of the following statements is NOT true?
   a. Larger tumors often abutted the capsule (subcapsular location).
   b. Hydro-dissection, to move the tumor away from a vital organ, was required twice as often for larger tumors than their smaller counterparts.
   c. There was no statistical difference in the number of MWA sessions required to achieve primary efficacy between the two groups.
   d. Primary efficacy, as defined by the authors, was similar for both groups.

3. Based on the results published in this study, approximately what percentage of HCCs demonstrate local tumor recurrence following successful MWA?
   a. 5–7%
   b. 10–12%
   c. 15–20%
   d. 25%

4. Which one of the following statements best summarizes the findings reported in this study?
   a. Local tumor progression as well as distant progression is statistically higher in HCCs >3 cm, validating the BCLC algorithm that ablation should be reserved for HCCs ≤ 3 cm.
   b. The proximity to large vessels and the subcapsular location contribute to the lower primary and secondary treatment efficacy following MWA for HCCs measuring 3.1–5 cm.
   c. Irrespective of the actual size, HCCs up to 5 cm have similar primary and secondary treatment efficacy rates following MWA, but larger tumors (3.1–5 cm) have a higher major complication rate and require more ablative sessions to achieve durable response.
   d. The primary and secondary treatment efficacy following MWA as well as major complication rates are comparable for all HCCs irrespective of size.