Hepatic Microwave Ablation With Multiple Antennae Results in Synergistically Larger Zones of Coagulation Necrosis

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Background: Microwave ablation is a promising treatment for unresectable liver tumors. Unlike radiofrequency ablation, microwave ablation may be performed with multiple simultaneously active antennae.

Methods: Microwave ablation was performed in an in vivo porcine liver model by using a single antenna (n = 11) or three antennae in a triangular array, activated either sequentially (n = 11) or simultaneously (n = 13). Lesions were measured and assigned a qualitative shape score.

Results: Single-antenna microwave lesions had a mean volume of 7.4 ± 3.9 cm³, compared with 14.6 ± 5.2 cm³ and 43.1 ± 4.3 cm³ for sequential and simultaneous multiple-probe ablations, respectively (P < .001; analysis of variance). Simultaneous lesions were rounder than sequential ablations and were more effective near blood vessels. Simultaneous lesions created with probe separation of ≤1.7 cm were round and confluent, whereas clefs were present with distances >1.7 cm (P < .001).

Conclusions: Microwave ablation has several theoretical advantages over currently available radiofrequency devices. Simultaneous three-probe microwave ablation lesions were three times larger than sequential lesions and nearly six times greater in volume than single-probe lesions. Additionally, simultaneous multiple-probe ablation results in qualitatively better lesions, with more uniform coagulation and better performance near blood vessels. Simultaneous multiple-probe ablation may decrease inadequate treatment of large tumors and decrease recurrence rates after tumor ablation.

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correspondingly larger zone of active heating. This may allow for more uniform tumor kill both within a targeted zone and next to vessels. RF is also limited by the increase in impedance with tissue boiling and charring, because water vapor and char act as electrical insulators. MW energy does not seem to be subject to this limitation; thus, lesion temperature may be driven considerably higher.

Like RF, MW ablation may be performed as an open, laparoscopic, or percutaneous procedure. Use of MW has been most prevalent in Asia to date, where a number of case series have shown it to be effective in local control of both hepatocellular carcinoma and metastatic colorectal carcinoma.

One limitation of MW has been the inability to treat large tumors without numerous overlapping ablations; in one study this required a mean of 46 ablations. Recent engineering advances have allowed the design of MW antennae that are tuned to the dielectric properties of liver, reducing feedback and increasing the amount of energy deposited into the surrounding tissue. This new MW ablation system (Vivant Medical Inc., Mountain View, CA) has the potential to create larger, hotter lesions than previously possible. Additionally, the prototype MW generator has the capacity to drive up to eight antennas at one time.

This ability to perform multiple ablations simultaneously may allow for the treatment of large tumors with concurrent overlapping lesions or for the ablation of several anatomically separate lesions at one time. Multiple probe ablation should reduce the need for repeat treatments, decrease inadequate treatment of larger tumors, and increase the speed of the therapy, thereby decreasing the complication rate. This study was designed to assess the feasibility of multiple-probe MW ablation in an in vivo porcine model. We hypothesized that sequential multiple-probe hepatic ablation would create larger zones of coagulation necrosis than single-probe ablation because of the additive effect of creating multiple overlapping lesions. We further hypothesized that simultaneous multiple-probe MW ablation would create synergistically larger lesions than either single-probe or sequentially activated multiple-probe ablation because of shielding of the lesion center from blood flow–mediated cooling.

![Microscope image](image)

**FIG. 1.** (a) Microwave generator capable of driving eight channels at 915 MHz (bottom), controlled by LabView software on a laptop computer (top). (b) Prototype microwave antenna with a 13-gauge diameter, 15-cm length, and 3.6-cm actively radiating segment.

1. The antenna has an echogenic coating that allows for easy visualization under ultrasound. This probe is connected by a flexible coaxial cable to a generator capable of producing 60 W of power at 915 MHz for each of eight channels. A laptop computer controls the generator output by using LabView software (National Instruments Corp., Austin, TX) and is connected to a four-channel fiberoptic temperature measurement system (model 790; Luxtron Corp., Santa Clara, CA).

**Animals, Anesthetic, and Surgical Technique**

Protocol approval for this procedure was obtained from our institutional animal research committee, and the policy on humane care and use of laboratory animals was met for all experimentation. Thirteen female domestic swine were used in this study. The pigs were anesthetized with tiletamine and zolazepam 7 mg/kg (Telazol; Fort Dodge Animal Health, Fort Dodge, IA) and xylazine 45 mg/kg intramuscularly (Rompun; Phoenix Pharmaceutical, St. Joseph, MO). Animals were intubated, and anesthesia was maintained with inhaled isoflurane gas. The liver was exposed through a bilateral subcostal incision.

**MW Protocol**

For single-probe ablations (n = 11), a solitary MW antenna was inserted into porcine liver under direct visualization. A fiberoptic temperature probe was inserted next to the antenna. MW energy was then applied for 10 minutes at 40 W, based on preliminary experiments (data not shown). The probe was removed, and any bleeding

**MATERIALS AND METHODS**

**Description of MW Device**

The ablation probe used in this study (Vivant Medical Inc.) is a 15-cm, 13-gauge dipole antenna designed to confine MW energy to a 3.6-cm radiating segment (Fig.
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from the surface puncture site was controlled by manual pressure, Bovie electrocautery, or both.

Sequential multiple-probe ablations were also performed with a single MW antenna. The probe was placed under direct visualization, energy was applied for 10 minutes at 40 W, and the probe was removed. The probe was then replaced to the same depth and activated twice more, forming an equilateral triangle. The distance between probe placements was varied from .5 to 2.0 cm.

For simultaneous multiple-probe ablations, three parallel antennae were inserted to the same depth in an equilateral triangle. Because we anticipated larger lesions with multiple-probe ablation, the separation between probes was varied from .5 to 3.0 cm. A fiberoptic temperature probe was placed in the center of the lesion, equidistant from the three antennae. MW energy was then simultaneously applied to all three probes for 10 minutes at 40 W. Again, probes were removed, and any bleeding from the surface puncture site was controlled by manual pressure, Bovie electrocautery, or both.

Pathology

After each procedure, animals were anticoagulated with 5000 U of heparin and killed using a combination of pentobarbital (40 mg/mL) and phenytoin (1 mg/mL) (Euthasar .2 mL/kg; Delmarva Laboratories, Midlothian, VA). The liver was removed and the portal vein cannulated. The liver was then perfused with 1000 mL of 10% neutral buffered formalin. Individual lesions were immersed in formalin to complete tissue fixation. Specimens were sectioned at regular 3-mm intervals transverse to the longitudinal axis of the MW probe track. A Umax Astra 4000U scanner (Umax Technologies, Inc., Fremont, CA) was used to generate a digital image of each section at 300 dpi. ImageJ (National Institute of Mental Health, Bethesda, MD) image-analysis software was used to determine the area of each section and the cross-sectional minimum and maximum diameter of the largest section. Lesion length was calculated by multiplying the number of sections times the section thickness. Lesion volume was derived by integrating the section areas over the lesion length. For the multiple-probe lesions only, the actual distances between MW antenna tracts were measured and averaged. Also, multiple-probe lesions were scored for deviation from roundness on a five-point scale (1, discontinuous; 2, >25% deflection from round; 3, 10% to 25% deflection; 4, <10% deflection; 5, round). Representative specimens were stained with hematoxylin and eosin and examined microscopically.

Statistics

An analysis of variance was used to determine the effect of the use of a single probe versus three probes activated sequentially versus three probes activated simultaneously on the maximum diameter, minimum diameter, length, and volume of a lesion. The average separation and the shape of the lesion were also compared between the two three-probe settings. Because the separation may have influenced the volume and shape of the lesion, we also compared these measures between the three-probe settings after adjusting for separation. Before analysis, all lesion characteristics were log-transformed to better meet the assumptions of analysis of variance. Spearman’s correlation coefficients were also calculated to help understand the relationship between volume, shape, and probe separation. All analyses included pig as a random effect and were performed with SAS statistical software (SAS Institute Inc., Cary, NC). Significance was determined by a P value of <.05.

RESULTS

Lesion Size

Simultaneous multiple-probe ablations were nearly six times larger in volume than single-probe lesions (43.1 ± 4.3 cm³ vs. 7.4 ± 3.9 cm³, respectively; P < .001; Fig. 2) and almost three times larger than sequential ablations (43.1 ± 4.3 cm³ vs. 14.6 ± 5.2 cm³; P < .001). Sequentially activated multiple-probe lesions were approximately twice as large as single-probe ablations (P < .002). Lesion volume was not significantly correlated with probe separation for either sequential or simultaneous multiple-probe lesions.

Simultaneous multiple-probe lesions also had the greatest maximum and minimum diameter of all three groups. The maximum diameter was 4.8 ± .3 cm, compared with 2.1 ± .3 cm for single lesions (P < .001) and 2.9 ± .3 cm for sequential lesions (P < .002) (Fig. 3). The minimum diameter was 3.5 ± .3 cm, compared with 1.5 ± .3 cm for single lesions (P < .001) and 1.8 ± .4 cm for sequential lesions (P < .001). Compared with single-probe lesions, sequential ablations had a greater maximum diameter (P < .01) but a similar minimum diameter (P = .27). Lesion length was not significantly different among the three groups (4.4 ± .4 cm for single-probe lesions, 5.2 ± .4 cm for sequential lesions, and 4.3 ± .4 cm for simultaneous lesions; P = .29).

Temperature was not significantly different between single-probe (112.5°C ± 9.4°C) and simultaneous-probe (109.6°C ± 22.3°C) lesions (P = .41). The maximum single-probe temperature was 124°C, whereas the maximum multiple-probe temperature was 150°C.

Pathology

On gross inspection, single-probe and both sequential and simultaneous multiple-probe lesions had a central pale zone of coagulation surrounded by a red hyperemic zone (Fig. 4). There were no differences between single and sequential or simultaneous multiple-probe ablations by microscopic analysis. On hematoxylin and eosin staining, hepatocytes in the coagulated zone had amorphous cytoplasm and had lost their cell walls but retained their nuclei. Cells lining the hepatic sinusoids were separated from the cell plates. Gas bubbles were visible in the central zones of the ablation lesion.

Lesion shape significantly correlated with separation between probes for both sequential (Spearman's correlation coefficient, $-0.75; P < .01$) and simultaneous (Spearman's correlation coefficient, $-0.76; P < .01$) lesions (Fig. 5). Some multiple-probe lesions had discontinuous areas where the coagulation zones produced by individual MW antennae did not merge. No simultaneous lesions with probe separations of $\leq 1.6$ cm had discontinuities. With a 1.7-cm measured separation as a cutoff, ablations with smaller distances between probes were significantly closer to round (score, 4.1 $\pm$ 1.1 vs. 1.8 $\pm$ .6; $P < .01$; Fig. 6). Several simultaneous multiple-probe lesions showed extension of coagulation necrosis along blood vessels up to a centimeter away from the main body of the lesion (Fig. 7).

DISCUSSION

On the basis of this study, simultaneous multiple-probe MW thermal ablation therapy acts synergistically to increase ablation lesion size, whereas sequential multiple-probe ablation is only additive. Sequential activation of three MW antennae resulted in lesions twice as large as those created by a single probe, whereas simultaneous activation led to lesions nearly six times larger. Additionally, simultaneous multiple-probe ablation resulted in qualitatively rounder lesions, with more uni-
form coagulation and better performance near blood vessels.

The synergism of simultaneous activation may be due to thermal protection of the area between MW probes. A single-probe ablation is subject to blood flow-mediated cooling from all sides. In simultaneous multiple-probe ablation, however, the central area of the developing thermal lesion is protected from vascular cooling. This is probably due to an increase in energy deposition and a decrease in local blood flow in the tissue between antennae.

Among simultaneously ablated lesions, there does seem to be a limit to how far apart MW antennae can be separated. In this system, probe separations of <1.7 cm yielded significantly more confluent, rounder lesions. At probe separations beyond 1.7 cm, however, clefts started to appear, and the overall lesion shape became less round. In some cases, areas of coagulative necrosis failed to merge, leaving nonablated tissue between probes. We therefore recommend that simultaneous multiple-probe ablations be performed with an antenna separation of 1.5 cm, at the settings of 40 W of power and 10 minutes’ duration. It is possible that increased applied power or longer times of MW application may create round lesions with greater probe spacing, but this was not addressed by our study. Although this study was limited to ablation with one or three probes, the MW system may drive up to eight probes simultaneously.

FIG. 3. Lesion dimensions of single-probe microwave ablation compared with sequential and simultaneous multiple-probe microwave ablation with three parallel antennae. $P < .001$; $\dagger P < .002$.

FIG. 4. (a) Single-probe microwave ablation at 40 W for 10 minutes. (b) Sequential multiple-probe ablation with three parallel antennae separated by 1.1 cm. (c) Simultaneous multiple-probe ablation with antenna separation of 1.6 cm.
Using a different MW system, Sato et al.\textsuperscript{23} described their experience with multiple-probe MW ablation in a small clinical series. Using a disk-shaped introducer to guide placement of seven antennae, they were able to create lesions from 5 to 6 cm in diameter, successfully treating three of six tumors. However, in this instance, the multiple antennae were activated sequentially, rather than simultaneously. Similarly, Lu et al.\textsuperscript{24} used sequential multiple-probe ablation to treat tumors >2 cm in 61 patients with a 92% technical success rate and 8% recurrence after a mean 18-month follow-up.

The superiority of simultaneous over sequential multiple-probe ablation is suggested by two experimental studies of multiple-probe RF ablation.\textsuperscript{25,26} In each study, sequential activation of three or more RF electrodes was less effective than simultaneous application. Lesion sizes were smaller in the sequential groups, and lesion geometry was poor, with areas of nonablated tissue between electrodes. The synergistic effects of simultaneous multiple-probe ablation are confirmed by our study. This has important clinical applications, because many tumors require multiple overlapping ablations for complete treatment. The high rate of recurrence seen in some studies of RF ablation may be due to irregularities in the areas between sequentially delivered overlapping lesions. While there is a water-cooled RF cluster electrode with three needles, these needles are fixed in configuration and are electrically in parallel.\textsuperscript{26,27} Simultaneous multiple-probe RF ablation is theoretically limited by electrical interference between probes. This was seen in a study by Goldberg et al.\textsuperscript{25} as inadequate heating of the central electrode in a five-electrode array that led to incomplete coagulation in the center of a 3.8-cm lesion. It may be theoretically possible to overcome this limitation through rapid switching of current between multiple RF probes.\textsuperscript{28} Much work will be necessary, however, before such a system could be made widely available.

In addition to the potential for synergistic use of multiple MW antennae in the treatment of solitary lesions, the ability to drive multiple probes simultaneously may be useful in the treatment of multiple tumors. With
RF ablation requiring up to 45 minutes per lesion, the procedure time can be quite lengthy, especially when multiple tumors are treated. Significant time savings could be achieved through multiple-probe MW ablation.

Numerous studies have shown increased ablation lesion size and improved lesion geometry with hepatic inflow occlusion during RF ablation.\textsuperscript{11,29,30} Using a different MW ablation system, Takamura et al.\textsuperscript{31} found that ablation lesions were significantly larger with occlusion of the portal or hepatic veins, but not with hepatic arterial occlusion alone. Because we do not routinely perform hepatic inflow occlusion during RF or cryotherapy of liver tumors, we did not assess the effect of inflow occlusion on multiple-probe MW ablation.

An unexpected finding of this study was the presence of selective tracking of coagulative necrosis outward along blood vessels. This was present in several of the simultaneous-ablation lesions and involved vessels up to 5 mm in diameter. Coagulation extended up to 1 cm away from the main body of the lesion. On the basis of pathologic appearance, it seems that blood inside the vessel is also coagulated.

We speculate that the preferential tracking of the ablation zone along vascular pathways is due to the creation of high-temperature water vapor that follows blood vessels as the path of least resistance. This effect may not be seen in RF ablation because of the lower temperatures generated by RF. Additionally, the large zone of active heating created by MW ablation may cause larger amounts of heated water vapor to develop in a shorter amount of time than in RF ablation, which relies primarily on passive thermal conduction. Alternatively, MW energy may selectively affect perivascular tissue. Heating by MW energy is determined by the permittivity of tissue.\textsuperscript{32} Permittivity varies depending on tissue type and cellular water content, but it is not known whether there is a difference in permittivity between perivascular liver and tissue more distant from blood vessels.

The selective tracking of the MW lesion along blood vessels may decrease the tumor recurrence near blood
vessels that has heretofore limited thermal (and, to some extent, cryotherapeutic) hepatic ablation. However, it may also present the risk of thrombosis of major vessels, leading to areas of hepatic infarction. Although major vessel thrombosis and infarction were not seen in this study, due caution should be observed when tumors are ablated near large vessels such as the hepatic veins and branches of the portal venous and hepatic arterial system.

Local hepatic ablation is currently used to increase the number of patients amenable to curative or palliative treatment of liver tumors. All current systems have unique advantages and disadvantages. Cryotherapy is relatively cumbersome, has variably high complication rates, and is not amenable to a percutaneous technique in most patients but has low rates of postprocedure recurrence. RF ablation is limited to a single lesion and seems to have higher recurrence rates, especially near blood vessels. MW thermal ablation is not yet available clinically in the United States. However, it does have several theoretical advantages over RF ablation, including higher temperatures and a broader field of power distribution. The capability of multiple-probe MW ablation offers the potential for synergistically increased lesion size, enhanced control of lesion shape and size, and improved lesion geometry, as well as decreased procedure time, cost, and anesthetic risk. Simultaneous multiple-probe
MW ablation may also help overcome the cooling effect of local blood flow and decrease the rate of recurrence near blood vessels.

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REFERENCES