

Original article

Comparison of the effects of in-vivo thermal ablation of pig liver by microwave and radiofrequency coagulation

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Abstract Microwave and radiofrequency coagulation is frequently used for the treatment of hepatic tumors. However, differences between these types of therapy have not been clearly demonstrated so far. We performed both types of thermal ablative treatment on pig liver, and compared the size and shape of the coagulated areas produced. The effects of combining both treatments and interrupting hepatic blood flow were also evaluated. The liver of an anesthetized pig was thermally coagulated, with or without interruption of hepatic blood flow, using a needle electrode at 40 W for 150 s with 2450-MHz microwaves and/or with a 460-kHz radiofrequency current. The diameters of the coagulated areas in the liver were 20 ± 3 mm (mean \pm SD; $n = 4$) after microwave coagulation and 28 ± 3 mm following radiofrequency coagulation when blood flow was not interrupted, whereas they were 31 ± 2 mm and 37 ± 3 mm, respectively, when blood flow was interrupted. When these treatments were combined sequentially, the diameters of the lesions were 43 ± 3 mm and 29 ± 2 mm with and without blood flow interruption, respectively. The ellipticity of the coagulated area, as measured by the largest-to-smallest ratio of its diameters, was 2.3 ± 0.4 after microwave coagulation and 1.1 ± 0.1 following radiofrequency coagulation. We conclude that radiofrequency coagulation produces a larger and more spherical coagulated area in the liver ($P < 0.01$) than does microwave coagulation. The lesion becomes larger ($P < 0.05$) with both treatments when hepatic blood flow is interrupted during the treatment. The sequential combination of these treatments produces a much larger lesion ($P < 0.05$) than that produced by either treatment alone.

Key words Microwave coagulation · Radiofrequency ablation · Pig liver · Thermal ablation · Blood flow

Introduction

The liver is a common site for primary and metastatic tumors of the gastrointestinal system.^{1,2} Although surgical resection can offer patients with primary or metastatic hepatic tumors a chance for long-term survival, some patients are not good candidates for surgery, either when the tumors are very large, there are many tumors, or hepatic reserve is inadequate. In such patients, alternative treatment is necessary. Recently, microwave (MW) coagulation³⁻⁸ and radiofrequency (RF) coagulation (ablation)⁹⁻¹⁵ have been applied to unresectable liver tumors. MW coagulation therapy of a hepatic tumor is based on the thermal denaturation of tumor tissue by MWs emitted from the tip of a needle electrode. Heat is generated by intermolecular collisions between polar molecules, mainly water molecules, in tissue placed under a strong electromagnetic field that is generated by high frequency (about 2 GHz) electromagnetic waves.³ In contrast, RF coagulation therapy is based on the thermal denaturation of tumor tissue caused by heat generated by an alternating current of about 500 kHz that runs from a needle electrode to a metal pad attached to the skin.¹²

Although the underlying principle common to both treatments is that tumor tissue is thermally denatured, the mechanisms of heat generation are completely different with these two treatments, as mentioned above. In addition, the advantages and disadvantages of the two treatments differ. With the MW treatment, hard tumors, such as metastatic gastrointestinal tumors, can be easily coagulated, but the area coagulated by this method frequently becomes ellipsoidal along the track of electrode insertion, especially so when the duration of treatment is long.⁶ This characteristic of MW coagulation makes it disadvantageous in the treatment of many spherical tumors. The reverse is true regarding RF coagulation. It is difficult to coagulate hard tumors by RF treatment, because, after the needle electrode is

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inserted in the tumor, the deployment of expandable tines (hooks) from the tip of the needle electrode is frequently hindered if the tumor tissue is very hard. However, it is relatively easy for RF treatment to coagulate target spherical tumor tissue.¹²

To date, these characteristics of MW and RF coagulation therapies have not been quantitatively compared; the difference in coagulations, e.g. in size, and shapes, cannot be compared directly, because the conditions of the treatments differ markedly depending upon the reports in the literature. It should also be noted that the relatively small sizes of the necrotic areas produced by MW and RF coagulations have long been the reason for the therapeutic limitation of these treatments.⁹ For instance, the therapeutic efficacy of MW coagulation has been demonstrated only for tumors less than 2 cm in diameter.⁸ The aim of this study was to compare how much normal liver tissue is coagulated by MW and by RF ablative treatment, and how the shapes of the coagulated areas in the liver differ from each other when treatment is conducted at the same output and for the same length of time. So far, there has been no such comparative study in the literature. We also evaluated whether sequential combination of these two methods (MW followed by RF) could increase the size of the coagulated area in the hepatic tissue and whether temporary interruption of hepatic blood flow had any effect on MW and RF coagulation.

Methods

Surgical techniques

Male domestic Landrace strain pigs (body weight, 35–40 kg) were anesthetized with ketamine hydrochloride and isoflurane. A vessel catheter was placed in the external jugular vein for drip intravenous administration of saline solution. Cardiac and respiratory functions were monitored throughout the procedures. Laparotomy was performed by transverse incision just below the costal margin. Special care was taken to avoid bleeding from the patent umbilical vein in the hepat umbilical ligament. The points of coagulation by MW and RF were chosen at random among the five lobes of the liver, a sufficiently thick area being chosen in each lobe. The animals were divided into groups (four pigs per group) according to treatment, as follows: MW coagulation (groups A and B), RF coagulation (groups C and D), and combined treatment (groups E and F). Groups A, C, and E were treated without hepatic blood flow interruption, whereas groups B, D, and F were treated with hepatic blood flow interruption.

Microwave coagulation

Coagulation of the liver by MWs was performed by inserting a needle electrode (2-mm diameter, 25 cm long; MD-20; Azwell, Osaka, Japan) (Fig. 1, upper) perpendicularly into the anterior side of the liver to a depth of 2 cm; 1 cm of the tip of the electrode (antenna) was active. MWs of 2450 MHz were emitted immediately after insertion of the needle electrode, using a MW generator (Microtaze OT-110M; Azwell) at an output of 40 W. The MWs were transmitted from the generator to the needle electrode via a flexible coaxial cable. During treatment of the liver, gentle, manual rotation of the shaft of the needle electrode around its axis was performed to prevent it sticking to coagulated tissue. The treatment was continued for 150 s, and the needle electrode was then removed. During treatment, the temperature of the liver parenchyma near the needle electrode was monitored with a needle-type (1-mm-diameter) electronic thermometer (Omega Engineering, Stamford, CT, USA) inserted in the liver to a depth of 5 mm and 1 cm distant from the point of the insertion of the electrode. In another experiment, in which hepatic blood flow was temporarily interrupted during the period of the treatment (group B), a vessel tape was first placed loosely around the portal vein and common hepatic artery en bloc. The needle electrode was then inserted. Immediately after the vessel tape was squeezed to interrupt hepatic blood flow (Pringle's maneuver), MWs were emitted, as described above, for 150 s. The vessel tape was released soon after the MW emission.

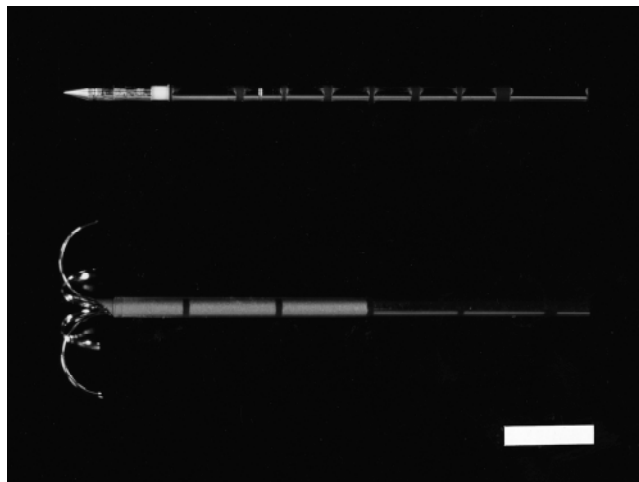


Fig. 1. Tips of the needle electrode used for microwave coagulation (*upper*) and radiofrequency coagulation (*lower*). Scale bar indicates 1 cm

Radiofrequency coagulation

In the experiment using RF coagulation, an insulated stainless-steel needle electrode (2-mm outer diameter, 15 cm long; Leveen needle electrode 26-207; Boston Scientific, Tokyo, Japan) (Fig. 1, lower) was inserted perpendicularly into the anterior side of the liver to a depth of 2 cm. Immediately after insertion of the needle electrode, eight curved stainless-steel expandable tines (hooks, active electrodes) that had been housed in the shaft of the needle electrode were fully deployed (expanded) radially from its tip. Each tine makes the track of a round curve after complete deployment (Fig. 1, lower). The outermost tips of all the tines make a circle of about 2-cm diameter. Soon after deployment of the tines, a 460-kHz alternate current, of continuous unmodulated sinusoidal waveform, was run across the needle electrode and external grounding metal pads (5 cm × 10 cm) affixed to the medial side of the thighs at an output of 40 W for 150 s, using a constant-voltage RF generator (RF2000; Boston Scientific). The impedance of the circuit was monitored continuously during treatment. In some experiments (group D) hepatic blood flow was interrupted temporarily, as described above, by Pringle's maneuver. The temperature of the liver parenchyma near the needle electrode was monitored with a needle-type thermometer, as described above.

Combination of microwave and radiofrequency coagulation

We performed an experiment whereby both MW and RF treatments were combined sequentially. First, MW treatment was carried out at 40 W for 150 s; the MW needle electrode was removed and the RF electrode was then inserted into the same site within 10 s. The RF current was next run at 40 W for 150 s. If blood flow interruption was needed (group F), the portal vein and common hepatic artery were squeezed with a vessel tape, as described above, just before the sequential treatments of MW and RF.

Measurement of coagulated area size

Immediately after treatment by MW or RF coagulation, the animal was killed and the liver was excised. The area of the liver coagulated by the treatment was cut out, fixed in a 3.5% (w/v) formaldehyde solution in water, and photographed. The diameter of the coagulated area was measured in three dimensions. First, the diameter along the track of insertion of the needle electrode was determined. Second, the diameter measured in the plane perpendicular to the track of insertion of the needle electrode and which ran at the tip of the needle electrode was determined. Third, the diameter

in the same plane but perpendicular to the second diameter was determined. The data values are expressed as an average of these three diameters. All the above diameters included the zone of outer hemorrhagic necrosis (described in "Results"). The thickness of the zone of outer hemorrhagic necrosis was measured in the same plane as that used for measurement of the diameters, as reported above. The magnitude of the deviation of the shape of the coagulated area from a spherical form was assessed by taking the ratio of the largest to the smallest diameter among the above three diameters.

Statistical analysis

The values for the coagulated area size are shown as means ± SD. Means of the data from two groups were compared by a non-paired two-tailed Student's *t*-test. The difference was considered significant if $P < 0.05$.

Results

Thermal coagulation of pig liver in vivo

Following treatment by either MW or RF, the area of liver parenchyma surrounding the needle electrode became pale yellow, and this area was surrounded by a dark zone (Fig. 2). When histologically examined, it was confirmed that the pale yellow area was necrotic tissue and the outer dark zone was tissue with hemorrhagic necrosis. There was no qualitative difference in these necrotic tissues following MW and RF treatment (data not shown). The outer zone of hemorrhagic necrosis was dark red immediately after the treatment, but it became dark brown after fixation in formaldehyde solution (Fig. 2).

The size of the coagulated area in the liver was expressed as the mean ± SD value of three diameters, including the outer dark zone of hemorrhagic necrosis. It was larger ($P < 0.05$) after RF than after MW treatment, when compared at the same output (40 W) and for the same duration (150 s) of treatment without blood flow interruption (Table 1, group A vs group C). The sequential combination of 150-s MW treatment followed by 150-s RF treatment did not increase the coagulated area significantly (Table 1, group E) compared with RF treatment alone when hepatic blood flow was not interrupted. (We performed MW coagulation first in the combined treatment experiment, because we thought that it would be easier to insert a non-hollow MW needle than a hollow RF needle in an uncoagulated tissue or tumor.) Temporary and simultaneous interruption of hepatic blood flow (both the portal vein and common hepatic artery) increased the size of

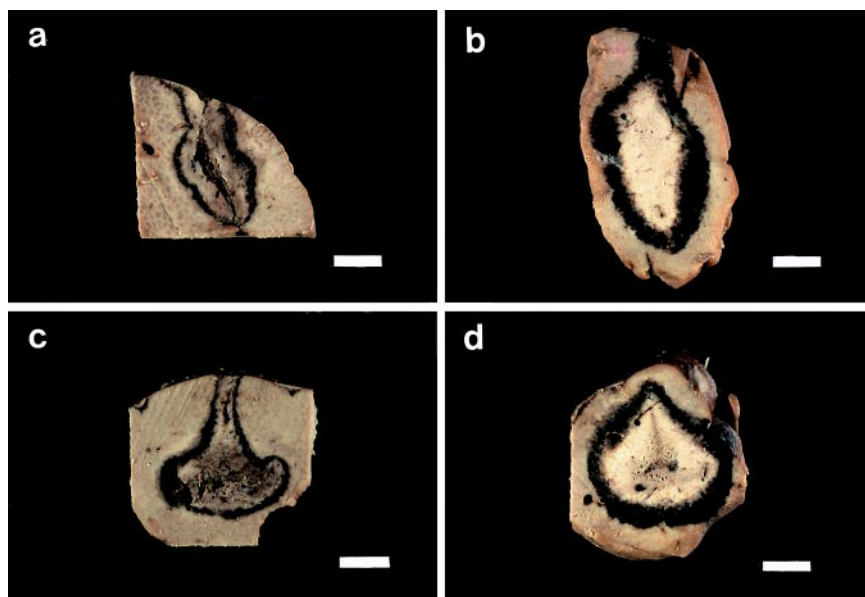


Fig. 2a-d. Section of normal pig liver after microwave and radiofrequency coagulation. The liver of an anesthetized pig was treated at 40W for 150s, either by microwave without hepatic blood flow interruption (**a**), by microwave with hepatic blood flow interruption (**b**), by radiofrequency without hepatic blood flow interruption (**c**), or by radiofrequency with hepatic blood flow interruption (**d**). A piece of the treated liver was fixed in formaldehyde solution, cut along the line of the insertion of the needle electrode, and photographed. Scale bar indicates 1 cm

Table 1. Diameters of coagulated areas in pig liver produced in vivo by microwave (MW) and radiofrequency (RF) coagulation

Treatment	Group	Blood flow interruption	Diameter of coagulated area (mm)	<i>P</i> value
MW	A	No	20 ± 3	0.0013 vs B
	B	Yes	31 ± 2	0.015 vs D
RF	C	No	28 ± 3	0.0078 vs D 0.020 vs A
	D	Yes	37 ± 3	0.025 vs F
Combination of MW and RF	E	No	29 ± 2	0.0044 vs A 0.00022 vs F
	F	Yes	43 ± 3	0.50 vs C 0.00021 vs B 0.025 vs D

Data values are given as means ± SD of four experiments. Hepatic blood flow was temporarily interrupted by simultaneous occlusion of the portal vein and common hepatic artery

the coagulated area following both MW and RF coagulation treatments (Table 1, group A vs group B, and group C vs group D) ($P < 0.01$). After combined MW and RF treatment, the size of the coagulated area was also markedly increased ($P < 0.05$) after blood flow interruption (Table 1, group E vs group F).

Although marginally significant ($P = 0.075$ for MW and $P = 0.034$ for RF), the absolute and the relative thickness of the zone of hemorrhagic necrosis (shown by a dark area surrounding the central pale yellow area in Fig. 2), also tended to increase with an increase in the diameter of the entire coagulated area (including the dark zone) after blood flow interruption, compared with the diameters without blood flow interruption (Table 2). However, there was only a small increase ($P = 0.90$)

in the relative thickness of the dark zone following combined MW and RF treatment (Table 2).

Deviation of coagulated area from spherical form

To determine the deviation of the coagulated area from a spherical form, we calculated the ratio of the largest diameter of the coagulated area to the smallest one (Table 3). MW coagulation without blood flow interruption produced a markedly ellipsoidal coagulated area, and the ratio of the largest to the smallest diameter was 2.3 ± 0.4 ($n = 4$). However, the area became less ellipsoidal (more spherical) when blood flow was interrupted (1.5 ± 0.3 ; $P < 0.05$). RF coagulation always produced a more spherical coagulated area ($P < 0.05$)

Table 2. Thickness of the zone of outer hemorrhagic necrosis in pig liver produced in vivo by microwave (MW) and radiofrequency (RF) coagulation

Treatment	Group	Blood flow interruption	Thickness (mm)	Relative thickness (%) ^a	<i>P</i> value ^b
MW	A	No	1.4 ± 0.8	7.1 ± 4.5	0.075 vs A
	B	Yes	4.6 ± 1.1	14.9 ± 3.4	
RF	C	No	1.9 ± 0.8	7.0 ± 2.9	0.034 vs C
	D	Yes	4.1 ± 1.1	10.9 ± 2.2	
Combination of MW and RF	E	No	2.3 ± 0.7	7.8 ± 2.0	0.90 vs E
	F	Yes	3.5 ± 1.8	8.1 ± 4.4	

Data values are given as means ± SD of four experiments. Hepatic blood flow was temporarily interrupted by simultaneous occlusion of the portal vein and common hepatic artery

^aRatio of the thickness of the zone of outer hemorrhagic necrosis to the entire diameter of the coagulated area, expressed as a percentage

^bCalculated for comparison of relative thickness

Table 3. Ratio of the largest to the smallest diameter of coagulated areas produced in vivo by microwave (MW) and radiofrequency (RF) coagulation

Treatment	Group	Blood flow interruption	Ratio of largest to smallest diameter	<i>P</i> value
MW	A	No	2.3 ± 0.4	0.022 vs B
	B	Yes	1.5 ± 0.3	0.32 vs D
RF	C	No	1.1 ± 0.1	0.012 vs A 0.024 vs D
	D	Yes	1.3 ± 0.1	0.35 vs F
Combination of MW and RF	E	No	1.4 ± 0.2	0.011 vs A 0.047 vs C 0.20 vs F
	F	Yes	1.2 ± 0.1	0.0034 vs A 0.17 vs B 0.35 vs D

Data values are given as means ± SD of four experiments. Hepatic blood flow was temporarily interrupted by simultaneous occlusion of the portal vein and common hepatic artery

than that produced by MW coagulation. The combination of both MW and RF treatments also produced a relatively spherical coagulated area, whether or not hepatic blood flow was interrupted.

Impedance and temperature changes during coagulation

The efficiency of coagulation during long-term constant-voltage RF treatment is limited by an increase in electrode impedance in the hepatic tissue (Fig. 3), because the current running through the tissue decreases with increasing impedance. For instance, impedance was about 70Ω at the start of treatment, it started to rise after about 90s, and then reached a plateau of about 80Ω after 120s with interruption of hepatic blood flow (Fig. 3; open circles). An increase in impedance inevitably decreases the efficiency of coagulation; this means a limitation of the method in terms of the size of the coagulated area in the liver. The temperature

measured near the needle electrode gradually rose with all conditions of treatment (Fig. 4). The rate of temperature increase and the maximum temperatures attained were higher when hepatic blood flow was interrupted with both the MW and the RF treatments. These findings were consistent with the result that the sizes of the coagulated areas were larger after blood flow interruption than without it (Table 1, group A vs group B and group C vs group D).

In summary, RF coagulation produces larger and more spherical coagulated areas than does MW coagulation, and interruption of hepatic blood flow produces larger coagulated areas with both treatments than those produced without interruption.

Discussion

Surgical devices that utilize MW or RF were originally developed as surgical knives for the electrocautery of

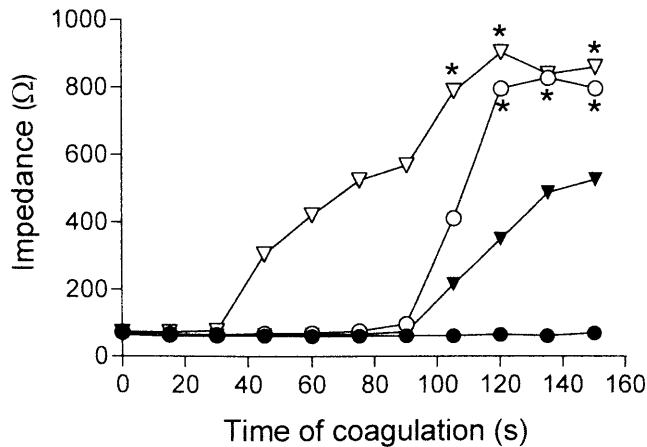


Fig. 3. Time course of impedance changes during radiofrequency coagulation of pig liver in vivo. Impedance was measured during radiofrequency treatment (*open and closed circles*) or during the session of radiofrequency treatment (*open and closed triangles*) that followed immediately after microwave treatment in a combined treatment experiment. The experiments were carried out with (*open circles and open triangles*) or without (*closed circles and closed triangles*) temporary interruption of hepatic blood flow. Each point represents the mean of four experiments. Asterisks indicate $P < 0.05$ comparing results in the presence and absence of hepatic blood flow interruption

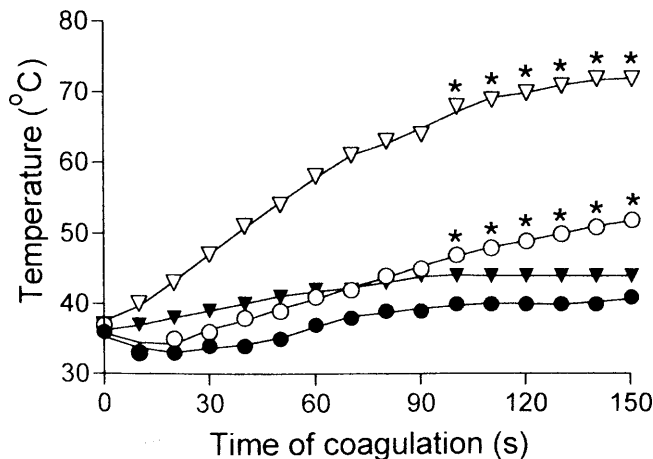


Fig. 4. Time course of temperature changes in pig liver during microwave and radiofrequency coagulation. The temperature measured in pig liver at a depth of 5 mm and 1 cm from the point of insertion of a microwave needle electrode (*open and closed triangles*) or a radiofrequency needle electrode (*open and closed circles*) with (*open circles and open triangles*) or without (*closed circles and closed triangles*) temporary interruption of hepatic blood flow is shown. Each point represents the mean of four experiments. Asterisks indicate $P < 0.05$ comparing results in the presence and absence of hepatic blood flow interruption

tissues.³ The surface created in the tissues when they are cut with these devices is coagulated simultaneously as the devices run through the tissue, and, consequently, bleeding from the cut surface is minimized. Because of

this hemostatic effect, these surgical devices are suitable for cutting highly vascularized tissues. According to Tabuse,³ the coagulated zone that forms on the cut surface is relatively thick when MW devices are employed for electrocautery. On the other hand, RF devices produce only a thin eschar that is usually unable to sufficiently control bleeding from highly vascularized parenchymal tissues.³ Contrary to Tabuse's report, we found that the reverse was true for the relative sizes of the coagulated areas created inside the hepatic tissue by the needle-type devices. The coagulated areas created by RF were found to be larger than those created by MW (Table 1).

One of the primary reasons for the limited lesion size attained with RF treatment is believed to be the charring effect of excessively high temperature around the needle electrode.⁹ Formation of charred tissue around the electrode presumably increases the impedance against the RF current and reduces heat generation. In fact, continuous saline infusion at the electrode tip, which is expected to keep the temperature of the needle electrode below the level of carbonization of tissue, is reported to increase the coagulated area.⁹

We hypothesized that hepatic blood flow cooled down the heat generated by MW or RF during coagulation. Based on this hypothesis, we postulated that interruption of hepatic blood flow during coagulation might increase the temperature of the target tissue and, thus, might increase the size of the coagulated area in the liver. In fact, as shown in Fig. 2 and Table 1, temporary interruption of hepatic blood flow increased the size of the coagulated area. Murakami et al.¹⁶ also demonstrated an increase in the size of the coagulated area with MW coagulation applied to patients with liver tumors when hepatic blood flow was interrupted. Patterson et al.¹⁷ demonstrated an increase in the size of the coagulated area in an in-vivo pig liver experiment after interruption of hepatic blood flow. Taken together, these results indicate that temporary interruption of hepatic blood flow during thermal coagulation by either MW or RF treatment increases the size of the coagulated area, presumably due to the suppression of the cooling effect of the blood flowing around the target tissue. Goldberg et al.¹⁸ reported that pig liver coagulated ex-vivo by RF treatment for 12 min produced an area of coagulative necrosis of 29 ± 2 -mm diameter, but the area in vivo was 24 ± 2 mm. However, they reported that occlusion of the portal vein produced an area of 29 ± 1 mm in vivo. Their results also support the finding that the perfusion-mediated cooling effect on the target tissue decreases the size of the coagulated area in the liver.

Hepatic blood flow can be temporarily interrupted during treatment by MW or RF by a vessel tape placed around the portal vein and hepatic artery if the liver is

treated under laparotomy. As demonstrated by Shibata et al.,⁶ interruption of hepatic blood flow is also possible by inflating two balloon catheters that have been inserted from femoral vessels, one being placed in the hepatic artery and the other in the hepatic vein, if the coagulation is to be performed percutaneously. It is noteworthy that blood flow in a region of the liver can be interrupted by this method without occluding the portal vein.⁶ During treatment with either MW or RF coagulation applied to primary or metastatic hepatic tumors, the cooling effect of blood that flows in and around the tumors may be different depending upon their vascularity. This means that one may not expect the same size coagulated area in normal liver tissue (Table 1) as that found when MW or RF coagulation is applied to tumor tissues. However, one would expect that the same relative order of lesion size would be reproduced by MW and RF coagulation with comparisons of tumors with the same vascularity. The effect of interruption of hepatic blood flow (Table 1) may also be reproduced in tumor tissues, although the absolute sizes of the coagulated areas may differ from these values observed in normal pig liver (Table 1) depending upon the differences in vascularity of the tumor tissues. The important points regarding the thermal ablative treatment of hepatic tumors indicated by our results are that intraoperative interruption of hepatic blood flow increases the size of the coagulated area both with MW and with RF treatment, and that the sequential combination of these treatments further increases the size of the coagulated area.

Based on our results, we recommend that small, fibrous, hard metastatic carcinomas be treated by MW coagulation therapy, because there is no need to expand tines from the electrode tip, which is frequently difficult to do in hard tissue. On the other hand, we recommend that large hepatocellular carcinomas, which are usually soft, be treated by RF coagulation (ablation) therapy, because it is easy to expand the tines and RF produces larger coagulated areas than MW coagulation does (Table 1, group A vs group C). Large metastatic carcinomas could be treated first with MWs and then with RF, as we did in the combined treatment experiment (Table 1, group E and group F).

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