의학박사 학위논문

No-touch Radiofrequency Ablation using Multiple Electrodes:

Comparative studies of Switching Monopolar versus Switching Bipolar Modes

다전극을 이용한 비접촉 고주파 열치료술:

교대 단극성 소작법과 교대 이극성 소작법의 비교 연구

2016 년 12 월

서울대학교 대학원
의학과 영상의학전공

장 원

A thesis of the Degree of Doctor of Philosophy in Medicine

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장원의 의학박사 학위논문을 인준함

2016년 12월

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Abstract

Introduction: To evaluate the technical feasibility, efficiency, and safety of switching bipolar (SB) and switching monopolar (SM) radiofrequency ablation (RFA) for no-touch ablation technique

Methods: Ex vivo and in vivo study were performed separately. In ex vivo study, A pork loin cube was inserted as a tumor mimicker in the bovine liver block; RFA was performed using the no-touch technique in the SM mode (2 groups, A1: 10 minutes, n = 10; A2: 15 minutes, n = 10) and SB mode (1 group, B: 10 minutes, n = 10).

In in vivo study approved by the animal care and use committee of the Institute, RFA was performed on 2 cm tumor mimickers in the liver using a no-touch technique in the SM mode (2 groups, SM1: 10 minutes, n = 10; SM2: 15 minutes, n = 10) and SB mode(1 group, SB: 10 minutes, n = 10).

The groups were compared technical success which was based on the creation of confluent necrosis with sufficient safety margins, and the ablation size, and the distance between the electrode and ablation zone margin (DEM).

To evaluate safety, small bowel loops were placed above the liver surface and 30 additional ablations were performed in the same groups of ex vivo study. Moreover in in vivo study, thermal injury to the adjacent anatomic organs were compared between SM-RFA (15 minutes, n=13) and SB-RFA modes (10 minutes, n=13).

Results: The technical success rate of the creation of confluent necrosis was higher in the group SB than group SM1 (both $p<0.05$) although confluent necrosis with sufficient safety margins were created in all specimens of ex vivo study. Gross ablation volume and DEM in SB-RFA mode was smaller than that in SM-RFA for 15 min ablation in both ex vivo and in vivo studies (both $p < 0.05$). The incidence of thermal injury to the adjacent organs and tissues was significantly less in the SB-RFA mode than that in SM-RFA mode ($p=0.001$ and $p=0.021$ in ex vivo and in vivo studies, respectively).

Conclusions: SB-RFA was more feasible for no-touch technique of liver tumors with a better safety profile than the SM-RFA.

Keywords: radiofrequency ablation, RFA, no-touch technique, HCC, hepatocellular carcinoma

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LIST OF ABBREVIATION

RFA = Radiofrequency ablation

SB = Switching bipolar

SM = Switching monopolar

DEM = Distances between electrode and outer margin of ablation zone

HCC = Hepatocellular carcinoma

INTRODUCTION

Radiofrequency ablation (RFA) is widely accepted as a nonsurgical option for treating primary and metastatic hepatic tumors, a potentially curative treatment for early-stage hepatocellular carcinoma (HCC), and as a bridge therapy for patients waiting for a liver transplant (1-5). Furthermore, according to the recent Barcelona Clinic Liver Cancer Staging and Treatment Strategy guidelines for HCCs, RFA is favored over surgical resection for very early stage HCCs (single nodule <2 cm) (3). However, one of the major disadvantages of RFA is a higher local tumor progression rate when compared to conventional surgery (6, 7). Conventionally, RFA is performed by inserting a monopolar electrode into the tumor. However, it is not always possible to generate an ablation zone with a sufficient peritumoral margin (>5 mm) when using single monopolar electrode, and so it is often necessary to perform multiple ablations with overlapping techniques or ablations with multiple electrodes (8). Various methods have been used to generate larger and more uniform ablation zones in a given time duration. These include switching ablation with or without a multipolar approach, modifying tissue characteristics using saline perfusion, and combination therapy with RFA or other therapies such as arterial chemoembolization (8-12). However, despite their success in generating a sufficient ablation margin, these approaches also increased treatment complexity and complications (8). The use of multiple ablation electrodes or multiple overlapping techniques can increase the risk of tumor seeding along the puncture route particularly for tumors located on the liver surface; however, this risk can be lowered by the use of tract ablation (13-16).

Recently, a number of studies (17-20) demonstrated the feasibility of multipolar RFA using multiple electrodes with no-touch techniques, and the promising outcomes of the no-touch RFA included high technical success, local tumor progression-free survival rates, and the absence of tract seeding episodes in HCC treatment. To avoid direct puncturing of the tumors, no-touch RFA is performed by inserting multiple electrodes outside of the tumor tissue. Thus, the risk of tract seeding is extremely low and a sufficient peritumoral margin is achievable. However, this technique requires a relatively long ablation time (18.5–27.2 minutes) and a significant amount of radiofrequency energy, which may result in parenchymal damage outside of the target tumor (17-20). Theoretically, delivery of a high-density current into target tissues could be obtained more quickly in a bipolar mode than a monopolar mode, and subsequently, the ablation of tissues lateral to the electrodes could be reduced (8). Although increased ablation efficiency is achieved using multipolar or switching bipolar RFA (21-23), a comparison between monopolar and bipolar RFAs for the no-touch technique has not been assessed in vivo.

Therefore, we evaluated the in vivo technical feasibility, efficiency, and safety of switching bipolar (SB) and switching monopolar (SM) radiofrequency ablation (RFA) as a no-touch ablation technique in the porcine liver.

MATERIALS AND METHODS

This study received technical support and a research grant from STARmed Co. (Goyang, Republic of Korea). All authors had complete control of the all experimental data and information submitted for publication at all times.

We perforemd two separate ex vivo and in vivo studies to evalaute the feasibility, efficiency, and safety of the no-touch technique.

The RFA Equipment

A prototype of the multichannel radiofrequency (RF) system was developed to deliver RF energy in the SB mode using three electrodes. This allows the automatic switching of energy to one electrode or electrode pair depending on changes in electrical impedance, using the inherent "off time" of the power pulsing algorithm (8, 11, 24). If the impedance of an active electrode or electrode pair increased to 50 ohms above baseline impedance, the energy delivery was switched to the inactive electrode pair or electrode (25). A separable clustered electrode (Octopus® electrode; STARmed, Goyang, Korea) with three internally cooled electrodes and a 2.5-cm long active tip, was used for the no-touch technique (25) (Fig. 1).

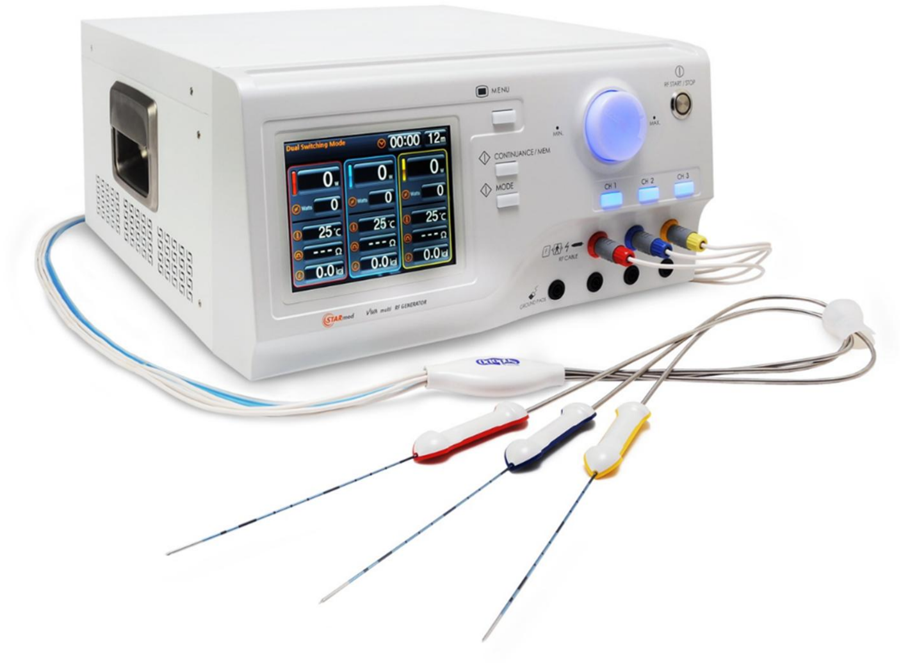


Figure 1. Photograph of a prototype RFA generator and a clustered separable Octopus® electrode.

Chilled normal saline solution was infused into the lumen of each electrode and a peristaltic pump (VIVA Pump; STARmed, Goyang, Korea) was used to ensure the tip temperature remained below 25°C. Technical parameters such as average power output, electrical impedance, currents applied, and total energy delivered were monitored continuously and recorded using a monitoring software (VIVA Monitor Software V 1.0; STARmed, Goyang, Korea).

Part 1. Ex vivo study

The Ex vivo Experimental Setting

We separately performed two-phase experimental studies to evaluate the efficacy and safety of the SM and SB modes of the no-touch RFA technique..

In the first experiment, to compare the efficacies of the SM- and SB-RFA techniques, we prepared 30 bovine liver blocks, slicing each explanted bovine liver into 12 × 12 × 7-cm^3 liver blocks. After we made a small incision at the center of each liver block, we inserted a 1.2 × 1.2 × 1.2-cm^3 pork loin cube with an approximate diagonal line length of 2 ($1.2 \times \sqrt{3} \fallingdotseq 2.0$) cm as a tumor mimicker while maintaining its diagonal line as parallel to the liver surface as possible.

Subsequently, we placed each of the Octopus electrodes meticulously using the no-touch technique in a triangular array with a 2.5-cm inter-electrode distance through an acrylic plate that contained multiple holes at 5-mm intervals (25). Three electrodes were inserted at the same depth (4~5cm) in the liver. We inserted a thermometer at the center of the ablation zone to monitor the tissue temperature in real time. Subsequently, we performed the RFA after immersing a liver block in a $50 \times 20 \times 25\text{-cm}^3$ saline-filled bath at room temperature. We then recorded the elapsed times to reach 50°C, 60°C, 70°C, 80°C, and 90°C of tissue temperature.

In the second experiment, to evaluate the safety of SM- and SB-RFA, we checked the presence of organ injury as a safety parameter. Specifically, we prepared 30 additional $10 \times 8 \times 7.5\text{- cm}^3$ bovine liver blocks and immersed them in a $30 \times 20 \times 20\text{- cm}^3$ saline-filled bath. We inserted electrodes in a triangular array using the same acrylic plate with a 2.5-cm inter-electrode distance and placed one of the electrodes 14 mm below the upper surface of the liver; subsequently, we placed bovine small bowel loops just above the liver block (Fig. 2). We then placed a thermometer between the liver and small bowel loops and recorded the temperature; we also measured the surface temperature of the small bowel in contact with the liver surface using a thermal imaging camera (Fluke Ti90; Fluke corp., WA, USA) at the end of each ablation.

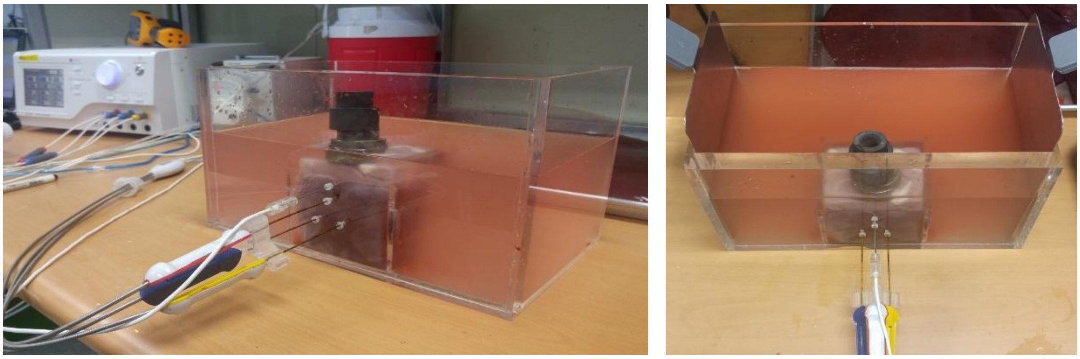


Figure 2. The ex vivo study to evaluate adjacent bowel injury during RFA. The photograph shows a segment of small bowel wall neighboring the upper surface of a liver block that was dipped into a 30 × 20 × 20-cm^3 saline-filled acrylic bath at room temperature. Note that one of the Octopus electrodes is inserted into the bovine liver 14 mm below the liver upper surface, and a thermocouple is placed between the small bowel wall and the liver surface for real time temperature measurement.

Ablation protocols of Ex vivo Study

In each experiment, we performed 30 ablations. In the SM mode, RF energy (maximum 200 W) was delivered to one of the three electrodes and was automatically switched among the three electrodes depending on the elevation of the tissue impedance for 10 minutes (group A1, n = 10) or 15 minutes (group A2, n = 10). In the SB mode, the RF energy (maximum 100 W) was delivered to one of the electrode pairs and was switched in the same manner for 10 minutes (group B, n = 10) (Fig. 3). The 10-minute ablation time in the SB mode was based on previous studies that reported that bipolar RFA could be performed with relatively faster ablation and monopolar RFA (8, 21, 23). Therefore, we evaluated the ablative efficiency of the SM mode in two groups using the same as well as a longer duration than the SB mode in groups A1 and A2 (10 and 15 minutes, respectively) (21, 23).

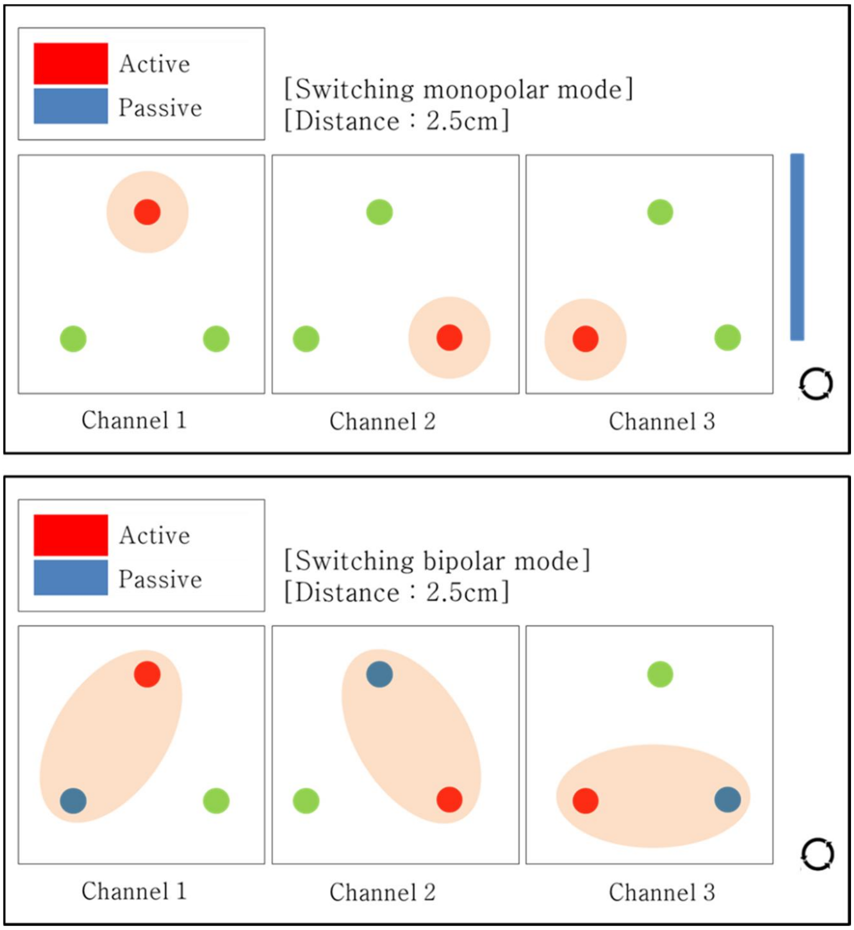


Figure 3. Diagram showing typical patterns of switching monopolar and switching bipolar modes. In the switching bipolar mode, a pair of electrodes is activated.

Part 2. In vivo study

Animals, anesthesia, and surgery

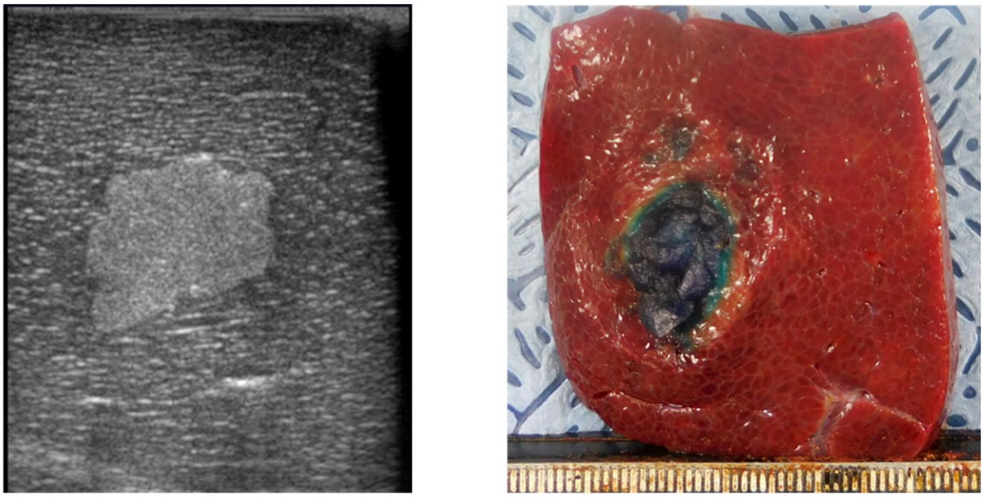
This in vivo study was approved by our Institutional Animal Care and Use Committee and all experiments were in accordance with the institutional guidelines. A total of 16 domestic male pigs (mean weight, 65 kg; range 60-70kg) were used in our in vivo studies.

Each animal was sedated with an intramuscular injection of zolazepam (5 mg/kg, Zoletil; Virbac, Carroscedex, France) and xylazine (10 mg/kg, Rompun; Bayer-Schering Pharma, Berlin, Germany), and the animals were then intubated and ventilated during the procedures. Anesthesia was maintained by the inhalation of 1%-4% isoflurane (IsoFlo®; Abbott Laboratories, North Chicago, IL) in pure oxygen gas with mechanical ventilation. The pigs were then placed in the supine position and then, a midline incision was made after sterile draping. One of the authors (W.C., with five years of experience in the RFA procedure and experiments) performed the ablation procedures through a midline incision under the guidance of ultrasonography (6-12-MHz linear transducer; Accuvix XQ; Medison, Seoul, Republic of Korea). Two to four ablation zones were generated in the liver of each animal; however, only one ablation was performed in each lobe of the liver.

Therefore, a total of 56 ablation zones were created in 16 pigs. The animals' vital signs, including pulse rate, electrocardiogram, and temperatures, were carefully monitored during the entire procedure.

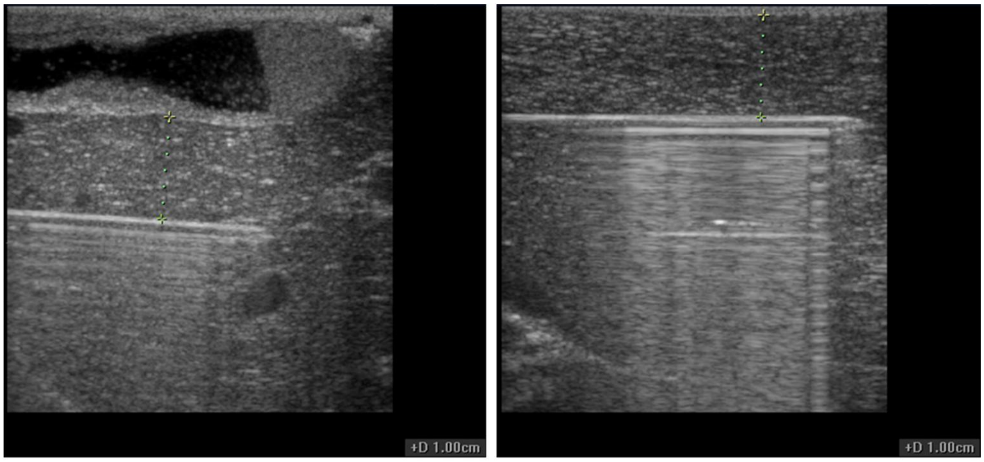
Tumor mimickers

For simulating the no-touch tumor ablation technique, tumor mimickers were made using a mixture of agarose, cellulose, glycerol and methylene blue as previously reported (26). Approximately 2.5 cc of the mixture was injected into the porcine liver under the guidance of ultrasonography to create a spherical or elliptical mass. In order to avoid the heat sink effect, care was taken not to inject tumor mimickers in the vicinity of large vessels. Tumor mimickers were detected *via* ultrasonography as hyperechoic lesions and blue nodules on gross specimens (Fig. 4). Three perpendicular diameters of each tumor mimicker were measured using the electronic caliper on the ultrasonograph, and the volume was calculated by approximating the shape of the lesion to an ellipsoid.



a b

Figure 4. (a) Ultrasonograph of the agarose-based tumor-mimicker, (b) Photograph of the tumor mimicker on a sliced specimen



a b

Figure 5. Ultrasonographs of an electrode inserted 1 cm apart from (c) the gallbladder and (d) liver surface. Electrodes were inserted parallel to the liver surface or gallbladder.

In vivo Experimental Setting

We performed two in vivo experimental studies to compare the efficiency and safety of performing no-touch RFA techniques in porcine livers, using SM and SB energy delivery modes. The first experiment compared the feasibility and efficiency of SM- and SB-RFA using no- touch ablation techniques. Tumor mimickers were generated and injected as previously described. Three electrodes were inserted around the tumor mimicker through a triangular acryl plate containing multiple holes to maintain an interelectrode distance of 2.5 cm (25).

The second experiment was conducted to evaluate the safety of SM- and SB-RFA techniques. As a safety parameter, we checked the presence of thermal injury in adjacent organs or structures including the stomach, gallbladder, small bowel, and biliary tract at each segmental level. One of the electrodes was inserted in the liver 1 cm away from the liver surface, gallbladder or biliary tract (Fig. 5). The other two electrodes were inserted through the same acryl plate used in experiment 1, thereby ensuring an inter-electrode interval of 2.5 cm. Thermal conductivity at the center of each ablation zone was measured in real-time using a thermometer placed at the center of the ablation zone. Moreover, times to reach tissue temperatures of 50°C, 60°C, 70°C, 80°C, and 90°C were recorded.

Ablation protocols of In vivo Study

In the first experiment, a total of 30 ablation lesions were made in either the SM mode (n = 20) or SB mode (n = 10). RF energy was applied in the SM mode for 10 minutes (group SM1, n = 10) or 15 minutes (group SM2, n = 10) and in the SB mode for 10 minutes (group SB, n = 10). The modes of the ablation were randomized to minimize a selection bias and other variations, including potential heat sink effects. The maximum RF delivered energy was 200 W in the SM mode and 100 W in the SB mode. The 10-minute ablation time used in the SB mode was based on previous studies reporting that bipolar RFA could be performed with a relatively faster ablation time than monopolar RFA (8, 21, 23). Therefore, we evaluated the ablative efficiency of SM mode in two subgroups using the same 10 minutes ablation time, as well as a longer 15 minutes ablation time; these subgroups were SM1 and SM2, respectively (21, 23).

In the second experiment, thermal injury was compared between 15 minutes SM ablation and 10 minutes SB ablation modes. The maximum RF energy and ablation times were the same as in experiment 1. The rates of thermal injury in our previous *ex vivo* study were 30% and 100% in SB-RFA and SM-RFA using the same ablation time. However, we considered the heat sink effect might decrease the rates to 20% and 80% in SB-RFA and SM-RFA, respectively. The sample size was calculated with 0.05 of alpha and 0.20 of beta and therefore 13 ablations per group were required. We performed 26 ablations and the presence of thermal injury in the stomach (n = 4), gallbladder (n = 4), small bowel (n = 3) and segmental intrahepatic biliary tract (n = 2) were checked in each group.

All animals were euthanized by intravenous injection of potassium chloride after the RFAs were performed and all livers were removed en bloc.

Assessment of Technical success and Ablation Zone

Ablated bovine liver blocks of ex vivo study and porcine liver segments containing ablation zones of in vivo study were cut along the electrode tract, then sliced in the transverse plane perpendicular to the axis of the electrode tracks at 5–7mm intervals so that sections included the largest areas of ablation and tumor mimicker. To prevent any bias in the measurements of ablation size, slices were photographed beside a ruler on a copy stand using a digital camera (Nikon Coolpix S6900;

Nikon Inc., Tokyo, Japan). Two observers (W.C., with 5 years of experience in the RFA procedure, and a technician with 10 years of experience in the RFA experiments) measured the vertical diameter (Dv) in the vertical plane as well as the long-axis diameter (Dmx) and the short-axis diameter (Dmi) of the RF-induced ablation zones at the transverse plane with the maximum area in consensus (27). Technical success of the no-touch technique, size and shape of the ablation zone were evaluated. A technical success in terms of ablation was defined as >5-mm peritumoral ablation margins outside the tumor mimicker in all directions on the slices (28-30) (Fig. 6).

The specimens of in vivo study were stained for 30 min in 2% 2,3,5-triphenyl tetrazolium chloride (TTC) (Sigma-Aldrich, St Louis, MO) at 20–25 °C to assess the cell viability. Distances between the electrode and outer margin of ablation zone (DEM) were measured on the plane with the maximum coagulation area (Fig. 7 and 8). If the ablation zone reached to the liver surface, DEM near to the saturated surface was not measured, and the mean value of the measurable DEMs was calculated. In cases with confluent or partial confluent necrosis, the shape of the RF-induced ablation zone was quantitatively evaluated on the same plane using the ratio between the Dmi and Dmx and the circularity defined by the following formula: circularity = $4\pi A/P^2$, where A is the area of the measured zone and P is the perimeter of the area (23). All measurements of the diameter, distance, and circularity were performed on image files of the slices using Image J software (https://imagej.nih.gov). The volumes of ablation zones were only calculated when technical success was achieved. In the case of confluent ablation, the volume was calculated by approximating the shape of the lesion to an ellipsoid. In cases where the ablation zone was non-confluent, an ellipse intersected by the tangent points of the coagulation zone was drawn; the maximum (Dmx-eff) and minimum (Dmi-eff) diameters of the ellipse were measured. The volumes of the ablation zones were evaluated according to the same approximation of the shape to an ellipsoid. In order to compare the variability in ablation volumes among the three groups, the coefficient of variation of the ablation volume was calculated as the ratio of the standard deviation to the mean value of gross ablation volume. The effective ablation volume (Volume-eff) was also calculated using the formula: Volume-eff = $\pi/6 \times Dmin^3$, where Dmin is the shortest diameter measured.

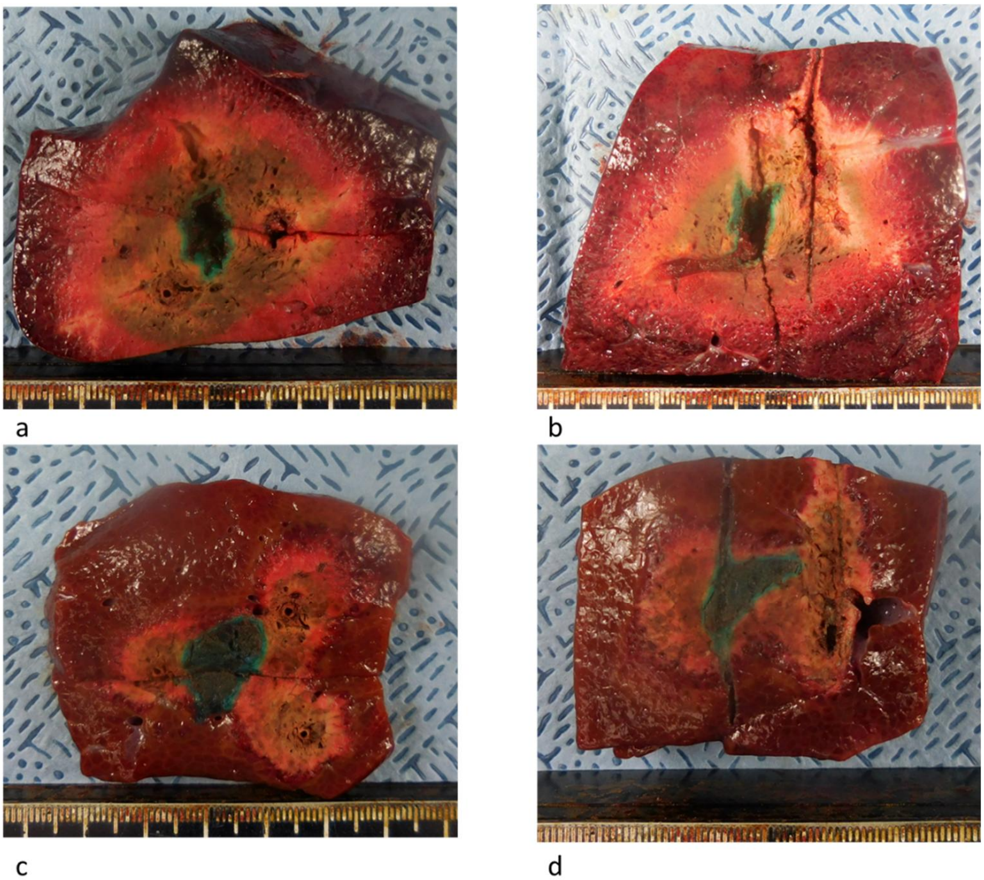
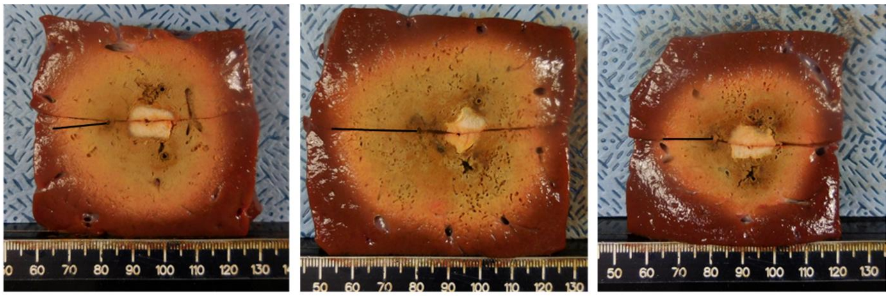


Figure 6. Photographs showing transverse and vertical planes of the specimen. (a, b) technical success with confluent necrosis. (a,b) and in the case of technical failure with partial confluent necrosis (c,d)



a b c

Figure 7. Comparison of radiofrequency ablation (RFA)-induced coagulation in ex vivo study.

A, B, C. Transverse cut surfaces of ablated specimens in groups A1, A2, and B, respectively. Black bars indicate distance between the outer margin of the ablation zone and the electrode.

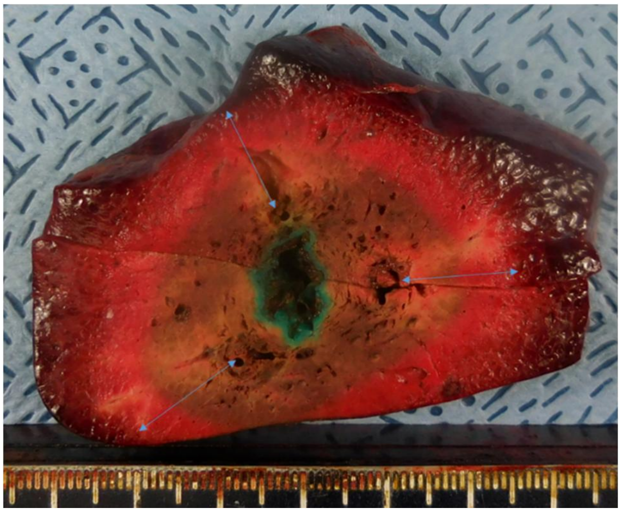


Figure 8. Photographs of the same specimen of Fig.6(a) after TTC treatment. Arrows indicate the distance between the outer margin of the ablation zone and the electrode.

Assessment of thermal injury

In ex vivo study, the presence of small bowel injury was checked immediately after the ablation procedure to evaluate adjacent organ injury; injured bowel segments or bowel segments most closely neighboring the ablation zone were fixed in 40 g/L formaldehyde solution, cut into 3-mm thick slices, embedded in paraffin, and stained with hematoxylin and eosin for light microscopy. The presence and depth of thermal injury to the small bowel was graded as follows; 0, no injury; 1, partial thickness injury of the muscular layer; and 2, full thickness injury of the small bowel wall including mucosal injury (31, 32).

In in vivo study, after sacrificing the animals, the adjacent stomach, small bowel, gall bladder and liver segment containing targeted biliary tract were also resected and processed for light microscopy in same manner of ex vivo study. One of the authors (K.B.L. with ten years of clinical experience in the interpretation of liver and gastrointestinal pathology) reviewed the slides for the presence and depth of thermal injury to the organs and biliary tract. The depth of thermal injury was recorded as the deepest layer with thermal injury for the stomach, small bowel and gallbladder (31-34).

Statistical Analysis

For each experiment, the results were presented as the mean value ± standard deviation (SD). In ex vivo study, the measured values and the technical parameters of the three groups (A1 vs. A2 vs. B) were compared using the analysis of variance (ANOVA) test. Bonferroni correction was used for post hoc analysis.

In in vivo study, results were compared between the SM-RFA groups (SM1 and SM2) and the SB-RFA group (SB) and then subgroup analyses among these three groups (SM1, SM2, and SB) were performed. The measured and calculated values as well as the monitored technical parameters were compared by t-test with unequal variances and the analysis of variance (ANOVA) test with Scheffe's method as a post hoc analysis. Regarding the rates of technical success and creation of confluent necrosis, we used the chi-square test and Marascuilo procedure for multiple comparisons of proportions (35). The rate of thermal injury was compared using the chi-square test; and times to reach certain temperatures were compared using the t-test with unequal variances. For all statistical analyses, p-values <0.05 were considered statistically significant but p-values <0.017 were considered statistically significant for Bonferroni correction. Statistical analyses were performed using the MedCalc statistical software, version 12.2.1 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Part 1. Ex vivo study

Technical parameters

The mean impedance of the SB mode was significantly higher than that of the SM mode (all $p < 0.001$) (Table 1) and the mean delivered RF power and total amounts of delivered energy were also significantly lower in the SB mode than in the SM mode (all $p < 0.001$).

Technical success, ablation size measurement, and shape analysis

None of the specimens showed technical failure or partial confluent or separated ablation (Table 2).

Ablation size measurements. – The mean Dmis of the ablation areas in groups A1, A2, and B were 4.98 ± 0.23 cm, 5.24 ± 0.26 cm, and 4.49 ± 0.13 cm, respectively ($p < 0.001$; Table 3). The SM-RFA (groups A1 and A2) generated significantly larger ablation volumes than SB-RFA (group B): 65.9 ± 8.6 cm^3 (group A1); 73.6 ± 10.0 cm^3 (group A2); and 52.1 ± 5.0 cm^3 (group B) ($p < 0.001$). The effective ablation volumes were 57.7 ± 9.8 cm^3, 57.9 ± 7.3 cm^3 and 46.8 ± 3.1 cm^3 in groups A1, A2, and B, respectively and were significantly larger for SM-RFA than for SB-RFA (A1 vs. B, $p = 0.006$; A2 vs. B, $p < 0.001$).

Ablation shape analysis. – The circularities of the ablative zones were 0.95 ± 0.05 in group A1, 0.97 ± 0.01 in group A2, and 0.94 ± 0.06 in group B (p = 0.334); thus suggesting that there were no significant differences in the quantitative values of the shape analysis among the three groups. However, DEM was significantly lower in group B (1.39 ± 0.08 cm) than in groups A1 (1.67 ± 0.10 cm) and A2 (1.86 ± 0.18 cm) (p < 0.001).

Elapsed time. – The elapsed times to reach 60°C, 70°C, 80°C, and 90°C were significantly faster in the SB-RFA group than in the SM-RFA group (groups A1 and A2, p = 0.002 for 60°C; p < 0.001 for 70, 80, and 90°C; p = 0.681 for 50°C) (Table 4).

Table 1. Measured Values of Technical Parameters according to the Power Application Modes in Ex Vivo Study

Parameters	Group A1 (n = 10)	Group A2 (n = 10)	Group B (n = 10)	p value	A1 vs. A2	A1 vs. B	A2 vs. B
Total delivered energy (Kcal)	12.0 ± 0.8	14.6 ± 1.3	9.0 ± 0.9	<0.001	<0.001	<0.001	<0.001
Average watt (W)	110.8 ± 6.1	95.5 ± 6.4	77.6 ± 5.2	<0.001	<0.001	<0.001	<0.001
Impedance (Ohm)	58.8 ± 1.4	61.5 ± 1.6	93.6 ± 12.4	<0.001	0.001	<0.001	<0.001

Table 2. Ex Vivo Results of Technical Success Rate, and Shape Analysis of RF-induced Ablation Zones in Each Group

Parameters	Group A1 (n = 10)	Group A2 (n = 10)	Group B (n = 10)	p value
Qualitative analysis of ablation				
Technical Success	100% (10/10)	100% (10/10)	100% (10/10)	1
Confluent ablation	100% (10/10)	100% (10/10)	100% (10/10)	1
Partial confluent ablation	0% (0/10)	0% (0/10)	0% (0/10)	1
Separated ablation	0% (0/10)	0% (0/10)	0% (0/10)	1
Quantitative analysis of Coagulation Necrosis				
Circularity	0.95 ± 0.05	0.97 ± 0.01	0.94 ± 0.06	0.334
Dmi/Dmx Ratio	0.95 ± 0.04	0.94 ± 0.04	0.94 ± 0.04	0.795

Dmx= maximum diameter of the ablative zone, Dmi = minimum diameter of the ablative zone

Table 3. Ex Vivo Results of Ablation Size Measurement in Each Group

Parameters	Group A1 (n = 10)	Group A2 (n = 10)	Group B (n = 10)	p value	A1 vs. A2	A1 vs. B	A2 vs. B
Dmx (cm)	5.24 ± 0.23	5.58 ± 0.29	4.78 ± 0.20	<0.001	0.01	<0.001	<0.001
Dmi (cm)	4.98 ± 0.23	5.24 ± 0.26	4.49 ± 0.13	<0.001	0.03	<0.001	<0.001
Dv (cm)	4.81 ± 0.29	4.79 ± 0.20	4.63 ± 0.24	0.384			
Gross Ablation volume (cm^3)	65.9 ± 8.6	73.6 ± 10.0	52.1 ± 5.0	<0.001	0.083	0.001	<0.001
Effective Ablation volume (cm^3)	57.7 ± 9.8	57.9 ± 7.3	46.8 ± 3.1	<0.001	0.963	0.006	<0.001
DEM (cm)	1.67 ± 0.10	1.86 ± 0.18	1.39 ± 0.08	<0.001	0.013	<0.001	<0.001
CV of the volume (%)	13	13.6	9.6				

Dmx= maximum diameter of the ablative zone, Dmi = minimum diameter of the ablative zone, Dv = vertical diameter of the ablative zone, DEM = distance between electrode and ablation zone margin, CV = coefficient of variation

Table 4. Elapsed Times to Reach Specific Temperatures in Ex vivo study

Temperature	SM-RFA (seconds)	SB-RFA (seconds)	p value
50°C	83.1 ± 22.8	80.8 ± 5.6	0.681
60°C	109.1 ± 14.5	96.2 ± 6.0	0.002
70°C	130.1 ± 15.2	108.6 ± 7.8	<0.001
80°C	154.0 ± 18.5	121.6 ± 9.6	<0.001
90°C	185.6 ± 26.0	137.9 ± 11.8	<0.001

The second experiments

Thermal injury to the small bowel was noted in 90% (9/10), 100% (10/10), and 30% (3/10) of the cases in groups A1, A2, and B, respectively (A1 vs. B, $p = 0.008$; A2 vs. B, $p = 0.001$, A1 vs. A2, $p = 0.317$) (Fig. 9. Six cases of grade 2 small bowel injury were observed only in group A2 (6/10), and all thermal injuries of the small bowel noted in group A1 and B were grade 1 injuries (A2 vs. A1 and B for grade 2 injury, $p = 0.004$). The mean final temperatures measured by a thermocouple placed between the liver surface and small bowel after the completion of ablation were 59.1 ± 7.4°C, 65.1 ± 8.6°C, and 49.4 ± 6.7°C in groups A1, A2, and B, respectively. The surface temperatures of the small bowel neighboring the ablation zone measured by a thermal imaging camera were also significantly lower in the SB group than in the SM groups, and significantly lower in group A1 than in group A2 (all $p < 0.001$): 48.4 ± 3.1°C, 56.7 ± 3.5°C, and 40.5 ± 2.3°C in groups A1, A2, and B, respectively.

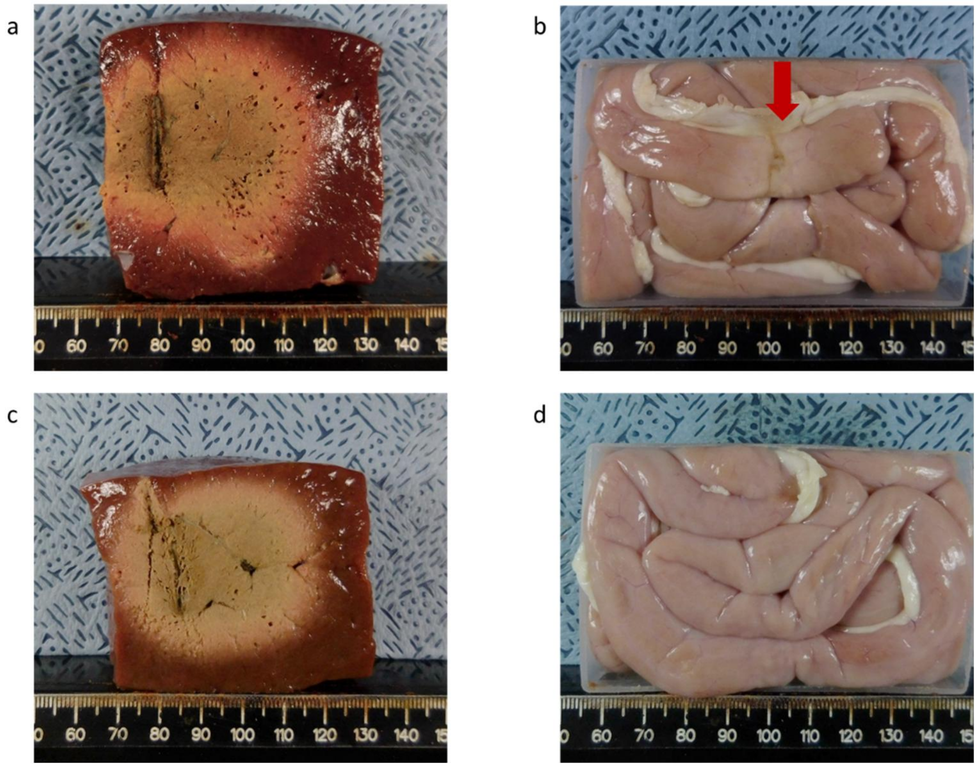


Figure 9. Comparison of adjacent small bowel thermal injury during RFA in groups A2 and B.

A, B. Vertical cut surface of ablated specimens and adjacent small bowel in group A2, respectively. Note that the ablated area extended to the liver surface and there is a color change of the small bowel wall by thermal injury (arrow).

C, D. Vertical cut surfaces of ablated specimens and adjacent small bowel in group B, respectively. Note that the liver surface was not ablated and adjacent small bowel showed no thermal injury.

Part 2. In vivo study

Technical parameters and tumor mimickers

The maximum diameters of tumor mimickers were 1.99 ± 0.25 cm, 2.04 ± 0.15 cm, and 2.08 ± 0.20 cm, and their volumes were calculated to be 2.78 ± 0.68 cm^3, 2.41 ± 0.69 cm^3, and 2.42 ± 0.50 cm^3 in the groups SM1, SM2, and SB, respectively. Despite efforts to avoid perivascular areas during implantation of tumor mimickers, we found that 30% (3/10), 40% (4/10), and 30% (3/10) of mimickers were contiguous to large vessels (> 3 mm) in the groups SM1, SM2, and SB, respectively (36).

The mean impedance of the SM mode was significantly lower than that of the SB mode (all $p < 0.001$) (Table 5). The average power and total amounts of energy delivered were significantly lower in the SB mode than in the SM mode (all $p < 0.001$)

There were no significant differences in the maximum diameter and volumes of tumor mimickers among the groups ($p = 0.580$ and 0.264, respectively).

Table 5. Measured Values of Technical Parameters according to the Power Application Modes

Parameters	Group SM1 (n = 10)	Group SM2 (n = 10)	Group SB (n = 10)	SM1 vs. SM2	SM1 vs. SB	SM2 vs. SB
Total delivered energy (Kcal)	11.3±0.7	16.2±2.0	8.2±0.8	<0.001	<0.001	<0.001
Average power (W)	105.7±5.8	102.2±7.8	79.1±4.4	0.266	<0.001	<0.001
Impedance (Ohm)	65.3±8.2	63.3±7.0	84.9±12.3	0.563	<0.001	<0.001

Note. – SM= switching monopolar, SB = switching bipolar.

Technical success, ablation size measurement, and shape analysis

Technical success. – – A 100% (10/10) technical success was achieved using SB-RFA, which was significantly higher than the success of SM-RFA (SM1 and SM2, 65% [13/20], p = 0.0357). Moreover, subgroup analysis determined the technical success rate to be higher in the SB group than in the SM1 groups (100% [10/10] vs. 60% [6/10], $p < 0.05$). Perivascular tumor mimickers reduced the technical success rates to 0% (0/3), 25% (1/4), and 100% (3/3) in the groups SM1, SM2, and SB, respectively. When cases of perivascular tumor mimickers were excluded, the technical success rates increased to 85.7% (6/7) and 100% (6/6) in the SM1 and SM2 groups. The rate of confluent necrosis was higher in the SB group than in either the SM1 group (90% [9/10] and 40% [4/10], $p < 0.05$) or SM2 group; however, the difference in the rate between the SB and SM2 groups was not statistically significant (Table 6, p>0.05).

Ablation size measurements.– The volume of gross ablation was significantly smaller in group SB than in group SM2 (39.8 ± 9.7 cm^3 and 59.2 ± 18.7 cm^3) (Table 7 The overall DEM was lower in SB-RFA than in SM-RFA (1.31 ± 0.19 cm, and 1.07 ± 0.10 cm, respectively, p < 0.001). DEM of SM1, SM2, and SB were 1.22 ± 0.14 cm, 1.39 ± 0.21 cm, and 1.07 ± 0.10 cm, respectively, and the SB group had a significantly lower DEM than the SM2 group (p < 0.05). Other size parameters including diameters and effective ablation volume were not significantly different between the groups.

Quantitative Ablation shape analysis. – Circularity was significantly higher when SB-RFA was used compared to that when SM-RFA was used (0.91 ± 0.03 vs. 0.86 ± 0.08, p = 0.027); however, a subgroup analysis did not reveal any significant differences between the groups.

Elapsed time to reach specific temperatures

The times to reach 50°C, 60°C 70°C, 80°C, and 90°C were 94.0 ± 54.1, 159.4 ± 87.1, 228.3 ± 143.5, 310.3 ± 193.1, 396.3 ± 212.3 seconds in SM-RFA and 62.8 ± 44.0, 109.0 ± 76.1, 114.5 ± 54.4, 171.4 ± 80.1, 221.8 ± 94.3 seconds in SB-RFA and significantly shorter in the SB-RFA group than in the SM-RFA group (p = 0.015, 0.030 and 0.048 for 70°C, 80, and 90°C; p = 0.091 for 50°C and p = 0.102 for 60°C) (Table 8).

Safety assessment

Thermal injury to adjacent organs and biliary tracts was less frequently noted with SB-RFA than with SM-RFA (23.1% (3/13) and 69.2% (9/13), respectively, p = 0.021) (Table 9; Fig. 10). Excluding injury to the biliary tract, the rate of thermal injury penetrating the muscle layer was lower when SB-RFA was used compared to that when SM-RFA was used; however, these differences were not statsitically significant (18.2% (2/11) and 54.5% (6/11), respectively, p = 0.084)

Table 6. In Vivo Results of Technical Success Rate, and Shape Analysis of RF-induced Ablation Zones in Each Group

Parameters	SM-RFA (n=20)	SB-RFA (n=10)	p-value	Group SM1 (n=10)	Group SM2 (n=10)	Group SB (n=10)	p-value	SM1 vs. SM2	SM1 vs. SB	SM2 vs. SB
Qualitative analysis of Coagulation Necrosis										
Technical Success	65% (13/20)	100% (10/10)	0.0357	60% (6/10)	70% (7/10)	100% (10/10)		NS	<0.05	NS
Confluent necrosis	55% (11/20)	90% (9/10)	0.0595	40% (4/10)	70% (7/10)	90% (9/10)		NS	<0.05	NS
Partial confluent necrosis	35% (7/20)	10% (1/10)	0.1512	40% (4/10)	30% (3/10)	10% (1/10)		NS	NS	NS
Separated necrosis	10% (2/20)	0% (0/10)	0.3088	20% (2/10)	0% (0/10)	0% (0/10)		NS	NS	NS
Quantitative analysis of Coagulation Necrosis										
Circularity	0.86±0.08	0.91±0.03	0.027	0.85±0.07	0.87±0.09	0.91±0.03	0.234			
Dmi/Dmx Ratio	0.88±0.05	0.86±0.10	0.982	0.84±0.11	0.88±0.09	0.86±0.10	0.756			

Note. – SM= switching monopolar, SB = switching bipolar, Dmx= maximum diameter of the ablative zone, Dmi = minimum diameter of the ablative zone, NS = not significant

Table 7. In Vivo Results of Ablation Size Measurement in Each Group

Parameters	SM-RFA (n=20)	SB-RFA (n=10)	p-value	Group SM1 (n=10)	Group SM2 (n=10)	Group SB (n=10)	p-value	SM1 vs. SM2	SM1 vs. SB	SM2 vs. SB
Dmx (cm)	4.91 ± 0.72	4.48 ± 0.37	0.114	4.57 ± 0.55	5.19 ± 0.76	4.48 ± 0.37	0.052			
Dmi (cm)	4.33 ± 0.91	3.98 ± 0.39	0.188	3.87 ± 0.87	4.71 ± 0.79	3.98 ± 0.39	0.209			
Dv (cm)	4.32 ± 0.65	4.24 ± 0.56	0.774	4.07 ± 0.63	4.53 ± 0.62	4.24 ± 0.56	0.383			
Gross Ablation volume (cm^3)	50.0 ± 19.5	39.8 ± 9.7	0.117	39.3 ± 15.3	59.2 ± 18.7	39.8 ± 9.7	0.023	NS	NS	<0.05
Effective Ablation volume (cm^3)	34.3 ± 12.7	29.5 ± 10.5	0.331	27.1 ± 12.6	40.4 ± 9.7	29.5 ± 10.5	0.863			
DEM (cm)	1.31 ± 0.19	1.07 ± 0.10	<0.001	1.22 ± 0.14	1.39 ± 0.21	1.07 ± 0.10	0.002	NS	NS	<0.05
CV of the volume (%)	39	24.2		38.9	31.6	24.2				

Note. – SM= switching monopolar, SB = switching bipolar, Dmx= maximum diameter of the ablative zone, Dmi = minimum diameter of the ablative zone, Dv = vertical diameter of the ablative zone, DEM = distance between electrode and ablation zone margin, CV, coefficient of variation

Table 8. Thermal injury to the adjacent organs and structures in In Vivo Study

Mode	Target	Thermal injury	Depth
SM-RFA	Stomach	75% (3/4)	Proper muscle (n=1); Mucosa (n=2)
	Gall bladder	50% (2/4)	Mucosa (n=2)
	Small bowel	100% (3/3)	Proper muscle (n=1); Submucosa (n=1); Mucosa (n=1)
	Biliary tract	50% (1/2)	
SB-RFA	Stomach	25% (1/4)	Subserosa (n=1)
	Gall bladder	50% (2/4)	Mucosa(n=2)
	Small bowel	0% (0/3)	
	Biliary tract	0% (0/2)	

Note. – SM= switching monopolar, SB = switching bipolar

Table 9. Elapsed Times to Reach Specific Temperatures in In Vivo study

Temperature	SM-RFA (seconds)	SB-RFA (seconds)	p-value
50°C	94.0 ± 54.1	62.8 ± 44.0	0.091
60°C	159.4 ± 87.1	109.0 ± 76.1	0.102
70°C	228.3 ± 143.5	114.5 ± 54.4	0.015
80°C	310.3 ± 193.1	171.4 ± 80.1	0.030
90°C	396.3 ± 212.3	221.8 ± 94.3	0.048

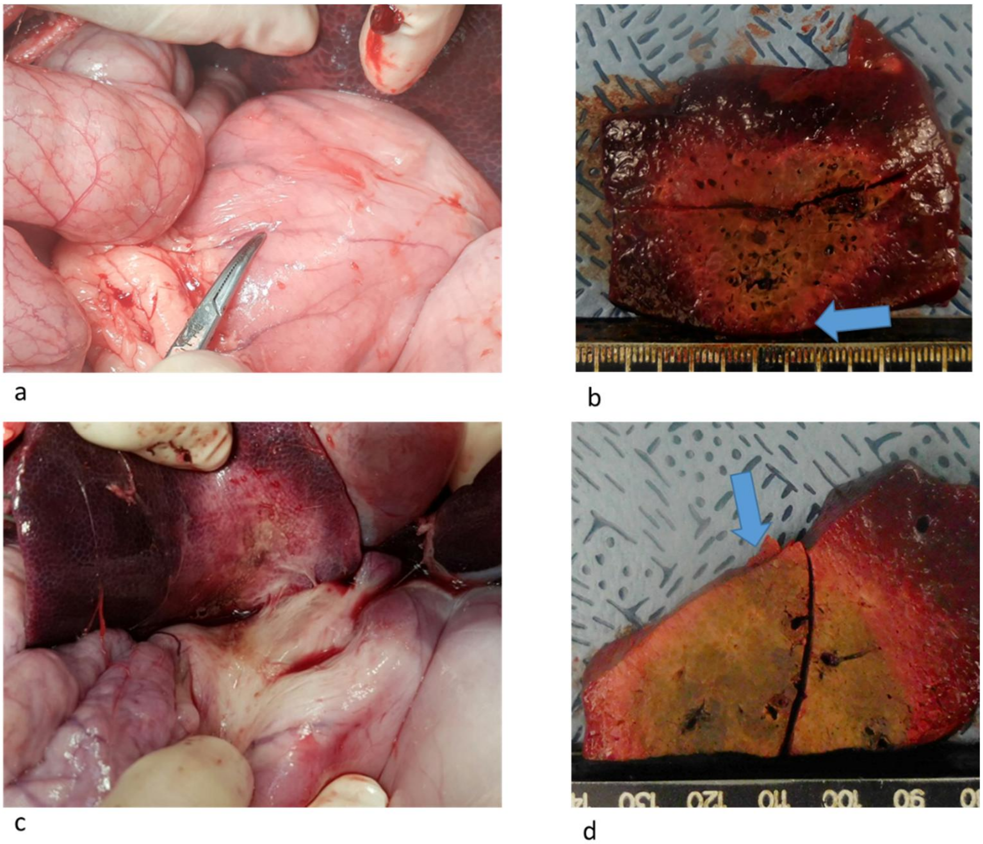


Figure 10. In vivo study for an adjacent stomach injury. (a) Photograph showing the absence of stomach injury after SB-RFA. (b) Corresponding liver specimen, showing the ablation zone did not reach the liver surface abutting the stomach (arrow). (c) Photograph showing discolored thickened whitish area of the stomach suggesting thermal injury. (d) Corresponding liver specimen, showing the ablation zone reached the liver surface abutting the stomach (arrow).

DISCUSSION

Our study demonstrated that the no-touch RFA technique using an Octopus electrode was feasible for treating a tumor in both the SM and SB modes. In ex vivo study, there was no technical failure and no non-confluent coagulation in neither of the SM and SB modes. Moreover, in in vivo study, with the exception of cases with perivascular tumor mimickers, technical success rates were 100% in both the SM2 and SB groups. However, the overall rates of technical success and confluent necrosis were significantly better in the SB group compared with the SM1 group. Technical success rates in SM-RFA could be increased with a longer ablation time; however, these differences are not statistically significant. Therefore, in order to achieve confluent necrosis with SM-RFA, it might be necessary to perform additional ablations whilst changing the position of electrodes; however, this will increase the complexity of the procedure and related complications. Our study results are in good agreement with the previous in vivo study which showed the superior performance SB RFA than in SM RFA in the creation of spherical confluent ablation zones (23). In this in vivo study, Technical failure was determined as insufficient peritumoral margin with partial or separated necrosis, and may be caused by the heat sink effect of adjacent vessels. With respect to energy delivery, monopolar RFA was vulnerable to the heat sink phenomenon, and the presence of large peritumoral vessels increased the risk of incomplete ablation (36, 37), whereas, SB-RFA was less affected by the heat sink phenomenon compared with SM-RFA in the perfused ex vivo bovine liver model (38). So the discrepancy of rates in technical success and confluent necrosis between ex vivo and in vivo studies was explicated by the heat sink effect.

In ex vivo study, the SB mode showed significantly smaller DEM than did the SM mode, which might indicate less injury to the adjacent liver parenchyma using no-touch RFA. Moreover, in in vivo study, although the volume of gross ablation was significantly larger in group SM2 than in group SB, DEM was significantly smaller in group SB than group SM2 ($p<0.05$). Since large-scale ablations around the perimeter of the tumor may be associated with a greater risk of thermal injury to adjacent structures, it is necessary to create a sufficiently large zone of confluent ablation zone to generate an adequate ablation margin; however it should not be too large as that could create unnecessary injury to the adjacent normal tissue (23). A higher technical success rate using the no-touch technique may be achieved with SB-RFA rather than with SM-RFA.

Theoretically, no-touch RFA techniques can provide several advantages over conventional tumor puncture RFA techniques, such as the absence of tract seeding or peritoneal seeding, and the absence of an increase in intratumoral pressure. However, the peritumoral ablation size could be larger for the no-touch RFA technique using multiple electrodes placed outside the tumor than for conventional RFA methods that puncture the tumor, and may therefore, increase the risk of thermal injury to adjacent structures. In the SM1 and SB groups, ablation time was the same, and ablation volume and DEM were not significantly different; however, the rates of technical success and confluent necrosis were significantly lower in the SM-RFA than in the SB-RFA group. According to previous studies, bipolar RFA has greater energy efficiency and enables a faster ablation time than monopolar RFA. The lower technical success observed in the SM-RFA group SM1 was in good agreement with these studies (21, 23). Thermal injury was evaluated in the cases of successful ablation and ablations were compared between SM-RFA (15 minutes) and SB-RFA (10 minutes). No-touch SB-RFA created less frequent thermal injury to adjacent organs and structures than SM-RFA, although the differences in mean DEM between SM2 and SB groups was only 0.33 cm. Moreover, in cases where there were successful ablations in both SM- and SB-RFA groups, the ablation volume following SB-RFA was significantly smaller than that in the SM2 group, and it showed less ablation of the liver tissue outside of the electrode (shorter DEM). Conversely, the temperature at the center of the ablation zone had risen more quickly in the SB mode than in the SM mode. These results could be explained by the basic physical differences in electrical current flow between the SM and SB RF energy delivery techniques. In monopolar RFA, the current spreads from each electrode centrifugally to the periphery, whereas during bipolar RFA the electrical current flows between a pair of electrodes and prevents the ablation zone from perfusion-mediated cooling, thereby resulting in a faster and more focal heating between the electrodes (8, 23). Based on our results, we believe that the SB mode may be the optimal energy delivery mode for the no-touch RFA technique than the SM mode, because it effectively increases tissue temperature at the center, and induces lesser thermal injury to the surrounding organs.

RFA is widely accepted as one of the curative treatment options for early stage HCC in patients who are not good surgical candidates, primarily because it is more cost-effective and less invasive than surgery (2, 39). Monopolar RFA is the most commonly used technique, and requires placement of the electrode within the target tumor. It creates an ablation zone centrifugally along the flow of electrical current in the tissue surrounding the electrode (40). Risk of tract or peritoneal seeding after RFA is inevitable (15); however, an increased risk of tumor seeding is associated with pericapsular tumors, poorly differentiated tumors, and high α-fetoprotein levels (41). After Llovet et al. reported a high rate (12.5%, 4/32 patients) of tumor tract seeding when treating HCC with RFA (41), it has been raised as a major issue, particularly in patients treated for a curative purpose (42). According to a systematic review of tumor seeding after percutaneous diagnostic and therapeutic procedures for HCC (14), the mean risk for tumor seeding after RFA alone was 1.73% (range, 0–5.56%), and after RFA with biopsy, the mean risk increased to 2.5%. Despite the relatively low risk of tumor seeding, and considering the cumulative risk of tract seeding for multisession RFAs or RFAs with multiple electrode insertions, the no-touch technique could be valuable for preventing tract seeding after RFA, particularly in patients waiting for liver transplants or patients with HCCs located on the liver surface (42, 43). In order to avoid capsular breach during ablation, the no-touch wedge ablation technique may reduce the potential risk of tumor rupture and consequent hemorrhage (44). Additionally, as the drainage vessels of HCC change from hepatic veins to peritumoral sinusoid or portal veins (45, 46), (44, 45), the no-touch technique can induce thrombosis in the draining peritumoral vessels which may be advantageous in decreasing the risk of metastases via the vessels. Until now, few studies have reported on the use of no-touch tumor ablation techniques using multipolar RFA with multiple bipolar electrodes, or multiple microwave antennae for liver tumors, especially for subcapsular tumors (17, 20, 43, 44). When a traditional ablation technique using the monopolar mode with placement of electrode in the tumor has been used, the areas near the ablation probe are heated to well greater than tumor-lethal temperatures; however this is not as readily achieved at the periphery of the ablation zone. Therefore, residual unable tumor is often seen as scattered, nodular, eccentric enhancement at the margin of the ablation zone (47).

The present study has several limitations. First, the feasibility and safety of the no-touch technique were evaluated intraoperatively; therefore, we were unable to assess the feasibility and safety of percutaneous RFA. Thus, the feasibility of the no-touch technique in percutaneous RFA should be evaluated. Since the use of RFAs with multiple electrodes is routine in clinical practice, the differences in safety profile between the intraoperative and percutaneous approaches are expected to be minimal. Second, we did not compare our SB-RFA system with the multipolar RFA system, which shows promising results for no-touch ablation (19, 20) nor conventional monopolar RFA system without no-touch technique. Third, this in vivo study was performed in a relatively small number of animals, so we could not demonstrate significant differences in technical success between the SM2 and SB groups. In the SM2 group, technical failure resulted from the perivascular location of tumor mimickers. Further studies to evaluate the heat sink effect, especially for perivascular tumors are required. Fourth, we only tested the no-touch technique with a single inter-electrode interval of 2.5 cm. Additional studies using larger interelectrode intervals would be valuable. Finally, the RF ablations were performed using a tumor mimicker; therefore, the thermal efficiency of the current RF system might not be translated into clinical practice owing to different tissue textures of target tumors.

In conclusion, our results demonstrate that SB-RFA is more feasible with a no-touch technique and provides a better safety profile with smaller adjacent parenchymal ablation zones, sufficient peritumoral margins, and lesser thermal injury to the adjacent organs compared with the SM-RFA techniques.

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국문 초록

서론: 이 연구에서는 비접촉 기법을 이용한 교대 이극성 고주파 소작술과 교대 단극성 소작술의 기술적 타당성, 효율성 및 안전성을 평가하고자 하였다.

방법: 이 연구에서 Ex vivo 와 In vivo 실험을 각각 시행하였다. Ex vivo 연구에서는 돼지 등심을 종양 유사체로 소 간 덩어리에 삽입하였다. 비접촉 기법을 이용한 고주파 소작술이 교대 단극성 (group A1; 10 minutes, n = 10, group A2; 15 minutes, n = 10)과 교대 이극성 (group B; 10 minutes, n = 10) 방법으로 시행되었다.

In vivo 연구는 동물실험윤리위원회의 승인을 받았다. 돼지 간에 2cm 크기의 종양 유사체를 만든 뒤 고주파 소작술을 비접촉기법을 이용하여 교대 단극성 (group SM1: 10 minutes, n = 10; group SM2: 15 minutes, n = 10)과 교대 이극성 (group SB: 10 minutes, n = 10) 방법으로 시행되었다.

충분한 안전역 확보 여부와 합류 괴사에 근거하여 기술적 성공여부를 평가하고 소작 병변의 크기, 전극과 소작경계까지의 거리 (DEM)를 측정하여 각 군에 비교하였다.

Ex vivo 연구에서는 안전성을 평가하기 위해 소장을 간 표면에 위치시킨 후 같은 군에 대해 30 개의 추가적인 소작을 시행하였다. 또

한 In vivo 연구에서는 이접한 장기에 대해 열 손상 여부를 교대 단극성 (15 minutes, n=13) 과 교대 이극성 (10 minutes, n=13) 방법에 대해 비교하였다.

결과: Ex vivo 연구에서는 모든 검체에서 합류괴사와 충분한 안전역이 확보되었으나 In vivo 연구에서는 SB 군에서 SM1 군보다 기술적 성공확률이 유의하게 높았다 (p<0.05). 소작 병변의 크기와 DEM 은 교대 이극성 방법으로 시행하였을 때 15 분간 교대 단극성 방법으로 시행하였을 때보다 유의하게 작았다 (p<0.05). 주변 장기와 조직의 열손상도 교대 이극성 방법에서 교대 단극성 방법보다 유의하게 적게 발생하였다 (Ex vivo 와 In vivo 연구에서 유의확률은 각각 p=0.001 과 p=0.021 임).

결론: 비접촉기법을 이용할 때, 교대 이극성 고주파 소작술이 교대 단극성소작술에 비해 시행하기 용이하며 더욱 안전하다.

주요어 : 고주파 소작술, RFA, 비접촉 기법, HCC, 간세포암.

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