BJR

Received: 3 July 2014

Cite this article as:

Yoon JH, Lee JM, Woo S, Hwang EJ, Hwang I, Choi W, et al. Switching bipolar hepatic radiofrequency ablation using internally cooled wet electrodes: comparison with consecutive monopolar and switching monopolar modes. Br J Radiol 2015;88:20140468.

FULL PAPER

Revised:

Switching bipolar hepatic radiofrequency ablation using internally cooled wet electrodes: comparison with consecutive monopolar and switching monopolar modes

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Objective: To evaluate whether switching bipolar radiofrequency ablation (SB-RFA) using three internally cooled wet (ICW) electrodes can induce coagulations >5 cm in porcine livers with better efficiency than consecutive monopolar (CM) or switching monopolar (SM) modes.

Methods: A total of 60 coagulations were made in 15 *in vivo* porcine livers using three 17-gauge ICW electrodes and a multichannel radiofrequency (RF) generator. RF energy (approximately 200 W) was applied in CM mode (Group A, n = 20) for 24 min, SM mode for 12 min (Group B, n = 20) or switching bipolar (SB) mode for 12 min (Group C, n = 20) in *in vivo* porcine livers. Thereafter, the delivered RFA energy, as well as the shape and dimension of coagulations were compared among the groups.

Results: Spherical- or oval-shaped ablations were created in 30% (6/20), 85% (17/20) and 90% (18/20) of coagulations

Radiofrequency (RF) tumour ablation is increasingly being utilized as an alternative option in patients with unresectable primary and secondary liver malignancies.^{1,2} In the treatment of small hepatocellular carcinomas (HCCs), RF ablation (RFA) has been shown to yield satisfactory local tumour control, with one study pathologically demonstrating complete tumour necrosis in 83% of HCCs <3 cm.³ Indeed, according to the recent Barcelona Clinic Liver Cancer staging and treatment strategy guidelines for HCCs, RFA is favoured over surgical resection for very early stage HCCs (single nodule <2 cm) in patients with Child–Pugh A liver cirrhosis.⁴ Furthermore, a recent systematic review paper by Cucchetti et al⁵ reported that for very early HCCs (single nodule <2 cm) in Child-Pugh Class A patients, RFA provided similar life expectancy and quality-adjusted life expectancy at a lower cost than did surgical resection.

in the CM, SM and SB groups, respectively (p = 0.003). SB-RFA created ablations >5 cm in minimum diameter (D_{min}) in 65% (13/20) of porcine livers, whereas SM- or CM-RFA created ablations >5 cm in only 25% (5/20) and 20% (4/20) of porcine livers, respectively (p = 0.03). The mean D_{min} of coagulations was significantly larger in Group C than in Groups A and B (5.1 ± 0.9, 3.9 ± 1.2 and 4.4 ± 1.0 cm, respectively, p = 0.002) at a lower delivered RF energy level (76.8 ± 14.3, 120.9 ± 24.5 and 114.2 ± 18.3 kJ, respectively, p < 0.001).

Conclusion: SB-RFA using three ICW electrodes can create coagulations >5 cm in diameter with better efficiency than do SM- or CM-RFA.

Advances in knowledge: SB-RFA can create large, regular ablation zones with better time-energy efficiency than do CM- or SM-RFA.

However, for single HCCs 3-5 cm in diameter, resection was shown to provide better life expectancy and to be more cost effective than RFA owing to high local tumour progression rates after RFA. $^{5-12}$ This is in large part owing to the limited ability of currently available RFA devices in creating a sufficiently large ablation zone encompassing HCCs 3–5 cm in diameter along with a safety margin.^{7,11,13,14} Therefore, an ideal RFA system would provide the capability to create coagulations >5 cm in short-axis diameter within a reasonable time frame (<30 min) for the treatment of tumours >3 cm in diameter considering a sufficient safety margin (5-10 mm in thickness). Currently, multiple overlapping ablations are often used for the treatment of liver tumours >2 cm in order to cover the complete tumour volume as well as to create a 1-cm-thick peripheral ablation margin.^{15,16} However, there is considerable technical difficulty in probe repositioning during overlapping ablations, especially under

ultrasound guidance, owing to gas bubble formations, ultimately resulting in incomplete ablations.^{17–19}

Recently, multiple-electrode RFA approaches, including the switching monopolar (SM) mode, bipolar mode and multipolar mode, have been attempted with each demonstrating efficiency in creating a larger ablation zone in liver tissue than in the standard monopolar RF technique.^{2,20–26} Theoretically, RFA in switching bipolar (SB) mode using multiple electrodes should further improve the thermal and electronic efficiency of RFA devices compared to conventional monopolar modes. However, until now, the efficacy of SB-RFA with internally cooled wet (ICW) electrodes, which allow simultaneous internal cooling and saline infusion, in creating 3- to 5-cm coagulation areas, have not been tested in previous *in vivo* studies.

Therefore, the purpose of this study was to evaluate whether SB-RFA using three ICW electrodes can induce coagulations >5 cm in diameter in porcine livers with better efficiency than consecutive monopolar (CM) or SM mode.

METHODS AND MATERIALS

This study received technical support and was partially funded by a research grant from RF Medical Co. (Seoul, Republic of Korea). All authors had full control of all data and information submitted for publication at all times.

Development of a switching bipolar radiofrequency ablation unit

Recently, a multichannel RF system (M-3004; RF Medical Co., Seoul, Republic of Korea) allowing automatic switching of RF energy among the three electrodes according to impedance changes in either monopolar or bipolar modes was developed.²⁰ The multiRFA system includes a generator with a maximum power of 200 W at a frequency of 400 kHz and provides three separate channels for the three electrodes. It can be used in either SM or bipolar mode to heat tissue in which power is applied in alternating fashion to the three electrodes (Figure 1a). In monopolar mode, the RF system allows continuous monitoring of impedance between the active portion of the electrode and the dispersive electrode (grounding pads). The RF power is controlled by impedance changes during RFA, and the duty cycle between the electrodes is automatically controlled by continuously measured impedance values. Maximal power is switched at approximately 30 s if there is no impedance rise >40% above the baseline value. However, if the impedance of one of the electrodes rises 40% above the baseline value, the current is reduced by 10% and switched to the other electrode automatically.^{21,27}

A three 17-gauge ICW electrode (RF Medical Co.) RFA system with a 3-cm exposed tip was used in this study (Figure 1b). The internal structure of the exposed tip of the ICW electrode was identical to that of a conventional internally cooled electrode except that the former contains two tiny (0.03-mm) side holes.²⁸ Approximately, 99% of the chilled 0.9% isotonic saline was used for cooling, and 1% was used for infusion, at rates of 1.2 and 1.4 ml min⁻¹, respectively.²⁹ A peristaltic pump (RFP-300) was used to infuse a normal saline solution at 5–10 °C into the

Figure 1. (a) Photograph of an internally cooled wet electrode with a hole in the active tip. (b) A prototype three-channel radiofrequency ablation system, which allows the use of multiple electrodes in either switching monopolar or bipolar modes.



(a)



lumen of the three ICW electrodes at a rate sufficient enough to maintain a tip temperature of 10–25 °C.

Animals, anaesthesia and surgery

Approval for this protocol was obtained from the Animal Use and Care Administrative Advisory Committee of Seoul National University Hospital. All experiments were performed in accordance with the general guidelines issued by the National Institute of Health (NIH) of the USA for the care of laboratory animals. 15 domestic male pigs (mean weight, 65 kg; range, 60–70 kg) were anaesthetized using an intramuscular injection of 50 mg kg⁻¹ of ketamine hydrochloride (Ketamine; Yuhan, Seoul, Republic of Korea) and 5 mg kg⁻¹ of Xylazine (Rumpun; Bayer Korea Ltd, Ansan, Republic of Korea) and prepared for surgery. Thereafter, endotracheal intubation was performed and anaesthesia was maintained with inhaled isoflurane (1–4% IsoFlo[®]; Abbott Laboratories, North Chicago, IL). The pigs were then placed in the supine position and prepared at the midline and draped.

One of the three operators (SW, WSC and EJH with assistance from two technicians) performed the ablation procedures by means of open laparotomy through a midline incision, and one ablation lesion was created in each lobe of each animal. Therefore, a total of 60 ablation lesions were created in the 15 animals. After creating four ablation zones in the liver of each pig, the liver was allowed to be cooled to body temperature, and the incision was closed using non-absorbable sutures.

Radiofrequency ablation protocol

Experiments were performed with the multichannel RF generator system (M-3004; RF Medical Co.) and three ICW electrodes (RF Medical Co.). As the goal of the RFA procedure was to create coagulations >5 cm in minimum diameter (D_{\min}), RF energy (power output, 200 W) was applied in CM mode (Group A, n = 20) for 24 min in *in vivo* porcine livers, while RF energy was applied in SM mode (Group B; n = 20) or SB mode for 12 min (Group C; n = 20) each, based on our preliminary study results on *ex vivo* bovine livers.

The location of the ablation lesions in the liver lobes was randomized, in order to minimize the bias from any potential variation of segmental perfusion. To avoid the influence of the increased temperature in the liver tissue, a minimum distance of 7 cm between ablation zones was maintained. RF electrodes were placed to ensure that the entire ablation zone would be within the liver parenchyma. Based on the results of our preliminary ex vivo study and considering the influence of tissue perfusion in an in vivo setting, the three cluster electrodes were placed in a triangular array with equidistant interprobe spacing of 2.5 cm using an acrylic puncture aid with multiple holes 3 mm in diameter at 5-mm intervals from the centre up to 4 cm. Ablation lesions were formed by placing the RF electrodes in the pig liver under visual guidance, and after insertion of the probes into the liver, ultrasound (7.5-MHz linear transducer; SonoAce 5500; Medison, Seoul, Republic of Korea) was used to guide and further position the probe away from vessels >5 mm in diameter. In CM mode, RF energy was consecutively applied to each of the three internally cooled electrodes for 8 min by changing the current flow to the second probe just after the ablation with the first probe. In SM mode, the RF energy was applied to one of the three ICW electrodes, and RF energy delivery was automatically changed among the three electrodes depending on impedance changes (Figure 2a). In SB mode, the RF energy was applied to a pair of the three ICW electrodes, and according to impedance changes, RF energy delivery was automatically changed between the three pairs of the three electrodes (Figure 2b). In CM and SM modes, RF power was manually increased to 200 W, and RF energy was applied consecutively or alternately to the electrode so that current flows from one electrode to the dispersive metallic pads. In SB mode, RF current flowed from one electrode to the other, and RF energy was applied alternately to the pair of electrodes.²⁴ The applied current, power output and impedance were continuously monitored by the generator during RFA and were recorded automatically using a computer program.

Assessment of coagulation necrosis

The 15 pigs were euthanized with intravenous pentobarbital 1 h after closing the incision of the abdominal wall on the day of the procedure, and immediately after sacrificing the animals, the liver was removed en block. Segments of the livers containing RF-induced coagulations were sliced perpendicular to the electrode tracks (transverse plane) at 5–7 mm intervals, and then the slices were cut in the longitudinal plane containing one of the three electrode tracks by one of the four authors. To assess cell viability, as indicated by mitochondrial enzyme activity, the specimens obtained were stained by incubating representative tissue sections for 30 min in 2% 2,3,5-triphenyl tetrazolium

chloride (TTC) (Sigma-Aldrich, St Louis, MO) at 20–25 °C,^{30,31} which was used to determine irreversible cellular injury during the early stages of RF-induced necrosis.¹⁹ In addition, after TTC staining, the slices were photographed using a digital camera (Canon EOS 300D; Canon Inc., Tokyo, Japan), and the images were saved to an image management software program (Photoshop®; Adobe®, San Jose, CA). All specimens containing the ablation lesions were independently examined in blinded fashion using NIH ImageJ (http://rsb.info.nih.gov) by two of the authors (JML and WSC, with >15 years' and >4 years' experience, respectively, in evaluating coagulation diameters). Using an electronic caliper, the observers measured the D_{\min} and the maximum diameter (D_{max}) of the central, white region of the RF-induced coagulation zones in slices showing the maximal coagulation diameter along the transverse plane. The vertical axis diameter $(D_{\rm v})$ along the electrode insertion axis was measured in the longitudinal plane. In addition, the effective volume of the ablation zone was determined as follows: $4/3\pi (D_{\min}/2)^{3.6}$ If it was central, white regions of the RF-induced coagulation zones around the electrodes were separated, then the diameters and volume of the largest region among the separated coagulation zones were calculated.

In order to analyse the shape of the ablation zone, the ablation lesions were evaluated by the isoperimetric ratio of each lesion in the most representative slice, using NIH ImageJ software.¹⁹ The closer the isoperimetric ratio to one, the more circular the lesion shape. In addition, to compare the configuration of the ablation zones in each group, the ratio of D_{\min}/D_{\max} was calculated. We also assessed whether the coagulation was confluent (round or oval shaped), partially confluent (clover or maple leaf shaped) or separated.³² The RFA zones of all cases were fixed in 10% formalin for routine histological processing and were finally processed by paraffin sectioning and haematoxylin–eosin staining.

Statistical analysis

The results of quantitative measurements of ablation lesions and electrical parameters were reported as mean \pm standard deviations. The prevalence of round- or oval-shaped lesions in each group was also compared using the χ^2 test. Parameters were tested using the Kolmogorov–Smirnov test for normality: the dimensions, areas, volume and effective volume of the ablation zones in the three groups were compared using the one-way analysis of variance test followed by the *post hoc* Tukey–Kramer test for group-to-group comparison. For all statistical analyses, a *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using commercially available software (MedCalc; MedCalc Software, Ostend, Belgium).

RESULTS

Electrical measurement of the three modes

The mean impedance of each RF energy delivery mode in Groups A, B and C were 57.9 ± 7.2 , 62.7 ± 12.7 and $61.3 \pm 11.9 \Omega$, respectively, with no significant differences between the groups (p = 0.394, Table 1). The mean delivered RF energy for Group C ($76.8 \pm 14.3 \text{ kJ}$) was significantly less than that of Group A ($120.9 \pm 24.5 \text{ kJ}$) and Group B ($114.2 \pm 18.3 \text{ kJ}$; p < 0.001). In addition, the average delivered RF energy during

Figure 2. Diagrams showing the radiofrequency (RF) energy delivery protocol in switching monopolar (SM) mode and switching bipolar (SB) mode. (a) In SM mode, RF energy was applied to one of the three internally cooled wet (ICW) electrodes, and RF energy delivery was automatically changed among the three electrodes depending on impedance changes. (b) In SB mode, RF energy was applied to a pair of the three ICW electrodes, and according to impedance changes, RF energy delivery was automatically changed between the three pairs of three electrodes. Note that there is no grounding pad in RF current circuitry. CH, change.



(a)



(b)

the procedure in Groups A, B and C were 84 ± 17 , 158.7 ± 25.4 and 106.68 ± 19.9 W, respectively (p < 0.001).

Analysis of the shape of ablation lesions

Groups B and C created 17 and 18 circular- or oval-shaped ablation lesions, respectively, whereas Group A created six circularor oval-shaped ablation lesions (Table 1). Groups B and C showed significantly larger numbers of confluent ablation lesions than did Group A (p = 0.003, Figure 3). In addition, three separated ablation lesions were observed in Group A, whereas none of the ablation lesions was separated in Groups B and C. On quantitative measurement, the mean ratio of $D_{\min}: D_{\max}$ of ablation lesions and the mean circularity (isometric ratio) were substantially higher in Groups B and C than in Group A (Table 1).

Quantitative measurement of the size of coagulation necroses

RFA in SB mode for 12 min using three ICW electrodes in Group C created significantly larger effective ablation volume than those created with CM ablation for 24 min in Group A (72.8 \pm 36.4 *vs* 39.0 \pm 27.7, respectively, *p* = 0.002, Figure 4). At the slice showing the largest ablation zone, the mean *D*_{min} and the mean

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Table 1. Measured values of technical parameters and shapes of coagulation necrosis according to radiofrequency power application modes

ŝ , , *D*_{max}, maximum diameter of the ablatic Values are mean ± standard deviation.

 $^{a}p\text{-values}$ indicate the statistical difference among Groups A–C. $^{b}\chi^{2}$ test results indicating the difference between the three groups.

Figure 3. Graph showing the distribution of coagulation necrosis shapes in the three groups according to the radiofrequency (RF) energy delivery mode. The *x*-axis indicates different RF energy delivery modes, and the *y*-axis indicates the number of RF ablation zones. Ablation zones were categorized into three shapes: round or oval shaped; partially confluent (clover leaf or maple leaf shaped); and separated. CM, consecutive monopolar; RFA, radiofrequency ablation; SB, switching bipolar; SM, switching monopolar.



areas of coagulations in Group C were substantially larger than those of Groups A and B (Table 2). However, there were no significant differences in effective ablation volume between Groups A and B (p = 0.49) and B and C (p = 0.062).

In addition, SB-RFAs had a significantly higher number of coagulations >5 cm in D_{min} than did CM- or SM-RFAs: 65% (13/20) in Group C, 20% (4/20) in Group A and 25% (5/20) in Group B (p = 0.03). In Group C, there were five lesions between 4 and 5 cm in D_{min} (25%, 5/20), and only two lesions between 3 and 4 cm in D_{min} (10%, 2/20).

DISCUSSION

Our study demonstrated that RFA in SB mode using three ICW electrodes was able to create coagulations >5 cm in 65%, and ablation zones >4 cm in 90% of cases within a relatively short duration (12 min) of energy application in perfused in vivo liver tissue. The mean D_{min} of ablation lesions created by SB-RFA was 5.1 cm, which is large enough to safely treat 3-cm-sized tumours. This fact has significant clinical implications including simplification of the RFA procedure, reduction in procedure time and improvement of the therapeutic results of RFA for hepatic malignancies. Our results surpass the results of a previous study that reported an ablation zone 3.2 cm in D_{min} using SM-RFA.^{20,33} Indeed, the bipolar mode has been shown to create larger, more regular coagulation necroses than do either monopolar simultaneous or alternating RFA methods. This is owing to its superior heat production efficiency at a given current level, since the current is confined between the tissue and the electrode.²⁵ In addition, ICW electrodes were used in our study instead of internally cooled electrodes. ICW electrodes are able to deliver a larger amount of RF energy to the tissue, as thermal and electrical conductance are improved by avoiding

Figure 4. Comparison of the radiofrequency (RF)-induced coagulations of the consecutive monopolar (CM), switching monopolar (SM) and switching bipolar (SB) groups. (a) Photograph of the cut surface of the coagulation created by CM-RF ablations demonstrates a 3.5×6.9 -cm-sized, confluent ablation zone with an irregular shape. Note that the size of each ablation zone along the three electrodes is relatively different. (b) Photograph of the cut surface of the coagulation created by SM-RF ablation demonstrates an oval-shaped, 4.5×5.3 -cm ablation area with an irregular margin. (c) Photograph of the cut surface of the coagulation area with a shaped, 6.1×6.5 -cm ablation area with a sharp margin. Note that the size of each ablation along the three electrodes is relatively be same.



(a)



(b)



(c)

Coagulation necrosis	Group A Consecutive mode RFA (n = 20)	Group B Switching monopolar RFA $(n = 20)$	Group C Switching bipolar RFA (n = 20)	<i>p</i> -value ^a	<i>p</i> -value A vs B	p-value A vs C	p-value B vs C
D_{\min} (cm)	3.9 ± 1.2	4.4 ± 1.0	5.1 ± 0.9	0.002	0.469	0.004	0.175
D_{\max} (cm)	5.8 ± 0.6	5.5 ± 0.8	5.9 ± 0.7	0.382	0.679	1.000	0.356
$D_{\rm v}~({\rm cm})$	4.6 ± 0.2	5.3 ± 0.4	5.5 ± 0.28	0.963	1.000	1.000	1.000
Area (cm ²)	21.2 ± 4.3	21.8 ± 5.3	25.1 ± 5.5	0.040	1.000	0.047	0.131
Effective volume (cm ³)	39.0 ± 27.7	50.2 ± 27.8	72.8 ± 36.4	0.004	0.768	0.003	0.073

Table 2. Measured values of the dimensions of coagulation necrosis according to radiofrequency (RF) power application modes

 D_{max} , maximum diameter of the ablation zone; D_{min} , minimum diameter of the ablation zone; D_{v} vertical diameter of the ablation zone; RFA, radiofrequency ablation.

Values are mean \pm standard deviation.

^ap-values indicate the statistical difference among Groups A-C.

tissue vaporization and charring using perfused saline in tissue.^{28,29,34} ICW electrodes are also helpful in avoiding tissue dehydration and charring, which have been more commonly reported with the bipolar mode.³⁵ Considering that there is a huge clinical demand regarding ablation devices that can allow the creation of larger zones of coagulation coupled with the need to secure an adequate "ablation margin",¹³ our SB-RFA system using triple ICW electrodes represents a potential advance in imaging-guided tissue coagulation, providing the ability to perform RFA in tumours >2 cm within a single application, with reduced treatment time, anaesthetic risk and treatment cost.^{22,36,37}

Our study also demonstrated that RFA in the SB mode with electrodes spaced 2.5 cm apart for 12 min was superior to the CM-RF mode in creating more round- or oval-shaped coagulation areas. Although reports of coagulation zones much >5.0 cm created primarily by CM-RFA using cluster electrodes combined with saturated saline infusion have been published,³⁸ the shape of the lesions was quite irregular. Previous studies using perfused electrodes demonstrated that irregularly shaped areas of coagulation have been observed at RFA and simultaneous saline injection, attributing to non-uniform saline distribution.³⁹ Given that most tumours treatable with RFA are spherical, the shape of the ablation area should also approximate a sphere, in order to create a sufficient ablative margin while minimizing the destruction of normal surrounding tissue.¹⁷ We believe that the reason why SB-RFA created a coagulation zone more spherical and confluent in shape as well as with a larger size than the standard CM- or SM-RFA technique can be explained by the better thermal efficiency of the SB mode,²⁵ and that this feature can help reduce recurrence following ablation therapy.

Despite of the fact that RFA using three ICW electrodes in the SB mode was able to create coagulations >5 cm in short-axis diameter in 65% of procedures, there are several technical considerations to think over prior to applying this technology for the treatment of liver malignancies percutaneously. First, since large-scale ablations may be associated with a greater risk of thermal injury to adjacent structures and have larger variability in coagulation diameters, further investigation regarding accurate

titration on interprobe distance, duration and power may be necessary to avoid unnecessary injury to adjacent normal tissue, as well as to better determine the predictability of coagulation size in the liver.^{22,25} Second, theoretically, RFA using three ICW electrodes in the SB mode has an increasing risk of bleeding and other injuries related to multiple-electrode insertions.³⁷ However, during our *in vivo* experiments, we did not observe severe bleeding from the electrode insertion sites. Last, the complexity of the SB-RFA procedure could be higher than that of CM-RFA with multitine electrodes. Based on our experience, however, although placing three probes into the index tumour under ultrasound guidance can make the RFA procedure difficult, it is only minimally more complicated for clinicians experienced in ultrasoundguided procedures than the insertion of a single probe.²²

Our study has several limitations to consider. First, this study established the initial feasibility of RFA in the SB mode using three ICW electrodes and a multichannel RF system, using the intraoperative approach. Thus, we may not be able to properly assess the risks of using the percutaneous approach, as we were able to avoid unwanted thermal injury by positioning electrodes away from adjacent tissue using the intraoperative approach. However, multiple electrodes are frequently used for imageguided percutaneous RFA in routine clinical practice.^{22,36,40,41} Second, in 35% (7/20) of cases, SB-RFA with three ICW electrodes failed to create coagulations >5 cm in diameter in a clinically acceptable time frame. Although we believe that the improved efficiency of SB-RFA in creating large ablation zones could be valuable for the treatment of large tumours and for decreasing local recurrence, further improvement in reproducibility in creating ablations >5 cm is warranted. Third, we did not compare SB-RFA using multiple electrodes with microwave ablations with multiple antennas. However, RF systems have been shown to provide better cost effectiveness, and it is also more widely available than microwave ablations.¹⁸ Further comparison between our RF device and microwave devices may be warranted. Last, RFAs were carried out in normal porcine livers, and therefore, the thermal efficiency of the current RF system in this study may not be translated into real clinical practice owing to the different tissue texture of target tumours. Despite these shortcomings, as far as we know, pig livers may be the best *in vivo* model to provide a reliable basis for testing the efficacy of RFA devices.

In conclusion, our results demonstrated that SB-RFA using multiple ICW electrodes can achieve coagulations >5 cm in diameter with better efficiency than SM- or CM-RFA in a relatively short time frame in 65% of cases. In addition, we believe that this technology may ultimately result in more effective

treatment of hepatic tumours 3–4 cm in diameter by reducing the treatment time and enabling more confident destruction of the entire tumour as well as the creation of a sufficient safety margin.

FUNDING

This study received technical support and research grant from RF Medical (Seoul, Republic of Korea).

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