

Switching Monopolar No-Touch Radiofrequency Ablation Using Octopus Electrodes for Small Hepatocellular Carcinoma: A Randomized Clinical Trial

Sae-Jin Park^a Eun Ju Cho^c Jeong-Hoon Lee^c Su Jong Yu^c Yoon Jun Kim^c
Jung-Hwan Yoon^c Hyo-Jin Kang^a Jeong Hee Yoon^{a, b} Dong Ho Lee^{a, b}
Se Hyung Kim^{a, b, d} Jae Young Lee^{a, b} Jeong Min Lee^{a, b, d}

^aDepartment of Radiology, Seoul National University Hospital, Seoul, Republic of Korea; ^bDepartment of Radiology, Seoul National University College of Medicine, Seoul, Republic of Korea; ^cDepartment of Internal Medicine and Liver Research Institute, College of Medicine, Seoul National University, Seoul, Republic of Korea; ^dInstitute of Radiation Medicine, Seoul National University Medical Research Center, Seoul, Republic of Korea

Key Results

- A sufficient ablative margin was more frequently achieved in the no-touch RFA group (57/60 = 95%) than in the conventional RFA group (50/64 = 78.1%) on immediate follow-up CT ($p = 0.02$, 95% CI = 0.02–0.26).
- The cumulative incidence of local tumor progression in the no-touch RFA group was significantly lower than that in the conventional RFA group ($p = 0.02$, HR = 3.95, 95% CI = 1.2–12.9).
- In the Cox regression model, conventional RFA was the predictive factor for local tumor progression ($p = 0.04$, HR = 4.95, 95% CI = 1.1–23).

Keywords

Hepatocellular carcinoma · Radiofrequency ablation · Local tumor progression

Abstract

Introduction: A switching monopolar no-touch radiofrequency ablation (RFA) technique is used for small hepatocellular carcinoma (HCC); however, there have not been any randomized clinical trials comparing this technique to the conventional RFA technique. **Objective:** This study aims to compare the results of two RFA techniques, and to comparatively identify more effective methods to reduce the pro-

gression of local tumors associated with small HCC (≤ 2.5 cm). **Methods:** This prospective randomized clinical trial (NCT03375281) recruited a total of 116 participants (M:F, 93:23; 68.3 ± 8.4 years) between October 2016 and September 2017. The primary outcome was the cumulative incidence of local tumor progression (LTP) after RFA. Secondary outcomes included technical success rate, technique efficacy, and RFA procedure characteristics. Kaplan-Meier analysis and the Cox proportional hazard regression model were used. **Results:** The mean follow-up period was 24.1 months. A sufficient ablative margin was more frequently achieved in the no-touch RFA group (57/60 = 95%) than in the conventional RFA group (50/64 = 78.1%) on immediate follow-up CT

($p = 0.01$). The cumulative incidence of LTP in the no-touch RFA group was significantly lower than that in the conventional RFA group ($p = 0.02$). In multivariable analysis, no-touch RFA was the only predictive factor for LTP ($p = 0.04$, hazard ratio = 0.2, 95% confidence interval = 0.04–0.94). **Conclusions:** A switching monopolar no-touch RFA technique is a favorable treatment option and provides lower LTP after RFA compared with conventional RFA for small HCC.

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Introduction

There has been a recent increase in the use of screening tests for high-risk groups of hepatocellular carcinoma (HCC), along with an increase in the proportion of small HCC [1]. Curative treatment options for small HCC include liver transplantation, hepatic resection, microwave ablation, and radiofrequency ablation (RFA) [2]. RFA is primarily used as a noninvasive local therapeutic modality for HCC, which is difficult to treat surgically [3].

RFA is performed by penetrating a tumor by inserting radiofrequency (RF) electrodes, using one or more RF electrodes depending on the size of the tumor and the desired ablation zone. It is suggested that inserting an electrode to concentrate high-frequency energy in the center of the tumor may enhance the therapeutic effect [4]. However, an important limitation of conventional RFA is that the local tumor progression (LTP) is more than 10% [5, 6]. Furthermore, it may spread the tumor along the insertion route of the electrode. In previous studies where RFA was performed, track seeding was observed in 0.2–0.5% of patients due to the dispersal of tumor cells [7, 8]. Also, there is a theoretical possibility that tumors may experience bubble production within the tumor due to temperature rise of the tissue near the electrode during thermal ablation, which subsequently increases the intratumoral interstitial pressure. Then, the increased interstitial pressure within the tumor during the ablation procedure may spread the tumor cells and increase the LTP [9–12].

Therefore, a method is needed to prevent such potential tumor spread without elevating the intratumoral interstitial pressure. Besides, if ablation can be performed without penetrating the tumor, it will fundamentally prevent the spread of the tumor along the electrode insertion route.

Consequently, the “no-touch” technique was introduced, avoiding the need for incisions into tumors during

surgery. In several retrospective studies, “no-touch” RFA (Nt-RFA) using multipolar RF technology showed a similar success and complication rate, and better LTP than conventional RFA using a monopolar RF technology [13–15]. Although one prospective cohort study compared conventional RFA with Nt-RFA, a different RF ablation system and different electrodes for each RFA technique were used [16]. Therefore, it is still uncertain whether the better therapeutic outcome originated from the different RF techniques (Nt-RFA vs. conventional tumor puncture technique) or the different hardware of RFA systems. Furthermore, to our knowledge, there have been no randomized clinical trials comparing Nt-RFA with conventional RFA using the same RFA system and electrodes.

Therefore, this study aimed to compare the results of conventional RFA and Nt-RFA using a switching monopolar RF technology and to evaluate which method is more effective in reducing the LTP prospectively.

Materials and Methods

This randomized clinical trial was performed from October 2016 to September 2017 in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of our institution (IRB No. 1604-137-758). This study was registered in ClinicalTrials.gov (<https://clinicaltrials.gov>, registration No.: NCT03375281). Financial support was provided by STARmed Corp. (No. 06-2016-2370).

Participants

Between October 2016 and September 2017, participants were recruited according to the following eligibility criteria: (a) age between 20 and 85 years, (b) Child-Pugh class A, (c) number of HCCs <3, (d) size ≤ 2.5 cm, (e) treatment-naïve HCC or newly developed HCC in participants who had had successful local tumor control for HCCs (within Milan criteria) by surgery, transarterial chemoembolization (TACE), RFA or percutaneous ethanol injection for at least more than 2 years, and (g) imaging within 60 days before RFA treatment. Based on our previous study [17] results showing that the minimum diameter of the ablation sphere created by switching monopolar RFA using the separable clustered electrodes (Octopus[®] electrode; STARmed, Goyang, Korea) was approximately 3.76 cm, we enrolled tumors smaller than 2.5 cm.

Exclusion criteria were as follows: (1) HCC abutting main hepatic veins or the first branches of the main portal vein (≥ 5 mm), (2) absence of a border under fusion image, (3) platelet count $\leq 50,000/\text{mm}^3$ or INR prolongation $\geq 50\%$, (4) presence of vascular invasion or extrahepatic metastasis.

The diagnosis of HCC was made based on the presence of risk factors and typical imaging appearance at CT or MRI according to the Liver Imaging Reporting and Data System [18]. We collected clinical information such as sex, age, origin of cirrhosis, and lab data. The shape of the HCC was classified as round, oval, or irregular according to the boundary of the tumor. The segmental

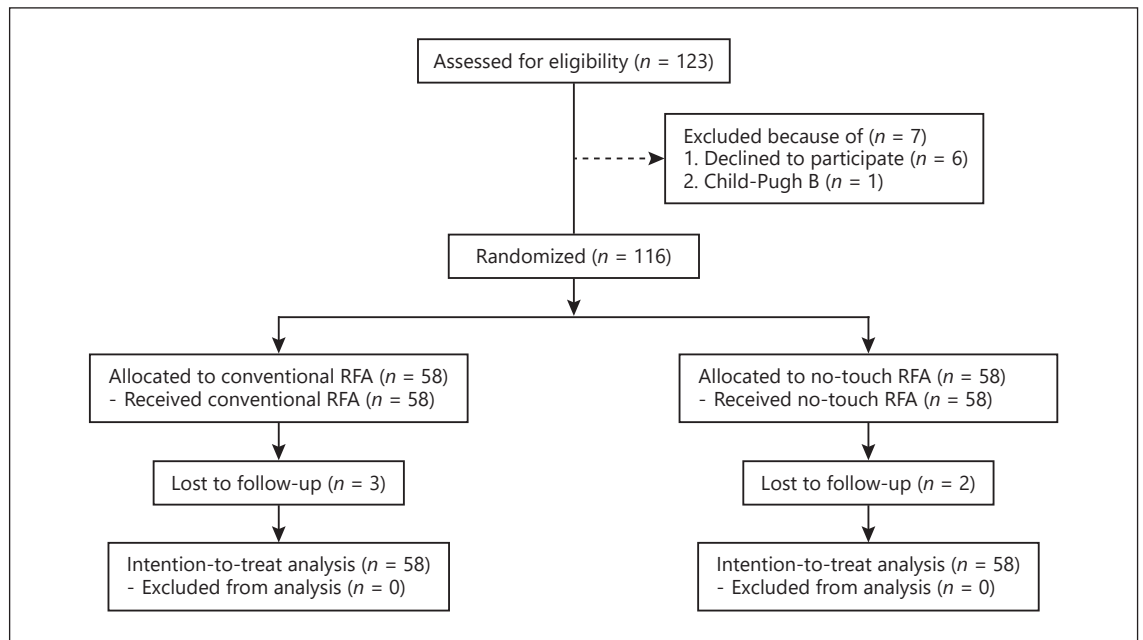


Fig. 1. Study diagram.

location of HCC was determined using the Couinaud classification [19]. Subcapsular HCC was defined as an index tumor located within 1 mm of the liver capsule [20]. Liver cirrhosis was diagnosed using the radiological diagnostic criteria (morphological criteria) using CT and/or MRI [2].

Enrollment and Assignment

All participants provided written informed consent before randomization. Participants who met the criteria and signed the consent forms were randomly assigned to two groups (the Nt-RFA and conventional RFA groups at a 1:1 ratio) by the stratified randomization and block randomization method beforehand, which was developed by the Medical Research Collaborating Center of our institution. This was determined by size (<2 cm or 2–2.5 cm), number (single or two), and type of HCC (naïve HCC or recurrent HCC). Group allocation was masked to the participants (Fig. 1).

RFA Procedures

The RFA system was a separable clustered electrode (Octopus® electrode; STARmed, Goyang, Korea) with 2 or 3 internally cooled electrodes, each with a 2- to 3-cm-long active tip (suppl. Appendix 1; see www.karger.com/doi/10.1159/000512338 for all online suppl. material) [21]. Percutaneous RFA procedures were conducted using real-time US-CT-MR fusion guidance (Navigator-GE & Siemens, Samsung, PercuNav-Phillips) with conscious sedation by one of four radiologists (D.H.L, S.H.K, J.Y.L, and J.M.L) who have 12–21 years of clinical experience in RFA [22]. Electrodes were placed using a free-hand technique. The goal of RFA was to achieve complete ablation of both the visible tumor and a 0.5- to 1-cm-wide ablation margin in the normal liver parenchyma surrounding the tumor [23]. We maintained each tip temperature below 25 °C by infusing normal saline solution at 0 °C into the lumen of each

electrode using a peristaltic pump (VIVA Pump; STARmed). Grounding was achieved by attaching 4 pads to the participant's back. We continuously monitored the technical parameters, such as power output, impedance, applied currents, and total delivered energy, and recorded them using VIVA Monitor Software V 1.0 (STARmed).

In the conventional RFA procedure, 2 or 3 electrodes were placed within the target tumor with approximately 10–15 mm interelectrode distance, ideally within the middle zone of the target tumor. One cycle of ablation was performed for approximately 8–10 min in tumors <2.5 cm, and if an optimal ablation margin was not achieved after the first cycle of ablation, additional cycle(s) of RFA were done followed by repositioning of the electrode(s), as appropriate [23]. The precise techniques of electrode insertion using the separable clustered electrode are described elsewhere [23, 24].

Nt-RFAs were performed as described by Seror et al. [13], which involved puncturing 3 electrodes into the tumor-free area adjacent to the lesion (Fig. 2), contrary to directly puncturing the tumor as in conventional RFA (Fig. 3). When the index tumor was located on the liver surface, best efforts were made to avoid direct puncture of the tumor by taking an oblique pathway to obtain a rim of nontumorous liver tissue while placing the electrode [25].

The number of electrodes and the geometric composition of their insertion depended on the tumor size in both Nt-RFAs and conventional RFAs (suppl. Appendix 2). In most cases, all 3 electrodes were used, and when the HCC with a size of less than 2 cm was treated in the conventional method, 1 or 2 electrodes were placed inside the HCC, and the remaining electrodes were placed in the surrounding parenchyma. In the RFA procedure, switching monopolar mode was used in both groups [26]. The switching monopolar mode is that switching between multiple electrodes oc-

Fig. 2. No-touch RFA of small tumor under fusion imaging guidance. A 60-year-old man with alcoholic liver cirrhosis, with a history of transarterial chemoembolization. On follow-up, there is still viable HCC in segment 5 (1.6 cm). **a** Arterial phase gadoxetic acid-enhanced MR image demonstrates 1.6-cm arterial enhancing nodular lesion in segment 5 of the liver (arrow). **b** Under fusion imaging guidance between real-time working US and reference hepatobiliary phase MR images, location of the index tumor is determined, and the electrode is inserted. **c** After RF energy delivery, an echo cloud of microbubbles is created and encompasses the index tumor. **d** Immediate follow-up contrast-enhanced portal venous phase transverse CT image displays complete ablation of the target tumor with a sufficient ablation margin.

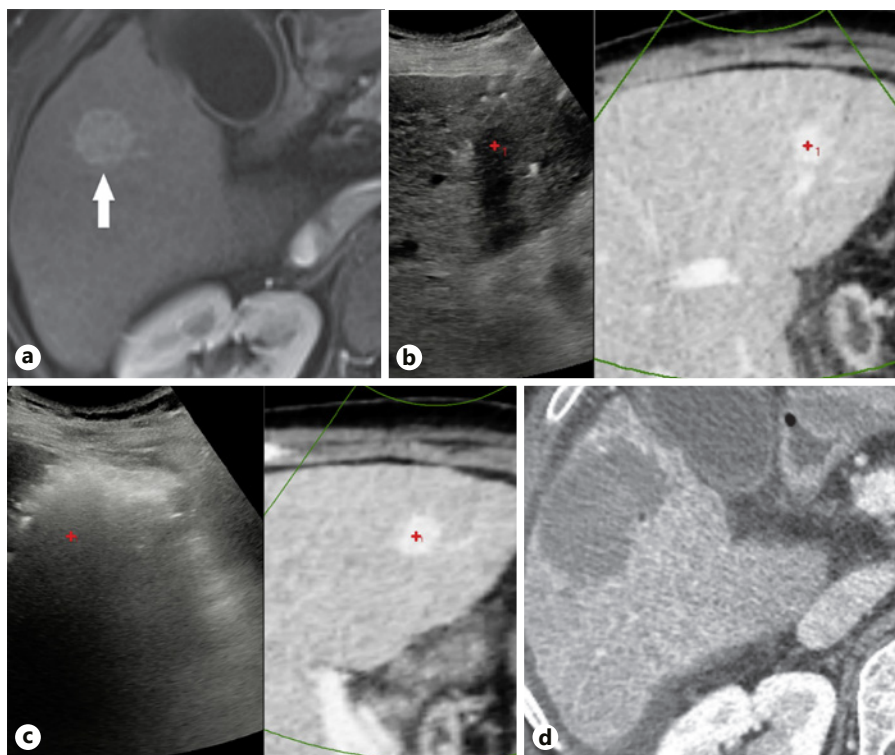
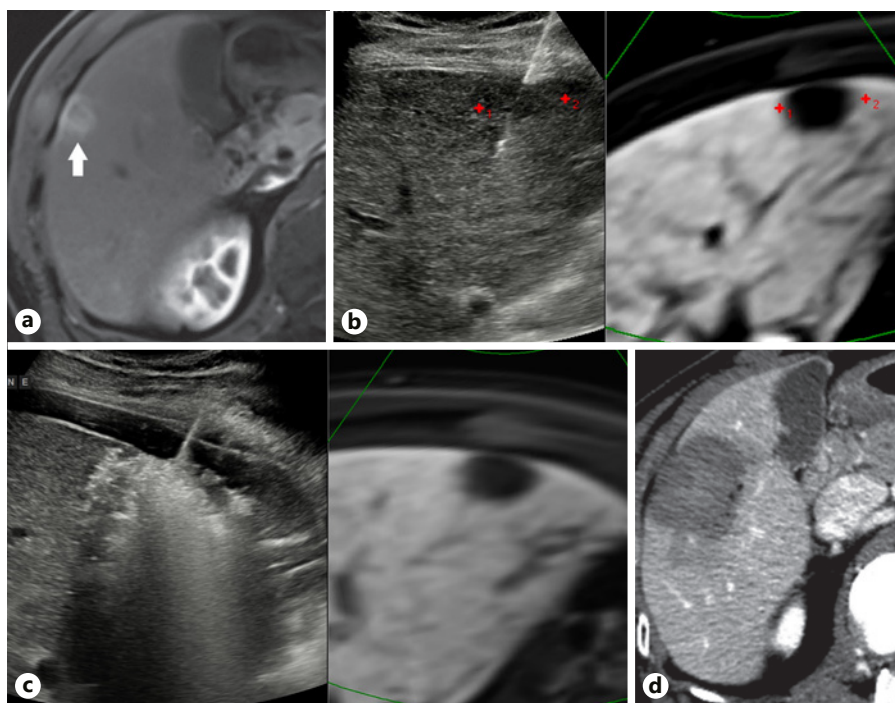


Fig. 3. Conventional RFA of small tumor under fusion imaging guidance. A 64-year-old man, a hepatitis B virus carrier, with a history of operation for HCC. On follow-up MRI, there is recurrent tumor in the segment 5 (2.4 cm) subcapsular portion. **a** Arterial phase gadoxetic acid-enhanced MR image demonstrates a 2.4-cm arterial enhancing nodular lesion in segment V of the liver (arrow). **b** Under fusion imaging guidance between real-time working US and reference hepatobiliary phase MR images, location of the index tumor is determined, and the electrode is inserted. **c** After RF energy delivery, an echo cloud of microbubbles is created and encompasses the index tumor. **d** Immediate follow-up contrast-enhanced portal venous phase transverse CT image displays complete ablation of the target tumor with a sufficient ablation margin.



curred according to impedance changes to transfer energy through other electrically independent electrodes using the power pulse algorithm [27]. Artificial ascites (5% dextrose water solution), used to ablate subcapsular tumors or tumors located near the diaphragm, were aspirated as much as possible after the procedures [23].

Follow-Up after Treatment

Participants with a complete response underwent imaging and measurement of serum α -fetoprotein every 3 months during the 1st year and every 3–6 months during the 2nd year [28].

Table 1. Demographics of participants (*n*, %) in two groups

Category	Total	No-touch RFA	Conventional RFA	<i>p</i> value
Sex				
Male	93 (80.2)	45 (77.6)	48 (82.8)	0.49
Female	23 (19.8)	13 (22.4)	10 (17.2)	
Age ^a , years	68.3±8.4	68.2±7.9	68.4±8.9	0.86
Origin of liver cirrhosis				0.43
Hepatitis B virus-related	92	46	46	
Hepatitis C virus-related	10	6	4	
Alcoholism	9	5	4	
NBNC	10	3	7	
Tumor number				0.15
One	108	56	52	
Two	8	2	6	
Previous treatment				0.31
TACE	80	41	39	
Operation	15	5	10	
RFA	34	13	21	
PEIT	8	4	4	
Tumor shape				0.71
Oval	85	43	42	
Round	31	13	18	
Irregular	8	4	4	
Type of tumor				0.65
Naive HCC	5	3	2	
Recurrent HCC	111	55	56	
Tumor segmental location				0.86
1, 2, 3, 4, 5, 6, 7, 8				
Tumor location				0.52
Subcapsular	17 (13.7)	7 (11.7)	10 (15.6)	
Central	107 (86.3)	53 (88.3)	54 (84.4)	
Tumor size ^a , cm	1.7±0.5	1.6±0.5	1.7±0.5	0.35
<2	76	39	37	
2–2.5	40	19	21	
Lab				
Total bilirubin ^a	0.7±0.4	0.6±0.4	0.8±0.4	0.78
Prothrombin time ^a	1.1±0.1	1±0.1	1.1±0.1	0.64
Albumin ^a	4±0.4	4±0.4	4±0.4	0.38
Platelets, <i>n</i> × 10 ³	135	135	136	0.88
Range	48–280	69–280	48–272	
AFP, ng/mL	91.9	15.4	168.4	0.2
Range	<1–6,840	<1–223.5	<1–6,840	
Follow-up period ^a , months	24.1±5.5	24.6±5.3	23.7±5.7	0.34

RFA, radiofrequency ablation; NBNC, hepatitis B surface antigen and hepatitis C antibody negative; TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; PEIT, percutaneous ethanol injection therapy; AFP, α-fetoprotein. ^a Mean ± SD.

Outcomes

The primary outcome was LTP, which was defined as the reappearance of HCC adjacent to the ablated zone after successful treatment. Secondary outcomes were technical success rate, technique efficacy, and RFA procedure characteristics. RFA procedure characteristics included total procedure time, ablation time, ablation volume, sufficient ablative margin, and complications. The ablation volume was determined using the following formula: $V =$

$4/3\pi \times r_x \times r_y \times r_z$ [29]. The term “sufficient ablative margin” was confirmed at the immediate follow-up CT and defined as 5 mm from the tumor margin.

Technical success was defined as full coverage of the index tumor with an ablative margin greater than or equal to 5 mm at immediate post-RFA CT [30]. Technique efficacy was defined as complete ablation of macroscopic tumor at 1-month follow-up CT or MRI.

Table 2. Procedure characteristics

Category	No-touch RFA	Conventional RFA	<i>p</i> value
Total procedure time ^a , min	47.4±28	45.2±13	0.59
Ablation time ^a , min	12.2±6.1	12.1±5.6	0.9
Ablation volume ^a , cm ³	50.3±31.6	56.2±32.4	0.32
Energy ^a , kcal	14.5±9.9	15.6±8	0.5
Hospital stay ^a , day	1.5±1	1.8±3	0.99
Sufficient safety margin ^b			0.01
Sufficient	57 (95%)	50 (78.1%)	
Insufficient	3	14	
Artificial ascites infusion	36 (62.1%)	38 (65.5%)	0.7
Complication	7 (12.1%)	6 (10.3%)	0.77
Ascites	6	6	
Pseudoaneurysm	1	0	
Bowel perforation	0	1	
Technical success	60 (100%)	64 (100%)	
Technique efficacy	59 (98.3%)	64 (100%)	0.3
RF mode			0.56
Switching monopolar	58	58	

RFA, radiofrequency ablation. Technical success was achieved in all patients. Two major complications of postprocedural pseudoaneurysm and bowel perforation occurred. ^a Mean ± SD. ^b Confirmed at immediate follow-up CT.

Statistical Analysis

The sample size was calculated using a reported cumulative incidence of LTP of 6–7% after Nt-RFA and 20–30% after conventional RFA [14, 31]. A total of 56 participants were required in each group to achieve a power of 80% and an α -level of 0.05 for a 2-sided statistically significant difference. We included 61–62 participants in each RFA group to allow an expected 10% dropout rate after randomization.

Intergroup demographic data, technical success, technique efficacy, and RFA procedure characteristics were analyzed by the Mann-Whitney test and by the Fisher exact test. Survival curves and cumulative incidence of LTP were generated by the Kaplan-Meier method and compared by the log-rank test. To determine the significant risk factors predicting LTP, we used Cox proportional hazards regression models and the Wald test.

All statistical tests were 2-sided, and the null hypothesis was rejected when $p < 0.05$. The statistical analyses were performed using MedCalc statistical software, version 19.1 (MedCalc Software, Mariakerke, Belgium).

Results

Demographic of Study Participants

Between October 2016 and September 2017, 123 participants were assessed for eligibility, of which 6 refused to participate and 1 did not meet the inclusion criteria before randomization. A total of 116 participants met the criteria and were randomly assigned to each group in a

1:1 ratio. In both the conventional and Nt-RFA groups, all participants received treatments as assigned. The study was completed on August 8, 2019. The mean follow-up period was 24.1 months. Three of 58 participants (5.2%) in the conventional RFA group and 2 of 58 participants (3.4%) in the Nt-RFA group were lost to follow-up (Fig. 1). The demographic data of the participants are presented in Table 1. There were 93 male participants. Among the etiology of liver cirrhosis, hepatitis B virus-related cases comprised the largest portion. There were 108 participants with one HCC and 8 participants with two HCCs. Eighty participants underwent TACE, and 34 participants underwent RFA as previous treatments. There were no target lesions due to LTP after TACE or RFA. Among the 80 participants who underwent TACE, 41 participants were enrolled in the Nt-RFA group. Five participants had naïve HCC. There were 76 HCCs under 2 cm, and 17 participants had subcapsular tumor locations. There was no significant difference between the two groups in the demographic data.

Procedure Characteristics

The procedure characteristics in the two groups are presented in Table 2. Technical success was achieved in all tumors. Technique efficacy was achieved in 59 (98.3%, Nt-RFA) and 64 (100%, conventional RFA) participants.

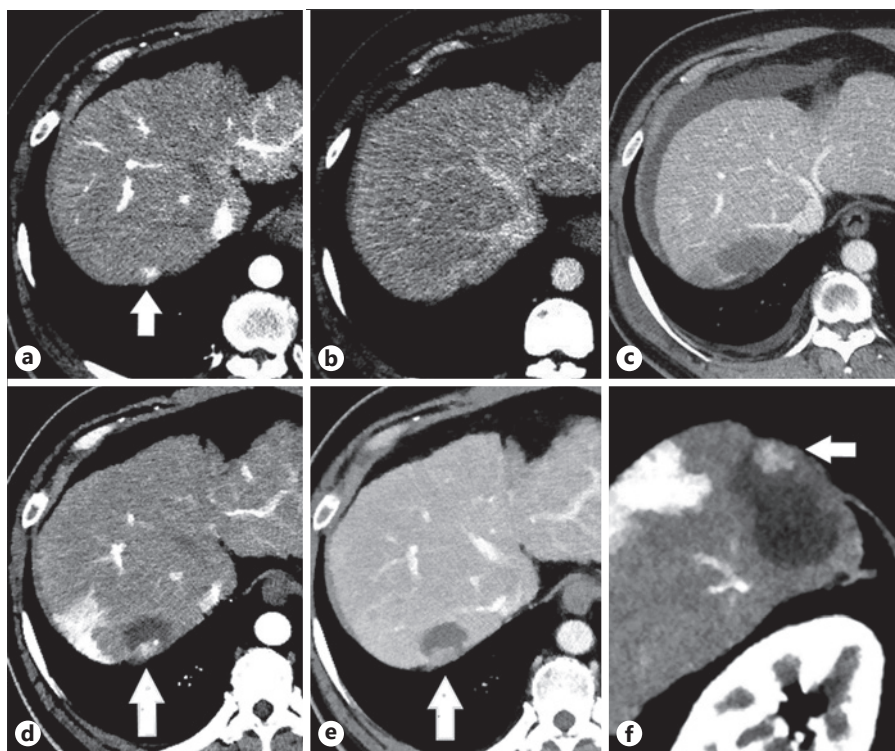


Fig. 4. Local tumor progression after conventional RFA. A 53-year-old man, a hepatitis B virus carrier, underwent conventional RFA for HCC in segment 7. On follow-up CT, there is HCC in segment 7 (arrows), at the margin of the treated lesion. After CT scan, he underwent additional TACE. **a** Arterial phase (before RFA). **b** Delay phase (before RFA). **c** Immediately after RFA. **d** Arterial phase (after RFA). **e** Portal phase (after RFA). **f** Coronal reconstruction image.

A sufficient ablative margin was achieved in 57 cases out of 60 (95%) in the Nt-RFA group and in 50 cases out of 64 (78.1%) in the conventional RFA group, indicating a statistically significant difference ($p = 0.01$).

Both groups did not demonstrate a significant difference in the total procedure time, ablation time, ablation volume, and complications. Thirteen participants demonstrated complications after RFA. In the Nt-RFA group, 7 participants reported complications, the major complication being pseudoaneurysm in 1 case. In conventional RFA, 6 cases were reported, with 1 case being bowel perforation. The intergroup complication rate was not significantly different ($p = 0.77$).

LTP between Conventional RFA and Nt-RFA

Two participants (3.4%) in the Nt-RFA group who achieved treatment success developed LTP (Fig. 4). In the conventional RFA group, 9 participants (15.5%) developed LTP. Of the 11 participants with LTP, 2 received RFA again and 9 received TACE.

The 1- and 2-year estimated cumulative incidences of LTP were 3.5 and 3.5% in the Nt-RFA group, and 8.9 and 13.5% in the conventional RFA group, respectively. The cumulative incidence of LTP in the Nt-RFA group was significantly lower than that in the conventional RFA

group ($p = 0.02$) (Fig. 5). Predictive factors for the development of LTP are summarized in Table 3. In the multivariable Cox regression analysis, only Nt-RFA was associated with a lower risk of LTP ($p = 0.04$, hazard ratio = 0.2, 95% confidence interval = 0.04–0.94).

Discussion

Our results demonstrated that Nt-RFA is more effective at controlling LTP than conventional RFA (2-year LTP rates: 3.5% in the Nt-RFA group and 13.5% in the conventional RFA group). The cumulative incidence of LTP was significantly lower in Nt-RFA, and conventional RFA was evaluated as a risk factor for LTP. Our study results were in good agreement with the results of the previous study by Seror et al. [13], which reported enhanced complete necrosis in Nt-RFA (26 out of 29, 89.6%) using a multibipolar approach compared with conventional RFA (14 out of 30, 46.6%). Similarly, another study by Kawamura et al. [32] also reported 2.9% LTP rates of Nt-RFA in comparison with 17.7% LTP rates of conventional RFA. The better results of Nt-RFA than conventional RFA in lowering LTP rates could be attributed to several technical advantages of Nt-RFA. First, Nt-RFA can first

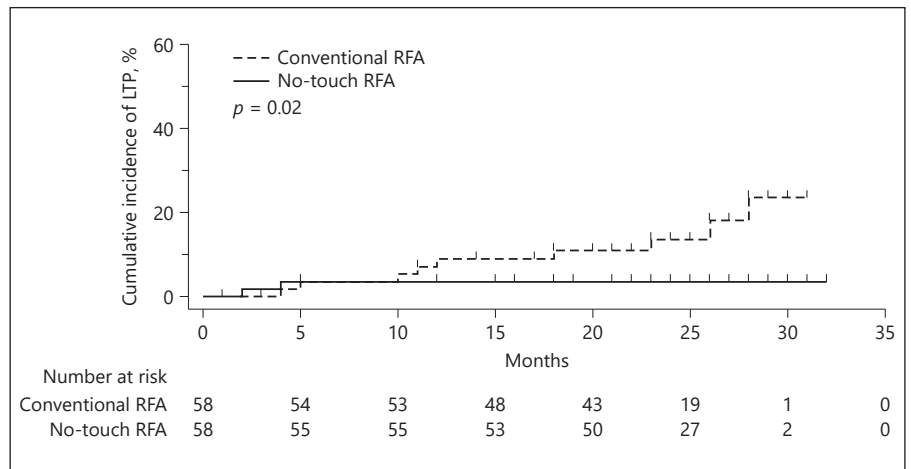


Fig. 5. Comparison of survival estimation and cumulative incidence of local tumor recurrence between the two groups.

induce vessel coagulation around the tumor, which may possibly result in less intratumoral pressure relative to conventional RFA [14] and lower tumor propagation. Second, Nt-RFA is known to improve the rate of complete necrosis resulting from a larger centripetal ablation volume, inducing sufficient ablative margins. As RFA was not the first-line treatment modality in our study population, we do not make a concrete conclusion whether the development of LTP significantly affected overall patient survival or not. However, according to a recent study by Lee et al. [33] which reported 10-year outcomes of RFA as first-line therapy for single HCC <3 cm, LTP was an important prognostic factor for overall survival after percutaneous RFA. So, even if the development of LTP may not significantly affect overall patient survival, we believe that the lower rate of LTP in the Nt-RFA group may contribute to lengthening the recurrence-free survival and lowering the need for additional interventional procedures to obtain a similar overall survival outcome [6].

There have been several studies comparing Nt-RFA and conventional RFA in the treatment of small HCCs showing that Nt-RFA has lower tumor recurrence than conventional RFA, which is consistent with our results [14–16, 34]. Most of these studies were retrospective, with that by Hirooka et al. [16] being a prospective cohort study. In our study, the estimated cumulative incidence of LTP was lower in the Nt-RFA group. LTP typically occurs early and is considered to be related to residual tumor cells in the peritumoral area that have spread microscopically beyond the ablative or resected margin. Therefore, LTP may be more significantly associated with the treatment methodology or result, or the local environment of the tumor such as contact with a vessel. As Nt-

RFA places probes at the surrounding liver parenchyma to the tumor margin without directly puncturing the tumor, there is a reduced risk of direct tumor implantation through the needle or bleeding from the tumor [11, 35, 36].

In addition, a sufficient ablative margin was more frequently made in Nt-RFA than in conventional RFA: 95% in the Nt-RFA group and 78.1% in the conventional RFA group ($p = 0.01$). Interestingly, however, there was no difference in the ablation volume between the two groups, possibly because the needle was moved several times to create a sufficient ablative margin during conventional RFA. Furthermore, with regard to total procedure time and ablation time, there were no significant intergroup differences. The superior results of Nt-RFA appeared to be consistent with the aforementioned principle of Nt-RFA. Moreover, recent advances in the fusion imaging technique have resulted in improved tumor visibility and technical feasibility when applied to Nt-RFA procedures [22]. This aided with RFA procedure monitoring, making the Nt-RFA technique easier to implement. Although a previous study by Shiina et al. [37] reported that conventional RFA using the multiple overlapping ablation technique with a single electrode provided an excellent LTP rate of 3.2% at 5- and 10-year follow-ups, these results seemed to be only possible by experienced operators in a high-volume center, and by repeated RFAs until creation of sufficient ablation including tumor and surrounding liver tissue during the hospitalization period. In fact, many other previous studies have reported a 10–30% recurrence rate after single-session RFA using the multiple overlapping technique [38–41]. The relatively higher recurrence rate of conventional RFA in many previous

studies could be related to the technical difficulty of precise placement of electrodes in an untreated area of the target tumor (overlapping ablation) in the presence of numerous microbubbles in the treated area following an earlier ablation session on ultrasound guidance [42].

Our study had several limitations. Firstly, our follow-up duration after RFA (mean 24.1 months) was short. However, since we aimed to evaluate LTP by comparing two techniques of RFA, there was no need for a long-term follow-up. Secondly, the effectiveness of RFA may depend on the operator's experience and skill. RFAs were performed by four radiologists in our study and the results may not be reproducible. This is a general limitation of many clinical studies. Thirdly, we used a switching monopolar mode as the RF energy delivery mode in our study. The previous studies have shown that the multibipolar mode produces centripetal energy, preventing the ablation zone from perfusion-mediated cooling, resulting in more focal heating between the electrodes and being less affected by the heat sink effect [14]. Moreover, according to our previous in vivo experimental study [26], the switching bipolar mode was more advantageous for Nt-RFA as it could create confluent necrosis more frequently and also had a better safety profile. Indeed, in our study, because the participants had small HCCs with a maximum diameter of 2.5 cm, a switching monopolar mode could be used. Further study is required to determine which RF energy delivery mode is better for improving tumor control rates using a "no-touch" ablation technique. Fourthly, most of the participants had prior HCC treatments. It can interfere with the result such as intrahepatic distant recurrence, recurrence-free survival, or overall survival. So, we focused on LTP to compare two techniques. Despite these limitations, this study is still meaningful given that it is a randomized prospective study.

In conclusion, a switching monopolar Nt-RFA is a favorable treatment modality and provides a lower LTP rate

compared with conventional RFA for small HCC. Therefore, it may contribute to lengthening the recurrence-free survival and also decrease the necessity of additional interventional procedures to obtain a similar overall survival outcome compared to conventional RFA.

Statement of Ethics

This randomized clinical trial was performed from October 2016 to September 2017 in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Participants have given their written informed consent, and the protocol was approved by the Institutional Review Board of our institution (IRB No. 1604-137-758).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

- Sae-Jin Park: data curation, formal analysis, investigation, software, writing original draft.
- Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon, Hyo-Jin Kang: data curation.
- Jeong Hee Yoon: data curation, writing review and editing.
- Dong Ho Lee: data curation, supervision, writing review and editing.
- Se Hyung Kim, Jae Young Lee: data curation.
- Jeong Min Lee: data curation, supervision, writing review and editing.

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