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No-Touch Radiofrequency Ablation Using Twin Cooled Wet Electrodes for Recurrent Hepatocellular Carcinoma Following Locoregional Treatments

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Objective: To evaluate the therapeutic outcomes of no-touch radiofrequency ablation (NT-RFA) using twin cooled wet (TCW) electrodes in patients experiencing recurrent hepatocellular carcinoma (HCC) after undergoing locoregional treatments.

Materials and Methods: We conducted a prospective, single-arm study of NT-RFA involving 102 patients, with a total of 112 recurrent HCCs (each ≤ 3 cm). NT-RFA with TCW electrodes was implemented under the guidance of ultrasonography (US)-MR/CT fusion imaging. If NT-RFA application proved technically challenging, conversion to conventional tumor puncture RFA was permitted. The primary metric for evaluation was the mid-term cumulative incidence of local tumor progression (LTP) observed post-RFA. Cumulative LTP rates were estimated using the Kaplan-Meier method. Multivariable Cox proportional hazard regression was used to explore factors associated with LTP. Considering conversion cases from NT-RFA to conventional RFA, intention-to-treat (ITT; including all patients) and per-protocol (PP; including patients not requiring conversion to conventional RFA alone) analyses were performed.

Results: Conversion from NT-RFA to conventional RFA was necessary for 24 (21.4%) out of 112 tumors. Successful treatment was noted in 111 (99.1%) out of them. No major complications were reported among the patients. According to ITT analysis, the estimated cumulative incidences of LTP were 1.9%, 6.0%, and 6.0% at 1, 2, and 3 years post-RFA, respectively. In PP analysis, the cumulative incidence of LTP was 0.0%, 1.3%, and 1.3% at 1, 2, and 3 years, respectively. The number of previous locoregional HCC treatments (adjusted hazard ratio [aHR], 1.265 per 1 treatment increase; P = 0.004), total bilirubin (aHR, 7.477 per 1 mg/dL increase; P = 0.012), and safety margin ≤ 5 mm (aHR, 9.029; P = 0.016) were independently associated with LTP in ITT analysis.

Conclusion: NT-RFA using TCW electrodes is a safe and effective treatment for recurrent HCC, with 6.0% (ITT analysis) and 1.3% (PP analysis) cumulative incidence of LTP at 2 and 3-year follow-ups.

Keywords: Hepatocellular carcinoma; Image guidance; Radiofrequency ablation; Local tumor progression

INTRODUCTION

Image-guided thermal ablation techniques, including radiofrequency ablation (RFA) and microwave ablation, are widely accepted curative treatment options for early-stage hepatocellular carcinoma (HCC) ≤ 3 cm in size and with

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up to three lesions [1,2]. Ablation is considered a viable alternative to surgical resection due to its comparable long-term survival and reduced morbidity, despite a higher rate of local tumor progression (LTP) [2-4]. However, a recent study identified LTP as an important prognostic factor for overall survival post-RFA [5], and also it can lead to the necessity for more interventions [6]. Therefore, optimizing ablation techniques to reduce LTP rates is critical for improving outcomes in patients with either de novo or recurrent HCCs.

No-touch (NT) RFA, using multi-bipolar electrodes [7,8], separable clustered electrodes [9,10], or twin cooled wet (TCW) electrodes [11] is a relatively novel technique designed to mitigate several drawbacks of conventional RFA in HCC management, including difficulties in creating sufficient safety margin (SM) around the tumor and the risk of track seeding or unwanted peritoneal seeding [12]. While NT-RFA has shown promise in addressing small naive HCCs, its application to recurrent HCC following locoregional treatments presents unique challenges. The varied tissue compositions within these recurrent tumors after locoregional treatments such as RFA or transarterial chemoembolization (TACE)—encompassing necrotic tissue, lipiodol, desiccated tissue, fibrosis, and sporadically distributed viable tumor cells—can compromise both electrical and thermal conductivity, thereby undermining effective ablation [13,14]. Notably, a lack of prospective studies specifically examining NT-RFA for recurrent HCC after locoregional treatments exist. Given the heterogeneous tissue compositions observed in recurrent HCC patients, there is an imperative to develop advanced methodologies that augment electrical and thermal conductivity, ensuring precise RF energy delivery to the targeted tumor sites [15]. Based on this rationale, we hypothesize that the integration of saline augmentation with TCW electrodes, and the synergistic use of bipolar and switching monopolar modes, could significantly enhance both electrical and thermal conductivity, thereby optimizing NT-RFA efficacy.

Therefore, this study aims to evaluate the mid-term cumulative incidence of LTP using NT-RFA with TCW electrodes in patients with recurrent HCC after locoregional treatments. Additionally, we will assess secondary outcomes, including RFA-related complications, and the estimated cumulative incidences of intrahepatic distant recurrence (IDR) and extrahepatic metastasis (EM).

MATERIALS AND METHODS

Compliance with Ethical Standards

This single-center, single-arm, prospective cohort study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1907-157-1050, ClinicalTrials.gov No. NCT05449860). All participants provided written informed consent for enrollment in the study. Financial support was provided by RF Medical (Seoul, South Korea). However, the authors maintained full control over patient recruitment, data collection, and analysis, ensuring an unbiased approach without any interference from the funding source. All study data are available for further scrutiny and can be obtained from the corresponding author upon request.

Study Design

This investigation was configured as a single-arm prospective study. Although the primary intent was to administer NT-RFA, a switch to conventional tumor puncture RFA was allowed in cases where NT-RFA was technically unfeasible.

Patients

Participant Recruitment

Before the study, participants were recruited according to the following eligibility/inclusion criteria: 1) age 20–85 years, 2) recurrent HCC after locoregional treatments (RFA or TACE) ≤ 3 cm in size or up to three HCCs ≤ 3 cm, and 3) Child-Pugh class A or B liver function. The exclusion criteria included: 1) untreated HCC, 2) invisible tumor on real-time ultrasonography (US)-MR/CT fusion imaging, 3) no safe access route, 4) tumors with macrovascular invasion and/or distant metastasis, 5) an interrupted RFA procedure due to poor patient cooperation, 6) RFA using single electrode, 7) presence of bleeding tendency defined as a platelet count < 50000 mm^3, or 8) prothrombin time international normalized ratio > 1.5. The size criteria were established based on a prior study that examined the ideal inter-electrode distance of NT-RFA using the TCW electrodes [11].

Recurrent HCC Diagnosis

Recurrent HCC was diagnosed based on the following criteria: 1) Liver Imaging Reporting and Data System (LI-RADS) treatment response (LR-TR) viable according to LI-RADS TR algorithm v2018: nodular, mass-like, or irregular

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thick tissue in or along the treated lesion with APHE, or washout, or enhancement similar to preablation [16], 2) LR-TR equivocal (indeterminate enhancement), accompanied by ancillary features favoring malignancy, such as restricted diffusion or mild-to-moderate T2 hyperintensity in the area of indeterminate enhancement [17].

RFA Procedures and Follow-Up

RFA Procedure

Percutaneous RFA procedures were conducted to implement NT-RFA under the guidance of a real-time US-CT-MR fusion (S-fusion; Samsung, Suwon, Korea). A seasoned radiologist, possessing 20 years of clinical experience in imaging-guided ablation, conducted the procedures with either a clinical body fellow or senior resident. If the tumor margin is not well delineated on real-time US CT-MR fusion, either SonoVue (Bracco, Milan, Italy) or Sonazoid (GE Healthcare, Milwaukee, WI, USA) was used to improve tumor localization [18]. When the tumor is situated in the subcapsular region without adequate peritumoral parenchyma, or when a safe electrode insertion pathway into the target tumor using the NT technique is unattainable under multimodality fusion imaging, we opted for conventional RFA over NT-RFA [9,12].

The RFA procedures were conducted using TCW electrodes (RF Medical), featuring two separable electrodes with perfusion holes on the active tips, in conjunction with a 200-watt multichannel generator. RF energy was delivered in the combined bipolar and monopolar modes for 8–12 minutes. Electrode active tip length was determined by the tumor size: electrodes with 2-cm active tips were chosen for tumors < 1.5 cm, while 2.5- or 3-cm active tips were used for tumors measuring 1.5–3.0 cm. As described in our previous study, the two tines of TCW electrodes were inserted into the perimeter of the index tumor (generally 3–5 mm from the tumor margin) at an inter-electrode distance of 2–3 cm under the guidance of fusion imaging [11]. The same RFA system and electrodes were utilized for both NT-RFA and conventional RFA groups in this study.

In both NT-RFA and conventional RFA groups, the ablation strategy for recurrent HCC differed based on prior treatment: for recurrences post-RFA, ablation was confined to the viable tumor portion alone; however, for recurrences following TACE, the approach involved whole-tumor ablation, encompassing both the viable tumor portion and previously treated areas, or areas with retained iodized oil, in alignment with the findings of previous multicenter studies [13]. Before initiating ablation, an electronic "virtual" target was placed on the recurrent tumor using real-time fusion US-MR/CT. During the ablation process, the formation of echogenic bubble clouds was continuously monitored. If the echogenic complex demonstrated a SM ≤ 5 mm around the electronic "virtual" target using real-time fusion US-MR/CT, the ablation was considered complete and subsequently terminated by the operator [19,20]. Otherwise, the electrode was repositioned to ensure an adequate SM [21]. An illustrativecase is shown in Figure 1.

Immediate Follow-Up CT

Following RFA procedures, immediate multiphasic liver protocol CT or MRI studies were conducted to assess post-procedural complications, complete tumor necrosis, ablation size, and technical success based on the reporting criteria suggested by the International Working Group on Image-guided Tumor Ablation [22]. Technical success of RFA was defined as complete coverage of the target tumor by the ablation zone achieved by RFA on immediate follow-up CT or MRI. Technical failure was defined as incomplete coverage, by using immediate follow-up imaging studies.

Furthermore, operators assessed their confidence in achieving a SM using a 4-point scale, based on pre- and post-procedure CT/MR image registration using nonrigid registration software (Hepacare: Siemens Healthineers, Erlangen, Germany), as previously detailed [23,24]: 1) residual viable tumor, 2) complete ablation but threatened SM creation < 2 mm, 3) complete ablation with borderline SM ≥ 2 and < 5 mm, and 4) complete ablation with sufficient SM ≥ 5 mm. If a residual tumor was detected, the ablation was repeated. However, for incomplete SM, the decision to redo the ablation depended on the patient's condition and the procedure's technical challenges, as judged by the operators.

Follow-Up Imaging

One month post-RFA, participants underwent follow-up imaging studies using either contrast-enhanced multiphasic liver CT or MRI. Additionally, measurements of serum α-fetoprotein levels and liver condition tests were performed. Technical efficacy was defined as complete coverage of the target tumor by the ablation zone assessed at 1-month follow-up imaging [22]. For participants with technical efficacy, follow-up liver CT or MRI was performed every 3 months until the end of the study (36 months

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maximum) to monitor for potential tumor recurrence (Fig. 1).

Tumor recurrence after RFA was further classified into three categories: LTP, IDR, and EM [22]. LTP was defined as the reappearance of enhancing tumor foci adjacent to the ablation zone after the achievement of treatment success. IDR was defined as the occurrence of HCC in the liver, excluding the ablation zone. When metastatic tumor foci were found outside of the liver, we considered them to be the appearance of EM.

Therapeutic Outcomes (End Points)

The primary endpoint of our study was the cumulative incidence of LTP, recorded from the date of RFA treatment to the first detection of LTP in whole study patients (ITT analysis) and in patients who received NT-RFA not requiring conversion to conventional RFA (PP analysis). Secondary endpoints included procedure time, major RFA-related complications, conversion rates from NT-RFA to conventional RFA with tumor puncture, technical success rate, technical efficacy rate, and cumulative incidence of IDR and EM.

Complication Assessment

Post-ablation complications were defined as problems noted within 1 month post-ablation as well as additional complications identified on follow-up imaging and judged to be likely caused by ablation. Post-ablation complications were graded according to the Clavien–Dindo classification by reviewing medical records and imaging studies [8]. Grade IIIa or higher complications were considered major complications, and the rest were considered minor.

Statistical Analysis

Technical success, technique efficacy, and LTP rates were assessed using per-nodule data, while demographic factors and technical parameters underwent statistical evaluation. For continuous variables, the independent *t*-test was employed, whereas categorical variables were compared using the chi-square test or, where suitable, Fisher's exact test. The Kaplan-Meier method was used to determine the cumulative incidence of various recurrence forms, including LTP, IDR, and EM. Factors associated with LTP were explored using the Cox proportional hazards regression analysis, with factors attaining a P-value < 0.1 in the univariable analysis progressing to multivariable evaluation. Significance was ascertained at a P-value < 0.05. All statistical analyses were conducted utilizing IBM SPSS Statistics (version 29.0; IBM Corp., Armonk, NY, USA) and MedCalc (version 22; MedCalc Software, Ostend, Belgium), with the methodology supported by our institution's Medical Research Collaborating Center.

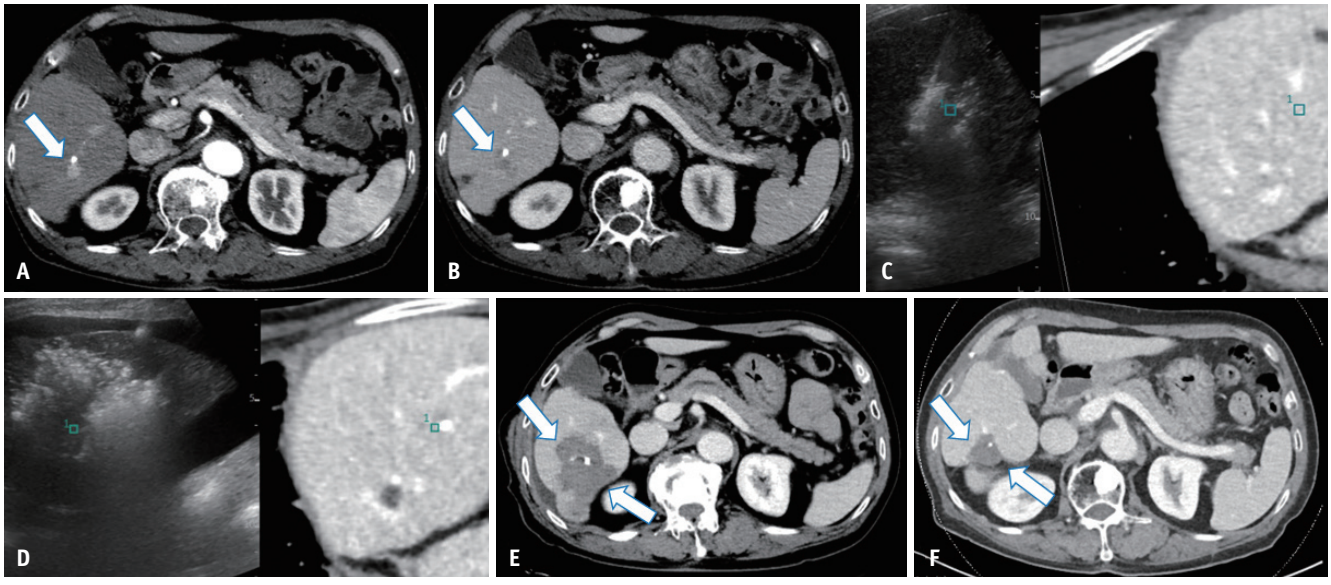

Fig. 1. Underlying hepatitis B virus-related liver cirrhosis patient with HCC. **A, B:** Contrast-enhanced CT imaging during arterial and portal phases revealed a 2 cm arterial enhancing nodule around the necrotic portion created by previous transarterial chemoembolization treatment on segment 6 of the liver, suggesting a recurrent HCC (arrows). **C:** Under real-time ultrasonography-CT fusion imaging guidance, a hypoechoic nodule was correlated to the arterial enhancing nodule. Two electrodes were inserted outside of the target tumor without tumor puncture with an inter-electrode distance of 2.5 cm. **D:** During the ablation procedure, the index tumor is covered by echogenic bubble clouds. **E:** On the portal phase of immediate follow-up CT, complete ablation of the target tumor with sufficient margin was shown to be achieved (arrows). **F:** On 36-month follow-up CT, there was no evidence of local tumor progression (arrows). HCC = hepatocellular carcinoma

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RESULTS

Participant Characteristics

Initially, 116 participants were screened for study enrollment between January 2020 and October 2021. Out of these, 14 patients were excluded for not meeting the inclusion criteria: more than 3 HCCs (n = 6), size > 3 cm (n = 1), low platelet (n = 1), poor visibility (n = 2), no safe access route (n = 1), RFA performed in a different region (n = 1), no use of TCW electrodes (n = 1), and interrupted RFA due to patient cooperation (n = 1). Consequently, 102 participants were ultimately enrolled in our study, with plans to undergo NT-RFA using TCW electrodes (Fig. 2). Before participating in this study, 32 participants had undergone RFA, 79 had received TACE, and one participant had been previously treated with both RFA and TACE for their target tumors. Table 1 provides an overview of the participants' baseline characteristics.

RFA Procedure Characteristics

Among the 102 study participants with 112 HCCs, NT-RFA using TCW electrodes was successfully performed in 88 HCCs in 79 patients, and conversion to conventional RFA was required in 24 HCCs in 23 patients (24/112, 21.4%) (Fig. 2). The transition to a conventional tumor puncture technique was necessitated by various factors, including insufficient peritumoral tissue for electrode placement (n = 10), perivascular tumors (n = 5), deep-seated lesions from entry (n = 4), unintentional and erroneous tumor puncture (n = 3), and inadequate sonic windows (n = 2). Therefore, the NT-RFA technical applicability rate was 78.6% (88/112). Artificial ascites were used in 85 patients (83.3%). The mean ablation time and mean procedure time were 8.18 ± 3.16 minutes and 45.1 ± 13.6 minutes, respectively. Detailed technical parameters of the participants group are summarized in Table 2.

Technical Success, Technical Efficacy, and Complications

One patient who had a conversion to conventional RFA due to a relatively poor sonic window showed technical failure on immediate follow-up CT. The patient received surgery later. Therefore, the technical success rate of RFA was achieved in 111 among the 112 ablation index tumors (99.1%, 111/112). An adequate SM > 5 mm around the tumor was created in 89 tumors (79.5%), and borderline SMs between 2 mm and 5 mm were obtained in 15 tumors (13.4%) (Table 2). No occurrences of major complications (Grade IIIa or higher) were observed. Also, on 1-month follow-up CT or MRI scan, all patients except the one participant who had treatment failure showed complete ablation of the index tumor, and therefore, technical efficacy was obtained in 111 index tumors (99.1%, 111/112)

Recurrence Outcomes after RFA

The median follow-up duration was 30.0 months (range:

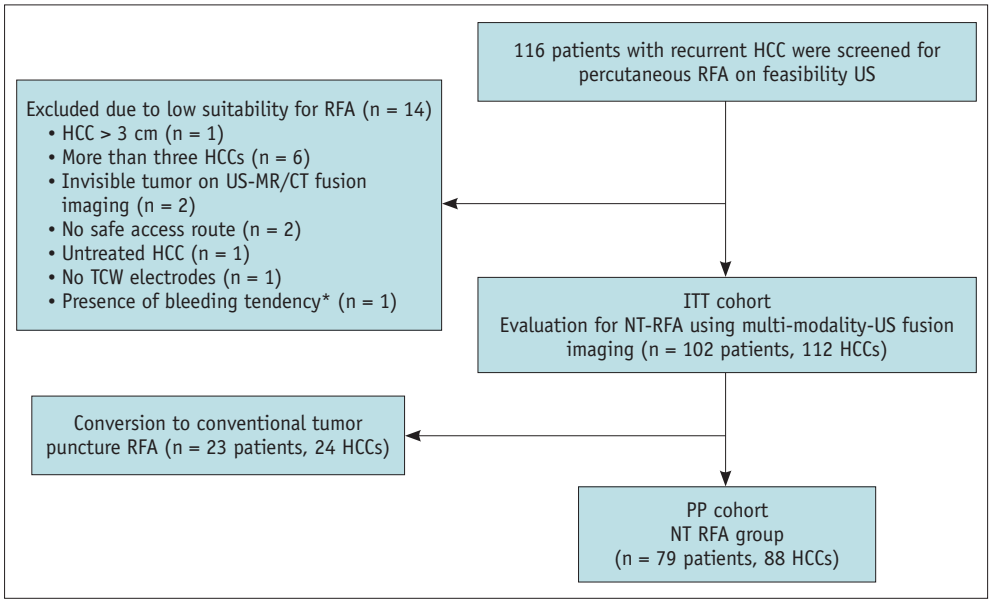

Fig. 2. Patient enrollment progress. *Presence of bleeding tendency was defined as a platelet count less than 50000 mm^3. HCC = hepatocellular carcinoma, RFA = radiofrequency ablation, US = ultrasonography, TCW = twin cooled wet, ITT = intention-to-treat, NT = no-touch, PP = per-protocol

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Table 1. Baseline characteristics of patients and tumors

Characteristic	Intention-to-treat analysis (102 patients with 112 HCCs)	Per-protocol analysis (79 patients with 88 HCCs)
Patient characteristics		
Age, yrs	69.3 ± 8.1	69.3 ± 8.3
Sex, M:F	78:24	59:20
Etiologic cause		
HBV	73 (71.6)	60 (75.9)
HCV	12 (11.8)	7 (8.9)
ALC	9 (8.8)	6 (7.6)
HBV and HCV	2 (2.0)	2 (2.5)
HBV and ALC	1 (1.0)	1 (1.3)
Others	5 (4.9)	3 (2.9)
Laboratory findings		
Albumin, g/dL	4.00 ± 0.51	4.01 ± 0.52
Total bilirubin, mg/dL	0.71 ± 0.44	0.68 ± 0.38
Prothrombin activity, INR	1.06 ± 0.09	1.06 ± 0.09
AFP, ng/mL	45.14 ± 166.18	48.55 ± 184.36
Platelet count, K/mm^3	117.99 ± 44.91	117.38 ± 46.40
Child-Pugh score A or B	102 (100)	79 (100)
Tumor characteristics		
Previous treatment for target tumors		
TACE	79 (70.5)	64 (72.7)
RFA	32 (28.6)	23 (26.1)
Both TACE and RFA	1 (0.9)	1 (1.1)
Number, single:two	92 (82.1):20 (17.9)	71 (80.7):17 (19.3)
Location, subcapsular:central	27 (24.1):85 (75.9)	18 (20.5):70 (79.5)
Tumor size, cm	1.55 ± 0.49	1.53 ± 0.48

Data are mean ± standard deviation or number of patients or tumors with percentage in parentheses.
HCC = hepatocellular carcinoma, HBV = hepatitis B virus, HCV = hepatitis C virus, ALC = alcoholic liver cirrhosis, INR = international normalized ratio, AFP = alpha fetoprotein, TACE = transarterial chemoembolization, RFA = radiofrequency ablation

Table 2. Technical prameters of RF ablation

Category	Intention-to-treat analysis (102 patients with 112 HCCs)	Per-protocol analysis (79 patients with 88 HCCs)
Hospital stay, day	1.2 ± 0.6	1.1 ± 0.5
Artificial ascites		
Yes	85 (83.3)	66
No	17 (16.7)	13
Ablation time, min	8.18 ± 3.16	8.28 ± 3.13
Procedure time, min	45.1 ± 13.6	45.5 ± 13.7
Mean delivered RF energy, kcal	12.9 ± 7.3	12.9 ± 7.0
SM assessed on immediate follow up CT scan		
Adequate (> 5 mm SM)	89 (78.8)	76 (86.4)
Borderline (2–5 mm SM)	15 (13.4)	8 (9.1)
Threatened (< 2 mm SM)	7 (6.3)	3 (3.4)
Incomplete necrosis	1 (0.9)	1 (1.1)
Diameter of ablation zone, mm	47.5 ± 12.9	48.0 ± 12.0

Data are mean ± standard deviation or number of patients or tumors with percentage in parentheses.
RF = radiofrequency, HCC = hepatocellular carcinoma, SM = safety margin

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3–36 months). Among the 111 tumors having complete necrosis on 1-month follow-up CT, six developed LTP, subsequently managed with repeated RFA or TACE. Therefore, according to ITT analysis, the estimated cumulative incidences of LTP in all participants were 1.9%, 6.0%, and 6.0% at 1, 2, and 3 years, respectively (Fig. 3A). The cumulative incidences of IDR at 1, 2, and 3 years were 45.9%, 57.9%, and 60.2%, respectively (Fig. 4A). Additionally, one patient experienced EM, resulting in a 2.2% cumulative incidence of EM at 3 years. According to PP analysis, the cumulative incidences of LTP in patients who received NT-RFA were 0.0%, 1.3%, and 1.3% at 1, 2, and 3 years, respectively (Fig. 3B). The cumulative incidences of IDR in them were 42.5% at 1 year and 53.7% at 2 and 3 years (Fig. 4B).

The results of LTP and IDR in patients who underwent conversion to conventional tumor puncture RFA during follow-up are detailed in the Supplementary Figure 1.

Risk Factors for LTP

In the ITT analysis, according to multivariable Cox regression analysis, the number of previous locoregional treatments for HCC, total bilirubin, and SM were independent predictive factors for LTP (Table 3). Previous locoregional treatments included RFA, TACE, percutaneous ethanol injection therapy, or transarterial radioembolization. Other factors also did not show statistical significance at the 5% level (Table 3).

The exploration of factors using Cox regression analysis was not possible in the PP analysis due to the presence of only one case of LTP.

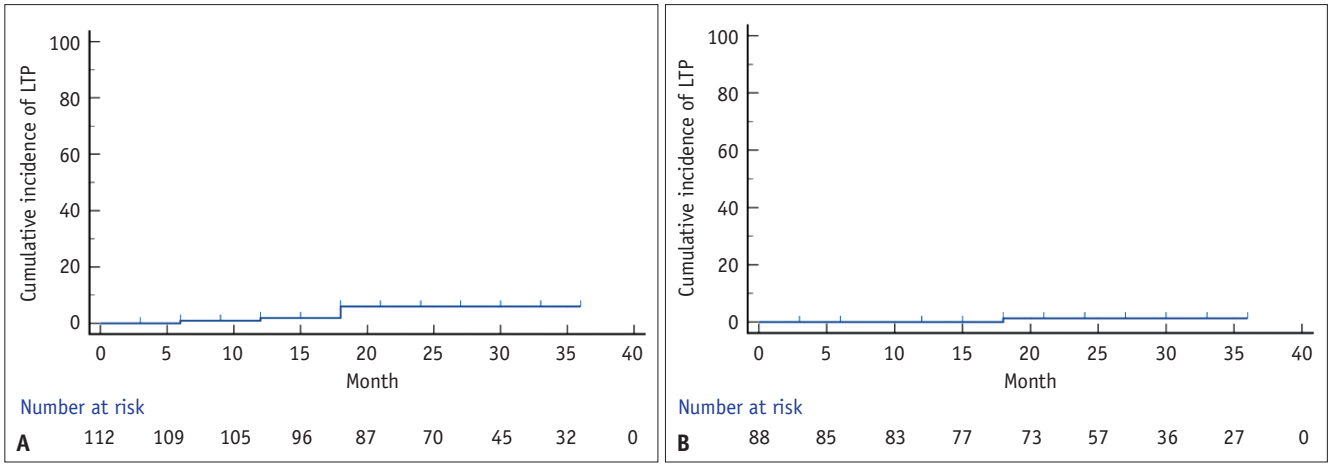

Fig. 3. Cumulative incidences of LTP according to **(A)** intention-to-treat analysis and **(B)** per-protocol analysis. LTP = local tumor progression

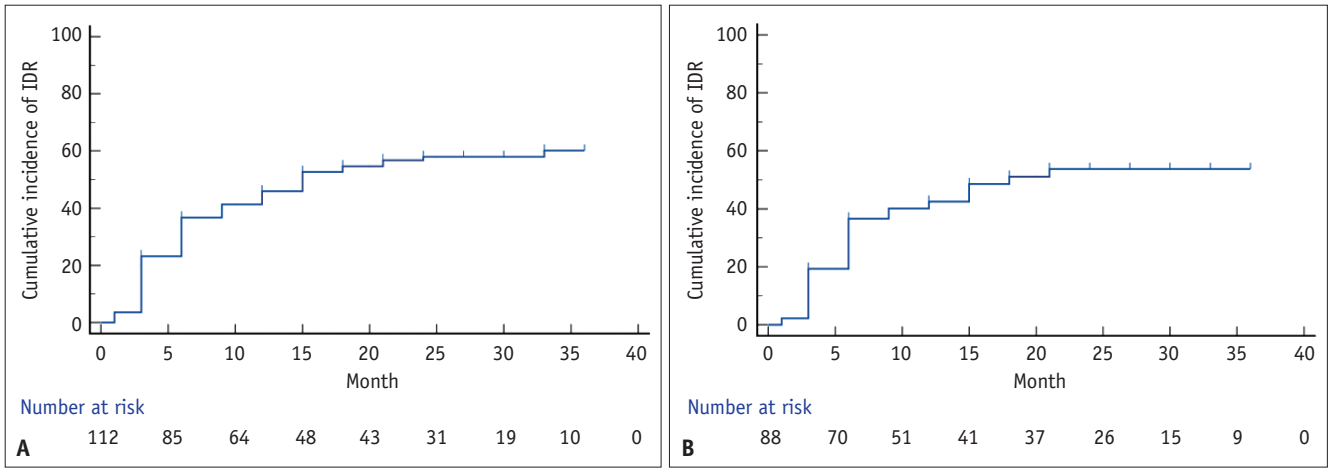

Fig. 4. Cumulative incidences of IDR according to **(A)** intention-to-treat analysis and **(B)** per-protocol analysis. IDR = intrahepatic distant recurrence

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Table 3. Univariable and multivariable Cox regression analysis of risk factors for local tumor progression according to ITT analysis

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	*P*	Adjusted hazard ratio	95% CI	*P*
Sex						
Female	Reference category					
Male	0.553	0.101–3.024	0.495			
Age, yr	01.08	0.97–1.20	0.157			
Tumor size, cm	0.175	0.02–1.66	0.129			
Tumor number						
One	Reference category					
Two	1.02	0.12–8.73	0.987			
Number of previous locoregional treatments for HCC	1.18	1.05–1.34	0.007	1.265	1.077–1.486	0.004
Previous treatment						
TACE	Reference category					
RFA	0.402	0.081–1.990	0.264			
TACE and RFA	NA	NA	0.993			
Tumor location						
Subcapsular	Reference category					
Central	0.16	0.03–0.85	0.031	0.348	0.046–2.627	0.306
Total bilirubin, mg/dL	3.53	1.31–9.54	0.013	7.479	1.551–36.073	0.012
Prothrombin activity, INR	263	0.32–2.16 x 10^5	0.103			
Albumin, g/dL	0.60	0.12–3.05	0.540			
Platelet count, K/mm^3	0.99	0.97–1.01	0.438			
Alpha fetoprotein, g/mL	1.00	0.99–1.01	0.887			
Ablation volume, mm^3	0.99	0.93–1.05	0.664			
Safety margin						
> 5 mm	Reference category					
≤ 5 mm	7.57	1.39–41.32	0.016	9.032		0.016

ITT = intention-to-treat, CI = confidence interval, HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, RFA = radiofrequency ablation, NA = not available, INR = international normalized ratio

DISCUSSION

Recurrent HCC presents a unique therapeutic challenge, given its tendency for recurrence even after locoregional treatments. The development of effective management strategies for recurrent HCC is critical for improving patient outcomes and survival rates. In this context, our study aimed to assess the viability and benefits of NT-RFA using TCW electrodes. Among the 112 index tumors, NT-RFA was successfully administered to 88 tumors, while 24 required conversions to conventional RFA (21.4%). Furthermore, the estimated cumulative incidences of LTP in all participants (ITT analysis) were 6.0% at 3 years. Notably, patients who received NT-RFA (PP analysis) exhibited a cumulative LTP rate of 1.3%. Moreover, on multivariable Cox regression analysis according to ITT analysis, the number of previous locoregional treatments for HCC, total bilirubin, and SM were identified as predictive factors for LTP.

Our study on NT-RFA demonstrated superior outcomes, with 2-year LTP rates lower than the 24.2% reported by Choi et al. [15] in their prior prospective study. This previous study, conducted at the same institute, employed conventional tumor puncture RFA with TCW electrodes for treating recurrent HCCs. In contrast to our results, a recent retrospective study by Park et al. [25], reported no significant difference in cumulative LTP when using either single or two internally cooled wet (ICW) electrodes between the conventional tumor puncture technique and NT-RFA technique. The differences between our study and the previous study [25] can be attributed to several factors. First, the study designs varied: ours was prospective, while theirs was retrospective, which adds to the strength of our study in terms of the robustness of data collection and analysis. Second, the previous study exhibited variations in

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the number of electrodes (one or two) and RF energy delivery modes (monopolar or bipolar), while our study consistently employed the same RF electrodes and a uniform RF energy delivery mode. Lastly, the previous study may have had a limited sample size for comparing the two techniques, with 34 patients in the conventional RFA group and 14 in the NT-RFA group using ICW electrodes. Thus, a direct comparison between our current study and their previous study may not be entirely justified. Based on our study results, we suggest that NT-RFA with TCW electrodes holds promise as a therapeutic option for recurrent HCC, showing favorable outcomes compared to previous studies, despite the challenges of direct comparisons.

Our findings from NT-RFA in patients with recurrent HCC after locoregional treatments align with previous studies focusing on NT-RFA for small, treatment-naive HCC, demonstrating consistent advantages of the technique [9-11]. The improved tumor control with NT-RFA using TCW electrodes can be attributed to early peritumoral vessel neutralization, expanded SM surrounding the tumor, and reduced intratumoral pressure [9-11,26]. Additionally, the synergistic combination of bipolar and switching monopolar modes contributes to optimal ablation zones compared with either monopolar or bipolar mode alone: the centripetal RF energy in bipolar mode effectively ablates inter-electrode tumors, while the centrifugal RF energy in monopolar mode fosters a protective margin around the tumor [12]. However, despite our study's excellent local tumor control rates and low complication rates, it is crucial to acknowledge potential drawbacks associated with this method. A potential concern is the increased technical complexity and possible complication risks, such as bleeding or damage to vital structures, related to multiple electrode insertions around the ablation index tumor [12]. For example, ideally, two electrodes should be placed parallel within a 2–3 cm distance in the peritumoral region to create a spherical ablation zone; however, achieving this in actual clinical practice can be challenging, especially under the guidance of ultrasound. Nevertheless, it's important to emphasize that NT-RFA may not be suitable for all target tumors.

In our study, we established a robust safety profile for the use of TCW electrodes in ablation treatments of recurrent HCC. We attribute a significant reduction in the risk of major complications, particularly in precise planning of the electrode insertion route, to the use of real-time US-CT-MR fusion imaging for guidance [19,27]. Additionally, our observations included an absence of major post-ablation complications that would necessitate extended hospital stays or further interventions. Notably, instances of track seeding or peritoneal seeding were also absent. These findings not only underscore the safety and efficacy of NT-RFA with TCW electrodes for treating recurrent HCC but also reinforce its potential as a preferred treatment option. Given the unique challenges presented by recurrent HCC, the use of NT-RFA with TCW electrodes emerges as a promising approach to enhance patient outcomes.

However, our study has certain limitations. Firstly, as a single-center, single-arm, prospective study with a relatively small sample size, there's a potential limitation in the generalizability of our results to broader populations. Secondly, the absence of a direct comparator group, specifically patients undergoing conventional RFA, limits our ability to conclusively establish the superior efficacy of NT-RFA using TCW electrodes. Nevertheless, our study demonstrated superior outcomes, with 2-year LTP rates falling below the 24.2% reported in a previous prospective study at the same institute that used conventional RFA with TCW electrodes [15]. Additionally, a prior randomized controlled trial at our center demonstrated that NT-RFA with TCW electrodes significantly reduced cumulative LTP rates compared to conventional RFA in smaller HCCs [11]. To further validate our findings, larger-scale studies, and randomized controlled trials are necessary.

In conclusion, our findings indicate that NT-RFA with TCW electrodes and combined RF delivery mode is an effective and safe treatment method for recurrent HCCs, providing 6.0% (ITT analysis) and 1.3% (PP analysis) cumulative incidence of LTP at 2- and 3-year follow-ups.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.1225.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jeong Min Lee, who hold respective positions on the Editorial Board Member of the *Korean Journal of Radiology*, were not involved in the editorial evaluation or decision to publish this article and reports grants from Philips

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Author Contributions

Conceptualization: Seong Jun Hong, Jae Hyun Kim, Jeong Hee Yoon, Jeong Hoan Park, Jung-Hwan Yoon, Yoon Jun Kim, Su Jong Yu, Eun Ju Cho. Data curation: Seong Jun Hong, Jae Hyun Kim. Formal analysis: Seong Jun Hong, Jae Hyun Kim. Funding acquisition: Jeong Min Lee. Investigation: Jeong Min Lee, Jae Hyun Kim. Methodology: Jeong Min Lee. Project administration: Jeong Min Lee, Jeong Hee Yoon. Resources: Jeong Min Lee. Supervision: Jeong Min Lee. Validation: Jeong Min Lee. Visualization: Jeong Min Lee. Writing—original draft: Seong Jun Hong, Jae Hyun Kim, Jeong Hee Yoon, Jeong Hoan Park. Writing—review & editing: Seong Jun Hong, Jae Hyun Kim, Jeong Hee Yoon, Jeong Hoan Park, Jung-Hwan Yoon, Yoon Jun Kim, Su Jong Yu, Eun Ju Cho.

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