의학박사 학위논문

식염수 분무형 갑상선 전극을 이용한 양성 갑상선 결절의 치료: 실험연구와 전향적 임상연구

Thyroid-dedicated Internally-Cooled Wet Electrode for Benign Thyroid Nodules: Experimental and Clinical Study

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이 논문을 의학박사 학위 논문으로 제출함

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국문요약

배 경: 이 연구는 체외 소의 간을 이용한 실험 연구를 통해 고주파 열치료 (radiofrequency ablation)에서 식염수 분무형 갑상선 전극 (internally-cooled wet electrode)이 응고 영역 (ablation zone)의 크기에 미치는 영향을 평가하고, 임상 연구를 통해 양성 갑상선 결절의 고주파 열치료에서 식염수 분무형 갑상선 전극의 적용 가능성을 평가 하고자 함에 있다.

방 법: 이 연구에서는 18 게이지 식염수 분무형 갑상선 전극을 개발 하였고, 식염수 분무형 갑상선 전극은 냉각된 (0 - 4℃) 등장성 식염수가 1.5 ml/분의 속도로 조직에 주입될 수 있도록 원위부 끝에 미세 구멍 (a microhole, 0.04 mm in diameter) 만들었다. 실험 연구에서는 체외 소의 간에 식염수 분무형 갑상선 전극과 내부 냉각형 전극 (internally cooled electrode)을 이용한 고주파 열치료를 시행하였다 (40 쌍, 1-cm active tip, 50 W, 1-분). 각각의 전극을 이용한 고주파 열치료 후 응고 영역 모양의 특징과 탄화 (carbonization) 유무를 비교하였다. 임상 연구에서는 전향적으로 등록된 5 ml 크기 이상의 양성 갑상선 결절을 가진 환자들을 대상으로 하였고, 모든 환자들은 식염수 분무형 갑상선 전극을 이용하여 초음파 유도하 고주파 열치료를 받았다. 치료 전, 치료 후 1 개월, 치료 후 6 개월에 초음파 검사, 증상 점수 (symptom score)와 미용 점수 (cosmetic score)를 분석하였다. 또한 치료 전과 치료 후 6 개월에 혈액검사(thyroid function [TSH, T3, T4], calcitonin, thyroglobulin, complete blood count, blood coagulation [prothrombin time and activated partial thromboplastin time])를 시행하고 분석하였다.

결 과: 실험 연구에서 식염수 분무형 갑상선 전극은 내부 냉각형 전극과 비교하여 유의하게 큰 응고 영역을 보였다 (auto-mode: 2189.0 ± 439.0 mm^3 vs. 891.7 ± 140.7 mm^3, $P < 0.001$; impedance-mode: 2425.9 ± 552.4 mm^3 vs. 886.3 ± 209.8 mm^3, $P < 0.001$). 임상 연구에서 모든 환자에게 식염수 분무형 갑상선 전극을 문제 없이 적용 할 수 있었다. 최종 추적 검사에서, 결절의 부피는 15.6 ± 12.1 ml 에서 4.1 ± 4.3 ml 로 감소하였고 ($P < 0.001$), 6 개월 추적 관찰에서 평균 부피 감소율은 73.3 ± 13.7%을 보였다. 미용 점수는 3.5 ± 1.0 에서 2.7 ± 0.9 로 감소하였고 ($P < 0.001$), 증상 점수는 3.1 ± 2.2 에서 0.9 ± 1.0 ($P < 0.001$) 로 감소하였다. 모든 환자에서 고주파 열치료 후 갑상선기능은 잘 유지되었다. 평균 티로글로불린 (thyroglobulin) 수치는 36.6 ± 52.1 ng/ml 에서 26.9 ± 62.2 ng/ml 로 감소하였다. 한 명의 환자가 치료 후 일시적인 목소리 쉼 현상을 보였고, 1 주일 이내로 저절로 호전을 보였다.

결 론: 실험 연구에서 응고 영역의 크기를 비교하였을 때 식염수 분무형 갑상선 전극은 내부 냉각형 전극보다 유의하게 큰 결과를 보였다. 임상 연구에서 식염수 분무형 갑상선 전극은 환자에게 적용 가능하였고, 양성 갑상선 결절의 치료에 효과적이었다.

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Introduction

Radiofrequency ablation (RFA) is used to treat benign thyroid nodules and thyroid cancers, with many studies reporting promising results, and several guidelines having been introduced [1-3]. For benign thyroid nodules, a conventional monopolar internally-cooled (IC) electrode is the standard device used; however, the small size of the ablation zone per unit time with such an electrode is less effective, especially in situation of relatively large benign thyroid nodule [4-6], and there is a need to increase the ablation volume per unit time in patients with large symptomatic benign thyroid nodules.

Several strategies have been proposed to solve this limitation, including saline injection before ablation, continuous infusion of saline through the electrode during ablation, bipolar RFA devices, and adjustable RFA electrodes [7-10]. Of these approaches, the continuous infusion of saline through the electrode can be an effective method because the injected saline can increase both electrical and thermal conductivity: NaCl alters tissue properties to permit greater RF energy deposition and the thermal conduction is improved within the tissues by more rapidly and effectively spreading heat by convection over a larger tissue volume. [9, 11]. Miao et al. reported that a cooled-wet electrode, which allowed simultaneous internal cooling perfusion and interstitial saline infusion with five side holes, was more efficient at creating large ablation zones in rabbit liver tumors than other monopolar electrodes [12].

It was firstly suggested in the liver that an internally-cooled wet (ICW) electrode makes a larger ablation zone than a conventional IC electrode. Therefore, we considered that ICW electrodes may be potential to be suitable for treating large benign thyroid nodules. Although ICW electrodes have been used for liver tumors [12-14], to the best of our knowledge, no studies have applied an ICW electrode to thyroid nodules. In addition, there are no suitable ICW devices for thyroid application.

Therefore, purpose of this study was to assess the effects on the ablation size of thyroid-

dedicated ICW electrode in *ex vivo* bovine liver and to evaluate the feasibility of an ICW electrode for treatment of benign thyroid nodules through a clinical trial.

Materials and Methods

The protocol for the experimental prospective clinical study was approved by the Ethics Committee of the Institutional Review Board of Asan medical center (Institutional Review Board number: 2019-0759). Written informed consent was obtained from all patients before RFA.

RF Devices

A thyroid-dedicated ICW electrode was developed by modifying an 18-gauge IC electrode. The 18-gauge ICW electrode had a microhole (0.04 mm in diameter) in the distal active tip area, allowing tissue infusion of (0 - 4℃) isotonic saline at a rate of 1.5 ml/minute (Figure 1). An 18-gauge IC electrode (RFTP-0710N; RF Medical) with a 1-cm active tip was used for comparison procedures.

The same 400 kHz generator (V-1000; RF Medical) and peristaltic pump (RFP-300; RF Medical) were used for both the ICW electrode and IC electrode. The peristaltic pump cooled the electrodes internally by delivering chilled (0 - 4℃) isotonic saline into the electrodes at a flow rate of 400 revolutions per minute.

Experimental Study

A series of RFA zones were induced in freshly excised bovine livers. The temperature of the bovine livers before ablation ranged from 23°C to 24°C, and they weighed approximately 7 kg each. The bovine livers were cut into 10 × 10 × 10 cm blocks and the 1-cm tip of the electrode was inserted into the liver blocks to a depth of 2 cm. An ablation time was 1 minute per electrode insertion, with the generator set to deliver 50 W of power using two ablation modes (auto and impedance) for a total of 80 bovine liver blocks (40 using IC electrodes and 40 using ICW electrodes). During ablation, the applied current, power output, and tissue impedance were recorded continuously using a computer program (Real Time Graphics Software version 1.2; RF Medical).

Liver blocks containing the RFA zones were dissected along the longitudinal plane passing through the axes of the electrode. As the white central area of the radiofrequency-induced ablation zone was previously shown to correspond with the zone of coagulation necrosis [15], two observers measured the maximum vertical diameter (D1) along the electrode and the transverse diameter (D2) perpendicular to it. The second transverse diameter of the ablation zone (D3) was measured in the perpendicular plane to the plane passing through the axes of the probe (Figure 2). The ablation zones were evaluated by calculating the lesion size as D1 × D2. The volumes of the ablation zones were calculated using the following equation: π (D1 × D2 × D3)/6. In auto-mode, number of cut-offs, which defined as shut down of power output to 0 automatically if the impedance was too high, were evaluated. In impedence-mode, number of lowering powers, which in proportion to the impedance increase rate, were evaluated. The formation of carbonization and the RFA parameters used were also evaluated.

Clinical Study

1) Patients

Between March 2020 and August 2020, 20 patients with benign thyroid nodules underwent US-guided RFA with the ICW electrode. The eligibility criteria for inclusion were as follows: (1) patients between the ages of 20 and 80 years; (2) benign cytology confirmed on evaluation of US-guided fine-needle aspiration or core needle biopsy; (3) a nodule volume larger than 5 ml. The exclusion criteria were as follows: (1) thyroid nodules with suspicious sonographic features; (2) abnormal thyroid function tests.

2) Pre-procedural Assessment

All patients underwent an US examination before RFA. An experienced radiologist (J.H.B., with 24 years of experience in neck US and 18 years of experience in thyroid RFA) conducted all US procedures and US-guided biopsies. The US system (RS 80, Samsung Medison Co., Ltd) was equipped with a high-frequency linear probe (5–14 MHz). Three orthogonal diameters (the largest diameter and two perpendicular diameters) were measured, and the volume of each nodule was calculated using the equation $V = \pi abc/6$, where V is the volume, a is the largest diameter, and b and c are the two perpendicular diameters. The nodule composition was graded into four categories on the basis of the proportion of the solid component: 1 solid, no obvious cystic content; 2 predominantly solid, cystic content ≤ 50%; 3 predominantly cystic, cystic content > 50%; and 4 cystic, no obvious solid content. Nodule vascularity was graded into four categories on the basis of a Doppler examination: grade 0, no intra-nodular vascularity; grade 1, peri-nodular vascularity only; grade 2, intra-nodular vascularity < 50%; and grade 3, intra-nodular vascularity > 50% [16].

Before RFA, a physician recorded a cosmetic score as follows [16]: 1, no palpable mass; 2, no cosmetic problem but a palpable mass; 3, cosmetic problem on swallowing only; and 4, readily and always detected cosmetic problem. Patient-determined symptom scores were rated using a visual analogue scale from 0 to 10 as baseline data.

Laboratory tests were also performed for thyroid function [thyroid stimulating hormone (TSH), triiodothyronine (T3), and free thyroxine (fT4)], calcitonin, thyroglobulin, complete blood count (CBC), and blood coagulation (prothrombin time and activated partial thromboplastin time).

3) Ablation Procedures

Each patient was placed in a supine position with the neck extended. After sterilization, vessels located along the approach route were identified, and 2% lidocaine was injected into the skin puncture and perithyroidal area. All procedures were performed by the same radiologist who evaluated the pre-procedural US images.

RFA was performed using an 18-gauge thyroid-dedicated ICW electrode with a 0.7 or 1.0 cm active tip (RFTSP-0710N; RF Medical). RFA was performed using the trans-isthmic approach and a moving-shot technique, with 30–90 W of radiofrequency power, depending on the size and characteristics of the target nodule and the active tip size. Ablation was terminated when the entire target lesion was covered with hyperechoic microbubbles.

Procedure-related pain was graded into four categories and recorded: grade 0, radiofrequency power did not have to be turned off because the patient experienced no pain; grade 1, radiofrequency power was turned off once or twice to reduce pain levels; grade 2, radiofrequency power was turned off more than three times; and grade 3, the procedure was incompletely terminated because of severe pain. [17, 18] Complications and side effects were defined according to the quality improvement guidelines of the Society of Interventional Radiology and a prior multicenter evaluation of complications [19, 20]. Each patient was monitored in the hospital for 1–2 hours after RFA.

4) Follow-up and Outcome Assessment

Follow-up US was performed at 1-month and 6-month after RFA, with changes in nodule size and volume being evaluated. Volume reduction was calculated as: volume reduction ratio (VRR) (%) = [(initial volume − final volume) 100]/initial volume. Therapeutic success was defined as a volume reduction > 50% of the initial nodule volume at the 6-month follow-up US examination [7]. The therapeutic success rate was defined as the percentage of successfully treated nodules [21]. Laboratory tests including thyroid function (TSH, T3, fT4) and thyroglobulin were assessed at 6-month follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 23.0 (SPSS, Chicago, IL). All p-values were two sided, and $P < 0.05$ was considered statistically significant.

1) Experimental study

The long-axis diameter, short-axis diameter, and calculated volumes of the RFA zones were reported as the mean ± standard deviation. The diameters, calculated volumes of the ablation zones, and the electrical parameters were compared using Student's *t*-test. The incidences of carbonization and power cut-offs in the experimental study were compared using Fischer's exact test.

2) Clinical study

The long-axis diameter, short-axis diameter, and calculated volumes of the ablated nodules were reported as the mean ± standard deviation. The diameters and calculated volumes of the ablated nodules in each follow-up exam were compared using Student's *t*-test.

Results

Experimental Study

The RFA parameters used in the experimental study are listed in **Table 1**. The incidences of cut-offs and lowering of power were significantly lower with the ICW electrode group than with the IC electrode group (cut-offs: 2/20 vs. 20/20, $P < 0.001$; lowering of power: 5/20 vs. 20/20, $P < 0.001$). Using the auto-mode, the true radiofrequency time (total ablation time – cut-off time) was significantly longer with the ICW electrode than with the IC electrode (58.6 ± 4.2 sec vs. 33.3 ± 3.4 sec, $P < 0.001$). As a consequence, the total delivered energy was much higher with the ICW electrode than with the IC electrode (2931.0 ± 212.4 J vs. 1664.2 ± 170.8 J, $P < 0.001$). The morphology of the ablation zone was elliptical in all specimens with both the IC and ICW electrodes. There were no carbonizations with either of the electrodes in either the auto-mode or impedance-mode.

After RFA, a well-defined area with a central white discoloration was observed. The mean long-axis diameter, short-axis diameter, vertical diameter, and calculated volumes for the ablation zones are summarized in **Table 2.** In the gross specimens, the mean long-axis, short-axis, and vertical diameters of the ablation zones in the ICW group were significantly larger than those in the IC group in both auto-mode and impedance-mode (all, $P < 0.001$). Therefore, the volumes of the ablation zones were also larger in the ICW group than in the IC group in both auto-mode and impedance-mode (auto-mode: 2189.0 ± 439.0 mm^3 vs 891.7 ± 140.7 mm^3, $P < 0.001$; impedance-mode: 2425.9 ± 552.4 mm^3 vs. 886.3 ± 209.8 mm^3, $P < 0.001$). With the impedance-mode, the volumes of the RF ablation zones were about 2.73 times larger in the ICW group than in the IC group.

Table 1. Radiofrequency ablation parameters used in the experimental study

Variable	Auto-mode[1]		**p-value**	Impedance-mode[2]		**p-value**
	IC (n = 20)	ICW (n = 20)		IC (n = 20)	ICW (n = 20)	
True RF time (s)[3]	33.3 ± 3.4	58.6 ± 4.2	< .001	60	60	
Number of cut-offs	20	2	< .001	-	-	
Lowering of power	-	-		20	5	< .001
Energy (J)	1664.2 ± 170.8	2931.0 ± 212.4	< .001	3000	3000	-

Note. IC, internally-cooled electrode; ICW, internally-cooled wet electrode.

[1]Auto-mode: power output was shut down to 0 automatically if the impedance was too high.

[2]Impedance-mode: power output was lowered in proportion to the impedance increase rate.

[3]True RF time = total ablation time – cut-off time.

Table 2. Radiofrequency ablation size and volume in the experimental study

Variable	Auto-mode		p-value	Impedance-mode		p-value
	IC (n = 20)	ICW (n = 20)		IC (n = 20)	ICW (n = 20)	
D1 (mm)	14.9 ± 1.0	18.6 ± 2.2	< 0.001	13.7 ± 1.4	18.4 ± 1.0	<0 .001
D2	10.4 ± 0.7	14.6 ± 1.2	< 0.001	11.0 ± 1.0	15.4 ± 1.7	< 0.001
D3 (vertical)	11.1 ± 0.9	15.3 ± 1.2	< 0.001	11.1 ± 1.0	16.2 ± 1.6	< 0.001
Volume (mm^3)	891.7 ± 140.7	2189.0 ± 439.0	< 0.001	886.3 ± 209.8	2425.9 ± 552.4	< 0.001

Note. IC, internally-cooled electrode; ICW, internally-cooled wet electrode.

Results are reported as mean ± standard deviation (%).

[1]Auto mode: power output was shut down to 0 automatically if the impedance was too high.

[2]Impedance mode: power output was lowered in proportion to the impedance increase rate.

Clinical Study

1) Patient Demographics and Clinical Characteristics

The baseline characteristics of the patients and their nodules are summarized in Table 3. The mean size and mean volume of the index nodule were 3.9 ± 1.1 cm and 15.6 ± 12.1 ml, respectively. All nodules were treated in a single session. The RFA parameters used in the clinical study are listed in Table 4.

The laboratory findings in the clinical study were as follows. The CBC and blood coagulation tests of all patients were normal at pretreatment evaluation. The initial mean TSH, fT_4, and T_3 were 2.1 ± 1.8 μU/mL (0.08–8.2), 1.3 ± 0.3 ng/dL (1.0–2.5), and 149.7 ± 23.0 ng/dL (116–202), respectively. The initial calcitonin and thyroglobulin were 2.1 ± 1.2 pg/ml (1.5–5.2) and 36.6 ± 52.1 ng/ml (1.5–233), respectively. In the initial laboratory test, eight patients had an elevated thyroglobulin level with a mean of 74.8 ± 67.4 ng/ml (range: 32.5–233). After RFA, thyroid function was well preserved in all patients, and the mean thyroglobulin level had significantly decreased to 26.9 ± 62.2 ng/ml at the 6-month follow-up ($P = 0.046$). Five out of the eight patients who had an initial elevated thyroglobulin level were normal on 6-month follow-up after RFA.

2) Treatment Outcomes in the Clinical Study

Table 5 shows changes in size and volume over time after treatment. After RFA, significant reductions in the mean volume of the ablated nodules were noted at 1- and 6-month follow-up ($P < 0.001$) (Figrue 3). After the procedures, both symptom and cosmetic scores showed significant decreases at 1- and 6-month follow-up (all $P < 0.001$).

Table 3. Baseline characteristics of patients and nodules included in the clinical study

Characteristics (n = 20)	
Age (years)	56.4 ± 13.2 (28–72)
Sex	
Male	4 (20%)
Female	16 (80%)
Nodule composition	
Solid	5 (25%)
Predominantly solid	14 (70%)
Predominantly cystic	1 (5%)
Nodule vascularity	
Grade 0	0
Grade 1	0
Grade 2	20 (100%)
Grade 3	0
Nodule diameter (cm)	3.9 ± 1.1 (2.4–6.6)
Nodule volume (ml)	15.6 ± 12.1 (5.4–49.3)

Results are reported as mean ± standard deviation (%).

Table 4. Radiofrequency ablation parameters used in the clinical study

		Clinical study (n = 20)
Active tip	0.7 cm	11
	1.0 cm	9
RF ablation time (s)		805 ± 405 (373–2130)
RF power (W)		54 ± 17.4 (30–90)
Total energy (J)		47654.8 ± 38539.7 (12000–170400)
Energy/ml (J/ml)		3508.2 ± 2030.1 (688.3–9380.0)

Table 5. Ultrasound features and cosmetic and symptom scores in patients before and after the procedures

	Baseline	1 month	6 months
Longest nodule diameter (cm)	3.9 ± 1.1	3.2 ± 0.9	2.4 ± 0.8
Nodule volume (ml)	15.6 ± 12.1	9.2 ± 8.1	4.1 ± 4.3
Volume reduction ratio (%)		42.2 ± 17.3	73.3 ±13.7
Cosmetic score (1–4)	3.5 ± 1.0	2.9 ± 0.6	2.7 ± 0.9
Symptom score (0–10)	3.1 ± 2.2	1.1 ± 0.9	0.9 ± 1.0
Pain during procedure (0–3)	1.0 ± 0.9		

Safety

Five patients who underwent RFA reported mild pain at the ablated site, or pain radiating to the head, ear, or shoulder during the procedure. However, the pain was reduced when the generator output was reduced or turned off during ablation. All patients tolerated the procedure. Transient voice change was observed in one patient, but the patient had recovered spontaneously after 1 week. No patient experienced a significant complication which needs hospitalization or delayed complication during the follow-up.

Discussion

In this study, we developed a thyroid-dedicated ICW electrode and tested it in an experimental and a prospective clinical study. In experimental study, we demonstrated that the thyroid-dedicated ICW electrode is effective in marking large ablation zone.

In terms of efficacy, the induced energy (J) delivered by the ICW electrode was higher than that delivered by the IC electrode in all experimental RF sessions. Therefore the ICW electrode created a larger ablation zone than the IC electrode. In addition, in the clinical study, thyroid-dedicated ICW electrode was technically feasible in treatment of benign thyroid nodule. RFA with ICW electrode was tolerated by all patients without any significant complication which needs hospitalization. We achieved a therapeutic success rate of 100% at 6-month follow-up with a mean volume reduction ratio of 73.3% ± 13.7%. To our knowledge, this study is the first clinical trial to evaluate the efficacy and feasibility of a thyroid-dedicated ICW electrode.

The effectiveness of the ICW electrode can be explained by the effect of the saline perfusion, which minimizes any rapid increase in impedance. The relatively small ablation size per unit time in the conventional monopolar RFA system is related to decreased current density, with a rate proportional to the inverse square of the distance from the electrode [4, 5]. That is because the resulting heating in the immediate vicinity of the electrode leads to rapid

charring and decreased current delivery. However, the ICW electrode overcomes these problems by infusing isotonic solution. The infused chilled (0 - 4℃) isotonic solution lowers the tissue temperature around the electrode and prevents charring at the electrode-tissue interface. Consequently, the ICW electrode allows a low impedance to be maintained during the procedure [9, 11].

The simplified "Bio-heat" equation describing RF induced heat transfer through tissue has been expressed by Goldberg et al.[22] as follows.

coagulation necrosis = energy deposited × local tissue interactions - heat loss

Infusion of isotonic saline can increase ablation volume by adjusting factors of 'local tissue interaction' or 'heat loss'; altering either local tissue characteristics of electrical conductivity or altering blood flow with use of adjuvants[11]. Another mechanism of increased ablation volume with isotonic saline is increased thermal conductivity; the injection of fluid improves the thermal conduction within the tissues by more rapidly and effectively spreading heat by convection over a larger tissue volume [11]. Also, the injection of isotonic solution with RFA make flattening of the heat distribution curve and permitting greater energy delivery with less tissue boiling [11].

Liver-dedicated ICW electrodes had multiple side holes with relatively proximal position. However, the position and number of the side holes of liver-dedicated ICW electrodes are not optimal for application to benign thyroid nodules with moving shot technique[10, 23]. During the moving shot technique, saline flowing from the proximal side holes flows to dependent portion by gravity, ablating an unexpected ablation zone. Therefore, we developed a thyroid-dedicated ICW with an effective design; one co-axial lumen, one distal microhole, and positioning of the microhole in the far distal tip portion. In thyroid RFA, the distal positioning of a microhole is important, as the moving-shot technique is the standard technique, and tissue coagulation starts at the distal portion of the electrode tip during the moving shot [24, 25].

In our *ex vivo* study, the thyroid-dedicated ICW electrode created a larger ablation zone than the IC electrode, and in our clinical study, we achieved a mean volume reduction ratio of 73.3 ± 13.7% at 6-month follow-up after a single-session of RFA. This result is similar or slightly superior to the 12 month results with a single procedure, reported in a recent systematic review (67% to 75% VRR)[26].

In all patients, thyroid function was well preserved after RFA. Among the eight patients who had an initially elevated serum thyroglobulin level, five had the level return to the normal range at 6-month follow-up. Additionally, the mean pretreatment serum thyroglobulin level was significantly lower at 6-month follow-up after RFA (36.6 ± 52.1 vs 24.8 ± 55.5, $P = 0.046$). In previous studies, a decrease in thyroglobulin level was attributed to reduction of tumor volume through RFA [27, 28].

Our study has several limitations. First, in the bovine liver experimental study, all the ablations involved normal liver parenchyma, not tumor tissue, and they were performed *ex vivo*. Greater variations in the ablation shape can be found *in vivo* because of the blood flow-related heat-sink effect, which results in rapid heat exchange. Second, increased ablation zone with thyroid-dedicated ICW electrode may increase the risk of complication, especially in case of the target nodule with narrow safety margin with important neck structures. In our study, all cases were performed by an experienced radiologist. Therefore, this thyroid-dedicated ICW electrode is applicable when the size of the nodule is large enough, and careful manipulation is needed when the RFA is done by physician with less expertise. Third, although we continuously measured the tissue temperature and monitored the impedance before and during RFA in each session, we did not set the electrical conditions to be similar to in *vivo* studies (e.g., by lowering tissue impedance by instilling saline before RFA). Consequently, it is unclear to what extent the results obtained in this study accurately represent the real situation. Forth, we only focused on comparing electrical parameters and ablation size between the two different electrodes; the optimization of the electrode profile,

including the saline infusion rate, should be validated in further studies. Lastly, although we achieved a VRR of more than 70% at 6 months after RFA, long-term follow-up results are necessary to evaluate the actual clinical impact of the ICW electrodes. Further studies with long-term follow-up are needed to validate the efficacy and feasibility of the thyroid-dedicated ICW electrode in clinical practice.

In conclusion, in the *ex vivo* study, the thyroid-dedicated ICW achieved significantly larger ablation zones than the IC. In the clinical study, the thyroid-dedicated ICW was feasible and effective in patients with benign thyroid nodules.

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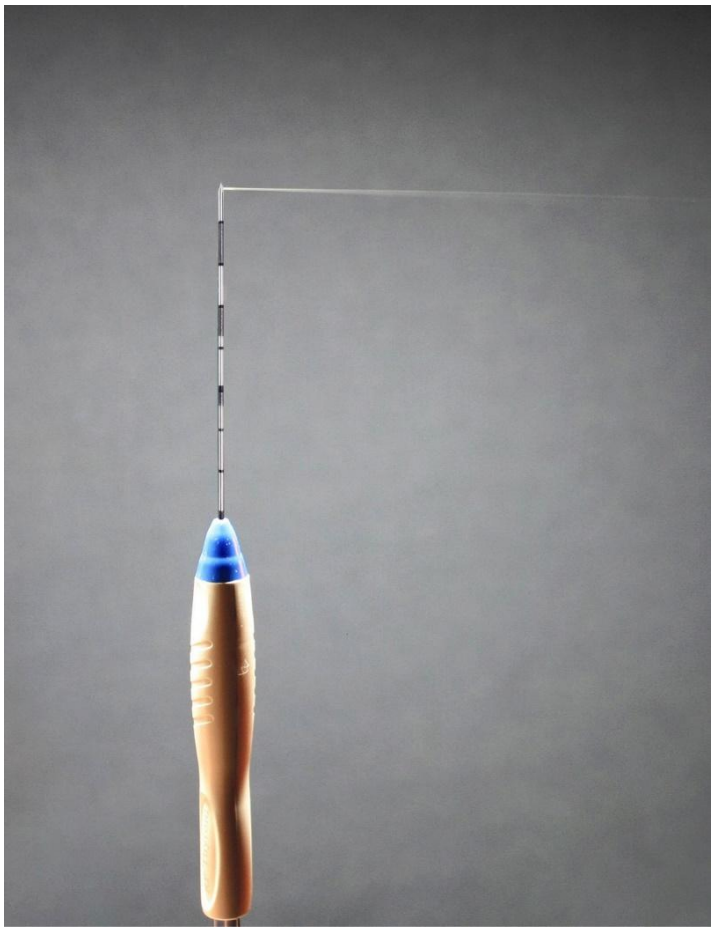
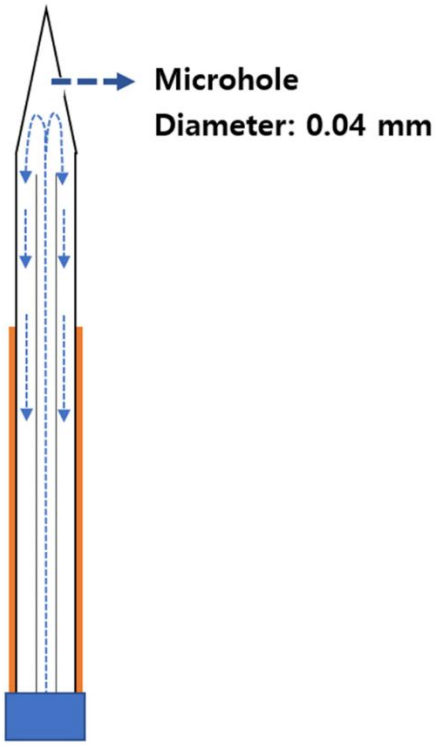
Figure 1. The thyroid-dedicated internally-cooled wet (ICW) electrode system. Photograph **(A)** and illustration **(B)** of the ICW electrode system show the propulsion of saline through the one microhole in the distal tip (rate = 1.5 ml/min).

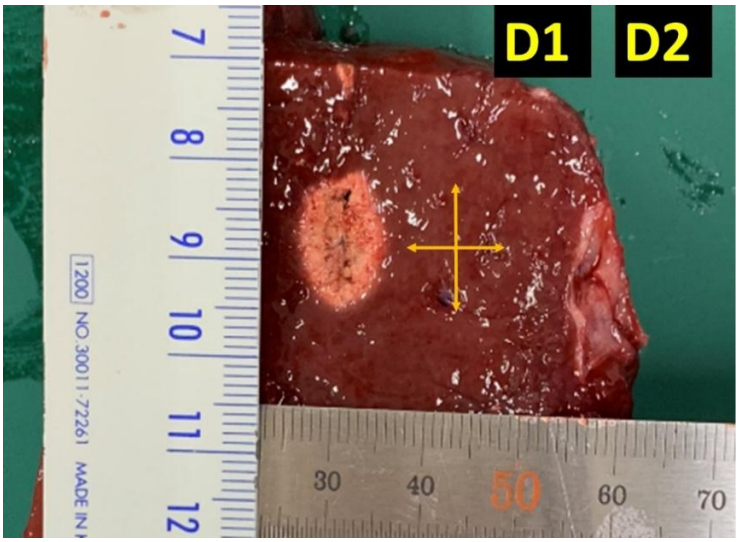


[Figure 1 A]

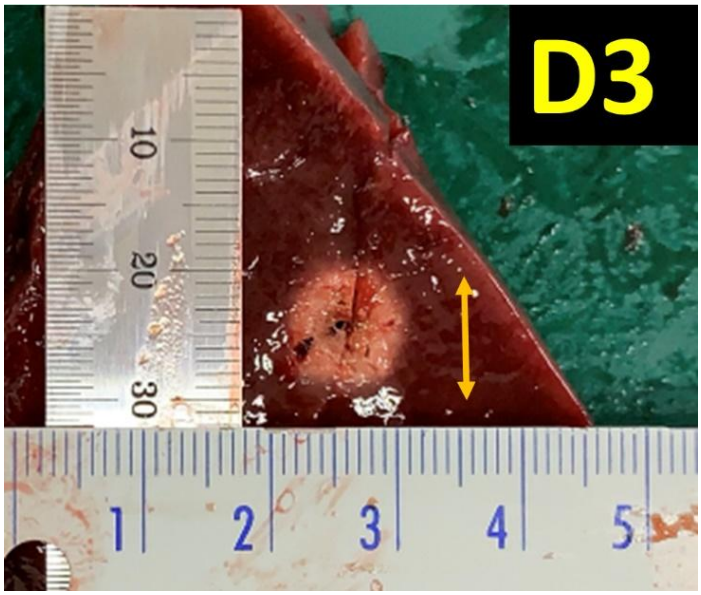


[Figrue 1B]

Figure 2. Measurement of the ablation zone. Photographs of specimen created by radiofrequency ablation with thyroid-dedicated internally-cooled wet electrode in the electrode insertion axis. **(A)** The maximum vertical diameter (D1) along the electrode and the perpendicular transverse diameter (D2) were measured. **(B)** The second transverse diameter of the ablation zone (D3) was measured in the perpendicular plane to the plane passing through the axes of the probe.

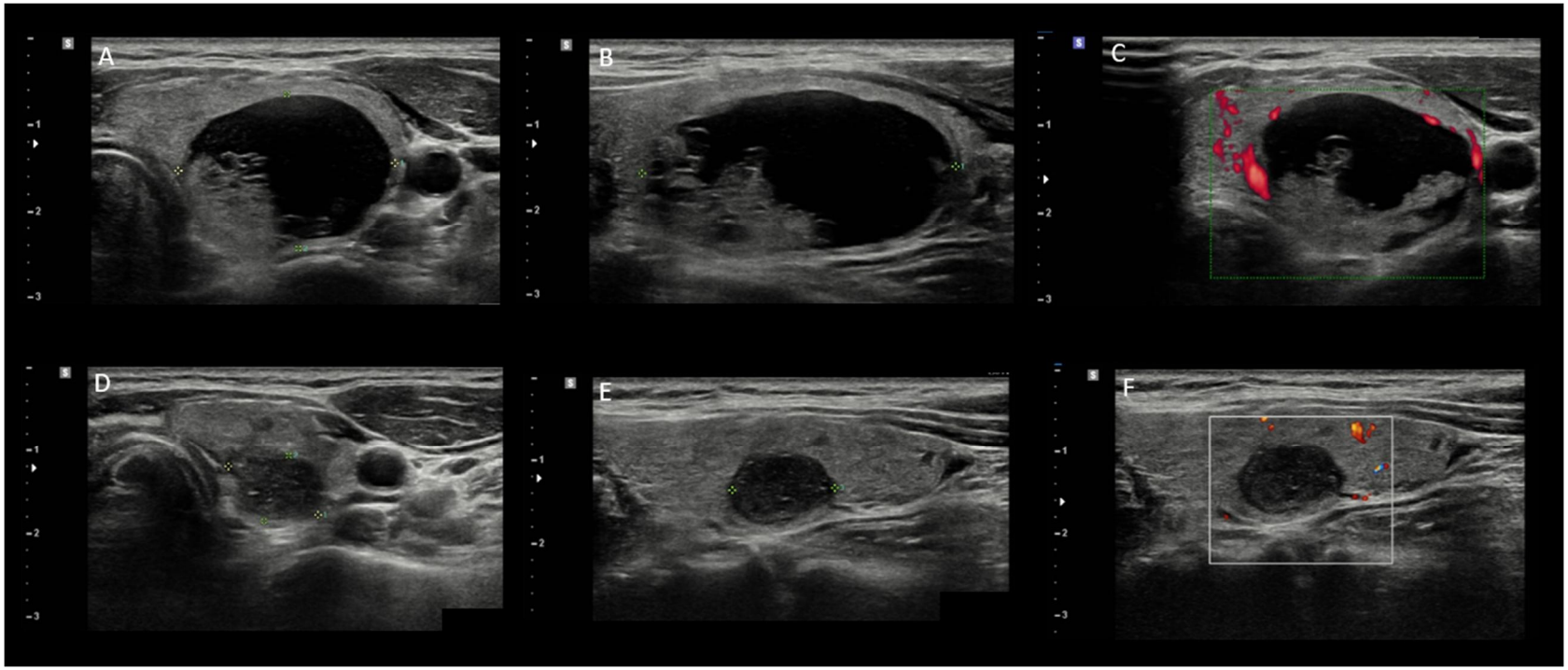


[Figure 2A]



[Figure 2B]

Figure 3. Gradual reduction of biopsy proven benign thyroid nodule after one session of RFA with thyroid-dedicated ICW electrode. **(A, B, C)** Initial ultrasonography (US) of a 51-year-old woman revealed 3.6 × 2.5 × 1.8 cm, volume 8.5-ml, and predominantly cystic mass in the left thyroid gland. **(D, E)** After one session of RFA, 6 month follow-up US revealed a smaller, 1.2 × 1.2 × 0.8 cm, volume 0.6-ml ablated nodule in the left thyroid gland. Volume reduction ratio was 93% on 6 month follow-up US. **(F)** On follow-up US, ablated nodule revealed no vascularity on Doppler exam.



영문요약

Background: To assess the effects on ablation size of radiofrequency ablation (RFA) using an internally-cooled wet (ICW) electrode in *ex vivo* bovine liver and evaluate the feasibility of the ICW electrode in treatment of benign thyroid nodules.

Methods: We developed an 18-gauge ICW electrode with a microhole at the distal tip for tissue infusion of chilled (0 - 4℃) isotonic saline (rate =1 .5 ml/minute). RFA using ICW and Internally-Cooled (IC) electrodes were performed in bovine livers (40 pairs, 1-cm active tip, 50W, 1-min). We compared the morphological characteristics of ablation zones and presence of carbonization. Twenty patients with benign thyroid nodules larger than 5 ml were prospectively enrolled into a clinical study and underwent ultrasound-guided RFA with ICW electrodes. Ultrasound examinations, laboratory data, and symptom and cosmetic scores were evaluated at preprocedure and 1 and 6 months after procedure.

Results: In the *ex vivo* study, the ICW achieved significantly larger ablation zones than the IC (auto-mode: 2189.0 ± 439.0 mm3 vs 891.7 ± 140.7 mm3, $P < 0.001$; impedance-mode: 2425.9 ± 552.4 mm3 vs. 886.3 ± 209.8 mm3, $P < 0.001$). In the clinical study, ICW electrodes were tolerable in all patients. At last follow-up, nodule volume had decreased from 15.6 ± 12.1 ml to 4.1 ± 4.3 ml ($P < 0.001$), and the mean volume reduction ratio was 73.3 ± 13.7% at 6.0 months follow-up. Cosmetic and symptom scores were reduced from 3.5 ± 1.0 to 2.7 ± 0.9 and 3.1 ± 2.2 to 0.9 ± 1.0 (both $P < 0.001$), respectively. After RFA, thyroid function was well preserved in all patients and mean thyroglobulin level decreased from 36.6 ± 52.1 ng/ml to 26.9 ± 62.2 ng/ml. One patient experienced temporary voice change that recovered within a week.

Conclusions: In the *ex vivo* study, the thyroid-dedicated ICW achieved significantly larger ablation zones than the IC. In the clinical study, the thyroid-dedicated ICW was feasible and effective in patients with benign thyroid nodules.