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CASE REPORT

Case Experience of Radiofrequency Ablation for Benign Thyroid Nodules: From an *Ex Vivo* Animal Study to an Initial Ablation in Taiwan

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Abstract Radiofrequency ablation (RFA) is a minimally invasive technique, used with ultrasound or computed tomography guidance, which can produce tissue coagulation necrosis in various kinds of tumors in the human body. In the past 10 years, numerous studies about RFA in benign thyroid nodules have been published. Reviewing these studies, we noticed that the effectiveness of ablation was higher when it was performed with the "moving-shot technique" via an internally cooled electrode. A consensus statement published from the Korean Society of Radiology also suggested the moving-shot technique as a standard ablation procedure for benign thyroid nodule ablation in Korea. In Taiwan, most symptomatic benign nodules are currently treated with surgical removal. RFA for mass lesions is primarily performed for the treatment of metastatic hepatic tumors. In our case, we have attempted to introduce RFA for benign thyroid nodules in Taiwan. Because endocrinologists in Taiwan were not familiar with this technique, we adopted a stepwise approach in learning how to perform RFA. We conducted *ex vivo* animal ablation exercises to gain experience in setting the radiofrequency generator for the right ablation mode and appropriate power output. The thyroid nodule volume reduction rate after 1 year of follow up was approximately 50% in this case. The most important thing we learned from this trial is that we confirmed the safety of thyroid nodule ablation. To the best of our knowledge, this is the first reported study of RFA of a thyroid nodule in Taiwan.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.
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Introduction

Radiofrequency ablation (RFA) is a technique used to destroy tissues with heat generated from a high-frequency alternating current. This current is created by a radiofrequency generator. When the generator is powered on, the alternating electric current oscillating between 200 kHz and 1200 kHz in the electrode causes nearby tissue ion agitation, which can create frictional heat [1]. With that amount of heat, the electrode can cause target tissue coagulation necrosis. This technique can be used for ablation of tumors in various kinds of tissue. There are several commercial vendors making various kinds of ablation systems, with different generators and electrodes. Some studies have adopted the Radiofrequency Interstitial Tissue Ablation Starburst ablation system with hook-expandable electrodes [2], however, other studies have used the Radionics Cool-tip ablation system with an internally cooled electrode [3,4]. In the past 10 years, emerging clinical trials have examined the efficacy of RFA for benign thyroid nodules. According to published articles, the effectiveness of these ablations is good, and the average volume reduction rate is usually more than 50%. The results are even better when ablation is performed using the "moving-shot ablation" technique [5,6]. Based on a published consensus statement from the Korean Society of Radiology, this ablation technique has become a standard procedure in Korea [7].

The goal of our trial was to introduce this technique in Taiwan. We adopted the Radionics Cool-tip ablation system with an internally cooled electrode and the moving-shot ablation technique, which targeted benign thyroid nodules. Our protocol was modified from Jeong et al's [4] study. It was approved by the institutional review board of the Far Eastern Memorial Hospital (FEMH IRB No. 97106) and the Taiwan Food and Drug Administration. Written informed consent was also obtained from the patients prior to the study. For the details of the protocol, please refer to Table 1; five individualized patients were enrolled in this study.

Because the training of endocrinologists in Taiwan does not include RFA techniques, for safety reasons, we suggest animal ablation practices prior to the ablation trial involving human patients. In this article, we describe the process of performing an *ex vivo* animal ablation study.

Ex vivo animal study and ablation system generator setting

Pig liver and pig thyroid gland are similar in size to those of humans, and they make good material for *ex vivo* animal studies. Before synthetic thyroid hormones became available, desiccated thyroid or thyroid extract derived from the thyroid gland of animals was the primary therapy for patients with hypothyroidism [8]. Most commercially available prescriptions of thyroid extract are derived from pigs. However, after the introduction of synthetic thyroid hormones, demand for pig thyroid glands fell sharply. Nowadays, if we need pig thyroid glands, we have to search for a nearby butchery market. In this trial, we obtained fresh pig thyroid glands from New Taipei City Butchery Market.

The RFA of pig liver has been previously reported in many studies [9,10]. Most studies evaluated the ablation volumes under different ablation conditions. In our study, the purpose of pig liver ablation was not to determine the ablation efficiency, but to practice doing the moving-shot technique (Figure 1A). Pig liver is adequately large and can be placed in a metallic container, which is connected to the ground pad of the radiofrequency generator. After inserting the electrode into the tissue and turning on the generator, coagulation began under the appropriate power output. Bubbles began to appear and could be seen under the ultrasound surveillance. We moved the electrode backward for 3–4 cm, stopped the power output temporarily, shifted the electrode to another direction, and ablated again. In this way, we learned how to perform the moving-shot technique with a steady hand.

The next step was pig thyroid gland ablation. Anatomically, the pig thyroid gland lies over the trachea and is easily found next to the larynx (Figure 2A). Just like the human thyroid gland, it is a butterfly-shaped organ, composed of right, left, and isthmus lobes (Figure 2B). The pig thyroid gland is much smaller than the pig liver. The echogenicity of the *ex vivo* pig thyroid gland is heterogenous and hypoechoic (Figure 2C). In this session, we did not try to ablate the gland with the moving-shot technique but attempted to ablate it using a different generator setting. The Cool tip RF system has two modes for power output: a manual mode and an impedance mode. Using the impedance mode, the power output will be shut down automatically if the impedance is too high. Using the manual mode setting and power output at 25 W, microbubbles appeared 2.5 minutes after the ablation began. However, with the impedance mode setting, microbubbles did not appear under the power output of 25 W. We increased the power output to 30 W, and microbubbles were noted at least 3 minutes after the ablation (Figure 2D). In this way, we demonstrated that the manual mode is better than the impedance mode in ablating pig thyroid glands. The ablation diameter under a power output of 30 W for 4 minutes was approximately 1.2 cm (Figure 2E). It is worth pointing out that some pig thyroid gland capsules ruptured during ablation when we tried to increase the power output to 50 W with longer ablation times (>5 minutes). This suggested that, although the ablation technique is very safe, the "safety margin" should be maintained between the thyroid capsule and the ablation target (Figure 2F).

Case report

A 53-year-old woman visited our hospital in 2012 for a left neck mass with compressive symptoms. She had a history of a left nodular goiter for 1 year and had been followed without Levothyroxin suppression therapy. The patient noted that the nodule had become larger in recent months. She felt neck discomfort during swallowing upon arrival to our outpatient clinic. The physical examination revealed a Grade II goiter on the left lobe of the thyroid. The nodule was approximately 3 cm in diameter by palpation, relatively soft in consistency, and was not attached to the adjacent tissue. Thyroid ultrasonography showed a solid but heterogeneous nodule in the left lobe. The volume of the nodule was

Table 1 Study protocol.

Patient selection
1. Inclusion criteria
   - Presence of subjective symptoms (foreign body sensation, neck discomfort or pain, compressive symptoms).
   - A poor surgical candidate or refusal to undergo surgery.
   - Fine-needle aspiration cytology (FNAC) showed benign results on two separate occasions.
   - Ultrasound (US) findings are compatible with a benign nodule.
2. Exclusion criteria
   - FNAC reveals follicular neoplasm or malignancy.
   - A nodule with the sonographic criteria for a malignancy (taller than wide, marked hypoechoic, microcalcifications, ill-defined margins).
   - Previous radiation or surgical history to the head and neck.
   - Previous sclerosing therapy.

Ablation machine
1. RF generator: Cool-tip RF system (Radionics, Valleylab, Tyco, Boulder, CO, USA)
2. Electrode: an internally cooled Cool-tip electrode (17 gauge, with 1-cm active tip)

Preablation assessment
1. Ultrasound examination
   - Record the size, characteristics, composition, intranodular vascularity, and any abnormal lymph nodes in the neck.
   - Measure volume of the tumor: $V = \pi abc/6$ (where V denotes volume, a is the largest diameter, and b and c are the other two perpendicular diameters).
2. Laboratory data
   - Thyroid function test: thyroid stimulating hormone (TSH), free thyroxine (FT4), thyroid autoantibodies (TSH-R antibody or anti-TPO antibody)
   - Bleeding tendency: bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (aPTT)
   - Routine complete blood count (CBC), biochemical tests including renal function test and liver function test
3. Ultrasound-guided fine-needle aspiration cytology (benign results to the same nodule on two separate occasions)

Procedure
1. Place the patient in the supine position with the neck extended.
2. Attach two ground pads in the patient's both thighs.
3. Local anesthesia with 2% lidocaine at the electrode puncture site (above isthmus).
4. Insert electrode under ultrasound guidance at isthmus (transisthmus approach). The electrode tip will be positioned in the deepest and most remote portion of the nodule.
5. Power output will begin with 20 W, and will be increased in 5-W increments up to 70 W.
6. When a transient hyperechoic zone appears at the periphery of the nodule, the electrode tip will be moved backward (moving-shot technique). In the more central area of the nodule, if the transient hyperechoic zone expands around the electrode tip, the electrode will be moved to an untreated area.
7. Check both thighs frequently to prevent skin burn during ablation.
8. Ablation will be terminated when all units of the nodule have changed to transient hyperechoic zones.

Post-RFA care
1. Let the patient rest for 1 h; then the patient will be observed for any sign of hemorrhage, voice change, or severe local pain.
2. Mild compression at the treatment site will be performed for 10—20 min.
3. Medication: Take oral analgesics (acetaminophen) for 1 d, if necessary.

Post-RFA follow up
- Follow up thyroid function test (Free T4 and TSH).
- Follow up ultrasonography at 1 wk, 1 mo, 3 mo, 6 mo, 9 mo, and 1 y after RFA; record nodule characteristics and volume.

Possible complication management
1. Pain during ablation: Reduce RF power, or stop ablation if severe pain. Medication (acetaminophen) after ablation.
2. Skin burn at electrode puncture site or pad attachment site: ice packing.
3. Voice change: Stop ablation and continue observation for 3 mo.
4. Intrathyroidal/intranodular or extrathyroid hematoma: direct compression and observation.
5. Tracheal thermal injury: Stop ablation and continue observation for 3 mo; surgical repair if necessary.
6. Esophageal thermal injury: Stop ablation and continue observation for 3 mo; surgical repair if necessary.

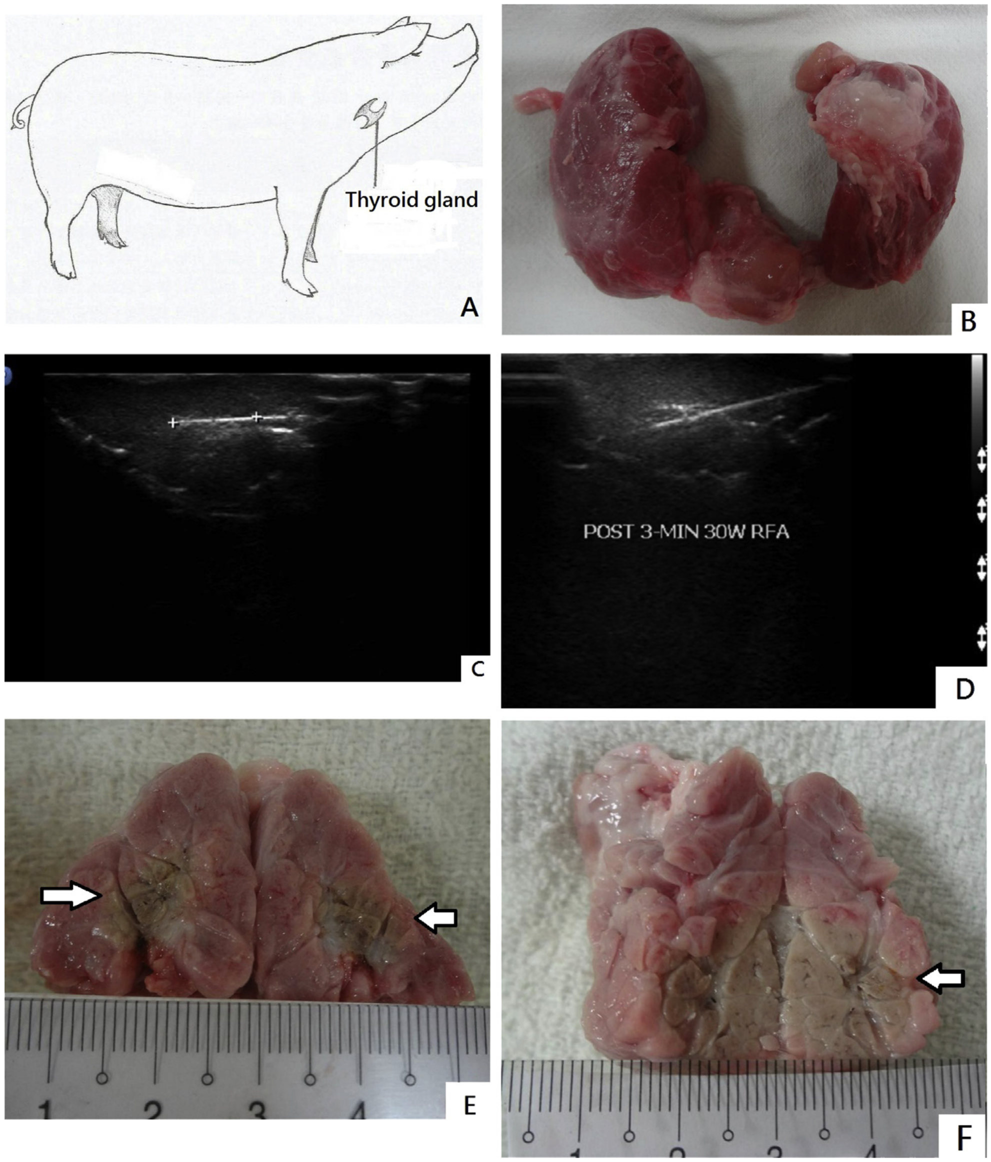

Figure 1 Radiofrequency ablation on a pig thyroid gland. (A) Schematic diagram showing the anatomic position of the pig thyroid gland. (B) Fresh pig thyroid gland, just removed from a slaughtered pig. (C) Ultrasonographic picture of *ex vivo* pig thyroid gland showing heterogenous and hypoechoic texture. The inserted electrode could be identified as a bright bold line. (D) Ablation performed with a power output of 30 W for 3 minutes under manual mode. Hyperechoic bubbles had already developed and could be seen under ultrasound surveillance. (E) Cross section of pig thyroid gland after fixed-needle ablation, with power output of 30 W for 4 minutes; ablation diameter, approximately 1.2 cm. (F) Cross section of another pig thyroid gland after ablation showed that the ablated area went beyond the thyroid capsule.

approximately 6.36 mL (Figure 3A), calculated as $V = \pi abc/6$ (where V denotes volume, a is the largest diameter, and b and c are the other two perpendicular diameters). The preablation sonographic images did not indicate malignancy. Ultrasound-guided fine-needle aspiration cytology (conducted twice to the same nodule) was also negative for malignancy or atypical cells. Laboratory examination results including blood test counts, bleeding time, and routine biochemistry were all normal. Thyroid functions were normal as the thyroid stimulating hormone level was 0.42 μIU/mL (normal range, 0.4–4.0 μIU/mL) and the free thyroxine (FT4) level was 1.78 ng/dL (normal range, 0.8–2.0 ng/dL). The thyroid autoantibodies tests produced negative results.

We adopted the Cool-tip RF system (Radionics, Valleylab, Tyco, Boulder, CO, USA) with an internally cooled electrode (17 gauge, with 1-cm active tip) as our ablation tool. The patient was treated with 2% lidocaine for local anesthesia at the puncture site just above the thyroid isthmus. The skin was slightly incised to facilitate the insertion of the electrode. With the guidance of ultrasonography, the electrode was inserted into the target nodule and the electrode tip was positioned at the most remote portion of the nodule from the isthmus. The ablation mode was set to the manual mode. We began ablating with 20 W of power output. In the first 30 seconds, there was no change at the tip. When we increased the power to 25 W,

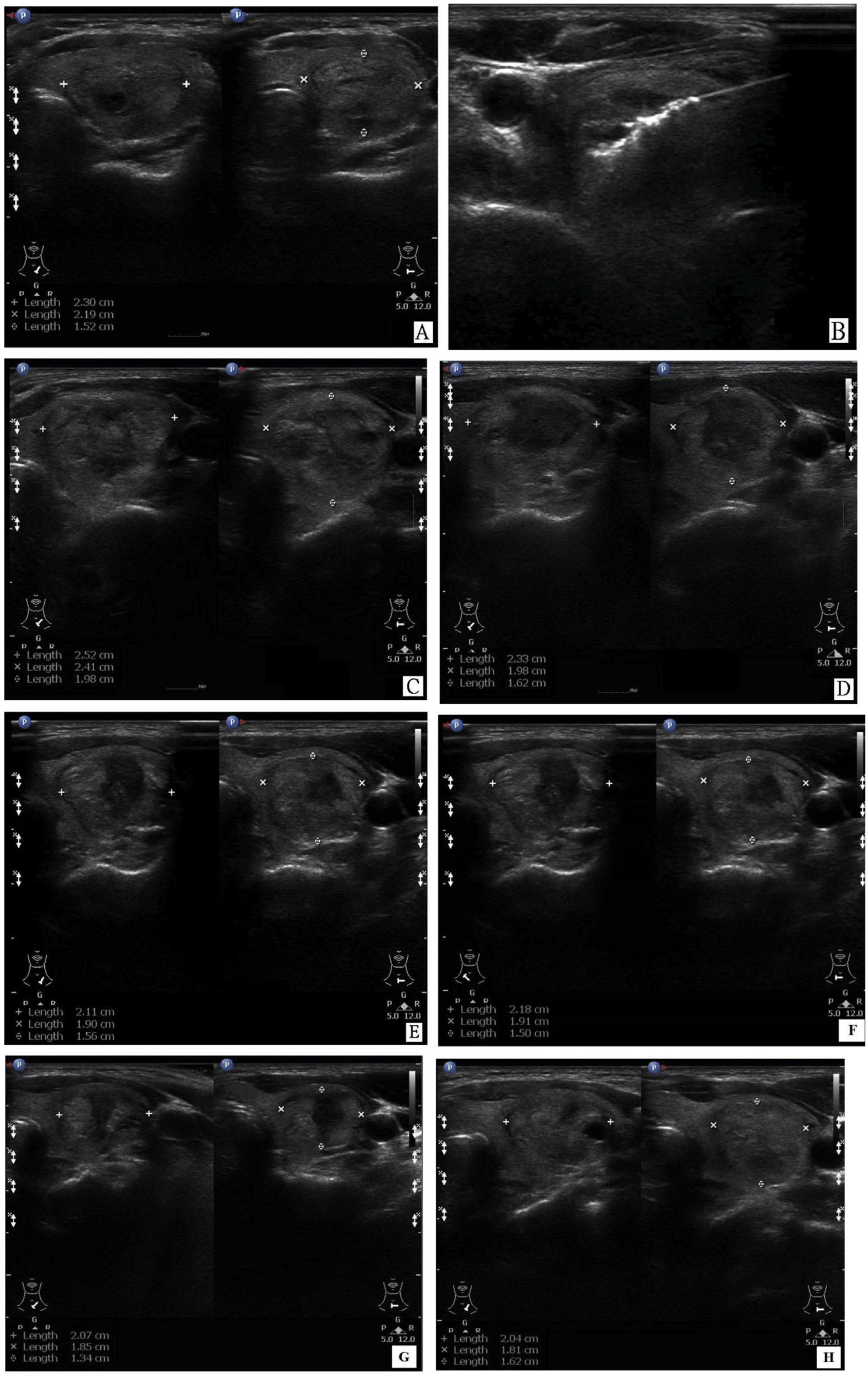

Figure 2 Target nodule ultrasonographic pictures prior to, during, and after radiofrequency ablation. (A) Nodule prior to ablation; estimated volume, 6.36 mL. (B) Nodule during ablation, with transient hyperechoic change. (C) Nodule 1 week after ablation; estimated volume, 6.30 mL. (D) Nodule 1 month after ablation; estimated volume, 3.91 mL. (E) Nodule 3 months after ablation; estimated volume, 3.52 mL. (F) Nodule 6 months after ablation; estimated volume, 3.27 mL. (G) Nodule 9 months after ablation; estimated volume, 2.68 mL. (H) Nodule 1 year after ablation; estimated volume, 3.13 mL.

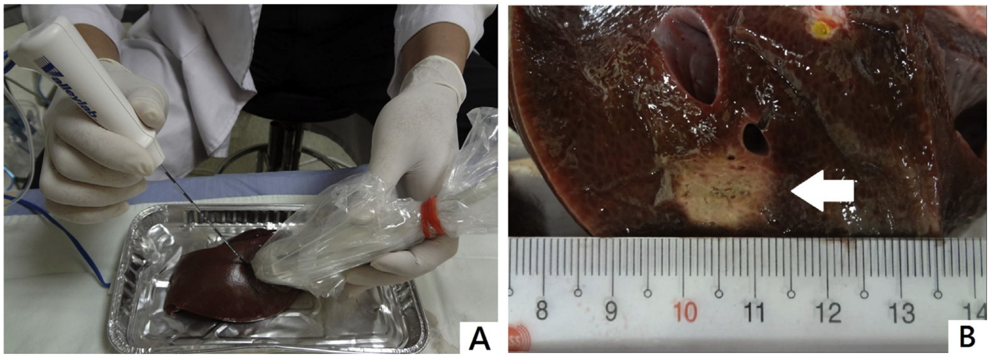

Figure 3 Radiofrequency ablation of pig liver. (A) Pig liver placed in a metallic container, ready for practicing the moving-shot technique. (B) Cross section of pig liver after moving-shot ablation; ablation diameter, about 1 cm.

the formation of a transient hyperechoic zone at the electrode tip appeared within 10 seconds. The electrode tip was moved backward slowly to ablate the untreated area (Figure 3B). Thirty seconds later, a transient hyperechoic zone along the needle tract was created after the electrode tip was moved to the opposite side of the nodule. Next, we turned off the power, tilted our electrode to another untreated portion, and inserted the electrode again to the most remote part of the nodule. Again, we set the power output to 25 W and another 30 seconds of ablation was performed. For safety reasons, we did not ablate the area that was very close to the nodule capsule. In this way, the moving-shot technique was performed for eight cycles (Table 2). Seventy percent of the nodular volume turned hyperechoic, and we discontinued ablation. The total ablation time was approximately 5 minutes. During the ablation, the patient could tolerate the procedure well without neck pain or discomfort. After mild compression for 30 minutes and rest for 60 minutes, the patient was discharged without any oral analgesics.

We scheduled to follow the patient with ultrasonography at 1 week, 1 month, 3 months, 6 months, 9 months, and 1 year after ablation to record the nodule characteristics and volume. The nodule volume at 1 week after ablation was 6.30 cm^3 (Figure 3C), representing 99% of the original size. The patient did not report any discomfort during that visit. The serial follow up with thyroid ultrasonography at 1 month, 3 months, 6 months, 9 months, and 1 year showed that the nodule volumes were 3.91, 3.52, 3.27, 2.68, and 3.13 cm^3, respectively (Figures 3D, 3E, 3F, 3G, and 3H). No complications were noted during the 1-year follow up. The thyroid function test conducted 3 months after ablation yielded normal results, and the thyroid nodule volume reduction rate was approximately 50%. The test indicated that the ablation procedure did not affect thyroid function.

Table 2 Ablation parameters.

Power (W)	Impedance (Ω)	Time (s)	
20	125–127	30	
25	124–128	30	Bubbles began to appear
25	130–135	30	Electrode shifted to another direction
25	125–130	30	Electrode shifted to another direction again (8 cycles)

MODE: manual mode. Total ablation time: 5 minutes 0 seconds.

Discussion

To the best of our knowledge, this is the first reported study on the RFA of nodular goiters in Taiwan. Our initial experience with RFA showed that this is a safe and effective procedure. The ablation was performed in an outpatient setting without hospital admission. We confirmed that general anesthesia was not necessary, and a 2% lidocaine injection at the electrode puncture site above the isthmus as local anesthesia was adequate for pain management prior to ablation. The ablation time was short, and the course of the moving-shot technique lasted only about 5 minutes. The power output from the generator was very low (20–25 W). This means that the patient will not experience much pain during the ablation. Oral painkillers were totally unnecessary after the procedure. We just pressed the wound firmly for 30 minutes and recommended bed rest. The course of postablation follow up was also very smooth. The procedure did not leave any scar on the patient's neck. In the post-ablation 1-month follow-up visit, we could not identify the electrode puncture site. No side effects, such as voice change, intrathyroid hematoma, skin burn, and tracheal or esophageal injury were observed during the 1-year follow up. The result of ablation was also satisfactory. Prior to ablation, the volume was 6.30 mL. After the ablation, the recorded volume was 3.13 cm at the last follow up. The volume reduction rate was 51%. The neck compressive symptoms also improved subjectively. The patient was satisfied with the treatment experience and efficiency. Thus, we demonstrated that thyroid nodule ablation could be performed safely and effectively in Taiwan.

RFA for benign thyroid nodules has been shown as an effective way to reduce thyroid nodule size in many studies [5,6]. However, to the best of our knowledge, this technique has not yet been performed in Taiwan. In Taiwan, most symptomatic benign nodules are treated with surgical removal [11]. RFA for mass lesions is performed primarily for the treatment of metastatic hepatic tumors [12].

There are obstacles for an endocrinologist in Taiwan to perform RFA if patients have thyroid nodules with cosmetic problems or compressive symptoms. The most important reason for this is that the training of endocrinologists in

Taiwan does not include RFA techniques. The preferred thyroid nodule ablation technique, the moving-shot technique [13], is even more complicated than the fixed-needle technique, which is usually performed for hepatoma ablation. To minimize the risk of possible ablation complications, physicians need stepwise practice prior to performing ablation in human patients. Our recommendation is that an *ex vivo* animal study should be tried first. This allows the physician to learn how to set the ablation generator, how to perform the moving-shot technique, and how to precisely ablate small volume tissue.

In conclusion, RFA has been shown to be a safe and effective way to ablate thyroid nodules in many trials, when performed by a well-trained technician. For the beginner, a stepwise approach to learn how to perform RFA in thyroid nodules is needed. *Ex vivo* animal ablation is a good way to provide an opportunity to practice. The technician can set the radiofrequency generator for the right ablation mode and appropriate power output. The physicians can also learn to perform the moving-shot technique from pig liver ablation. With adequate animal ablation experience, we can ablate thyroid nodules instead of opting for invasive surgical intervention in benign nodular goiters or other metastatic thyroid cancer lesions. The follow-up course showed that the ablation was very safe without any significant complications.

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