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Efficacy of single-session radiofrequency ablation (RFA) in rendering euthyroidism for persistent/relapsed Graves' disease, a pilot study

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Abstract

Objectives Graves' disease (GD) is the most common cause of hyperthyroidism. Antithyroid drug (ATD) is often the first-line treatment but > 50% patients suffer a relapse when ATD is discontinued. Surgery or radioiodine remains the current options of definitive treatment in these patients. This pilot study examined the short-term efficacy of single-session thyroid radiofrequency ablation (RFA) as a novel definitive treatment for persistent/relapsed GD.

Methods Consecutive patients with persistent/relapsed GD requiring ATD were considered. Those with a clear surgical indication, either thyroid lobe volume ≥ 20 mL; those who were pregnant or lactating; and those who had any severe medical conditions that would pose extra treatment risks were excluded. Eligible patients received ultrasound-guided RFA of the entire bulk of thyroid gland. Thyroid function tests were monitored bi-monthly. The primary outcome was disease remission rate, defined as a state of biochemical euthyroidism or hypothyroidism without ATD. Secondary outcomes were complication rates.

Results Of the 68 patients considered, 15 (22.1%) patients were eligible. Most were females (93.3%). The median age was 37 (IQR 31–48) years old. The disease remission rates were 79.0% at 6 months and 73.3% at 12 months. Among the 4 patients who relapsed after RFA, three required less ATD dose than before RFA. RFA was well-tolerated in the ambulatory setting. There were no vocal cord palsy, skin burn, hematoma, or thyroid storm after RFA.

Conclusions In well-selected patients, single-session RFA of the thyroid gland may be a potential treatment for patients with persistent/relapsed GD. It is a safe and well-tolerated ambulatory procedure.

Key Points

- *Radiofrequency ablation of the thyroid gland is an efficacious treatment for persistent/relapsed Graves' disease in well-selected patients.*
- *Radiofrequency ablation of the thyroid gland for the treatment of persistent/relapsed Graves' disease is a safe and well-tolerated ambulatory procedure.*
- *Radiofrequency ablation of the thyroid gland may be a potential alternative treatment for well-selected patients with persistent/relapsed GD who do not wish to undergo either thyroidectomy or radioactive iodine or continue antithyroid drugs.*

Keywords Radiofrequency ablation · Graves' disease · Ultrasonography · Iodine · Thyroidectomy

Abbreviations

AntiTSHR	Anti-thyroid stimulating hormone receptor antibody
ATD	Antithyroid drug
FNAC	Fine needle aspiration cytology
GD	Graves' disease
GO	Graves' ophthalmopathy
HIFU	High-intensity focused-ultrasound
LUSG	Laryngeal ultrasonography
RAI	Radioiodine therapy
RFA	Radiofrequency ablation
TSH	Thyroid-stimulating hormone
USG	Ultrasonography
VCP	Vocal cord palsy

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Introduction

Graves' disease (GD) is an autoimmune thyroid disorder caused by the presence of stimulating auto-antibodies to thyrotropin (thyroid-stimulating hormone receptor (TSHR)) on thyroid follicular cells. It is the most common cause of hyperthyroidism with approximately 3% of females and 0.5% of males developing GD in their lifetime [1]. In many parts of the world, antithyroid drugs (ATDs) have been the preferred upfront treatment in GD while definitive treatments like surgery or radioiodine therapy (RAI) are generally reserved for patients who remain hyperthyroid, despite daily maintenance of ATD for 18 months or longer (i.e., persistent/relapsed GD) [2, 3]. However, in practice, a greater proportion of patients with persistent/relapsed GD does not wish to proceed to either surgery or RAI because of perceived surgical risks and fear to radiation, respectively [1].

Radiofrequency ablation (RFA) is an image-guided thermal ablation technique that has been increasingly applied in various benign and malignant thyroid conditions [3–6]. Through a combination of frictional and conduction heat generated from the RFA needle, RFA is able to cause irreversible tissue necrosis of the target within the thyroid gland. Previous studies have found the functional capacity of the thyroid gland can be lowered when the bulk of the two (right and left) functional thyroid lobes has been ablated with thermal energy [7, 8]. As a result, we hypothesized that bilateral RFA to the thyroid gland could be an effective, non-surgical treatment in inducing disease remission for patients with persistent/relapsed GD. To the best of our knowledge, this has not been previously reported. The present pilot study aimed to examine the short-term efficacy of bilateral RFA as a treatment in inducing disease remission for patients with persistent/relapsed GD.

Methods

Patients

This study followed the principles in the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 22–504). Patients were recruited after informed consent. From March 2020 to December 2021, consecutive patients with persistent or relapsed GD were considered. To be eligible, first, the diagnosis of GD had to fulfill the standard clinical criteria for GD which included an elevated serum free T4, suppressed TSH level, positive TSHR antibody, and a clinically detectable diffuse goiter. Second, patients had to remain hyperthyroid despite maintaining ATDs for at least 18 months. Third, patients had no strong wish to undergo surgery or RAI as a definitive treatment of their persistent or relapsed GD. Lastly, patients had to be aged 18 years or over. The exclusion criteria were patients with a clear and immediate surgical indication (such as a compressive goiter, suspected or documented thyroid malignancy, planning pregnancy within 6 months or with moderate to severe Graves' ophthalmopathy (GO)), either the right or left lobe volume ≥ 20 mL by sonographic volumetry or who were pregnant or lactating and had any medical conditions that would make them too ill to undergo intravenous sedation or treatment.

Pre-treatment preparation and evaluation

All patients were rendered biochemically euthyroid prior to RFA treatment. Baseline serum TSH, Free-T4 (FT4), antithyroglobulin antibodies, antithyroid-peroxidase antibodies, TSHR antibodies levels, platelet count, and clotting profile were checked before RFA. The same ultrasound (USG) machine (Samsung HS30) and transducer (Samsung LN5-12) were used for evaluation and ablation. Dimensions of the thyroid lobes (width [W], depth [D], and length [L]) were measured and the volume of each thyroid lobe (V) was calculated by the formula $V = W \times D \times L \times 0.523$ [9]. Total thyroid volume was calculated by the sum of the volume of both lobes [10]. If necessary, USG-guided fine-needle biopsy with cytology would be performed to prove the benign nature of thyroid nodules. Vocal cord mobility was assessed by trans-laryngeal ultrasonography (LUSG) before, during and after ablation [11]. Vocal cord palsy (VCP) was defined as any reduction in one of the three vocal cord landmarks, i.e., true vocal cord, false vocal fold, and arytenoid cartilage. Flexible laryngoscopy was performed on day 7 after ablation to assess vocal cord status.

RFA procedure

All RFA procedures were performed by the same surgical team consisting of two experienced endocrine surgeons, each having performed more than 100 RFA procedures before. The same RF generator (STARmed VIVA RF generator) and needle (star RF Electrode–Fixed, 18G 70 mm, 10-mm active tip length) were used. Before ablation, approximately 10 mL of 1% lignocaine was injected in the perithyroidal space on each side of the thyroid gland. In addition, intravenous boluses of midazolam (Cheplarpharm) (1–3 mg) and pethidine (Martindale Pharmaceuticals) (10–30 mg) were given [12]. After insertion of the needle into the thyroid lobe, ablation began at 50 to 60W of power under USG guidance,

with the aim to ablate as much of the vascularized thyroid parenchyma as possible and this included the right lobe and left lobe as well as the isthmus if its thickness was >0.5 cm. The trans-isthmic approach and moving-shot technique were used as described previously [4, 13]. Each target lobe was divided into imaginary transverse planes with each comprising imaginary subunits. The ablation typically began from deep to superficial, and from lateral to medial. Each subunit was considered successfully ablated when microbubbles were observed at the site of ablation, after which the needle tip was shifted to the next subunit. The entire transverse plane was considered ablated completely when it was entirely filled with microbubbles. The USG transducer and RFA electrode was then advanced to the next imaginary transverse plane. Ablation close to the "danger triangle" of tracheal esophageal groove was avoided [13].

During the procedure, the patient's heart rate, blood pressure, respiration rate, and peripheral oxygenation were monitored. Adverse events that occurred during and after RFA were recorded. Pain associated with the treatment was subjectively rated by using a 0–10 numeric rating scale shortly after RFA and just before hospital discharge. The patients were closely observed for 4 h and discharged when the patient had eaten and did not complain of nausea or vomiting.

Post-ablation follow-up

In the first 2 weeks, patients were advised that palpitations or exacerbation of other thyrotoxic symptoms may occur. ATDs were immediately stopped after RFA. Patients were instructed to take propranolol, a beta-blocker, if they develop palpitations. All patients had their thyroid function checked at 2 weeks, 4 weeks, 2 months, 4 months, 6 months, 8 months, 10 months, 12 months, and every 2 months afterwards while thyroid USG and eye assessment were done at 6 and 12 months.

Study outcome

The primary outcome was the complete remission rate after RFA at 6 months. Complete remission was defined as a state of being biochemically euthyroid (FT4 12–23) or hypothyroid (FT4 <12 pmol/L) without the use of ATD following RFA. Relapse was defined as a state of being biochemically hyperthyroid (FT4 >23 pmol/L), or requiring ATD to maintain a euthyroid state. Other outcomes included partial treatment response which was defined as the ability to maintain a biochemically euthyroid state with a lower ATD dose than that of the baseline, complications such as vocal cord palsy (VCP), hematoma, skin complications, thyroid storm, and changes in GO activity after RFA.

Biochemical results

All measurements of TSH, FT4, and anti-thyroid antibodies were performed at our institution's laboratory. The normal reference values for TSH were 0.35 to 4.78 mIU/L, while T4 ranged from 12 to 23 pmol/L. Serum antithyroglobulin and antithyroid peroxidase antibodies were determined with radioimmunoassay (Bio Code; Izasa), and any values greater than 99 IU/mL were considered positive, while for anti-TSHR antibodies, any values 1 IU/L or greater were considered positive.

Statistical analysis

Statistical analysis was performed by using software (SPSS version 20, IBM). Data was expressed as mean ± standard deviation or median with interquartile range as appropriate. Datasets were compared by using the Student two-tailed *t* test for variables with normal distribution and Man-Whitney *U* test for non-parametric data. No adjustment was made for multiple testing. Comparison of categorical variables was performed by means of the χ^2 test. The threshold for a statistically significant difference was considered to be a *p* value of <0.05.

Results

Over the study period, 68 consecutive patients with persistent/relapsed GD were managed at our unit. Among them, 53 were excluded due to goiter with severe compressive symptoms ($n=27$), severe GO ($n=3$), planning for pregnancy within 6 months ($n=3$), concomitant thyroid malignancy or indeterminate thyroid nodules on FNAC ($n=5$), and refusing to participate or wishing to undergo surgery directly ($n=15$). Therefore, only 15 (22.1%) patients were eligible and agreed for treatment. Table 1 shows patients' baseline characteristics. The majority (93.3%) were females. The median (IQR) age at treatment was 37 (31–48) years old. The median (IQR) follow-up time was 14 (12–26) months. All patients suffered persistent/relapsed GD for at least 60 months before treatment. All patients were put on daily carbimazole maintenance prior to RFA treatment. While taking the daily carbimazole maintenance dose, none were placed under block and replacement therapy. The majority of patients (80%) were taking a low carbimazole daily regimen of 5 mg or less to render them biochemically euthyroid before RFA. Only 4 patients (26.7%) suffered from mild GO (clinical activity score (CAS) of 1). All patients had raised anti-TSHR (median 1.5 IU/L, IQR 1.4–3.6). The median (IQR) total thyroid volume was 16.1 mL (13.7–26.9), with the right thyroid lobe 10.5 mL (7.28–14.9) and left lobe 8.66 mL (5.74–12.1). Only one patient had a partial

Table 1 Baseline characteristics ($n = 15$) of patients undergoing single-session radiofrequency ablation (RFA) for persistent/relapsed Graves' disease

Characteristics	Median (IQR)/number (%)
Age at treatment (years)	37 (31–48)
Sex, *n* (%)	
- Male	1 (6.7)
- Female	14 (93.3)
Body weight (kg)	55 (53–62)
Body height (m)	1.60 (1.56–1.64)
Body mass index (kg/m^2)	22.2 (21.7–27.4)
Median follow-up (months)	14 (12–26)
Time from initial diagnosis to RFA (months)	96 (69–126)
Duration of antithyroid drug use since diagnosis (months)	50 (40–54)
Daily maintenance dose of carbimazole before RFA	
- 2.5 mg	2 (13.3)
- 5 mg	10 (66.7)
- 10 mg	2 (13.3)
- 30 mg	1 (6.7)
Activity of GO (according to CAS, 0–7)	0 (0–1)
Serum preablation Free T4 (pmol/L)	20 (15–23)
Serum preablation TSH (mIU/L)	1.6 (0.01–3.70)
Serum preablation antithyroglobulin auto-antibody (IU/mL)	275 (63–648)
Serum preablation antiperoxidase auto-antibody (IU/mL)	492 (104–3214)
Serum preablation anti-TSHR (IU/L)	1.5 (1.4–3.5)
Dimensions of the right thyroid lobe	
- Width (mm)	22.7 (18.9–25.0)
- Length (mm)	47.5 (41.7–53.1)
- Depth (mm)	18.3 (17.0–24.4)
- Estimated volume (mL)	10.5 (7.28–14.9)
Dimensions of the left thyroid lobe	
- Width (mm)	21.3 (16.0–25.6)
- Length (mm)	48.0 (40.0–49.4)
- Depth (mm)	16.2 (15.5–18.2)
- Estimated volume (mL)	8.66 (5.74–12.1)

GO Graves' ophthalmopathy, *CAS* clinical activity score, *anti-TSHR* anti-TSH receptor antibodies

thyroidectomy 10 years ago and her GD relapsed from a large right thyroid remnant.

Table 2 shows the treatment parameters of the cohort. Bilateral thyroid lobe ablation was achieved in all patients. For that patient who had previous partial thyroidectomy, only the large right remnant was ablated. The median (IQR) total energy applied was 39,246 (27,530–52,426) Joules while the median (IQR) total energy applied per unit volume being 2050 (1506–2510) Joules/mL. The median (IQR) duration of bilateral thyroid lobes ablation was 17.7 (14.7–20.7) min. Most patients (79%) had RFA treatment completed within 20 min. Each unilateral lobe was ablated with one single skin puncture, and therefore the 14 patients with whole gland (bilateral) ablation received two skin punctures. The patient with previous partial thyroidectomy had one single skin puncture for the RFA treatment. The median (IQR) pain score by visual analogue scale was 6 (4–7) immediately after RFA, and lowered to 3 (2–8) upon discharge from hospital. All patients were discharged within the same day, approximately 6 h after ablation. No patients suffered from treatment-related complications including VCP, skin burn, and hematoma formation. No patients developed thyroid storm or developed acute thyrotoxic symptoms that required treatment. At the latest follow-up, no patients suffered worsening of their pre-existing or new development GO.

Figure 1 shows the rate of complete remission after bilateral thyroid lobe ablation by RFA for our cohort. The disease remission rate at 6 months was 79.0% and at 12 months, the remission rate was 73.3%. Figures 2 and 3 show the ultrasonographic changes in the thyroid gland 3 months after RFA. The ablated zones could be seen as hypoechoic areas in the thyroid parenchyma. This patient remained in complete remission at her last follow-up at 12 months. Figure 4

Table 2 Treatment parameters and complications

	N = 15
Total energy given (Joule)	
- Right thyroid lobe	20,501 (12,970–30,292)
- Left thyroid lobe	17,196 (10,794–22,844)
- Both thyroid lobes	39,246 (27,530–52,426)
Energy given per unit lobe volume (Joules/mL)	
- Right thyroid lobe	2050 (1130–2469)
- Left thyroid lobe	1925 (1673–2427)
- Both thyroid lobes	2050 (1506–2510)
Total ablation time (minutes)	
- Right thyroid lobe	10.0 (6.3–12.1)
- Left thyroid lobe	8.3 (7.2–9.5)
- Both thyroid lobes	17.7 (14.7–20.7)
Ablation time per unit volume (minutes/mL)	
- Right thyroid lobe	0.89 (0.64–1.09)
- Left thyroid lobe	0.89 (0.69–1.43)
- Both thyroid lobes	0.91 (0.71–1.14)
Pain scores by visual analogue scale	
- At end of procedure	6 (4–7)
- Upon discharge	3 (2–8)
Treatment-related complications	
- Vocal cord palsy	0 (0.0)
- Skin burn	0 (0.0)
- Bleeding/hematoma formation	0 (0.0)
- Thyroid storm	0 (0.0)

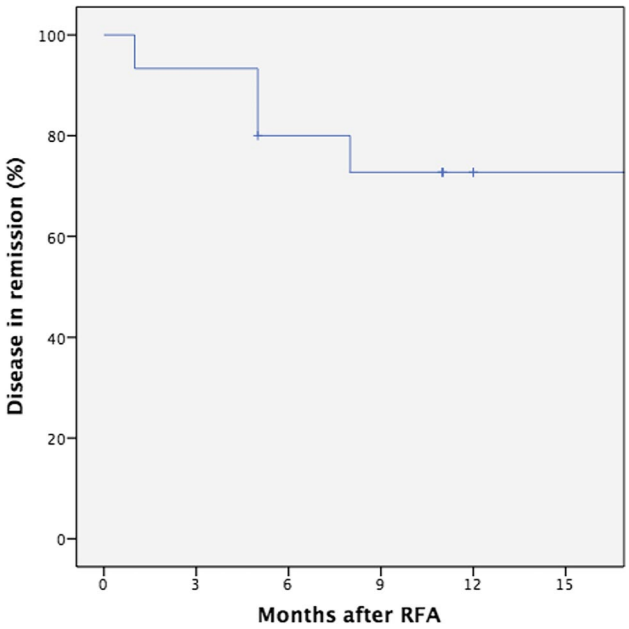

Fig. 1 Kaplan Meier analysis of the rate of complete remission after bilateral thyroid lobe radiofrequency ablation ($n = 15$). The disease remission rate at 6 months was 79.0% and at 12 months, the remission rate was 73.3%

shows the reduction in vascularity of the ablated gland of another patient who remained in remission at last the follow-up (12 months).

Table 3 summarizes treatment efficacy following RFA at the time of analysis. After a median (IQR) follow-up time of 14 (12–26) months, 11 (73.3%) patients had complete disease remission. Among them, 8 were biochemically euthyroid (7 normal FT4 and TSH, 1 normal FT4 and mildly suppressed TSH) without the need for either ATD or thyroxine supplement while 3 were put on 50 mcg daily thyroxine maintenance because of biochemical hypothyroidism after RFA. Among the 4 patients found not to be in remission at the time of analysis, all had a variable period of remission (i.e., biochemically euthyroid without ATD). The period of remission ranged from 4 weeks to 8 months after RFA. Three patients had a biochemical relapse within 6 months and they occurred at 4 weeks, 5 months, and 5.5 months, respectively. One patient had a relapse 8 months after RFA. Among these 4 patients not in remission at the time of analysis, 3 patients were able to maintain biochemically euthyroidism at a reduced daily ATD dose (when compared to that prior to RFA). The percentage of dose reduction ranged between 50 and 83.3%. They were regarded as a partial response to RFA. The remaining patient required a higher dose of carbimazole (relative to that prior to RFA) to control hyperthyroidism. No further patients developed relapse after 8 months. Table 4 illustrates the changes in thyroid function before RFA and at the last follow-up. Baseline characteristics and treatment parameters of patients who relapsed were compared to those who remained in remission in an attempt to identify factors associated relapse (Table 5). However, no significant clinical predictors for remission after RFA were identified.

Discussion

To the best of our knowledge, the present study was the first to evaluate the short-term efficacy of bilateral RFA as a definitive treatment for patients with persistent/relapsed GD. Our study found that in a well-selected group of patients, ablating both thyroid lobes with RFA could induce disease remission in a majority of the patients for 6 months or longer. Our data found 79.0% and 73.3% of patients at 6 and 12 month were able to be completely weaned off ATD daily maintenance. Therefore, bilateral RFA could be considered another option when patients do not wish to undergo surgery or RAI.

The high efficacy of RFA for benign thyroid nodules was well proven [3–6], but its use on Graves' disease is novel.

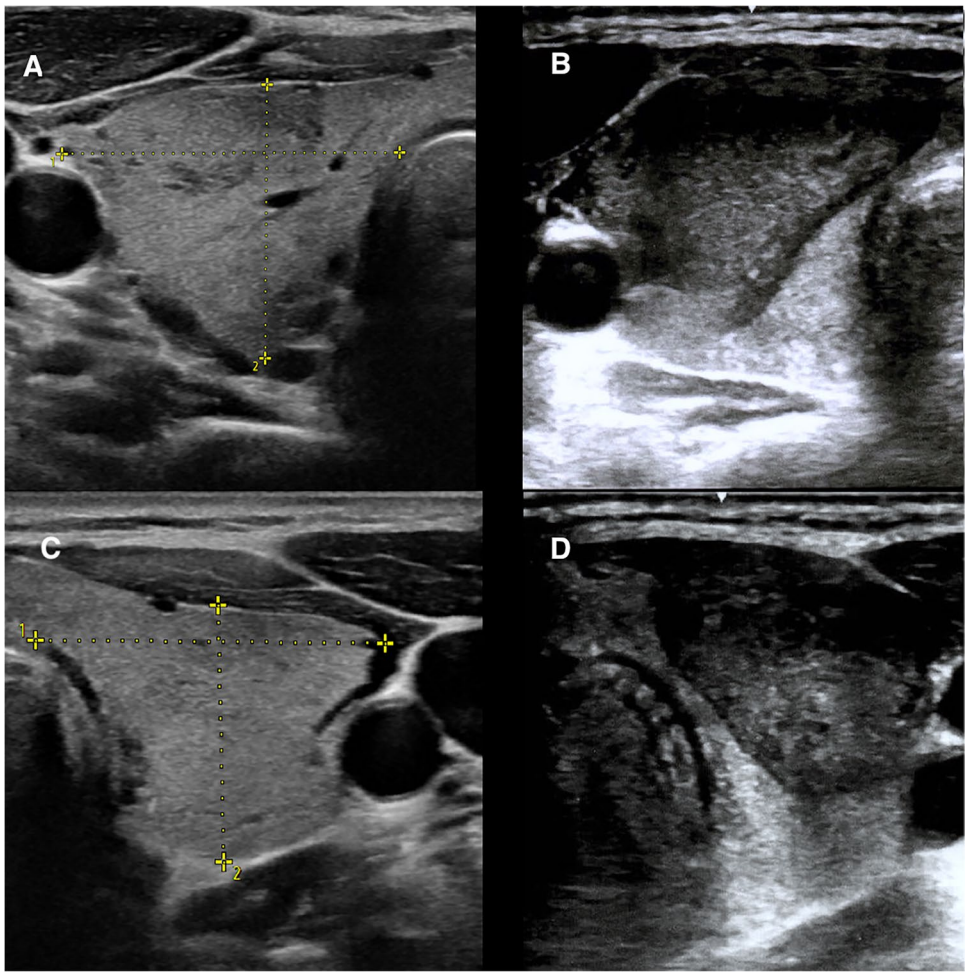

Fig. 2 Ultrasonographic images of a 38-year-old lady who underwent bilateral thyroid lobe radiofrequency ablation for Graves' disease. She remained in complete remission at her last follow-up at 12 months. Transverse view of the right lobe, before (**A**) and 3 months after ablation (**B**). Transverse view of the left lobe, before (**C**) and 3 months after ablation (**D**). Hypoechoic changes in the thyroid parenchyma were noted after ablation (**B**, **D**), signifying the ablated zones. Isoechoic areas signify un-ablated areas, which were close to the recurrent laryngeal nerves (the danger triangle)

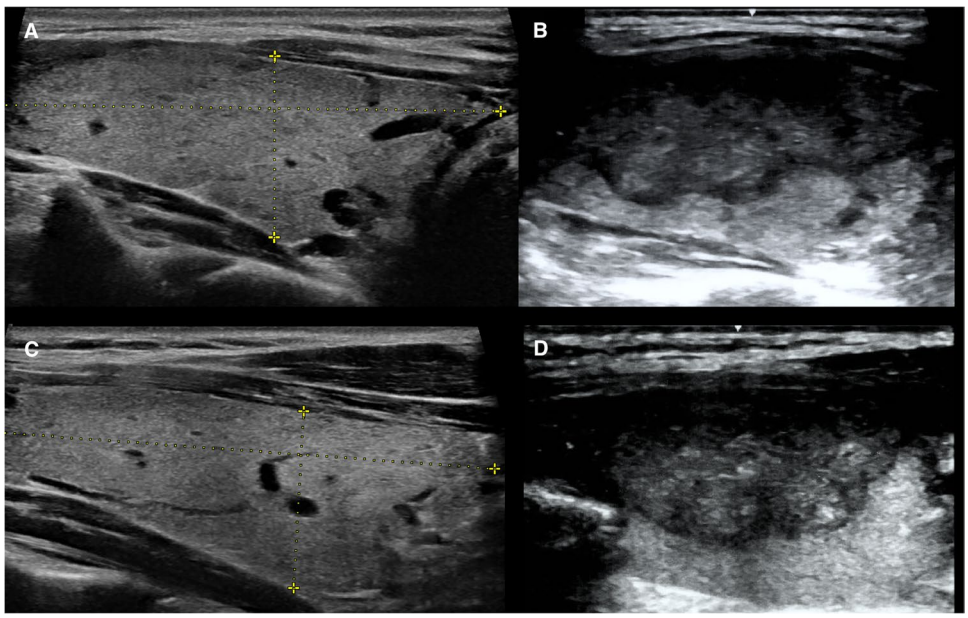

Fig. 3 Ultrasonographic images of the same patient in Fig. 2 who underwent bilateral thyroid lobe radiofrequency ablation for Graves' disease. Longitudinal view of the right lobe, before (**A**) and 3 months after ablation (**B**). Longitudinal view of the left lobe, before (**C**) and 3 months after ablation (**D**). Hypoechoic changes in the anterior thyroid parenchyma were noted after ablation (**B**, **D**), signifying the ablated zones. Isoechoic areas at the posterior region signify un-ablated areas, which were close to the recurrent laryngeal nerves

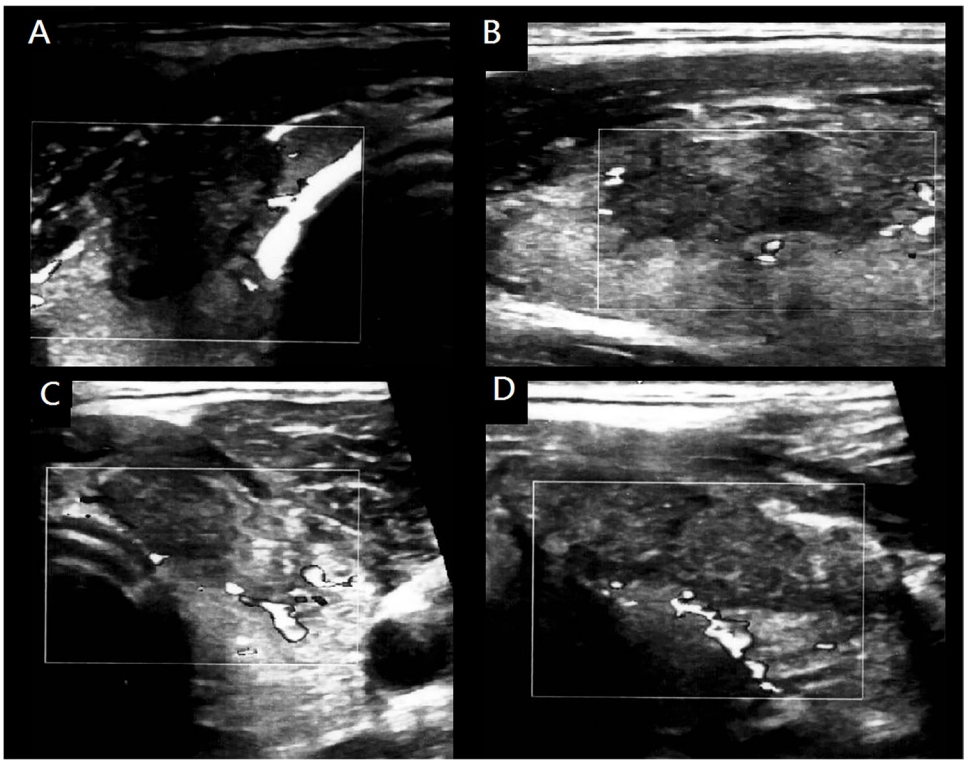

Fig. 4 Ultrasonographic image with Doppler assessment of the thyroid gland at last follow-up (12 months) of a 31-year-old man who remained in complete remission. Reduction in vascularity, in particular in the ablated hypoechoic zones, was observed in both lobes. **A**, **B** Right lobe, transverse and longitudinal view; **C**, **D** left lobe, transverse and longitudinal view

Table 3 Disease status following single-session radiofrequency ablation of Graves' disease ($n = 15$)

	N (%)
Number of patients in disease remission at:	
- 2 weeks	15 (100.0)
- 4 weeks	15 (100.0)
- 2 months	14 (93.3)
- 4 months	14 (93.3)
- 6 months	12 (80.0)
- 8 months	12 (80.0)
- 10 months	11 (73.3)
- 12 months	11 (73.3)
- 14 months	11 (73.3)
Disease status at last follow-up	
- Disease remission	11 (73.3)
- Biochemically euthyroid*	8 (53.3)
- normal FT4 and TSH	7 (46.7)
- normal FT4 and mildly suppressed TSH	1 (6.7)
- Biochemically hypothyroid#	3 (20.0)
- Persistent or relapsed GD	4 (26.7)
- On reduced daily maintenance ATD dose +	3 (20.0)
- On higher daily maintenance ATD dose +	1 (6.7)

*Serum Free T4 level within the normal range without daily ATD maintenance

#Serum Free T4 level below the normal range without daily ATD maintenance

+Relative to daily maintenance dose before RFA

GD Graves' disease, *ATD* anti-thyroid drug

Conventional treatment for persistent/relapsed Graves' disease include radioactive iodine therapy (RAI), surgery, and long-term ATD, each bearing certain disadvantages. Relative to single RAI for the treatment of persistent/relapsed GD, our remission or success rate with RFA appeared to be higher (79.9% vs. 52.5% at 6 months) [14]. The overall rate of hypothyroidism after RFA necessitating thyroxine replacement was 13.3%, which was much lower than RAI (41%) [15]. The other benefits of RFA over RAI in GD included no exposure and fear for radiation, as there were concerns of potential increased risk of malignancy after RAI [16]. RFA also does not require isolation precautions, which is a particular concern in our locality due to the crowded living conditions. For surgery, a scar is inevitable, as well as permanent hypothyroidism, necessitating lifelong thyroxine replacement. Surgery also carries the risk of permanent hypoparathyroidism. Although the risk of hypoparathyroidism may be reduced in the hands of high-volume surgeons, in reality, not all patients have the privilege. In fact, a recent study have shown that the risk of permanent hypoparathyroidism after total thyroidectomy can be as high as 11.2% in the community setting [17]. On the contrary, RFA has the clear advantage of zero risk of hypoparathyroidism. VCP is another serious complication after surgery. In particular, some reports have suggested that Graves' disease itself is a risk factor for VCP after surgery [18, 19]. On the contrary, RFA appeared to be safe as none of the patients in our cohort developed VCP. We certainly acknowledge ours is a small cohort and a larger sample size

Table 4 Thyroid function before radiofrequency ablation (RFA) and at 12-month follow-up. All medication doses were expressed as daily dose

Patient no	Before RFA			At 12-month follow-up				
	ATD dose* (mg)	TSH (mIU/L)	FT4 (pmol/L)	ATD dose* (mg)	Thyroxine dose (mcg)	TSH (mIU/L)	FT4 (pmol/L)	Disease status
1	5	1.2	15	0	0	1.98	20	Remission
2	10	0.01	22	0	50	3.2	16	Remission
3	5	3.7	15	0	0	5.8	18	Remission
4	2.5	5.3	21	0	0	1.2	18	Remission
5	5	0.01	20	0	0	2.0	16	Remission
6	30	0.01	29	5	0	1.3	15	Relapse
7	5	3.7	18	0	0	0.4	20	Remission
8	5	5.8	15	2.5	0	4.2	13	Relapse
9	10	0.01	24	0	50	1.2	16	Remission
10	5	0.3	24	2.5	0	0.2	20	Relapse
11	2.5	0.3	20	0	0	2.3	18	Remission
12	5	2.8	18	10	0	1.4	20	Relapse
13	5	2.4	20	0	0	2.0	18	Remission
14	5	1.1	23	0	50	2.2	18	Remission
15	5	1.6	16	0	0	2.0	15	Remission

ATD anti-thyroid drug

*Carbimazole was used as the ATD

Table 5 A comparison of patient characteristics and treatment parameters between those who remained in remission (group I) and those who relapsed (group II) after single-session radiofrequency ablation (RFA) for persistent/relapsed Graves' disease at last follow-up

Variable	Group I ($n=11$) Median (IQR)/number (%)	Group II ($n=4$) Median (IQR)/number (%)	p-value
Age at treatment (years)	38 (31–50)	31 (28–40)	0.177
Sex, *n* (%)			
- Male	1 (9.0)	0 (0.0)	0.733
- Female	10 (91.0)	4 (100.0)	
Body weight (kg)	54 (52–69)	61 (56–63)	0.400
Body height (cm)	159 (155–166)	165 (157–169)	0.500
BMI (kg/m^2)	22.1 (21.6–23.1)	22.3 (21.3–23.2)	> 0.999
Total duration of GD before RFA (months)	96 (72–120)	84 (60–98)	0.604
Total duration of carbimazole use before RFA (months)	48 (40–54)	53 (28–81)	0.833
Daily dose of carbimazole before RFA (mg)	5 (5–5)	5 (5–30)	0.489
Activity of GO (according to CAS, 0–7)	0 (0–1)	0 (0–0)	0.949
Serum preablation fT4 (pmol/L)	20 (15.8–22.3)	18 (15–20)	0.573
Serum preablation TSH (mIU/L)	1.4 (0.01–3.70)	2.8 (0.01–3.2)	> 0.999
Serum preablation antithyroglobulin antibody (IU/mL)	510 (77–648)	82 (63–687)	0.610
Serum preablation antiperoxidase antibody (IU/mL)	1033 (104–3474)	330 (89–3236)	0.762
Serum preablation anti-TSHR (IU/L)	1.4 (1.2–3.5)	1.6 (1.4–14.2)	0.413
Right thyroid lobe volume (mL)	10.9 (7.0–15.6)	7.9 (7.9–7.9)	0.889
Left thyroid lobe volume (mL)	8.7 (5.8–12.4)	8.6 (3.1–10.6)	0.692
Total thyroid volume	16.1 (14.5–29.3)	12.9 (11.0–18.0)	0.225
Total energy delivered (Joule)	37,447 (18,702–51,840)	37,949 (25,062–134,431)	0.753
Energy delivered per unit thyroid volume (Joule/mL)	2008 (1172–2552)	2050 (1840–2134)	0.769
Total ablation time (min)	18 (12–20)	17 (14–42)	0.851
Ablation time per unit volume (min/mL)	0.85 (0.57–1.14)	0.97 (0.74–1.10)	0.456

RFA radiofrequency ablation, *anti-TSHR* anti-TSH receptor antibodies, *ATD* antithyroid drug, *GO* Graves' ophthalmopathy, *CAS* clinical activity score

would be required to determine the true complication rates. Long-term ATD has been suggested as an alternative treatment for persistent Graves' disease, with the advantage of potential cure in the long run [20]. However, such protocol would require no interruption of ATD for at least 60 months. Furthermore, ensuring full compliance of ATD and continuous monitoring and follow-up for such a long period can pose a challenge. On the contrary, RFA is a one-off procedure and a majority (73.3%) of our patients remained medication free (in remission) since after the procedure. Based on the above advantages of RFA, we believe it could be a viable and attractive option for well-selected patients who do not find surgery, RAI, or long-term ATD acceptable.

Interestingly, when compared to a similar cohort treated by single-session high-intensity focused ultrasound (HIFU), our remission rates were remarkably similar and comparable over time [7]. Perhaps, this was because both ablation techniques shared similar underlying treatment principle (i.e., using thermal ablation to destroy the bulk of the functional thyroid parenchyma and thereby lowering overall glandular function). In our view, one benefit of RFA over HIFU in the treatment of persistent/relapsed GD appeared to be the significantly shorter treatment time (17.7 min vs. 64.3 min) [7]. However, a direct comparison in a clinical trial would be needed to see if one technique is favored over the other. The other advantages of RFA over HIFU would be more economic and accessible.

In terms of relapse afterwards, it is worth noting that the chance of disease relapse appeared higher in the first 6 months of treatment. In our cohort, 3 out of 4 (75.0%) relapses occurred within the first 6 months of treatment while only one (25.0%) patient had a relapse at 8 months after RFA. Also, it is worth noting that of the 4 patients who had a relapse, 3 were able to be put on a lower maintenance dose of ATD afterwards. Therefore, in terms of overall response, one could argue that effectively almost all or 14 of the 15 patients treated had either a full or partial response to RFA. The fact that 3 patients had a partial response would suggest RFA already resulted in some reduction in overall functional capacity of the thyroid gland. Based on this assumption, perhaps, further ablation leading to better thyroid function control is plausible.

In order to avoid damage to the recurrent laryngeal nerves, the "safety triangle" was not ablated. This inevitably left behind an area of "safety margin" that was unablated. The volume of this safety margin may have implications on the rate of relapse and more data on this aspect would be helpful. It would be interesting to know whether the use of more generous, posterior hydro-dissection would affect the volume of total ablation zone and safety margin, the rate of relapse, cure or hypothyroidism, and the rate of recurrent laryngeal nerve injury.

Another finding worth mentioning was that RFA to the thyroid gland was well-tolerated and safe. All patients could be discharged within the same day. None of the 15 patients suffered from complications of VCP, voice change, skin burn, or hematoma formation. The authors believed that during thyroid RFA, the use of sedation together with perithyroidal local anesthesia and the use of intra-operative laryngeal ultrasonography for the real-time monitoring of vocal cord status offered the best combination for improved patient experience and procedural safety [11, 12]. We acknowledge that in many parts of the world, thyroid RFA is commonly done without sedation due to various reasons. Therefore, we would not put intravenous sedation as a mandatory part of RFA, as our ablation procedures involved at most two punctures and would end within 20 min, which is similar to ablation of a large thyroid nodule. In the case of RFA-induced vocal cord palsy, real-time monitoring of vocal cords by laryngeal ultrasonography enables timely cessation of procedure to avoid further damage; and timely remedies such as injection of cold 5% dextrose injection around the tracheoesophageal groove may lead to voice recovery [21, 22]. In the event of unsuccessful laryngeal ultrasonography in visualizing the vocal cords, we recommend the use of voice checks during RFA, after ablation of the first lobe, and after ablation of the second lobe. Detection of unilateral vocal cord palsy after ablation of the first side, either with laryngeal USG or voice checks, could potentially avoid bilateral vocal cord palsy (and hence tracheostomy) by withholding ablation to the second side until the first side recovers.

The other important point to note would be that a thorough thyroid USG assessment, with or without FNAC before RFA, would be essential to rule out suspicious lesions, since the typical hypoechoic appearance of the thyroid gland after ablation (as in thyroid nodule ablation) could cause confusion in the future. Serial comparison of USG images before and after RFA would be helpful to detect any changes.

Despite our findings, there were limitations which should be acknowledged. First, our study was a pilot one and so, the sample size is small. This may be the reason why we were unable to identify predictors for remission or relapse after RFA. There is also a lack of control group. Second, our cohort was a highly selected one with only one-fifth of patients in our practice eligible for the treatment. Our exclusion criteria of unilateral thyroid lobe volume $\geq$20 mL would have excluded patients with considerably large goiter. However, from the literature, the mean total thyroid volume in patients with Graves' disease ranged from 24.8 to 40.2 mL [23–27]. Therefore, we believe using the upper limit of 20 mL per lobe, i.e., 40 mL total thyroid volume, would have already made half of the patients in the community eligible for the size criteria. We believe one of the major reasons for our high exclusion rate would be that our patients were seen at a surgical thyroid unit, and therefore they were more likely to have other conventional indications for surgery apart from refractoriness to ATD, e.g., very large

goiter, Graves' ophthalmopathy, and suspicion for thyroid malignancy. The third limitation would be that the technique of whole-gland RFA was somewhat more technically challenging and, perhaps, should be carried out by a team familiar with thyroid ablation in general. Fourth, evaluation of health-related quality of life would have been relevant. Fifth, one may worry the massive destruction of thyroid parenchyma may predispose to the development or worsening of existing autoimmune disease. However, we did not observe such phenomenon in the first year of the study. We shall continue to monitor this possibility. Finally, the presence of viable thyroid remnant as evident by the euthyroid status in 8 of our patients may raise the concern of potential disease relapse in the long run, as in subtotal thyroidectomy. The counter-argument would be that the nature of the thyroid remnant after RFA would be ablated tissues, which is different from that of subtotal thyroidectomy (normal thyroid tissue). Nevertheless, whether RFA can have a lasting treatment efficacy for Graves' disease remains to be elucidated by studies with longer follow-up.

Conclusion

In well-selected patients, single-session radiofrequency ablation of the thyroid gland may be a potential treatment for patients with persistent/relapsed GD who do not wish to undergo either surgery or RAI or continue ATD. In our experience, it is a safe and well-tolerated ambulatory procedure.

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- experimental
- performed at one institution

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