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ULTRASOUND

Two-year outcomes of single-session high-intensity focused ultrasound (HIFU) treatment in persistent or relapsed Graves' disease

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Abstract

Objective To evaluate the longer-term disease relapse of ultrasound (US)-guided high-intensity focused ultrasound (HIFU) ablation as a treatment for persistent/relapsed Graves' disease (GD).

Methods After ethics approval, consecutive patients with persistent or relapsed GD who underwent bilateral US-guided HIFU ablation from 2016 to 2017 were retrospectively analyzed. Altogether, 75 patients received HIFU ablation of the central portion of the right and left thyroid lobes with areas near the trachea–esophageal groove and common carotid artery un-ablated. They were followed for 24 months or longer. Baseline thyrotropin (TSH), free T4, anti-thyroid autoantibodies, and TSH receptor (TSHR) antibody were checked. Primary outcome was the 24-month relapse rate. Relapse referred to hyperthyroidism (free T4 (FT4) > 23 pmol/L) afterwards. Variables associated with relapse were analyzed by binary logistic regression.

Results The cohort comprised mostly females (84.0%) with a mean age of 42.05 ± 10.74 years. The 24-month relapse rate was 41.3% with 31 patients suffering a relapse. No patient suffered from hypothyroidism. Three patients (4.0%) suffered from temporary vocal cord palsy but these injuries recovered spontaneously after 2 months. In univariate analysis, higher daily dose of carbimazole (OR = 1.125, 95% CI = 1.023–1.237, $p = 0.015$) and higher baseline TSHR level (OR = 1.085, 95% CI = 1.022–1.152, $p = 0.007$) were significant factors for disease relapse. In the multivariate analysis, higher baseline TSHR level was a significant independent factor for disease relapse within 24 months (OR = 1.079, 95% CI = 1.014–1.148, $p = 0.016$).

Conclusions US-guided HIFU of the thyroid gland was a safe and relatively efficacious treatment in the longer term for patients with persistent or relapsed GD.

Key Points

- *US-guided HIFU ablation is relatively efficacious in the longer term.*
- *US-guided HIFU ablation of the thyroid is safe.*
- *Higher TSHR level may lead to higher disease relapse after treatment.*

Keywords Interventional ultrasonography · High-intensity focused ultrasound ablation · Graves' disease · Thyrotoxicosis · Ablation techniques

Abbreviations

ATD	Anti-thyroid drug
BMI	Body mass index
CMZ	Carbimazole
FT4	Free T4
GD	Graves' disease
HIFU	High-intensity focused ultrasound
RAI	Radioactive iodine
TSH	Thyroid-stimulating hormone or thyrotropin
TSHR	Thyroid-stimulating hormone receptor
US	Ultrasonography
VAS	Visual analogue scale

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Introduction

Graves' disease (GD) is an autoimmune thyroid disorder caused by the presence of stimulating autoantibodies to the thyrotropin (thyroid-stimulating hormone receptor (TSHR)) on thyroid follicular cells. It is the most common cause of hyperthyroidism and approximately 3% of women and 0.5% of men develop GD in their lifetime [1, 2]. In many parts of the world, anti-thyroid drugs (ATDs) remain the first-line treatment for GD [3]. However, once the disease has persisted or relapsed after a prolonged period of ATDs (i.e., persistent or relapsed GD), more definitive treatments such as surgery or radioactive iodine (RAI) therapy are recommended [2]. However, many patients still prefer to continue ATDs to maintain euthyroidism because of the fear of surgical risks and radiation exposure [4, 5].

High-intensity focused ultrasound (HIFU) is a form of thermal ablation that utilizes focused ultrasound energy to cause tissue ablation in a target area beneath the skin and soft tissue. It has been shown to be an effective and safe non-surgical treatment in patients with symptomatic benign thyroid nodule [6, 7]. Because of its ability in inducing precise tissue necrosis within the thyroid parenchyma, it was postulated that by ablating the central portion of the two major thyroid lobes (i.e., the right and left thyroid lobes), the functional capacity of the thyroid gland would be reduced and this may lead to GD remission. In a pilot study of 30 patients with persistent/relapsed GD who underwent this novel treatment, approximately two-thirds of patients were able to maintain euthyroidism at 12 months without ATDs [8]. However, because it was a pilot study with a short follow-up period, it was important to have a larger, confirmatory study with a longer follow-up period. Therefore, our study aimed to evaluate the longer-term outcomes (specifically, disease relapse and safety) of ultrasound (US)-guided HIFU ablation as a treatment for persistent/relapsed GD.

Methods and patients

This retrospective analysis was approved by the local institutional review board. All relevant clinical and treatment data were recorded prospectively after obtaining informed consent from patients. At our institution, most patients with GD were initially managed by the endocrinologists with ATDs for a period of 18 months or more before they were referred for more definitive treatment of their disease. The benefits and risks of the three definitive treatment options including surgery, RAI, and HIFU were explained before HIFU treatment. For the present study, consecutive patients with persistent or relapsed GD who chose to undergo bilateral HIFU ablation from January 2016 to February 2017 were analyzed. To be eligible, first, patients had to have a follow-up of 24 months or longer after treatment. Second, the diagnosis of GD had to fulfill the standard clinical criteria for GD (i.e., an elevated serum free T4, suppressed TSH level, and presence of TSHR autoantibody at treatment). Third, patients had to be suffering from persistent/relapsed GD (i.e., remained hyperthyroid despite completing a ≥ 18-month course of ATDs). Fourth, patients had to express no strong desire for immediate surgery or RAI as a definitive treatment for their disease. Fifth, the center or mid-point of both the right and left lobes had to be within the treatable perpendicular distance from the skin (i.e., 5–30 mm) [6, 7]. Patients with a clear indication for surgery (i.e., a compressive goiter, suspected or documented thyroid malignancy, planning pregnancy within 6 months, or with moderate to severe Graves' ophthalmopathy (GO) or patients who were not eligible for HIFU treatment (such as aged ≤ 18 years or ≥ 70 years, had pre-existing vocal cord palsy, restricted neck movement or extension)) were excluded. Also, patients with either right or left lobe volume ≥ 30 mL by US volumetry, concomitant indeterminate or malignant thyroid nodules on fine needle aspiration cytology (FNAC), active or severe GO, were pregnant or lactating, and had any medical conditions making them too ill to undergo intravenous sedation or treatment were excluded.

Pre-treatment evaluation

All patients with thyroid swelling were clinically graded according to the World Health Organization (WHO) grading system [9]. Lobe dimensions were measured by US using a LOGIQ e (GE Healthcare) scanner equipped with a 10–14-MHz linear matrix transducer. All measurements were done by an independent experienced sonographer with over 10 years of diagnostic US experience. Three orthogonal measurements of the right and left lobes (their longest diameter and two other perpendicular diameters) were made. In general, the longest diameter was the cranio–caudal dimension (length) of the lobe while the other two perpendicular diameters were the medio–lateral (width) and antero–posterior (depth) dimensions of the lobe. All measurements were made to the nearest 0.1 mm. To estimate the volumes of the right and left lobes, the ellipsoidal formula was used: volume (mL) = (width (in cm) × depth (in cm) × length (in cm)) × (π/6) where π was taken as 3.1416. In addition, the perpendicular distance from the skin to the center of each lobe and the number of concomitant nodules > 1 cm were recorded. The former was defined as the distance from the skin to the half-way point between the anterior and posterior aspects of the lobe based on the transverse US view. For those with concomitant nodules ≥ 1 cm, an US-guided FNAC was done to rule out malignancy.

Preparation

All patients were rendered biochemically euthyroid by ATDs. A beta adrenergic blocker was added 2 weeks before HIFU treatment. All patients continued their medications up to the day of treatment and were instructed to fast overnight before the day of treatment. On admission, patients' body weight (in kg), height (in cm), and baseline blood tests including serum TSH (mIU/L), FT4 (pmol/L), anti-thyroglobulin (anti-Tg) antibody, anti-thyroid peroxidase (anti-TPO) antibody, and TSHR antibody were drawn.

Treatment

All treatment sessions were carried out at our HIFU center. Each patient received a session of HIFU ablation using an US-guided HIFU device (EchoPulse). This device comprised an energy generator, a treatment head, a skin cooling device, and a touch-screen interface for planning. The treatment head incorporated an US transducer (7.5 MHz, 128 elements, linear array) and a HIFU transducer (3 MHz, single element, 60 mm in diameter). One person (B.H.L.) with > 3 years of HIFU experience carried out all the treatments. Each patient was positioned in supine position with the neck extended. Before treatment, each patient received intravenous diazemuls (Actavis) (10–15 mg) and pethidine (Martindale Pharmaceuticals) (50–100 mg). The treatment head was then positioned to target the middle layer of each lobe. Under US imaging, the treated lobe was converted into a voxel map with each voxel receiving a continuous 8-s HIFU pulse before the treatment head automatically moved to the adjacent voxel. To ensure safety, the device automatically selected the following safety margins: (a) 0.5 cm from the skin, (b) at least 0.3 cm from the trachea, and (c) 0.2 cm from the ipsilateral carotid artery. A laser-based movement detector enabled immediate power interruption if the patient moved or swallowed during ablation. The treatment aim was to ablate as much of the right and left lobes as possible while avoiding the areas close to the recurrent laryngeal nerve in the trachea–esophageal groove medially and the cervical sympathetic nerve fibers along the common carotid artery laterally. In general, approximately 2–3 mL of thyroid parenchyma on each side would be left unablated. The reason for not leaving a larger amount of unablated parenchyma is because from the experience in subtotal thyroidectomy, leaving > 6 mL of normal parenchyma may diminish the long-term remission rate [10]. The ablated volume of each treated lobe was calculated by multiplying the number of voxels treated with the volume of each voxel (≈ 102 mm^3 or 0.102 mL). To avoid skin burn, the skin was protected by a cooling device. All ablations started at 204 Joules (J) per pulse and increased up to 280 J per pulse until hyperechoic marks appeared (i.e., a sign of tissue necrosis) (Fig. 1). The total treatment time included treatment head positioning, treatment planning, and actual treatment (or "on-beam") delivery. During treatment, the patients' heart rate, blood pressure, respiration rate, and peripheral oxygenation were monitored. Under conscious sedation, patients were able to make a hand sign if the pain became intolerable. If so, either the power was lowered or in certain circumstances, more intravenous sedation was given. Any skin burn, swelling, and hoarseness of voice immediately after HIFU were recorded. Patients were asked to rate their pain during, immediately after treatment, and before discharge on a visual analogue scale (VAS) (0 = no pain and 10 = worse possible pain). Afterwards, a transcutaneous laryngeal US (TLUS) was done to assess the mobility of both vocal cords [11].

Post-treatment follow-up evaluation

In the first 2 weeks, patients were advised that palpitations or exacerbation of other thyrotoxic symptoms may occur, especially when they were severely thyrotoxic at the time of treatment. ATDs were immediately stopped after treatment but patients were advised to continue the beta adrenergic–blocking agent (such as propranolol 20–40 mg three times daily for 1 more week).

All patients had their thyroid function checked at 2 weeks, 4 weeks, 2 months, 4 months, 6 months, 8 months, 10 months, 12 months, 18 months, and 24 months after treatment. Following HIFU treatment, if the patient became biochemically hyperthyroid afterwards, ATDs were resumed and surgery or RAI was offered as a definitive treatment.

Study outcomes

The primary outcome was the 24-month rate of relapse after HIFU treatment. Relapse was defined as biochemical hyperthyroidism (FT4 > 23 pmol/L) following treatment while remission was defined as a state where there was biochemical euthyroidism (FT4 within the normal range) or hypothyroidism (FT4 < 12 pmol/L) following treatment. Other secondary outcomes included treatment-related complications. To determine factors associated with relapse, baseline characteristics including patient demographics, extent of neck swelling, body mass index, duration of ATDs, FT4, TSH, and anti-thyroid autoantibodies were compared between those who remained in remission (group I) and those who relapsed within the first 24 months (group II).

Biochemistry/laboratory

All measurements of TSH, FT4, and anti-thyroid antibodies were carried out 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 anti-Tg and anti-TPO antibodies were determined by radioimmunoassay (Bio Code) and any

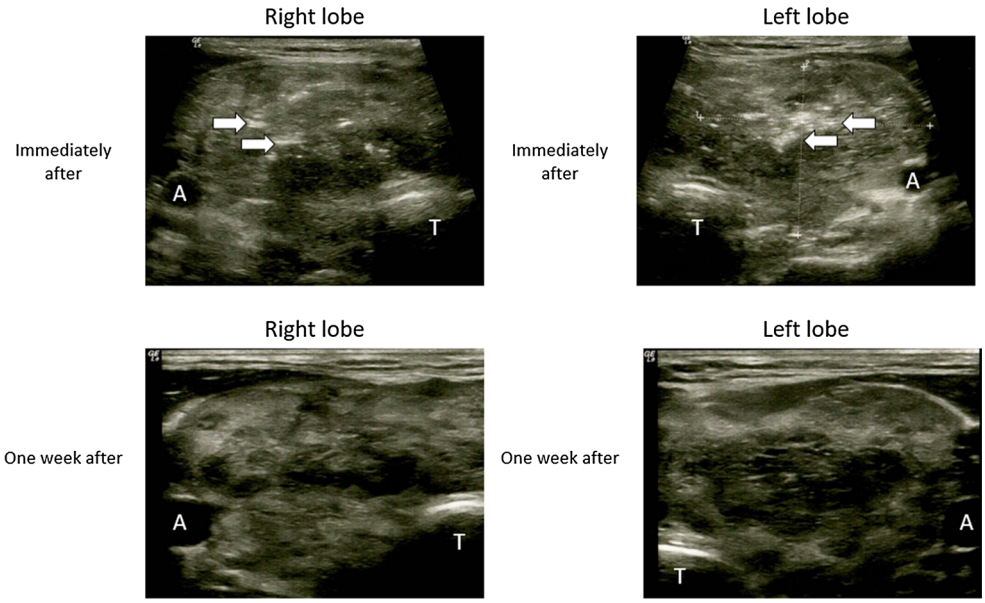

Fig. 1 Ultrasound pictures showing the effect of ablation to the central portion of the right and left thyroid lobes immediately after and 1 week after treatment

values > 99 IU/mL were considered positive while for TSHR autoantibody, any values ≥ 1 IU/L were considered positive.

Statistical analysis

Continuous data were expressed in mean ± standard deviation (SD). For comparison of categorical variables, chi-square tests and Fisher's exact tests were used while for continuous variables, the Mann–Whitney *U* test was used. The time to relapse was taken from the date of HIFU treatment to the date of relapse or last follow-up whichever was earlier. The cumulative risk of GD relapse was evaluated using Kaplan–Meier analysis and compared with log-rank test. Variables which were significant in the univariate analysis (by binary logistic regression) were entered into the multivariate analysis. All statistical analyses were performed using SPSS version 18.0 (SPSS). $p < 0.05$ was considered statistically significant.

Results

During this period, 78 patients underwent bilateral HIFU treatment for their persistent or relapsed GD and of these, 2 (2.6%) patients had missed their scheduled visits and 1 (1.3%) was lost to follow-up. Therefore, altogether, 75 (96.2%) patients completed their scheduled blood tests and visits and were eligible for the present study. None had concomitant nodules ≥ 1 cm necessitating an US-guided FNAC. All except one (98.7%) patient completed their HIFU treatment within one session and were discharged on the day of treatment. That patient failed to complete treatment within one session because of nausea and had to undergo a second session 1 week later.

The mean age at treatment was 42.1 ± 10.7 years old and the present cohort comprised mostly of females (84.0%) (Table 1). Almost half of the patients (46.7%) had a thyroid gland that was only palpable and not visible on neck extension. The mean duration of ATD use before treatment was 67.00 ± 26.33 months. The majority of patients (71/75 or 94.7%) were placed on carbimazole before treatment while the rest were placed either on propylthiouracil (3/75 or 4.0%) or lithium (1/75 or 1.3%) before treatment. None of the 75 patients had any evidence of active GO as assessed by ophthalmologists and the mean clinical activity score was 0 out of 7.

At baseline, the majority of patients had a concomitant elevated anti-Tg ($n = 63$, 84.0%) or anti-TPO ($n = 71$, $n = 94.7\%$) while all (100.0%) had an elevated TSHR (> 1 IU/L) antibody level. The overall total gland volume was relatively small with a mean of 21.78 ± 4.11 mL. The right lobe had a similar volume as the left lobe (11.03 mL vs. 10.68 mL, $p = 0.339$). However, there were no significant differences in lobe width, length, or depth between the two sides ($p = 0.213$, $p = 0.359$, $p = 0.717$, respectively).

In treatment parameters (Table 2), total energy delivered, energy per pulse, and total "on-beam" time were not statistically different between right and left lobes ($p = 0.097$, $p = 0.648$, and $p = 0.348$, respectively). The ablated volume (mL) was also not statistically different between the two lobes ($p = 0.123$).

Thyroid function status and disease remission

In the first 4 weeks, none of the 75 patients experienced any thyrotoxic symptoms and their serum TSH and FT4 levels were within the normal ranges. However, by the third visit

Table 1 Baseline patient characteristics

Parameters	Total no. of patients ($n = 75$)
Age at treatment (years)	42.05 ± 10.74
Sex (male:female)	12:63
Extent of neck swelling at presentation (by WHO classification)	
- Grade 1a (palpable but not visible when neck is extended)	35 (46.7)
- Grade 1b (palpable and visible when neck extended)	22 (29.3)
- Grade 2 (visible when neck is in the normal position)	18 (24.0)
Body weight (kg)	61.10 ± 12.85
Body height (m)	1.63 ± 0.07
Body mass index (kg/m^2)	23.11 ± 4.23
Total duration of ATDs use before ablation (months)	67.00 ± 26.33
Daily dose of carbimazole before ablation (mg)*	9.81 ± 5.84
Daily dose of propylthiouracil before ablation (mg)*	100 ± 0.00
Activity of Graves' ophthalmopathy (by CAS, 0–7)$^+$	0 ± 0
Serum pre-ablation free T4 (pmol/L)	17.61 ± 5.16
Serum pre-ablation TSH (mIU/L)	1.67 ± 3.02
Serum pre-ablation anti-thyroglobulin antibody (IU/mL)	686.95 ± 1212.69
Serum pre-ablation anti-peroxidase antibody (IU/mL)	2798.90 ± 3046.23
Serum pre-ablation TSHR antibody (IU/L)	9.50 ± 10.97
Perpendicular distance from skin to center of right lobe (mm)	1.81 ± 0.21
Perpendicular distance from skin to center of left lobe (mm)	1.81 ± 0.21
Pre-ablation thyroid dimensions and volume on ultrasonography	
Right lobe	
- Width (cm)	2.28 ± 0.37
- Length (cm)	5.28 ± 0.60
- Depth (cm)	1.74 ± 0.26
- Estimated volume (mL)	11.03 ± 2.55
Left lobe	
- Width (cm)	2.22 ± 0.34
- Length (cm)	5.35 ± 0.60
- Depth (cm)	1.71 ± 0.23
- Estimated volume (mL)	10.68 ± 2.64

Continuous data are expressed in mean ± standard deviation (SD)

For categorical data, numbers in parentheses are percentages

WHO, World Health Organization; *ATDs*, anti-thyroid drugs; *CAS*, clinical active score (0–7; severity classification); *TSH*, thyrotropin; *FT4*, free thyroxine; *TSHR*, thyrotropin receptor

*71 patients were taking carbimazole; 3 patients were taking propylthiouracil, and 1 patient was taking lithium before treatment

$^+$ Based on the most affected eye

(2 months), 5 patients became hyperthyroid and ATD was resumed. By the fourth visit (4 months), 9 more patients became hyperthyroid and ATD was resumed. By the fifth visit (6 months), 4 more patients became hyperthyroid. By the eighth visit (12 months), 31 (41.3%) patients had hyperthyroidism requiring the resumption of ATD. Interestingly, in the following 12 months, there was no further patient becoming hyperthyroid. At the time of analysis (February 2019), among the 31 patients who experienced a relapse, almost one-half (17/31 or 54.8%) chose to continue with ATD while 5 patients decided to undergo surgery and 8 patients had RAI. One patient had a second HIFU application and remained euthyroid.

The overall 12- and 24-month relapse rates following bilateral HIFU treatment were 41.3% and 41.3%, respectively (Fig. 2). Throughout the entire 24-month period, of the 44 who did not suffered a relapse, none became hypothyroid (FT4 = 11 pmol/L) and they all maintained euthyroidism without replacement.

Baseline characteristics including patient demographics, extent of neck swelling, body mass index, duration of ATDs, pre-

Table 2 Treatment parameters, pain score, and disease status at 24 months after HIFU ablation

	Cohort ($n = 75$)
Total energy delivered (kJ)	
- Right lobe	11.67 ± 4.24
- Left lobe	10.88 ± 2.97
Energy delivered per treatment pulse (J)	
- Right lobe	280.16 ± 28.43
- Left lobe	278.64 ± 26.39
Total "on-beam" time (min)	
- Right lobe	42.42 ± 17.68
- Left lobe	36.09 ± 10.08
Ablated volume (mL)*	
- Right lobe	5.47 ± 1.11
- Left lobe	5.28 ± 0.75
Pain scores by visual analogue scale (0–10)	
- During ablation	5.94 ± 2.59
- Immediately after ablation	2.91 ± 2.83
- Before hospital discharge	2.00 ± 2.09
Number (%) of patients in disease remission at:	
- 2 weeks	75 (100.0)
- 4 weeks	75 (100.0)
- 2 months	70 (93.3)
- 4 months	61 (81.3)
- 6 months	57 (76.0)
- 8 months	50 (66.7)
- 10 months	45 (60.0)
- 12 months	44 (58.7)
- 18 months	44 (58.7)
- 24 months	44 (58.7)

Continuous data are expressed in mean ± standard deviation (SD)

For categorical data, numbers in parentheses are percentages

WHO, World Health Organization; *US*, ultrasonography

*Estimated by the number of treated voxels multiplied by volume of each voxel (≈ 0.102 mL)

ablation thyroid function, and anti-thyroid autoantibodies were comparable between group I and group II (Table 3). Group I was taking significantly lower daily doses of carbimazole (CMZ) (8.21 mg vs. 11.78 mg, $p = 0.028$) and had a significantly lower mean pre-ablation TSHR antibody level than group II (5.76 IU/L vs. 13.72 IU/L, $p < 0.001$). Meanwhile, the total gland volume ($p = 0.546$), total energy delivered ($p = 0.121$), and duration of treatment time ($p = 0.639$) were also not significantly different between the two groups.

Factors leading to disease relapse at 24 months

In univariate analysis, higher daily dose of CMZ before ablation (OR = 1.125, 95% CI = 1.023–1.237, $p = 0.015$) and higher serum pre-ablation TSHR level (OR = 1.085, 95% CI = 1.022–1.152, $p = 0.007$) were significant factors leading to disease relapse. In the multivariate analysis, only higher serum TSHR level was a significant independent factor for disease relapse within 24 months (OR = 1.079, 95% CI = 1.014–1.148, $p = 0.016$) (Table 4).

Treatment-related complications

All patients except for one (98.7%) completed the bilateral treatment in one session. Pain was moderate during treatment (mean VAS = 5.94 ± 2.59) but improved immediately afterwards (mean VAS = 2.91 ± 2.83). On discharge, the mean pain score fell further (mean VAS = 2.00 ± 2.09) and 20 (26.7%) patients reported no pain (VAS of 0). Three (4.0%) patients reported residual neck discomfort at the first visit. No patients suffered skin burn. Three patients (4.0%) suffered hoarseness of voice from temporary vocal cord palsy. They all resolved without intervention at 4 weeks, 2 months, and 2 months, respectively. Minor skin redness and swelling were noted in 50 (66.7%) patients. Skin redness quickly subsided within a few hours and the general swelling gradually subsided over a period of 2 weeks.

Discussion

For patients with persistent or relapsed GD after adequate medical therapy, surgery and RAI have long been the recommended definitive treatment of choice [2, 12]. However, the decision for either modality does vary among institutions. For surgery, the benefits are the rapid control of hyperthyroidism, relief of any compressive symptoms, and nearly 100% cure rate while for RAI, the benefits are low treatment risks, no need for hospitalization, and relatively good efficacy (70–80% resolution of hyperthyroidism at 12 months) [2, 12]. Although RAI is a non-surgical option, the disadvantages are radiation exposure, slow induction of euthyroidism, potential worsening of GO, and deferral of pregnancy [2, 12, 13].

To overcome these shortcomings and avoid surgical risks, our group proposed the use of thermal ablation (namely, HIFU) as a treatment alternative. The treatment principle of HIFU ablation in GD is not dissimilar to that of a subtotal thyroidectomy in that a large proportion of thyroid parenchyma is destroyed in order to render euthyroidism while a small, non-ablated thyroid remnant maintains normal thyroid function. Our small pilot study confirmed the feasibility and safety of this modality [8] but to be confirmatory, a larger study with a longer follow-up period was necessary. The present study had twice as many patients as our earlier study and patients were followed for a minimum of 2 years.

Despite adopting similar study criteria and ablation technique as in the pilot study, the 12-month relapse rate appeared to be higher (41.30% vs. 26.70%). One explanation might be

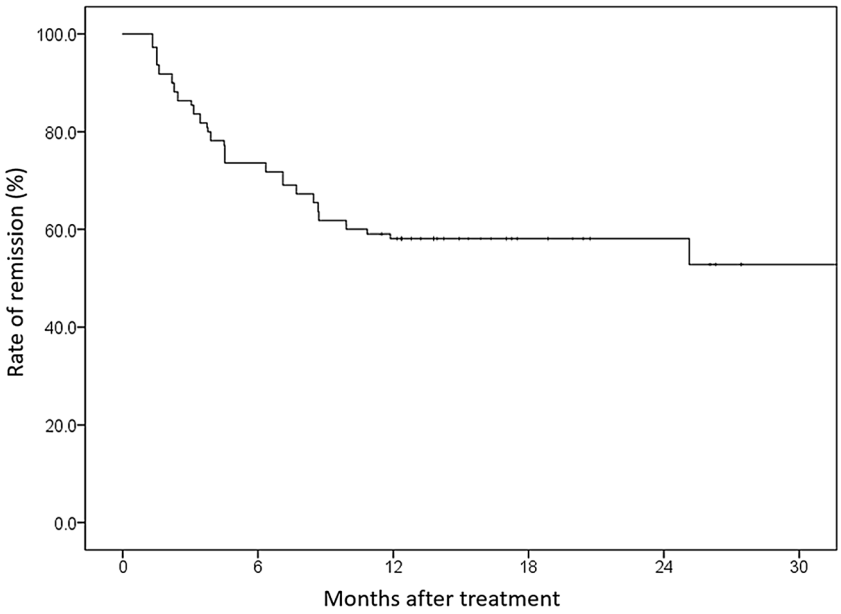

Fig. 2 Remission rate (%) after bilateral high-intensity focused ultrasound (HIFU) treatment (by Kaplan–Meier analysis)

Table 3 A comparison of patient characteristics and treatment parameters between those who remained in remission (group I) and those who relapsed (group II) at last follow-up

	Group I ($n = 42$)	Group II ($n = 33$)	p value
Age at ablation (years)	43.96 ± 11.06	39.72 ± 10.00	0.088^
Sex (male:female)	6:36	6:27	0.499+
Neck swelling (by WHO classification)			0.137+
- Grade 1a	4 (9.5)	3 (9.1)	
- Grade 1b	32 (76.2)	15 (45.5)	
- Grade 2	6 (14.3)	14 (42.4)	
- Grade 3	0 (0.0)	1 (3.0)	
Body mass index (kg/m^2)	22.95 ± 4.10	23.31 ± 4.45	0.499^
Duration of prior ATDs use (months)	65.24 ± 26.86	69.26 ± 25.89	0.147^
Daily dose of carbimazole (mg) before ablation	8.21 ± 3.89	11.78 ± 7.15	*0.028*^
Pre-ablation FT4 (pmol/L)	16.78 ± 3.18	18.65 ± 6.80	0.087^
Pre-ablation TSH (mIU/L)	2.14 ± 3.76	1.97 ± 1.67	0.141^
Pre-ablation anti-thyroglobulin antibody (IU/mL)	742.70 ± 1360.03	619.36 ± 1022.72	0.345^
Pre-ablation anti-peroxidase antibody (IU/mL)	3393.00 ± 3633.60	2090.91 ± 1960.69	0.186^
Pre-ablation TSHR antibody (IU/L)	5.76 ± 7.63	13.72 ± 12.64	< *0.001*^
Perpendicular distance from skin to center of right lobe (mm)	1.80 ± 0.21	1.83 ± 0.21	0.513^
Perpendicular distance from skin to center of left lobe (mm)	1.84 ± 0.18	1.78 ± 0.24	0.491^
Pre-ablation total thyroid volume (mL)	22.41 ± 4.21	21.08 ± 3.94	0.546^
Total energy delivered (kJ)	21.66 ± 7.00	25.44 ± 8.81	0.121^
Total "on-beam" time (min)	77.75 ± 27.20	80.50 ± 25.48	0.639^
Total ablated volume (mL)*	11.74 ± 2.84	11.59 ± 2.04	0.252

Continuous data are expressed in mean ± standard deviation (SD)

For categorical data, numbers in parentheses are percentages

Number in italics signifies statistical signifciance (i.e. p <0.05)

^ By Mann–Whitney U test

+ By chi-square test

*Estimated by the device, i.e., number of voxels × 0.102 mL

WHO, World Health Organization; *ATDs*, anti-thyroid drugs; *TSH*, thyrotropin; *FT4*, free thyroxine; *TSHR*, thyrotropin receptor

Table 4 Regression analysis of factors leading to disease relapse within 24 months of HIFU ablation

	Disease relapse within 24 months		
	Univariate analysis		
Variable	OR	95% CI	*p* value
Age (years)	1.040	0.993–1.087	0.095
Body mass index (kg/m^2)	1.020	0.914–1.138	0.721
Duration of ATD therapy (months)	1.006	0.988–1.024	0.512
Daily dose of CMZ (mg) before ablation	1.125	1.023–1.237	*0.015*
Serum pre-ablation FT4 (pmol/L)	1.078	0.976–1.189	0.138
Serum pre-ablation TSH (mIU/L)	1.163	0.929–1.456	0.860
Serum pre-ablation anti-Tg antibody (IU/mL)	1.000	0.995–1.006	0.664
Serum pre-ablation anti-peroxidase antibody (IU/mL)	1.000	0.999–1.001	0.089
Serum pre-ablation anti-TSHR (IU/L)	1.085	1.022–1.152	*0.007*
Perpendicular distance from skin to center of right lobe (mm)	1.749	0.590–10.128	0.622
Perpendicular distance from skin to center of left lobe (mm)	1.717	0.765–6.220	0.209
Pre-ablation total thyroid volume (mL)	1.085	0.958–1.229	0.922
Total energy delivered (kJ)	1.065	0.989–1.148	0.097
Total "on-beam" treatment (min)	1.004	0.983–1.025	0.704
Total ablated volume (mL)*	1.033	0.746–1.433	0.843

ATDs, anti-thyroid drugs; *CMZ*, carbimazole; *TSH*, thyrotropin; *FT4*, free thyroxine; *anti-Tg*, anti-thyroglobulin; *TSHR*, thyroid-stimulating hormone receptor

Number in italics signifies statistical signifciance (i.e. $p < 0.05$)

*Estimated by the device, i.e., number of voxels × 0.102 mL

because the baseline TSHR level was higher than that in the pilot study (9.50 IU/L vs. 4.30 IU/L), implying perhaps more severe GD in the present cohort [2]. This was somewhat supported by the fact that in the multivariate analysis, baseline TSHR level was the only significant, independent determinant of relapse for the first 2 years. Therefore, for the future, one should consider the baseline TSHR level as one of the important inclusions for this treatment modality.

Given that GD is essentially a disease affecting both thyroid lobes evenly, the amount of energy, treatment time, and power were similar between the right and left lobes.

The other finding worth highlighting was the fact that there was no additional patient with a relapse after 12 months. The 12-month relapse rate was essentially identical to that at 24 months. Therefore, it would appear that most, if not all, of the relapses occur in the first 12 months of treatment and perhaps, the interval before follow-up visits could be increased after 12 months. Another finding worth highlighting was that of those who remained relapse-free ($n = 44$ or 58.7%), none of them required levothyroxine replacement afterwards. This is important because of those who undergo RAI therapy, very few patients are able to maintain euthyroidism without levothyroxine replacement in the longer term because of the ongoing radiation damage [2, 12, 13]. Therefore, HIFU ablation might be the preferred non-surgical option if patients are overly concerned about treatment-related permanent hypothyroidism.

In terms of treatment safety, like in the previous study, vocal cord paresis remained to be the most common morbidity. However, it should be noted that this was not permanent and in our experience, all of the injuries recovered spontaneously within 2 months. The likely reason for this injury is likely due to the unintentional spread of heat energy to the nearby critical nerve structures like the recurrent laryngeal nerve. One possible way of reducing the risk of injury would be to avoid ablating areas close to the trachea–esophageal groove or to keep a safe distance from this dangerous area [14].

Despite our findings, we would like to acknowledge several limitations. First, this was a single-center/single operator' experience that may be difficult to be reproduced in other centers with less experience in HIFU ablation. In order to be a more acceptable technique, it would be important to have a multicenter study to confirm the current findings. Second, the present cohort was a highly selective group of patients with small-sized lobes and therefore, it remains unknown whether the results can be repeated in patients with bigger-sized GD. Third, the fact that only serum FT4 was used as a parameter for relapse might be inadequate because suppressed TSH levels at times can also be a sign of disease persistence after treatments and for some, a 24-month relapse rate of 41.3% is simply too high to be an acceptable treatment alternative. Fourth, we would like to acknowledge the fact that looking for hyper-echogenic changes might be insufficient in determining sufficient ablation as effective ablation could still

occur in the absence of these changes [15, 16]. The use of an US contrast agent during and after treatment might prove to be valuable when the thermally ablated region is not visible on standard B-mode images.

In conclusion, our study shows that US-guided HIFU ablation appears to be a relatively efficacious and safe therapeutic option for patients having persistent or relapsed GD. It might be a good treatment option in patients with a low baseline TSHR level.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Professor Stephen Cheng (Head of Department).

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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
- Retrospective
- Observational
- Single institution

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