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ULTRASOUND

Two sequential applications of high-intensity focused ultrasound (HIFU) ablation for large benign thyroid nodules

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Abstract

Objective High-intensity focused ultrasound (HIFU) ablation is a promising treatment for benign thyroid nodules but single application is less effective in larger-sized nodules. We aimed to assess the efficacy and safety of two sequential applications in larger-sized nodules.

Methods Fifty patients underwent ablation of a large-sized nodule (baseline volume ≥ 20 mL and diameter ≤ 50 mm). Thirty-one (62.0%) patients underwent single application (group I) while 19 (38.0%) underwent two sequential applications (group II). Nodule shrinkage (by volume reduction ratio or VRR), pain scores during and after ablation, and rate of vocal cord palsy (VCP), skin burn, and nausea/vomiting were compared between the two groups. *t* test or the Mann-Whitney *U* test was used for continuous variables while chi-square test was used for categorical variables. To determine factors for VRR, multivariate analysis was done by logistic regression analysis.

Results Total energy delivered and treatment time were significantly more in group II ($p < 0.001$ and $p = 0.001$, respectively). Total energy per nodule volume (kJ/mL) was also significantly greater in group II (1.01 kJ/mL vs. 0.57 kJ/mL, $p < 0.001$). The 6-month VRR was significantly greater in group II (56.74 ± 11.47% vs. 43.49 ± 12.03%, $p = 0.004$). Pain severity and rates of VCP, skin burn, and nausea/vomiting were comparable between the two groups ($p > 0.05$). Sequential application was an independent determinant of 6-month VRR (OR = 13.936, 95% CI = 1.738–197.399, $p = 0.036$).

Conclusions Sequential application led to better 6-month treatment efficacy than single application in large-sized nodules. Patients undergoing sequential application are not at greater risks of treatment-related side effects afterwards.

Key Points

- *Sequential application produces better 6-month efficacy over single application for large-sized nodules.*
- *Sequential HIFU application is well-tolerated and safe in patients with large-sized nodules.*
- *Sequential application takes longer and requires larger amount of pethidine and diazepam.*

Keywords Interventional ultrasonography · High-intensity focused ultrasound ablation · Nodular goiter · Ultrasound imaging · Ablation techniques

Abbreviations

HIFU	High-intensity focused ultrasound
Tg	Thyroglobulin
TSH	Thyroid-stimulating hormone
US	Ultrasonography
VAS	Visual analogue scale
VCP	Vocal cord palsy
VRR	Volume reduction ratio

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Introduction

Thyroid nodules are common. Although most are benign and will remain relatively unchanged over time, some do cause symptoms necessitating surgical resection [1–3]. However, surgery is not without risks and requires a general anesthesia and hospitalization. As a result, there has been a growing interest in developing less invasive, non-surgical techniques in treating benign thyroid nodules [4–6]. For predominantly solid or solid nodules, several thermal ablation techniques such as laser, microwave, and radiofrequency ablations have been shown to be effective [4–6]. High-intensity focused ultrasound (HIFU) is one of the new ablation techniques which is effective in causing significant nodule shrinkage and alleviating nodule-related symptoms [7–10].

However, it has been found that single application of HIFU ablation is generally less effective in causing shrinkage in larger-sized nodules [11, 12]. One possible reason for this is because a single application can only deliver a finite amount of energy into the target and so, the relative amount of energy per nodule volume in large-sized nodules can be significantly less than those in smaller-sized nodules [11]. In order to overcome this, one solution would be to apply more energy or two sequential applications to the same nodule within the same session. With improved techniques and increased experience [13], our group began to perform two sequential applications in nodules which would otherwise have been treated adequately by a single application. To our knowledge, the efficacy and safety of applying two sequential applications to these nodules have not previously been evaluated or reported. The present study aimed to compare the efficacy and safety of two sequential applications with those following single application in large-sized nodules.

Methods

This retrospective analysis was approved by local institutional review board. All relevant clinical and treatment data were recorded prospectively after obtaining informed consent from patients. Consecutive patients who underwent HIFU ablation for a symptomatic, solid, or predominantly solid (< 30% cystic areas) benign thyroid nodule from August 2015 to March 2018 were analyzed. At our institution, only patients who were indicated but refused surgery were considered for HIFU ablation. To be eligible for analysis, first, the nodule had to be proven benign on fine needle aspiration cytology (Bethesda category II) [14] with the center lying within the treatable depth (i.e., 5–30 mm from the skin). Second, the estimated baseline nodule volume had to be ≥ 20 mL on ultrasound (US) volumetry (see later). Third, the longest nodule dimension had to be ≤ 50 mm on US because from previous experience, nodules with a dimension > 50 mm could not have been adequately covered by a single application alone. Lastly, patients had to have normal serum levels of free T4 (FT4) and thyroid-stimulating hormone (TSH) levels. For the present study, any patients with previous ablation, follow-up of < 6 months, or missing data on sedation dose or pain level were excluded from analysis. Patient and nodule characteristics, treatment parameters, amount of sedation and analgesia used during treatment, the extent of nodule shrinkage (%) at 3 and 6 months, clinical nodule grade, symptom score, percentage rise in thyroglobulin (Tg) after treatment, severity of pain during and after treatment, and treatment-related complications were compared between those who underwent single ablation (group I) and those who underwent two sequential ablations (group II) within one session.

Case selection

At the beginning of the study, single application was applied to nodules of all sizes unless it was technically not feasible to be done with a single application (see inclusion criterion earlier). An example would be a nodule with a diameter > 50 mm. However, after April 2017, sequential application (i.e., one ablation followed immediately by another within the same session) was performed for all nodules with a baseline volume ≥ 20 mL.

Pre-treatment clinical evaluation

All thyroid swellings were clinically graded according to the World Health Organization (WHO) grading system [15] while the severity of pressure/local symptoms was rated on a visual analogue scale (VAS, 0–10 cm).

Single and sequential applications

All patients were asked to fast overnight and admit in the morning. Serum thyroid function tests (free T4 and TSH levels), Tg, and anti-thyroid autoantibodies were checked. All single and sequential ablations were performed by one person (B.H.L.) using a commercially available US-guided HIFU device. For single application, the objective was to ablate the entire nodule one time while for sequential application, the objective was to ablate the entire nodule twice (i.e., re-ablating the areas covered in the first application).

Before treatment, all patients were placed in a supine position with the neck slightly extended and received a bolus of intravenous diazepam (Actavis) (10–20 mg) and pethidine (Martindale Pharmaceuticals) (50–100 mg). Patients' heart rate, blood pressure, respiration rate, and peripheral oxygenation were monitored throughout. Patients were asked to show a hand sign if the pain became too severe. In that situation, either the energy was lowered or more medications were administrated.

The US-guided HIFU device comprised an energy generator, a treatment head, a skin cooling device, and a touchscreen interface for planning. The treatment head incorporated an image transducer (7.5 MHz, 128 elements, linear array) and HIFU transducer (3 MHz, single element, 60 mm in diameter). The device computer (Beamotion version no. TUS 3.2.2, Theraclion) automatically divided the nodule into multiple ablation voxels. Each voxel measured approximately 7.3 mm in thickness and 5 mm in width and received a continuous 8-s pulse of HIFU energy followed by 30–40 s of cooling time before the beam was moved to the adjacent voxel. Shortly after, sonographic changes like hypoechoic marks, hypoechogenic changes, and cavitations would normally be seen (Fig. 1).

To ensure safety, nearby structures like the carotid artery, trachea, and skin were marked out on the treatment screen before the start of treatment by the operator. To avoid inadvertent heat injury to important surrounding structures, the device automatically selected the safety margins for the skin, the trachea, and the recurrent laryngeal nerve and from the ipsilateral carotid artery. A laser-based movement detector enabled immediate power interruption when the patient moved or swallowed during ablation. To avoid skin burn, the skin was cooled by a balloon (filled with 10 °C liquids) at the tip of the treatment head. Both the total amount of energy delivered to the nodule (in kJ) and the "on-beam" (sonification) time taken (in min) were automatically recorded by the device's computer. The "on-beam" treatment time was the duration between the first to the last pulse (in min). Oral diet was resumed immediately afterwards and patients were discharged home a few hours after treatment. Afterwards, a transcutaneous laryngeal US was done to assess the mobility of both vocal cords as this was found to be a highly accurate alternative to laryngoscopy [16]. Vocal cord palsy (VCP) was defined as having an impaired or absent movement in one of the vocal cords corresponding to the ablated side. All patients were seen 4 days after treatment at the clinic where serum TSH, free T4, and Tg levels were checked again.

Pain assessment

Analgesics were not routinely prescribed after treatment. Upon completion of treatment, patients were asked to rate their overall (global) pain experience during treatment, 2 h after treatment, and the following morning. The pain level was scored on a VAS from 0 to 10 (0 = no pain and 10 = worse possible pain) by one dedicated person not directly involved with the study.

Nausea and vomiting assessment

Two hours after treatment, patients were specifically asked about whether they had any feeling of nausea which was defined as an unpleasant urge to vomit. If they had any vomiting episode afterwards, these were recorded. No antiemetic prophylaxis was routinely given in the study period.

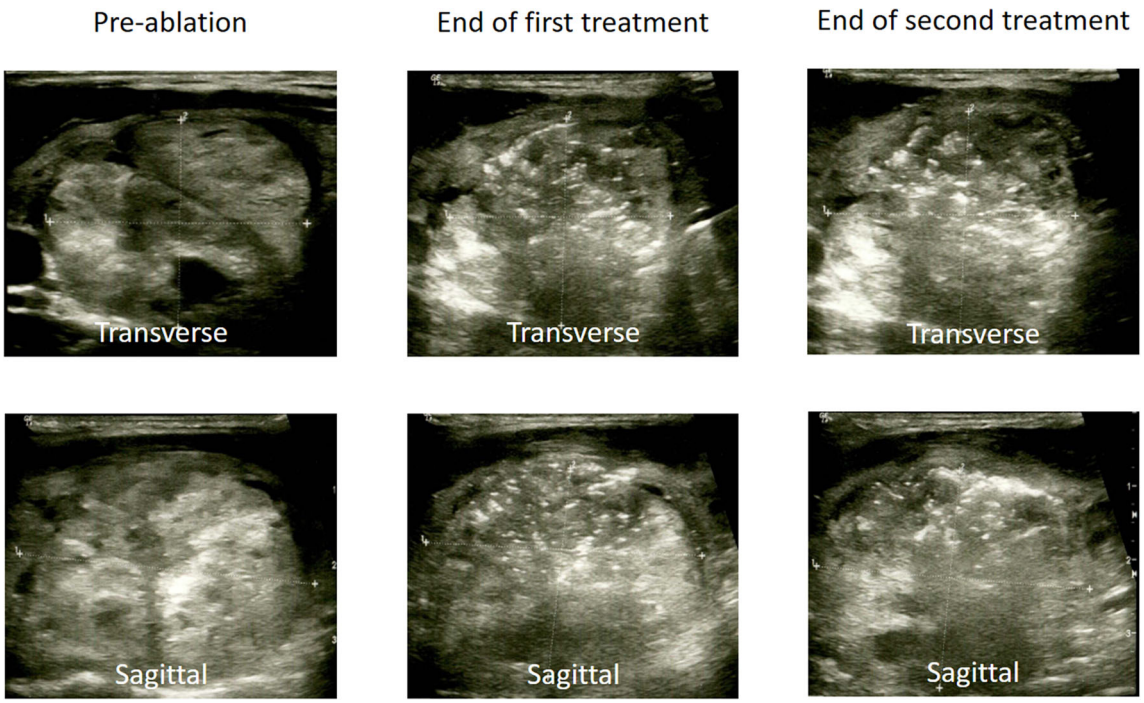

Fig. 1 Ultrasound pictures taken before and after first and second treatments in a patient who underwent sequential treatment. Note the increasing proportion of hyperechoic marks within the nodule at the end of the second treatment

Treatment efficacy

Each nodule was measured by US on the day of treatment (baseline) and at 3 months and 6 months. Nodule dimensions were measured using the LOGIQ e (GE Healthcare) scanner equipped with a 10–14 MHz linear matrix transducer. Three orthogonal diameters of the index nodule (its longest diameter and two other perpendicular diameters) were measured. In general, the longest diameter was the cranio-caudal dimension (length) of the nodule while the other two perpendicular diameters were the medio-lateral (width) and antero-posterior (depth) dimensions of the nodule. All measurements were made to the nearest 0.1 mm. To estimate nodule volume, we used the formula: volume (mL) = (width (in cm) × length (in cm) × depth (in cm)) × (π 6) where π was taken as 3.14159. The volume reduction ratio (VRR) was calculated based on the formula: [Baseline volume − volume at visit] − [Baseline volume] × 100. Treatment success was defined as ≥ 50% volume reduction at 6 months from baseline. At 3 and 6 months, patients in both groups had their swelling assessed clinically using the WHO grading system [15] and were asked to rate how much their obstructive and/or local pressure symptoms had improved from baseline (0 = same; 1 = slight improvement; 2 = moderate improvement; 3 = significant improvement).

Treatment cost

Only direct medical costs were calculated. These included the procedure, associated esthesia, and length of hospitalization. Indirect costs such as loss of productivity and wages were not included. The unit cost of each service has been listed in the Government Gazette [17].

Statistical analysis

The primary endpoint was the 6-month VRR. Continuous variables were expressed as mean ± SD and/or median and interquartile range (IQR) when appropriate. For comparison of continuous variables, *t* test was used when the data followed a normal distribution. Otherwise, the Mann-Whitney *U* test was used. Chi-square or Fisher's exact test was used to compare categorical variables. For comparison between the baseline and 3- and 6-month VRRs, the significance level was adjusted based on Bonferroni correction. To determine factors affecting 6-month VRR, univariate and multivariate analyses were done by logistic regression analysis. For multivariate analysis, only parameters significantly associated with 6-month VRR were entered together using the step-down procedure. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc.). All significance tests were two-tailed and those with a *p* value less than 0.05 were considered statistically significant unless they were Bonferroni corrected.

Results

During the study period, 338 consecutive patients completed their treatment for a benign thyroid nodule. Of these, 57 (16.9%) patients had a nodule with a baseline volume ≥ 20 mL but with none of the three dimensions ≤ 50 mm on pre-ablation US. Among them, two (3.5%) patients underwent a previous ablation, 3 (5.3%) patients had a follow-up < 6 months, and 2 (3.5%) patients had missing pain scores during or after treatment. As a result, 50 (87.7%) were analyzed. Of these, 31 (62.0%) complete single application (group I) and 19 (38.0%) completed two sequential applications (group II). All patients completed their respective treatment successfully within the same session and were able to be discharged home on the same day.

Patient baseline characteristics, treatment parameters, and amount of sedation and analgesia required were compared between groups I and II (Table 1). Patient age, sex ratio, body weight, body height, body mass index, WHO nodule grade, and symptom score were comparable between the two groups. Side of nodule, longest nodule dimension, baseline nodule volume, and distance from skin to center of nodule were also comparable between the two groups. Baseline thyroid function and anti-thyroid autoantibody levels were not significantly different between the two groups ($p > 0.05$).

However, as anticipated, the total energy delivered and total "on-beam" treatment time in group II were significantly more than those in group I (41.76 kJ vs. 20.90 kJ, $p < 0.001$ and 70.52 min vs. 59.03 min, $p = 0.001$, respectively). The total energy per nodule volume (kJ/mL) was also significantly greater in group II (1.01 kJ/mL vs. 0.57 kJ/mL, $p < 0.001$). However, the total "on-beam" time per nodule volume did not differ between the two groups (1.65 min/mL vs. 1.81 min/mL, $p = 0.285$). Given the longer treatment time, the amounts of pethidine and diazepam given were significantly greater in group II than in group I (89.08 ± 23.16 mg vs. 67.21 ± 20.93 mg, $p = 0.002$ and 18.82 ± 5.73 mg vs. 9.53 ± 3.07 mg, $p < 0.001$, respectively).

On day 4 after treatment, serum TSH significantly dropped while FT4 rose relative to baseline for both groups (Table 2). For group I, TSH significantly dropped from 1.32 ± 1.19 mIU/L to 0.90 ± 0.85 mIU/L ($p = 0.029$) while FT4 rose from 16.47 ± 1.93 pmol/L to 18.18 ± 2.82 pmol/L ($p = 0.020$). In group II, TSH also significantly dropped from 1.07 ± 0.70 mIU/L to 0.47 ± 0.40 mIU/L ($p = 0.011$) while FT4 rose from 16.94 ± 2.36 pmol/L to 20.00 ± 5.27 pmol/L ($p = 0.015$).

For Tg, in group I, the mean level significantly rose from 552.13 ± 902.27 ng/mL to 2269.63 ± 1932.35 ng/mL ($p < 0.001$). The mean Tg rise was 1143.95 ± 1583.01%. In group II, the mean level also increased from 786.53 ± 1328.41 ng/mL to 2509.60 ± 2252.21 ng/mL and the mean serum Tg rise after treatment was 1526.31 ± 1232.91%. However, the extent of Tg rise was comparable between the two groups ($p = 0.934$).

Table 1 A comparison of patient baseline characteristics, treatment parameters, and amount of sedation and analgesia required between those who underwent single HIFU ablation treatment (group I) and those who underwent two sequential HIFU ablation treatment (group II)

Variable	Group I ($n = 31$)	Group II ($n = 19$)	p value
Patient characteristics			
- Age at treatment (years)	50.87 ± 9.84	52.89 ± 16.15	1.000^
- Sex (male:female)	9:22	4:15	0.742+
- Body weight (kg)	63.55 ± 7.89	59.84 ± 5.84	0.091^
- Body height (m)	1.66 ± 0.07	1.62 ± 0.05	0.082^
- Body mass index (kg/m^2)	23.36 ± 2.85	23.40 ± 2.42	0.639^
WHO nodule grade at baseline			0.717+
- Grade 1a (palpable but not visible when neck is extended)	0 (0.0)	0 (0.0)	
- Grade 1b (palpable and visible when neck is extended)	7 (22.6)	3 (15.8)	
- Grade 2 (visible when neck is in the normal position)	19 (61.3)	11 (57.9)	
- Grade 3 (visible from distance)	5 (16.1)	5 (26.3)	
Pressure symptom score by VAS at baseline (in median (IQR))	4 (2.0)	4 (2.0)	0.612*
Characteristics of the index nodule			
- Side of the nodule (right:left)	13:17	5:14	0.362+
- Longest nodule diameter (cm)	4.26 ± 0.70	4.36 ± 0.69	0.345^
- Nodule volume at baseline# (mL)	38.76 ± 13.49	44.88 ± 13.45	0.059^
- Distance from skin to center of nodule (cm)	1.73 ± 0.41	1.72 ± 0.39	0.712^
Baseline blood tests			
- Serum TSH (mIU/L)	1.32 ± 1.19	1.07 ± 0.70	0.797^
- Serum free T4 (pmol/L)	16.47 ± 1.93	16.94 ± 2.36	0.208^
- Anti-Tg autoantibody (IU/mL)	118.34 ± 114.11	223.53 ± 480.84	0.081^
- Anti-TPO autoantibody (IU/mL)	185.35 ± 323.89	173.84 ± 337.06	0.102^
Treatment parameters			
- Total energy delivered (kJ)	20.90 ± 4.23	41.76 ± 10.19	< 0.001^
- Total energy/nodule volume (kJ/mL)	0.57 ± 0.13	1.01 ± 0.37	< 0.001^
- Total "on-beam" treatment time (min)	59.03 ± 15.60	70.52 ± 11.38	0.001^
- Total "on-beam" time/nodule volume (min/mL)	1.65 ± 0.62	1.81 ± 0.50	0.285^
- Energy per each pulse (J)	321.38 ± 26.27	329.89 ± 40.25	0.511^
Amount of analgesia and sedation required during ablation			
- Intravenous pethidine (mg)	67.21 ± 20.93	89.08 ± 23.16	0.002^
- Intravenous diazepam (mg)	9.53 ± 3.07	18.82 ± 5.73	< 0.001^

Continuous variables are expressed in mean ± standard deviation

TSH thyroid-stimulating hormone, *Anti-Tg* anti-thyroglobulin, *TPO* thyroid peroxidase

Nodule volume at baseline = (width × depth × length) × (π 6) where π was taken as 3.14159

^By two-sample *t* test

+ By chi-square test

*By Mann-Whitney *U* test

In terms of efficacy, the 3- and 6-month VRRs of the index nodule were significantly greater in group II than in group I (47.69 ± 11.77% vs. 36.19 ± 13.23%, $p = 0.015$ and 56.74 ± 11.47% vs. 43.49 ± 12.03%, $p = 0.004$) (Fig. 2). The proportions of nodules with VRR ≥ 50% at 6 months in groups I and II were 8/31 (25.8%) and 16/19 (84.2%), respectively ($p < 0.001$). In group I, the mean nodule volume was reduced from 38.76 ± 13.49 mL at baseline to 22.17 ± 10.31 mL at 6 months ($p < 0.001$) while in group II, the mean nodule volume was reduced from 44.88 ± 13.45 mL at baseline to 19.78 ± 9.85 mL at 6 months ($p < 0.001$). WHO nodule grade was also significantly lower at 6 months after ablation in group II ($p < 0.001$), despite the similar 6-month symptom score in both groups ($p = 0.663$).

In terms of pain score, the two groups did not differ significantly during treatment (5.65 ± 3.18 vs. 5.63 ± 3.57, $p = 0.837$), at 2 h after treatment (2.92 ± 2.77 vs. 3.16 ± 1.81, $p = 0.617$) and on the following morning after treatment

Table 2 A comparison of blood parameters, treatment efficacy, and clinical outcomes between those who underwent single HIFU ablation treatment (group I) and those who underwent two sequential HIFU ablation treatment (group II)

Variable	Group I ($n = 31$)	Group II ($n = 19$)	p value
Serum TSH (mIU/L)			
- Baseline	1.32 ± 1.19	1.07 ± 0.70	0.797^
- Day 4 after treatment	0.90 ± 0.85*	0.47 ± 0.40*	0.197^
Serum FT4 (pmol/L)			
- Baseline	16.47 ± 1.93	16.94 ± 2.36	0.208^
- Day 4 after treatment	18.18 ± 2.82*	20.00 ± 5.27*	0.173^
Serum thyroglobulin (ng/mL)			
- Baseline	552.13 ± 902.27	786.53 ± 1328.41	0.633^
- Day 4 after treatment	2269.63 ± 1932.35*	2509.60 ± 2252.21*	0.955^
- Percentage rise (%)[#]	1143.95 ± 1583.01	1526.31 ± 1232.97	0.934^
Serum anti-Tg autoantibody (IU/mL)			
- Baseline	118.34 ± 114.11	223.53 ± 480.84	0.081^
- Day 4 after treatment	38.52 ± 36.47*	32.46 ± 30.41*	0.102
Serum anti-TPO autoantibody (IU/L)			
- Baseline	185.35 ± 323.89	173.84 ± 337.06	0.457^
- Day 4 after treatment	192.66 ± 237.81	199.37 ± 210.37	0.381^
Treatment efficacy/extent of shrinkage (%)			
- 3-month VRR	36.19 ± 13.23*	47.69 ± 11.77*	0.015^
- 6-month VRR	43.49 ± 12.03*	56.74 ± 11.47*	0.004^
WHO nodule grade at 6 months			< 0.001[+]
- Grade 1a (palpable but not visible when neck is extended)	1 (3.2)	10 (52.6)	
- Grade 1b (palpable and visible when neck is extended)	7 (22.6)	5 (26.3)	
- Grade 2 (visible when neck is in the normal position)	18 (58.1)	3 (15.8)	
- Grade 3 (visible from distance)	5 (16.1)	1 (5.3)	
Symptom improvement score at 6 months			0.663[+]
- 0 (no improvement)	0 (0.0)	0 (0)	
- 1 (slight improvement)	3 (9.7)	2 (6.5)	
- 2 (moderate improvement)	11 (35.5)	5 (26.3)	
- 3 (significant improvement)	14 (45.2)	12 (63.2)	
Treatment-related complication			
- Vocal cord palsy	1 (3.2)	0 (0.0)	1.000[+]
- Skin burn	0 (0.0)	0 (0.0)	–
- Nausea or vomiting	1 (3.2)	3 (15.8)	0.355[+]

Continuous variables are expressed in mean ± standard deviation

VRR volume reduction ratio, *VAS* visual analogue scale (0 = no pain; 10 = worst possible pain), *Tg* thyroglobulin

[#] Based on the formula: [Serum Tg on day 4 − serum Tg at baseline] [serum Tg at baseline] × 100

*$p < 0.025$ (with Bonferroni correction), compared with baseline, by paired t test

^By two-sample t test

[+] By chi-square test

(1.55 ± 1.77 vs. 1.28 ± 1.22, $p = 0.300$). Rates of VCP and skin burn were not significantly different between the two groups. The incidence of nausea or vomiting was higher in group II but not significantly different (3.2% vs. 15.8%, $p = 0.355$). Only one (3.2%) patient in group I suffered from nausea while in group II, one (5.3%) had nausea and two (10.5%) had vomiting afterwards. The total cost of single application was USD 1987.20 while the total cost of sequential application was USD 2036.50. The cost difference of USD 49.30 was solely due to the longer treatment time in group II. There were no additional consumables used during sequential application.

In the univariate analysis, factors associated with VRR ≥ 50% were sequential application (OR = 15.333, 95% CI = 3.517–66.844, $p < 0.001$), total energy delivered (OR = 1.099,

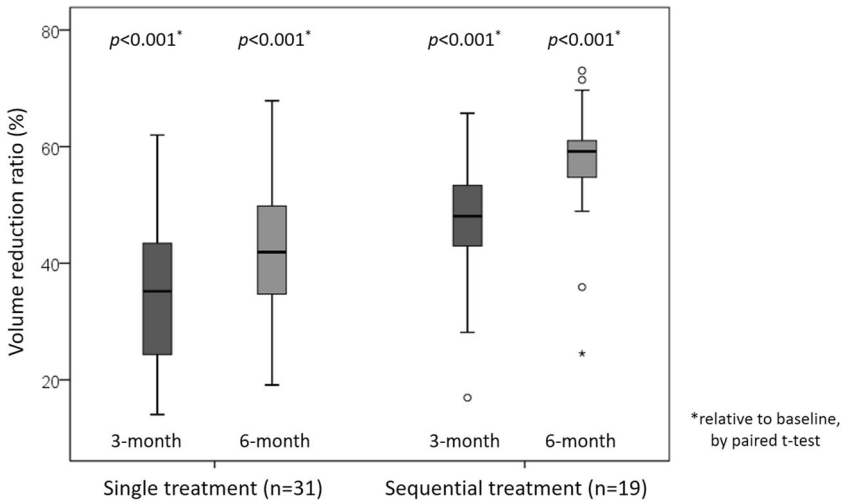

Fig. 2 A box plot showing the volume reduction ratio (VRR) (%) in single and sequential HIFU treatments in large-sized (≥ 20 mL) nodules

95% CI = 1.030–1.173, $p = 0.004$), total energy per volume nodule (OR = 30.066, 95% CI = 2.492–362.765, $p = 0.007$), and total "on-beam" treatment time (OR = 1.062, 95% CI = 1.014–1.111, $p = 0.010$) (Table 3). When all these factors were entered into the model at the same time, only sequential application was an independent factor for 6-month VRR ≥ 50% (OR = 13.936, 95% CI = 1.738–197.399, $p = 0.036$).

Discussion

The major advantages of HIFU over other established thermal ablation techniques such as laser, microwave, or radiofrequency ablation are first, it does not require the insertion of a needle into the target (i.e., it is truly non-invasive) and second, the entire ablation can be automated with little inputs from the operator [18–21]. However, similar to other ablation techniques, single application is often less effective in causing shrinkage in larger-sized nodules [11, 12, 22]. The overall shrinkage rate (or VRR) at 6 months following single HIFU treatment in small (< 10 mL), medium (10–30 mL), and large (>30 mL) nodules was reported to be 77.6%, 67.9%, and 48.1%, respectively [11]. One postulation is because there is a limit on how much energy can be deposited in a single application. In fact, the amount of energy per volume can be up to four times less in large-sized nodules [11]. The primary objective of the present study was to see whether by applying more energy (in the form of two sequential applications) to large-sized (≥ 20 mL) nodules could result in a significantly better shrinkage (VRR) after 6 months.

In agreement with the initial postulation, our data showed that sequential application resulted in significantly better

Table 3 Binary logistic regression analysis of factors associated with volume reduction ratio (VRR) ≥ 50% at 6 months

Variable	VRR ≥ 50% at 6 months^		
	Univariate analysis		
	OR	95% CI	*p* value
Age (years)	0.979	0.935–1.025	0.371
Sex	1.689	0.465–6.135	0.426
Body mass index (kg/m^2)	0.995	0.807–1.227	0.963
Baseline nodule volume (mL)	0.999	0.958–1.040	0.943
Side of nodule	1.125	0.686–2.337	0.667
Sequential application	15.333	3.517–66.844	< 0.001
Total energy delivered (kJ)	1.099	1.030–1.173	0.004
Total energy per nodule volume (kJ/mL)	30.066	2.492–362.765	0.007
Total "on-beam" treatment time (min)	1.062	1.014–1.111	0.010
Total treatment time per nodule volume (min/mL)	2.315	0.817–6.558	0.114
Average energy per each pulse (J)	0.996	0.978–1.014	0.668

^Entered as a dichotomized variable (≥ 50% or < 50%); there were 24 (48.0%) patients achieving VRR ≥ 50% at 6 months

3- and 6-month VRRs than single application (47.69 vs. 36.19%, $p = 0.015$ and 56.74% vs. 43.49%, $p = 0.004$, respectively). Also, the proportion of nodules reaching a VRR ≥ 50% at 6 months was greater following sequential application (84.2% vs. 25.8%, $p < 0.001$). This was despite the fact that group II actually had a greater baseline nodule volume than group I (44.88 mL vs. 38.76 mL, $p = 0.059$). More importantly, of all the potential factors, sequential application was the only independent factor associated with a better 6-month VRR (OR = 13.936, 95% CI = 1.738–197.399, $p = 0.036$). In addition, the clinical response (as measured by WHO nodule grade) at 6 months following sequential application was significantly more than that following single application ($p < 0.001$).

Although prolonged treatment time, patient tolerability, and risk of complications were some of the concerns with sequential application, our data found that both pain score and complications were comparable with those in single application. The only noticeable side effect was the higher incidence of nausea and vomiting (15.8% vs. 3.2%, $p = 0.355$) but this should not come as a surprise as higher doses of pethidine (an opioid medication) and diazepam were used during sequential application.

One point worth highlighting was that although the total energy delivered was doubled in sequential application (41.76 kJ vs. 20.90 kJ, $p < 0.001$), the treatment time increase was less than doubled (70.52 min vs. 59.03 min, $p = 0.001$). This could be explained by the fact that in the latter period, the ablation computer software was upgraded to allow a shorter treatment cycle between treatment pulses.

Another point worth noting was that although the increase in energy per nodule volume was a significant factor attributing to better shrinkage following sequential application, it was unclear to what extent the shrinkage could be increased further with more energy. Most likely, beyond a certain level of energy, the extent of shrinkage would reach a plateau. Perhaps, future studies might evaluate this and optimize treatment efficacy for benign thyroid nodules.

Despite these findings, we would like to acknowledge several shortcomings. First, our study was only a moderate-sized study and so, some of the non-significant findings were prone to type II errors. Second, given the study design (i.e., non-randomized assignment) and the fact that sequential applications were mostly carried out in the latter study period, it was impossible to tell whether the favorable outcomes might have been related to the better patient selection and treatment experience over time. Nevertheless, at least, our study showed that with appropriate patient selection, sequential application was feasible and safe and was able to produce superior efficacy. Third, given that our study was based entirely on early nodule characteristic changes after ablation [23], it would have been more interesting to evaluate the changes in blood flow within the treated nodule by color-power Doppler or contrast-enhanced US/US elastography as they can provide further insights into how nodules might respond following single or sequential application [24, 25].

Conclusion

Our study showed that sequential application was associated with superior 3- and 6-month efficacy and comparable safety profile as single application in large-sized (≥ 20 mL) thyroid nodules. Sequential application was the only independent factor for 6-month VRR. However, patients undergoing sequential application are expected to need significantly longer treatment time and receive greater amount of analgesia and sedation during treatment.

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Compliance with ethical standards

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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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