European Radiology (2019) 29:1469–1478
https://doi.org/10.1007/s00330-018-5671-0

ULTRASOUND

Role of second high-intensity focused ultrasound (HIFU) treatment for unsatisfactory benign thyroid nodules after first treatment

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Received: 14 May 2018 / Revised: 3 July 2018 / Accepted: 13 July 2018 / Published online: 7 August 2018

Abstract

Background We aimed to assess the efficacy and safety of second high-intensity focused ultrasound (HIFU) ablation treatment in benign thyroid nodules that had failed to shrink by > 50% 6 months after the first treatment.

Methods Twenty-eight patients who did not achieve 50% volume reduction at 6 months after the first HIFU treatment underwent a second HIFU treatment. Nodule volume was measured on ultrasound at baseline, 3 months and 6 months. Extent of nodule shrinkage (by volume reduction ratio) (VRR) = [Baseline volume – volume at 6 months]/[Baseline volume] * 100. Treatment success was defined as VRR > 50%. Obstructive symptom score (by 0–10 visual analogue scale, VAS) was evaluated for 6 months after treatment.

Results No complications occurred after the second treatment. The mean 6-month VRR was 21.78 ± 16.87% with a median (range) of 16.16 (1.63–54.07)%. At 6 months, only two (7.1%) patients achieved treatment success, while nine (32.1%) patients had VRR < 10%. However, relative to baseline (3.96 ± 1.04), the mean VAS significantly improved at 3 and 6 months (2.96 ± 1.43, $p<0.001$ and 2.58 ± 1.39, $p<0.001$, respectively). There was a significant correlation between VRR and improvement in VAS score at 6 months ($\rho=0.438$, $p=0.025$). Greater nodule volume before the second treatment (OR=1.169, 95% CI=1.004–1.361, $p=0.045$) was a significant factor for greater VRR after the second treatment.

Conclusions Although subjective obstructive symptoms continued to improve after the second treatment, the actual extent of nodule shrinkage was small. Larger-volume nodules tended to shrink more significantly than smaller-volume nodules in the second treatment.

Key Points

- *Second treatment resulted in small shrinkage in unsatisfactory nodules after first treatment.*
- *Obstructive symptoms tended to continue to improve after second treatment.*
- *Larger-size nodules tended to respond better in the second treatment.*

Keywords Interventional ultrasonography · High-intensity focused ultrasound ablation · Treatment efficacy · Ultrasound imaging · Ablation techniques

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Abbreviations

HIFU	High-intensity focused ultrasound
TSH	Thyroid stimulating hormone
US	Ultrasonography
VCP	Vocal cord palsy
VRR	Volume reduction ratio

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 anaesthesia and hospitalisation. As a result, there has been an increasing interest in developing less invasive, non-surgical techniques in treating benign thyroid nodules [4, 5]. For predominantly solid or solid nodules, several image-guided thermal ablation techniques like laser ablation, microwave and radiofrequency ablation have been shown to be effective [4, 5]. As a result, they have been suggested as an alternative to surgery or radioiodine therapy [6, 7]. High-intensity focused ultrasound (HIFU) is a new ablation technique that has also been shown to cause significant nodule shrinkage and improve obstructive symptoms shortly after single treatment [8–10]. It is a technique that can be performed successfully without either sedation or anaesthesia [11, 12].

However, it appears not all thyroid nodules can shrink satisfactorily with a single treatment. From previous studies, approximately 20% of benign thyroid nodules failed to shrink by > 50% at 6 months [13, 14]. Although surgical resection remains a therapeutic option when an ablated nodule has failed to shrink satisfactorily and is causing persistent obstructive symptoms, many of these patients still prefer a less invasive option like a second ablation treatment to the same swelling. Although the results of two or more treatments after the first treatment have been encouraging in other forms of thermal ablation [15, 16], they are less well-described in HIFU ablation. Therefore, the present study aimed to evaluate the efficacy and safety of second HIFU ablation treatment in benign thyroid nodules that had failed to shrink satisfactorily (i.e. a volume shrinkage < 50% at 6 months following the first treatment) and to identify factors that may affect the efficacy of the second treatment.

Methods

This retrospective analysis was approved by the local institutional review board and registered at *www.clinicalTrials.gov* (NCT03331172). All relevant clinical and treatment data were recorded prospectively after obtaining informed consent. Consecutive patients who underwent a second HIFU treatment for a solid or predominantly-solid (< 30% cystic areas) benign thyroid nodule from 2015 to 2017 were included. During the study period, the eligibility for the second treatment included: first, the nodule had to be proven benign on fine needle aspiration cytology (Bethesda category II) [17] after the first treatment; second, the centre of the nodule had to be within the treatable depth of 7–30 mm from the skin surface; third, the swelling (which can either be a solitary or dominant nodule in a multinodular gland) had to be causing a degree of obstructive discomfort; fourth, the nodule had to be shrunk by < 50% 6 months after the first treatment; fifth, the swelling had to have its longest diameter ≥ 20mm but ≤ 60mm on ultrasonography (US). All second treatments were carried out within 6 weeks of the 6-month visit after the first treatment. Any patients with < 6 months' follow-up following the second treatment were excluded from analysis.

Before (i.e. baseline), 3 and 6 months after the second treatment, the three orthogonal dimensions of the index nodule were measured on US by an independent experienced sonographer. 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 recorded. In general, the longest diameter was the cranio-caudal dimension (length) of the nodule while the other two perpendicular diameters were the mediolateral (width) and antero-posterior (depth) dimensions of the nodule. All measurements were to the nearest 0.1 mm. To work out the nodule volume, we used the formula: volume (ml) = (width (in cm) × depth (in cm) × length (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 VRR > 50%.

Clinical assessments

In addition to US assessments, the thyroid swelling was clinically graded by the World Health Organization (WHO) goitre grade system [18] before the second treatment. Also, at each visit (baseline, 3 and 6 months), patients were asked to rate their obstructive symptoms on a visual analogue scale (VAS) (0–10) (0 = no symptoms; 10 = most severe symptoms).

Application of the second HIFU treatment

All second treatments were carried out similarly to the first treatment by one person (B.H.L.) using the same commercially-available US-guided HIFU device (see later). All patients were instructed to be fasted overnight and to admit to the hospital in the early morning where baseline blood tests including serum thyroid function tests (Free T4 and thyroid stimulating hormone (TSH) levels), thyroglobulin (Tg) and anti-thyroid autoantibodies were checked.

At treatment, all patients were placed in a supine position with neck slightly extended and received a bolus of intravenous diazepam (Actavis) (10–15 mg) and pethidine (Martindale Pharmaceuticals) (50–100 mg)). Patients' heart rate, blood pressure, respiration rate and peripheral oxygenation were monitored throughout the procedure. Patients were asked to show a hand sign without moving the neck if the pain became too severe during treatment. In that situation, either the energy setting 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 touch-screen 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 treatment head was placed on the neck of the patient on the side of the index nodule and was finely adjusted until the nodule was within the treatable depth of 7–30 mm from skin surface. Once marked on the treatment screen, 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 20–30 s of cooling time before the beam was moved to the adjacent voxel. 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 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 ^{o}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 mins) were automatically recorded by the device's computer. The 'on-beam' treatment time was the duration between the first to the last pulse (in minutes). Oral diet was resumed immediately afterwards and patients were discharged home 2–3 h after treatment. Afterwards, a transcutaneous laryngeal US was done to assess the mobility of both vocal cords [19]. Vocal cord palsy (VCP) was defined as having an impaired or absent movement in one of the vocal cords corresponding to the ablated side. Other possible complications including skin burn, Horner's syndrome and infection were recorded.

Statistical analysis

Continuous variables were generally expressed as mean ± SD. Median and range was also presented when appropriate. Groups were compared using the Mann-Whitney U test. Chi-square tests were used to compare categorical variables. For correlation between two continuous variables, the Spearman's correlation test was performed. To identify which factors might determine the efficacy of the second treatment, patients were categorised into two groups based on their 6-month VRR after the second treatment. Patients with a 6-month VRR greater than the group median were categorised into Group I while those with a 6-month VRR less than or equal to the group median were categorised into Group II. Binary logistic regression model was used to evaluate factors leading to treatment success. Both the univariate and multivariate analyses were done by logistic regression analysis. Any significant parameters in the univariate analysis were entered into multivariate analysis. Obstructive symptoms were rated on a VAS of 0–10 at baseline, 3 and 6 months. Any changes in VAS between groups over time and their interactions were evaluated by Wilcoxon signed-rank test. 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.

Results

Figure 1 shows how patients were selected for the second treatment. Six months after the first treatment, 120 (76.9%) patients had a nodule shrinkage (VRR) of > 50% while 36 (23.4%) had a VRR ≤ 50%. In the latter group, the mean (SD) 6-month VRR was 31.80 ± 16.34F% and median (range) was 34.11 (-0.72–49.67)%. There was one (0.6%) patient whose baseline nodule volume was 4.97 ml and at 6 months after the first treatment, the nodule ended up slightly larger (5.01 ml) with VRR of -0.72%. There were three (1.9%) other patients whose baseline nodule volume changed very little 6 months after the first treatment. Their 6-month VRRs were 4.59%, 5.02% and 5.03%, respectively. In this subgroup that failed to achieve a 6-month VRR > 50% after the first treatment, 28 (77.8%) patients were eligible. The other eight (22.2%) patients were not eligible because of the lack of symptoms.

Table 1 shows the baseline characteristics and treatment parameters of patients who underwent a second HIFU treatment (n=28). In this cohort, the mean (± SD) nodule volume before the first treatment was 20.34 ± 16.73 ml and the 3- and 6-month VRR after the first treatment were 24.47 ± 17.19% and 27.69 ± 17.19%, respectively. Before the second treatment, the mean nodule volume was 13.72 ± 11.29 ml and the median (range) was 10.96 (4.42–44.24 ml). Half of them (50.0%) had a clinical size of grade 3 WHO nodule grade before the second treatment. None of the 28 patients suffered complications from the second treatment.

Figure 2 shows the 3- and 6-month nodule shrinkage (VRR) after the second treatment. The mean ± SD and median (range) nodule volume at 6 months after the second treatment were 10.10 ± 8.28 ml and 8.82 (3.29–37.40) ml, respectively. The mean 6-month VRR was 21.78 ± 16.87% and the median (range) was 16.16 (1.63–54.07)%. At 3 months, none of patients had a treatment success (VRR > 50%) while at 6 months, only two (7.1%) patients had a treatment success. There were nine (32.1%) patients whose baseline nodule volume shrunk by less than 10% (i.e. VRR < 10%) 6 months after the second treatment.

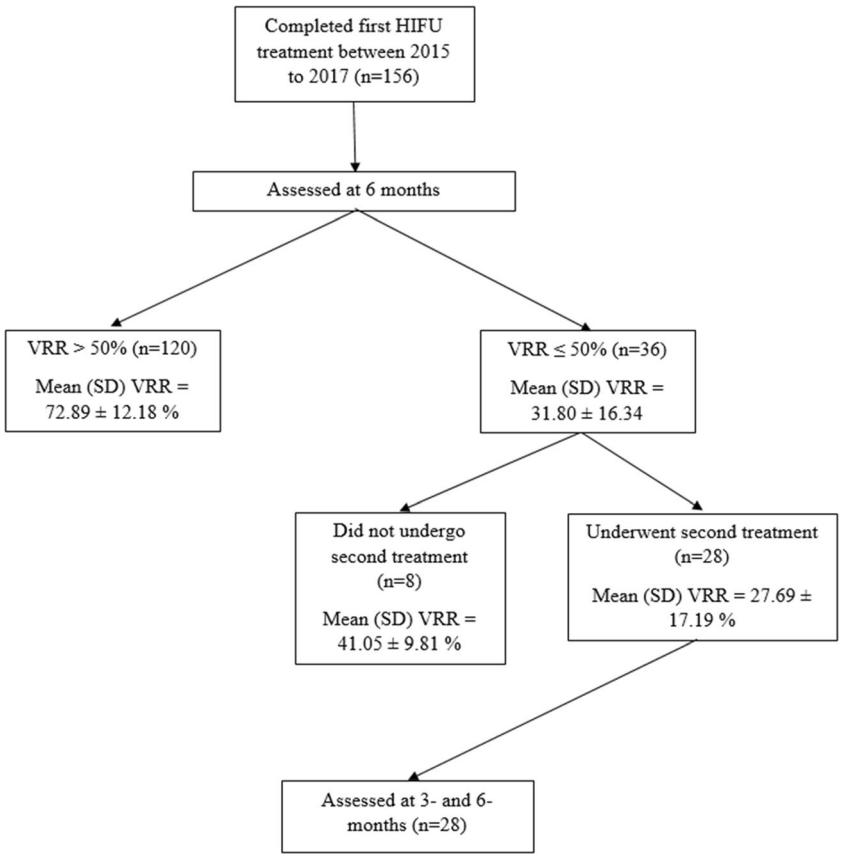

Fig. 1 Patient flowchart

Change in symptom score (by VAS) in the first 6 months after second treatment

At baseline, the mean VAS was 3.96 ± 1.04. After the second treatment, the VAS score at 3 and 6 months were significantly less than baseline (2.96 ± 1.43 vs. 3.96 ± 1.04, $p<0.001$ and 2.58 ± 1.39 vs. 3.96 ± 1.04, $p<0.001$, respectively) (Fig. 3). At 3 months, 17 (60.7%) patients had a lower (or improved) VAS score than that at baseline. Among those who did not report a lower VAS score, ten (35.7%) patients reported the same VAS score as that of baseline while only one (3.6%) patient reported a higher (or worse) VAS score higher than that of baseline. At 6 months, 21 (75.0%) patients had a lower (or improved) VAS score than that at baseline and seven (25.0%) patients reported the same VAS score as at baseline.

Association between VRR and symptom score (by VAS) over time

At 6 months, patients reporting an improved symptom score (i.e. reporting a lower 6-month VAS score than baseline) (n=21) had a significantly greater VRR than those who reported a similar (n=7) to baseline (27.38 ± 16.30% vs. 6.60 ± 4.62%, $p=0.002$, respectively). There was a significant correlation between VRR at 6 months and the absolute difference in VAS score at 6 months from baseline ($\rho=0.438$, $p=0.025$).

Factors determining treatment efficacy at 6 months

Figure 4 shows an example of a retreated nodule that had shrunk above the median after the second treatment.

Table 2 compares baseline characteristics and treatment parameters between those whose nodules had shrunk above the median (6-month VRR > 16.0%) (Group I, n=14) and those whose nodules had shrunk below or equal to the median (6-month VRR ≤ 16.0%, n=14) (Group II) 6 months after the second treatment. Most of the baseline characteristics including age at treatment, sex, WHO nodule grade, BMI, thyroid function and anti-thyroid auto-antibodies were comparable between the two groups. However, the baseline nodule volume in group I was significantly larger than that in group II (17.42 ml vs. 10.02 ml, $p=0.016$). Also, both the total energy delivered and total 'on-beam' time were significantly higher in groups I and II ($p=0.014$ and $p=0.016$, respectively). If 13.0 ml was used as the cut-off, those with nodule volume >13.0 ml had significantly higher 6-month VRR than those with nodule volume ≤ 13.0 ml (28.67 ± 14.64% vs. 15.88 ± 16.88%, $p=0.031$). In

Table 1 Baseline characteristics at the second HIFU treatment (n=28)

Variable	Mean ± SD/no. (%)
Age at treatment (years)	50.63 ± 12.47
Sex (male : female)	4 (14.3) : 24 (85.7)
Clinical nodule size by WHO nodule grade	
- Grade 1a (*palpable but not visible when neck is extended*)	0 (0.0)
- Grade 1b (*palpable and visible when neck extended*)	3 (10.7)
- Grade 2 (*visible when neck is in the normal position*)	11 (39.3)
- Grade 3 (*visible from distance)*	14 (50.0)
Body mass index (kg/m^2)	23.73 ± 3.38
Serum TSH (mIU/L)	1.32 ± 0.99
Serum free T4 (pmol/L)	16.50 ± 1.50
Anti-Tg autoantibody (IU/ml)	108.04 ± 137.87
Anti-TPO autoantibody (IU/ml)	1,336.65 ± 1,037.59
Nodule dimensions and volume	
- Width (cm)	2.75 ± 0.87
- Length (cm)	3.59 ± 1.17
- Depth (cm)	2.37 ± 0.58
- Volume (ml)[a]	13.72 ± 11.29
Distance from skin to the centre of the nodule (mm)	14.03 ± 5.27
Side of nodule (right / left / isthmus)	13 (46.4) / 14 (50.0) / 1 (3.6)
Location within the lobe (upper / middle / lower third)	4 (14.3) / 12 (42.9) / 12 (42.9)
Obstructive symptom score (0–10 by VAS)	3.27 ± 1.37
Treatment parameters	
- Total energy delivered (KJ)	16.53 ± 3.99
- Total 'on-beam' time (minutes)	68.07 ± 22.74
- Average energy per each pulse (J)	308.96 ± 31.13

WHO World Health Organization, *TSH* thyroid stimulating hormone, *SD* standard deviation, *Anti-Tg* anti-thyroglobulin, *TPO* thyroid peroxidase, *VAS* visual analogue scale

[a] Volume of a nodule = (width × depth × length) × (π/6), where π was taken as 3.14159

agreement with these findings, the baseline nodule volume at the first treatment was also significantly larger in group I than in group II (25.39 ml vs. 15.28 ml, p=0.016).

In the univariate analysis by logistic regression, larger nodule volume before second treatment (OR=1.169, 95% CI=1.004–1.361, p=0.045), total energy delivered at second

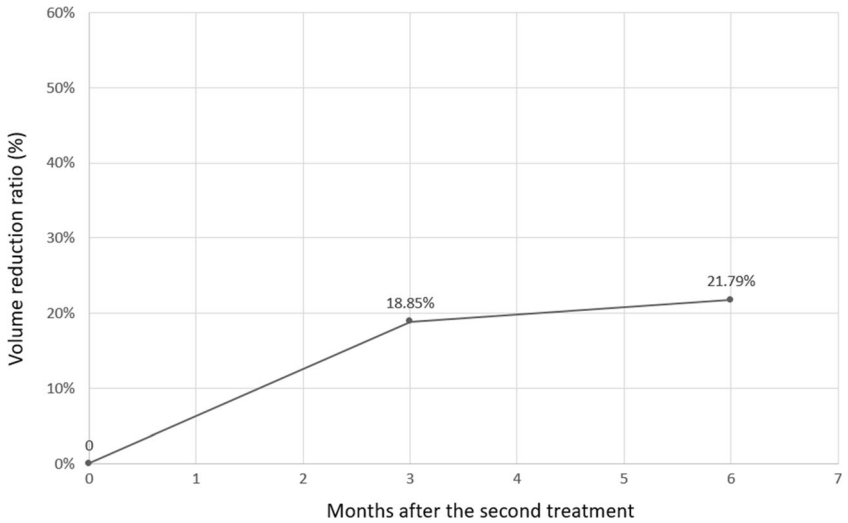

Fig. 2 Change in volume reduction ratio (VRR) from baseline to 3 and 6 months after the second HIFU treatment

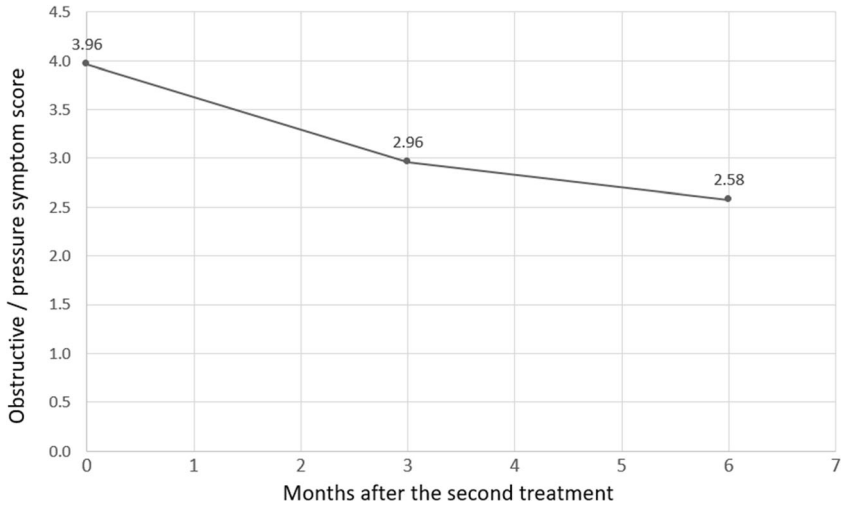

Fig. 3 Change in obstructive symptom score by visual analogue scale (0–10) from baseline to 3 and 6 months after the second HIFU treatment

treatment (OR=1.288, 95% CI = 1.027–1.615, p=0.028) and total "on-beam" time (OR=1.029, 95% CI=1.001 - 1.190, p=0.047) were significant factors for VRR > 16.0% at 6 months after the second treatment (Table 3). However, the latter two factors were inter-related to the nodule volume (p<0.05). When these three factors were entered into a multivariate analysis, none were significant (p>0.05).

Discussion

Relative to RFA and laser ablation, HIFU is considered a relatively new thermal ablation technique in the treatment of benign thyroid nodules [5–7]. To our knowledge, this was the first study to assess the role of second treatment in benign thyroid nodules that had not shrunk by > 50% in volume after the first HIFU treatment. In terms of shrinkage, our data showed that the overall shrinkage (or the 6-month VRR) after the second treatment was small (VRR of 21.78 ± 16.87% at 6 months). In fact, it was less than that in the first treatment (VRR of 27.69 ± 17.19% at 6 months, p=0.086). This meant that as a group, only a small amount of shrinkage was able to be gained from the additional treatment. There are several reasons for this. One reason could be due to the altered nodule content following the first treatment, making the subsequent ablation less effective. Another reason might be because it was generally more difficult to accurately focus the HIFU beam to the peripheral residual vital zone of the nodule. In fact, it was recently shown that HIFU is less

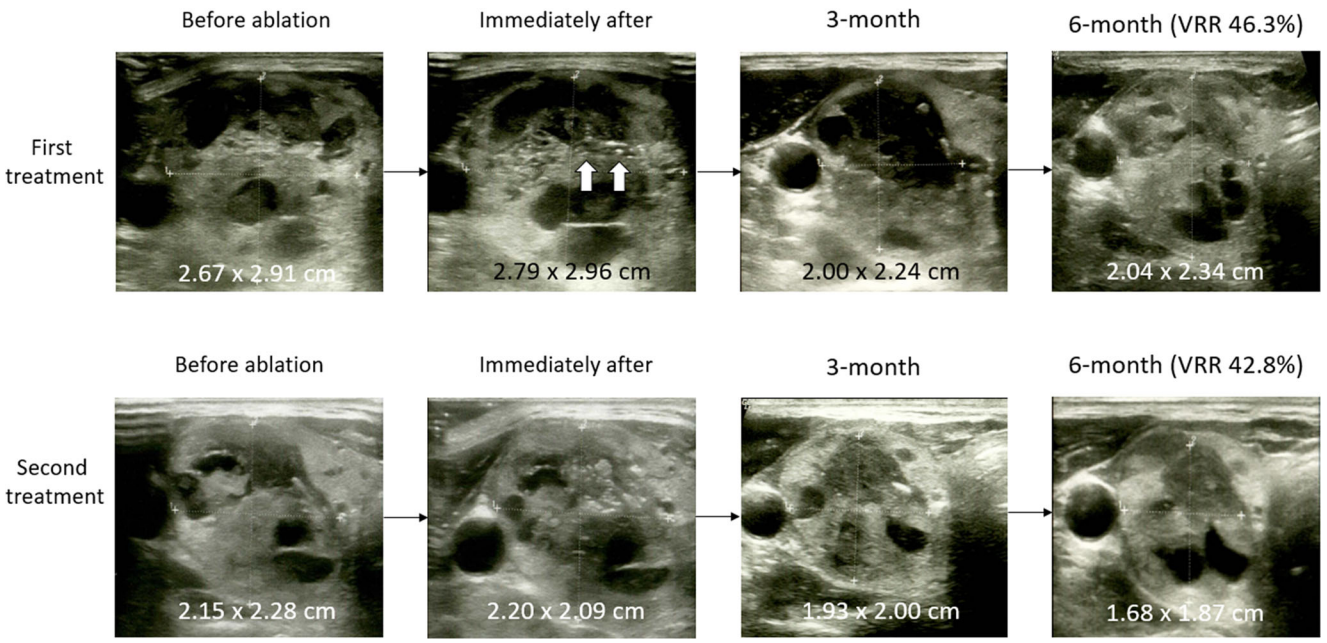

Fig. 4 Transverse view of a nodule following first and second HIFU treatments

Table 2 Comparison of baseline characteristics, treatment parameters and volume reduction ratio between those who achieved nodule shrinkage above the median (VRR > 16.0%) (Group I) and those who did not (VRR ≤ 16.0%) 6 months (Group II) after second HIFU treatment

Variable	Group I (n=14)	Group II (n=14)	*p*-value
Age at initial treatment (years)	54.15 ± 10.14	45.85 ± 13.64	0.125
Sex (male : female)	3 (21.4) : 11 (78.6)	1 (7.1) : 13 (92.9)	0.277
WHO nodule grade on presentation			0.143
- Grade 1a (*palpable but not visible when neck is extended*)	0 (0.0)	0 (0.0)	
- Grade 1b (*palpable and visible when neck extended*)	0 (15.4)	3 (21.4)	
- Grade 2 (*visible when neck is in the normal position*)	5 (35.7)	6 (42.9)	
- Grade 3 (*visible from distance)*	9 (64.3)	5 (35.7)	
Body mass index (kg/m^2)	23.15 ± 2.37	24.32 ± 4.18	0.418
Serum TSH (mIU/L)	1.38 ± 1.15	1.25 ± 0.84	0.932
Serum free T4 (pmol/L)	16.58 ± 1.56	16.42 ± 1.51	0.630
Anti-Tg autoantibody (IU/ml)	100.50 ± 122.77	116.27 ± 158.40	0.880
Anti-TPO autoantibody (IU/ml)	1,277.67 ± 4,086.14	1,401.01 ± 4,182.07	0.740
Dimensions of the index nodule on ultrasound			
- Width (cm)	2.99 ± 0.61	2.34 ± 1.01	0.059
- Length (cm)	4.02 ± 1.03	3.06 ± 1.14	0.059
- Depth (cm)	2.22 ± 0.59	1.99 ± 0.58	0.499
- Volume (ml)[a]	17.42 ± 10.37	10.02 ± 11.33	**0.016**
Distance from skin to the centre of the nodule (mm)	14.83 ± 4.94	13.19 ± 5.19	0.676
Side of nodule (right / left / isthmus)	4 (28.6) / 10 (71.4) / 0 (0.0)	9 (64.3) / 4 (28.6) / 1 (7.1)	0.439
Location within the lobe (upper / middle / lower third)	1 (7.1) / 5 (35.7) / 8 (57.1)	3 (21.4) / 7 (50.0) / 4 (28.6)	0.431
Baseline nodule volume+ at the first treatment (ml)[a]	25.39 ± 12.77	15.28 ± 19.10	**0.016**
3-month VRR after the first treatment (%)	25.70 ± 8.88	26.08 ± 11.58	0.724
6-month VRR after the first treatment (%)	30.05 ± 17.50	33.54 ± 15.63	0.614
Treatment parameters at the second treatment			
- Total energy delivered (KJ)	16.89 ± 3.96	12.25 ± 4.56	**0.014**
- Total 'on-beam' time (minutes)	70.55 ± 16.66	49.78 ± 13.51	**0.016**
- Average energy per each pulse (J)	309.83 ± 31.24	297.87 ± 37.22	0.079
VRR after the second treatment (%)			
- 3 months	31.87 ± 9.87	5.84 ± 3.88	**<0.001**
- 6 months	36.09 ± 11.38	7.48 ± 4.51	**<0.001**
Obstructive symptoms by VAS			
- Baseline	3.54 ± 1.33	3.00 ± 1.41	0.287
- 6 months	1.62 ± 0.96	2.31 ± 1.75	0.311

Continuous variables are expressed in mean ± standard deviation. Bold signifies statistical significance ($p<0.05$)

WHO World Health Organization, *TSH* thyroid stimulating hormone, *SD* standard deviation, *Anti-Tg* anti-thyroglobulin, *TPO* thyroid peroxidase, *VAS* visual analogue scale (0 = no symptom; 10 = most severe symptom), *VRR* volume reduction ratio

+volume estimated using the formula: (width × depth × length) × (π/6) where π was taken as 3.1416

[a] Calculated using the formula: [Baseline volume – volume at visit] / [Baseline volume] * 100

effective in treating autonomously functioning nodules than radioiodine therapy [20].

The fact that the shrinkage was limited is clinically relevant as there is currently no information on how nodules would behave following two or more HIFU treatments. However, the question of whether it is worth doing a second treatment for those unsatisfactory nodules in the first treatment remains unclear because in our experience, many patients still prefer a second ablation over surgery. Therefore, in our opinion, despite the limited shrinkage, a second treatment might still have a role for nodules that did not shrink satisfactorily in the first treatment.

Nevertheless, it should be pointed out that this cohort was a rather heterogeneous group with some nodules responding very well while others responding less satisfactorily. At 6 months, there were two (7.1%) patients who had > 50% shrinkage after the second treatment while there were nine (32.1%) patients who had little

Table 3 Logistic regression analysis of factors associated with the extent of nodule shrinkage above the median (i.e. VRR > 16.0%) at 6 months

Variable	Treatment success (> 50% volume reduction at 6 months)		
	Univariate analysis		
	OR	95% CI	*p*-value
Age (y)	1.069	0.985–1.160	0.110
Sex	0.278	0.025–3.104	0.298
Body mass index (kg/m^2)	0.897	0.705–1.141	0.897
Serum TSH (mIU/L)	0.866	0.375–1.998	0.736
Nodule width (cm)	2.586	0.823–8.125	0.104
Nodule length (cm)	2.441	0.946–6.299	0.065
Nodule depth (cm)	20.81	0.460–9.419	0.341
Nodule volume before second treatment (ml) [a]	1.169	1.004–1.361	**0.045**
Distance from skin to centre of nodule (mm)	1.018	0.793–1.249	0.683
Side of nodule (right / isthmus / left)	1.402	0.436–4.508	0.571
Location of nodule (upper / middle / lower)	2.156	0.644–7.211	0.213
Nodule volume before first treatment (ml) [a]	1.041	0.985–1.111	0.143
3-month VRR after first treatment (%)	0.996	0.922–1.077	0.924
6-month VRR after first treatment (%)	0.986	0.940–1.035	0.581
Total energy delivered (KJ)	1.288	1.027–1.615	**0.028**
Total 'on-beam' time (minutes)	1.092	1.001–1.190	**0.047**
Average energy per each pulse (J)	1.022	0.994–1.052	0.127

Bold signifies statistical significance ($p<0.05$)

TSH thyroid stimulating hormone, *VRR* volume reduction ratio

[a] Nodule volume estimated using the formula: (width × depth × length) × (π/6) where π was taken as 3.1416

(< 10%) shrinkage. Although it remains unclear why this might be, one explanation might be related to the nodule's consistency and composition before and after the ablation [21]. It has been shown that a certain type of nodules (namely, the spongiform type) tend to shrink more for the first 3 years after thermal ablation than other types [22]. Given this finding, perhaps future studies could examine more closely on the consistency and composition of these nodules and evaluate the relationship between nodule composition and extent of shrinkage after HIFU ablations.

However, interestingly, despite the relatively moderate nodule shrinkage, the mean symptom score (VAS) continued to improve in the first 6 months of the second treatment. The mean symptom score fell from 3.96 ± 1.04 to 2.96 ± 1.43 at 3 months ($p<0.001$) and 2.58 ± 1.39 at 6 months ($p<0.001$). Similar to previous studies [23, 24], our data also showed a significant correlation between improvement in symptom score and the extent of nodule shrinkage. For example, those reporting an improved symptom score did have a greater nodule shrinkage than those reporting no symptom improvement (27.38 ± 16.30% vs. 6.60 ± 4.62%, $p=0.002$). Also, there was a significant positive correlation between the 6-month VRR after the second treatment and the absolute difference in 6-month VAS score ($\rho=0.438$, $p=0.025$). Nevertheless, given the small overall nodule shrinkage, there was a definite discordance between physical nodule shrinkage and reporting of symptom score. One reason might be because there was a placebo effect where patients who received treatment tended to think the treatment really did help their problem.

In terms of safety, despite the small number of patients, our study showed that repeating the treatment to the same nodule was safe. None of the patients suffered any complications which were directly related to the treatment itself and because all the treatments were carried out on outpatient basis, there was no need for hospitalisation.

In terms of factors associated with the efficacy of the second treatment, our data showed larger nodules before the second treatment had significantly greater shrinkage than smaller nodules (Group II) ($p=0.016$). One reason might be because smaller nodules tended to be more difficult to treat because of the smaller target area. Although the experience of the operator is an important determinant of treatment success [5], this was less applicable as all the treatments were done by one operator.

Despite these findings, we would like to acknowledge several shortcomings. First, our study was only a relatively moderate in size as this was a highly selective cohort (< 20%) and so, some of the findings were prone to type II

errors. This may have explained why there were no significant factors identified in the multivariate analysis. Second, a longer period of follow-up would be necessary to evaluate the durability of the second treatment.

Conclusion

Although subjective obstructive symptoms continued to improve after the second treatment, the extent of shrinkage was relatively small (21.78 ± 16.87% at 6 months) for unsatisfactory nodules in the first treatment. Given a great variability in the extent of nodule shrinkage observed, a better nodule selection is required for the second treatment. In the present cohort, those with larger volume nodules before the second treatment tended to respond more significantly in the second treatment than those with smaller volume nodules.

Acknowledgements We would like to thank Mr. Hill Yu and Ms. Li Wing Kar for conducting all the symptom (or VAS score) assessments for the entire study period and Professor Stephen Cheng (Head of Department of Surgery, University of Hong Kong) for agreeing to be the guarantor of this paper.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

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

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

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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