Benign Solid Thyroid Nodules: US-guided High-Intensity Focused Ultrasound Ablation—Initial Clinical Outcomes[1]

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Purpose: To assess the short-term efficacy and safety of ultrasonographically (US)-guided high-intensity focused ultrasound (HIFU) ablation for treatment of benign solid thyroid nodules.

Materials and Methods: This prospective study was approved by the institutional ethics committee, and written informed consent was acquired. HIFU ablation was performed in one session with US guidance and conscious sedation in 20 euthyroid patients (mean age, 44.5 years) with a benign solitary or dominant thyroid nodule. Thyroid nodule volume, US structure, and Doppler pattern were assessed at baseline, at 1 week, and at 1, 3, and 6 months after treatment. Adverse events associated with HIFU were evaluated. Statistical analysis was conducted by using repeated measures analysis of variance, the Student t test, χ^2 test, and correlation analysis.

Results: The mean ± standard deviation nodule volume was 4.96 mL ± 2.79 at the start of the study. Nodule volume had decreased to 3.05 mL ± 1.96 at the 3-month follow-up examination ($n = 20$, $P < .001$), and reached 2.91 mL ± 2.43 by the 6-month follow-up examination ($n = 16$, $P < .001$). By then, the mean volume reduction was 48.7% ± 24.3 ($P < .001$). Isoechoic nodules showed greater reduction at 1 month than did hypoechoic nodules (31.6% ± 18.1 vs 16.4% ± 8.6, $P = .053$). Nodules with markedly increased blood flow showed smaller volume reduction at 3 months than did less-vascularized nodules (10.9% ± 14.5 vs 41.5% ± 20.3, $P = .054$). Minor transient complications (eg, subcutaneous edema, mild skin redness) were observed in two patients.

Conclusion: Early data suggest that US-guided HIFU ablation is an effective and safe procedure for treatment of benign solid thyroid nodules. Initial US echogenicity and vascularization influence the ablation outcome.

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The prevalence of thyroid nodules found by means of palpation is approximately 5%, but an estimated 50% of unselected populations have nodules that can be discovered at ultrasonography (US) (1). Ninety-five percent of all thyroid nodules are benign, and one-third of them show continuous growth (2). However, some of these nodules should be treated because patients report compression symptoms or cosmetic concerns. Although surgery is still the main therapeutic strategy, it carries a 2%–10% risk of complications such as hypocalcemia, transient or permanent recurrent laryngeal nerve palsy, bleeding, or postoperative infection (3). For this reason, various nonsurgical, minimally invasive techniques have been developed at specialized treatment centers. Percutaneous ethanol injection has been shown to be effective for cystic thyroid nodules (4); yet its application in benign solid nodules is limited due to the possibility of serious complications including recurrent nerve palsy, Horner syndrome, neck hematoma, thrombosis of the ipsilateral jugular vein, necrosis of the larynx and skin, or facial dysesthesia with increased tear flow (1,5). Innovative percutaneous thermal procedures such as US-guided laser or radiofrequency ablation can reduce the thyroid nodule size considerably. Although both procedures are considered safe, transient adverse effects including impaired vocal cord mobility have been observed (6).

Advances in Knowledge

- At 6 months after US-guided high-intensity focused ultrasound (HIFU) ablation, thyroid nodule volume had reduced significantly ($P < .001$) and the mean volume reduction was 48.7%.
- The reduction in volume at 3-month follow-up examination was smaller in nodules with markedly increased blood flow than in less-vascularized nodules (10.9% vs 41.5%, $P = .054$).
- After HIFU treatment of thyroid nodules, no serious and long-term adverse effects were observed.

High-intensity focused ultrasound (HIFU) is a noninvasive procedure that involves application of a focused high-energy ultrasound beam for thermal tissue ablation inside the targeted zone, with minimal effect on the surrounding tissue. This method has been applied for treatment of a variety of medical conditions such as uterine fibroids and prostate, breast, pancreatic, and liver tumors (7). A favorable outcome also has been observed in patients with primary or secondary hyperparathyroidism (8–10).

HIFU also was proposed for thyroid nodule ablation (11,12). In a human feasibility study, 25 patients were treated 2 weeks before a scheduled thyroidectomy. Pathologic analysis demonstrated targeted tissue destruction of 2%–80% without any damage to neighboring structures (13). To our knowledge, studies of follow-up after HIFU ablation of thyroid nodules have not been published, except for one case report (14) of a patient with toxic adenoma in whom nodule shrinkage after HIFU intervention was reported. Thus, the purpose of this prospective study was to assess the short-term efficacy and safety of US-guided HIFU ablation for the treatment of benign solid thyroid nodules.

Materials and Methods

The device for US-guided HIFU treatment and financial support for the supplies were provided by Theraclion (Paris, France). The authors had complete control of the data and information submitted for publication.

Study Population

The study was approved by the institutional ethics committee, and all patients signed written informed consent forms before participation. The inclusion criteria were as follows: *(a)* age older than 18 years, *(b)* the presence of one or more thyroid nodules without signs of malignancy (eg, nonsuspicious clinical and US appearance, benign results at cytologic examination performed in the last 6 months, normal serum calcitonin level), *(c)* a nodule measured at US greater than or equal to 10 mm in three orthogonal dimensions, *(d)* less than 30% of the targeted nodule comprising cystic area, *(e)* HIFU accessibility of the targeted nodule (distance between the skin and the anterior surface of the nodule less than 17 mm, with no interference of the collarbone with HIFU unit movements), *(f)* normal thyrotropin concentration; and *(g)* absence of vocal cord immobility at laryngoscopy.

The exclusion criteria were as follows: *(a)* head and/or neck disease preventing hyperextension of the neck, *(b)* history of thyroid cancer or other malignant tumors in the neck region, *(c)* history of neck irradiation, *(d)* intranodular macrocalcifications inducing a shadow substantial enough to preclude treatment with HIFU, *(e)* nodules next to the posterior margin of the thyroid lobe with anteroposterior diameter less than 15 mm, *(f)* pregnancy or lactation, and *(g)* any contraindication related to intravenous moderate sedation.

A total of 37 consecutive patients with a euthyroid nodular goiter were considered for HIFU treatment between December 2012 and July 2013. Among them, 11 patients did not meet

Implication for Patient Care

- US-guided HIFU ablation of benign solid thyroid nodules is a noninvasive procedure.

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Abbreviations:
BMI = body mass index
HIFU = high-intensity focused ultrasound

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Conflicts of interest are listed at the end of this article.

selection criteria (technical inaccessibility in nine patients, malignant results at cytologic examination in one patient, and epilepsy in one patient) and six patients declined enrollment. Twenty patients were eligible for HIFU ablation; their characteristics are presented in Table 1.

Table 1

Demographic, US, and Treatment Data of 20 Patients Who Underwent US-guided HIFU Ablation of Benign Thyroid Nodules

Characteristic	Value
Patients	
Age (y)	44.5 ± 11.7 (24–65)
Sex*	
Female	18 (90)
Male	2 (10)
Time since diagnosis of goiter (y)	3.6 ± 3.8 (0–14)
Previous thyroid surgery*	
No	17 (85)
Yes	3 (15)
BMI (kg/m^2)	24.82 ± 3.85 (18.96–34.4)
Thyrotropin (mIU/L)	1.7 ± 0.97 (0.5–3.6)
Thyroid nodule	
Type†	
Solitary	8 (40)
Dominant	12 (60)
Lobe†	
Left	5 (25)
Right	15 (75)
Basal volume (mL)	4.96 ± 2.79 (1.56–9.35)
Depth (mm)	7.8 ± 2.8 (3.0–12.8)
Treatment data	
Total energy (kJ)	16.4 ± 7.7 (5.5–31.7)
Energy per nodule volume (kJ/mL)	3.8 ± 1.5 (2.1–7.2)
Hyperechoic marks (%)	45.4 ± 18.6 (0–74)
Treatment time (min)‡	86.8 ± 31.7 (37–152)

Note.—Unless otherwise indicated, data are mean ± standard deviation, with the range in parentheses.

* Data are number of patients, with percentage in parentheses.

† Data are number of nodules, with percentage in parentheses.

‡ Treatment time included sonication, cooling, and repositioning.

Preablation Evaluation

Thyrotropin level (reference range, 0.3–4.0 mIU/L) was determined by means of radioimmunoassay (Brahms, Henningsdorf, Germany). Body mass index (BMI) at baseline was calculated as weight in kilograms divided by height in square meters. The physician (J.D.V., with 13 years of experience in US) evaluated the patients and assigned each a cosmetic score by using a 1–4 grading scale (1, no palpable nodule; 2, palpable but not visible nodule; 3, visible nodule on swallowing; 4, readily visible nodule) (15). The physician who assigned the score was different from the person who performed the HIFU.

US assessment of the targeted thyroid nodule was performed by a single examiner (R.K., with 29 years of experience in US) who used a real-time harmonic imaging 8-MHz transducer and a color Doppler US machine (Prosound Alpha 7; Aloka, Tokyo, Japan). All US features were additionally and independently evaluated by another physician (K.Z., with 15 years of experience in US) who was not technically involved in the HIFU procedure. The maximum nodule diameters were measured in three orthogonal planes. The nodule volume was calculated by using the ellipsoid model ($W \cdot L \cdot T \cdot \pi/6$, where W is width, L is length, and T is thickness). Depth of the thyroid nodule was estimated as the distance between the skin and the anterior nodule surface. The nodule echogenicity was compared with the surrounding thyroid parenchyma, and it was classified as hypoechoic, isoechoic, and hyperechoic. Depending on its homogeneity, the nodule was determined to be homogeneous or heterogeneous. Intranodular color flow Doppler pattern was evaluated as previously described (16): type 0, absence of flow; type 1, presence of flow with patchy, uneven distribution; type 2, clearly increased color Doppler signal intensity with patchy distribution; type 3, marked increase in blood flow with diffuse homogeneous distribution. US-guided fine-needle biopsy with cytology was performed in each patient to prove the benign nature of the targeted nodule.

US-guided HIFU System

The HIFU session was performed with a real-time US-guided HIFU system (EchoPulse; Theraclion, Paris, France), a mobile unit consisting of a corpus with energy generator, an articulated arm with a treatment head, a cooling system, and a touch-screen interface for procedure planning and follow-up. As described previously (8,10), the treatment head incorporated both the imaging transducer (7.5 MHz, 128 elements, linear array) and the HIFU transducer (3 MHz, single element, 60 mm in diameter) for delivering energy to the target. The treatable area was 5–28 mm from the skin, and the intended size of the HIFU ablation unit was 9 mm in length and 1.8–2.5 mm in orthogonal dimensions (Fig 1). The depth of each ablation unit was adjusted automatically to be centered with the anteroposterior diameter of the target. The safety of the adjacent structures was ensured by using a laser-based movement detector that enabled immediate power interruption in case a patient moved or swallowed.

US-guided HIFU Procedure

Each patient was treated in a single session on an outpatient basis by a single physician (R.K., with 5 years of experience in US-guided HIFU therapy). The patients were placed in supine position with the head hyperextended and were administered intravenous moderate sedation with fentanyl (0.1–0.325 mg) and ketoprofen (100–200 mg). The physician positioned the treatment head facing the targeted nodule. The planned treatment volume and the vulnerable structures (carotid artery, trachea, and skin) were outlined on a touch-screen interface on two axes. On the basis of this information, the device software defined the treatment units and safety margins (Fig 2, *A*). When planning was completed, the treatment head automatically moved to cover the whole treatment volume. The procedure consisted of HIFU repeated pulses for ablation of the whole targeted tissue. Skin integrity was secured by means of a cooling system. The physician supervised the beam focus, and if necessary, repositioned the treatment head. The treatment was started in all patients with the same energy level: 160 J per pulse. During the procedure, the physician adjusted the applied energy according to the occurrence of hyperechoic marks, because such phenomena may be associated with tissue coagulation (Fig 2, *B*). When hyperechoic marks did not appear at maximal admissible energy, the treatment was continued at submaximal level to avoid extranodular thermal damage. In each nodule, the proportion of hyperechoic marks obtained to all treated units was calculated. The complete procedure duration consisted of time for installation, positioning, planning, and treatment. Treatment duration included time for sonication (4 seconds per ablation unit) that varied with treatment volume, time for cooling (15–30 seconds), which depended on the energy level and the nodule distance from the skin, and time for repositioning.

During therapy, the patient's heart rate, blood pressure, respiration rate, and peripheral oxygenation were monitored. Patients were asked to make a sign (shake hand) if they felt pain or increased pressure from the treatment head. Adverse events that occurred during and after the HIFU procedure were evaluated. Pain associated with the treatment was subjectively rated by using a 0–10–cm visual analog scale. The patients were observed 1–2 hours after the procedure. Before and up to 24 hours after HIFU treatment, vocal cord mobility was assessed with indirect laryngoscopy.

Postablation Follow-up

US assessments at 1 week, 1 month, and 3 months after a single HIFU procedure were performed in all patients

Figure 1

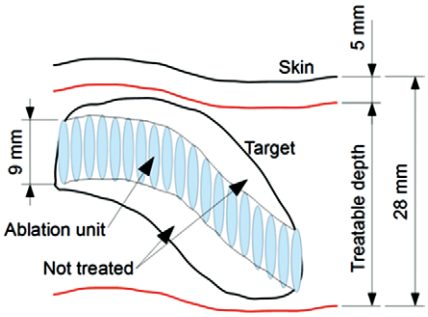

Figure 1: Schematic illustration shows the area treatable with US-guided HIFU system and adjusted placement of ablation units.

Figure 2

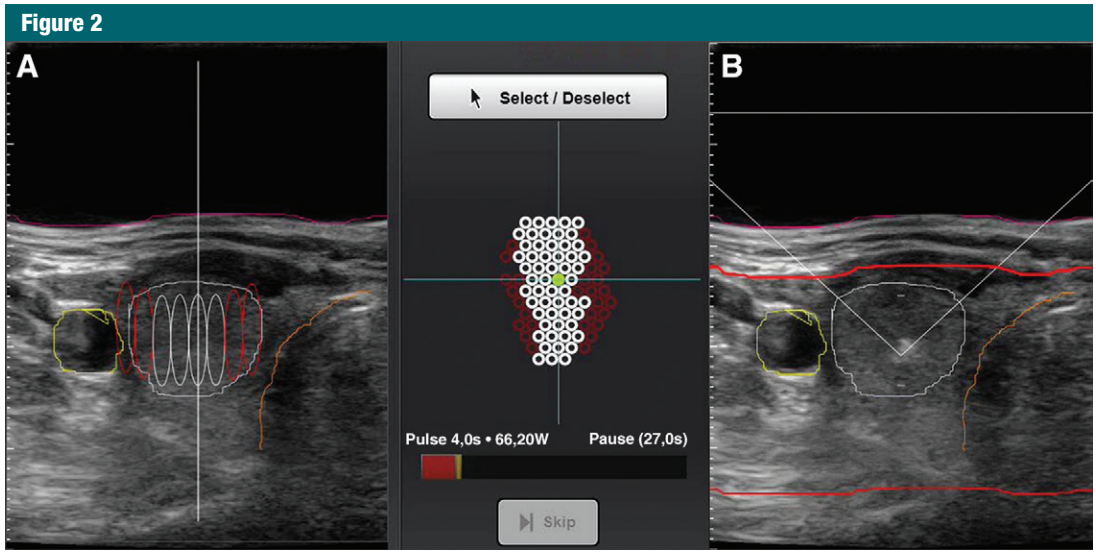

Figure 2: Touch-screen interface of US-guided HIFU system with treatment plan top view reconstruction (central panel) based on information collected in a set of parallel and regularly spaced US images. US images of transverse scan show isoechoic solid nodule in right thyroid lobe of a 43-year-old woman with euthyroid nodular goiter. *A*, Nodule and adjacent trachea and carotid artery were outlined by physician; treatment units outside the safety margins were eliminated automatically by the software (in red). *B*, Hyperechoic mark on the top of treatment cone after first sonication.

Figure 3

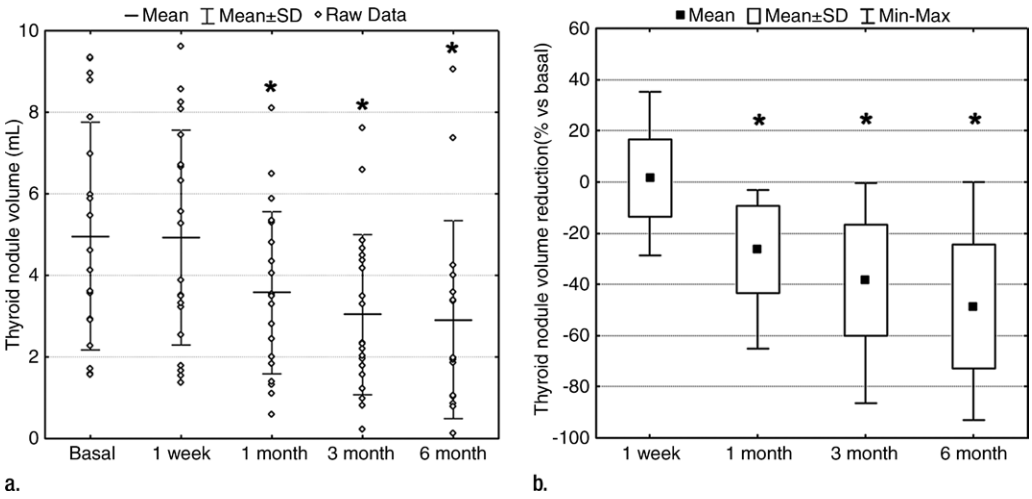

Figure 3: **(a)** Dot graph shows mean thyroid nodule volume change, and **(b)** box and whisker plot shows percentage of volume reduction during follow-up after HIFU ablation. * = $P < .001$ compared with basic value before treatment. *P* values were obtained with repeated measures analysis of variance and Student *t* tests. *SD* = standard deviation.

to record changes in thyroid nodule volume, echogenicity, homogeneity, and vascularization. Volume reduction percentage was calculated as: $([Vol_{basal} - Vol_{final}] \cdot 100)/Vol_{basal}$. At 3-month follow-up, the patients with nodule reduction of less than 30% were offered the possibility of additional HIFU treatment. In the remaining patients, all nodule characteristics were estimated also at 6 months. The cosmetic score was evaluated 6 months after initial HIFU treatment and a patient satisfaction survey was performed by using 10-cm visual analog scale score, with 0 for complete dissatisfaction and 10 for complete satisfaction.

Statistical Analysis

Statistical analysis was performed by using software (Statistica version 7.1; StatSoft, Tulsa, Okla). Data were expressed as mean ± standard deviation. Longitudinally recorded data were analyzed by using repeated measures analysis of variance. Otherwise, datasets were compared by using the Student two-tailed *t* test for variables with normal distribution. No adjustment was made for multiple testing. Comparison of categorical variables was performed by means of the χ^2 test. Correlations were calculated by using the Pearson correlation test. The threshold for a statistically significant difference was considered to be a *P* value of .05.

Results

Clinical and Treatment Characteristics of Patients

The nodule features and the treatment characteristics are presented in Table 1. Cosmetic scores for the 20 patients were 4 for six (30%) patients, 3 for two (10%) patients, 2 for 11 (55%) patients, and 1 for one (5%) patient. We found a significant negative correlation between cosmetic score and BMI ($r = -0.458$, $P = .042$). There was a significant positive correlation of the applied energy per volume tissue with nodule depth ($r = 0.447$, $P = .048$). No correlation was found between applied energy and age ($r = 0.163$, $P = .494$), BMI ($r = 0.046$, $P = .847$), the proportion of hyperechoic marks ($r = -0.351$, $P = .140$) or treatment duration ($r = -0.200$, $P = .426$). A significant negative correlation between the proportion of hyperechoic marks and BMI was shown ($r = -0.548$, $P = .015$). All patients completed the treatment. As indicated in Table 1, the mean treatment duration was 86.8 minutes.

Reduction in Nodule Volume after HIFU Therapy

The mean nodule volume did not change significantly from baseline to 1 week after HIFU therapy (4.96 mL ± 2.79 vs 4.94 mL ± 2.64, respectively; $P = .923$) (Fig 3a). In eight (40%) of 20 patients the nodule had enlarged, with a mean volume increase of 17.2% ± 9.2 (range, 4.7%–35.1%), whereas in 12 (60%) patients, the nodule had shrunk, with a mean volume reduction of 8.7% ± 6.9 (range, 2.3%–28.6%) (Fig 3b). In 20 patients, the mean nodule volume decreased to 3.58 mL ± 1.99 at 1-month follow-up examination ($P < .001$) and to 3.05 mL ± 1.96 at 3-month follow-up examination ($P < .001$) (Fig 3a). The mean volume reduction was 26.3% ± 16.9 at 1-month follow-up ($P < .001$) and 38.5% ± 21.6 at 3-month follow-up ($P < .001$) (Fig 3b). After 3-month follow-up, three patients with less than 30% volume reduction underwent a second HIFU treatment and one patient did not return for the follow-up visits. In the remaining 16 patients, nodule volume decreased to 2.91 mL ± 2.43 at 6-month follow-up ($P < .001$) with volume reduction of 48.7% ± 24.3 ($P < .001$). At that follow-up visit the maximum nodule reduction was 92.9% (Fig 3b).

Figure 4

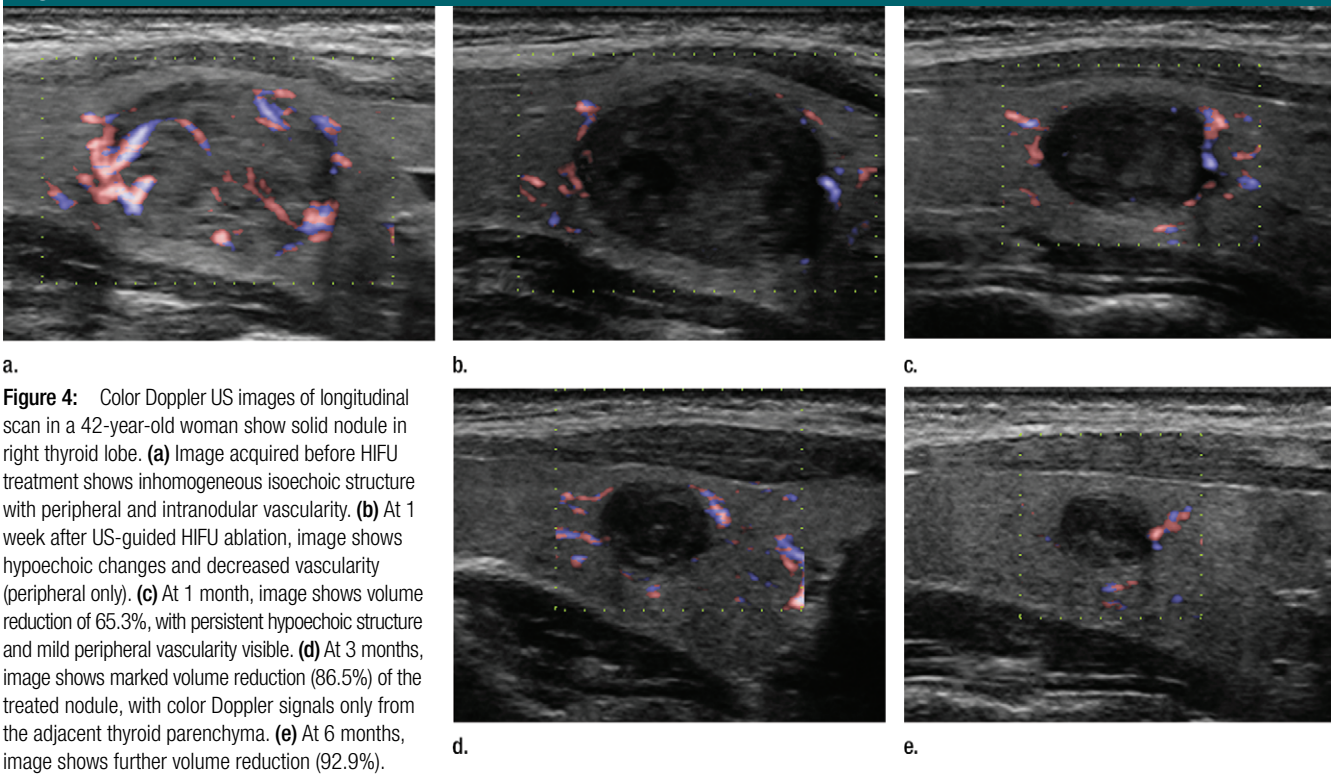

Figure 4: Color Doppler US images of longitudinal scan in a 42-year-old woman show solid nodule in right thyroid lobe. **(a)** Image acquired before HIFU treatment shows inhomogeneous isoechoic structure with peripheral and intranodular vascularity. **(b)** At 1 week after US-guided HIFU ablation, image shows hypoechoic changes and decreased vascularity (peripheral only). **(c)** At 1 month, image shows volume reduction of 65.3%, with persistent hypoechoic structure and mild peripheral vascularity visible. **(d)** At 3 months, image shows marked volume reduction (86.5%) of the treated nodule, with color Doppler signals only from the adjacent thyroid parenchyma. **(e)** At 6 months, image shows further volume reduction (92.9%).

There was no correlation between 6-month volume reduction and basal volume ($r = -0.205$, $P = .446$) or nodule depth ($r = -0.094$, $P = .730$). Similarly, no correlation was found between 6-month volume reduction and the applied energy per volume tissue ($r = -0.047$, $P = .862$) or the proportion of hyperechoic marks ($r = 0.345$, $P = .191$). The mean cosmetic score significantly decreased from 2.6 ± 1.0 to 1.9 ± 0.9 ($P = .022$), whereas the satisfaction visual analog scale score was 8.8 ± 2.0 (range, 3–10).

US Pattern before and after HIFU Therapy

Postablation changes in echogenicity and intranodular vascularization are shown in Figure 4. Ten of 13 (77%) nodules that were isoechoic became hypoechoic as early as 1 week after the treatment, while all initially hypoechoic nodules did not change. The posttreatment transformation of nodule echogenicity and homogeneity was significant until 1 month after therapy (Table 2). Compared with hypoechoic nodules, isoechoic nodules showed greater but not significant volume reduction at 1 month ($P = .053$), although the applied energy per volume tissue was significantly lower ($P = .033$) (Table 3). No significant differences in any clinical and treatment parameters except age were observed between patients with and without echogenicity change (Table 3).

Nodule vascularity decreased significantly 1 week after the HIFU procedure ($P = .002$) and it remained significantly lower 3 and 6 months after therapy ($P = .050$ and $P = .016$, respectively) (Table 2, Fig 4). In nodules with an initial color Doppler pattern of type 1 or 2, the mean volume reduction at 1-, 3-, and 6-month follow-up was 27.9% ± 17.1, 41.5% ± 20.3, and 50.7% ± 23.7, respectively. In comparison, the volume reduction in nodules with initial color Doppler pattern type 3 was 11.7% ± 0.3 ($P = .207$) and 10.9% ± 14 ($P = .054$) at 1-month and 3-month follow-up, respectively. At 6-month follow-up, the volume reduction in one patient was 18.1%, whereas the second patient was not included in the follow-up.

Adverse Events

HIFU was well tolerated by all patients. Pain visual analog scale score was 2.8 ± 2.0 (range, 0–7.5). It correlated significantly ($r = 0.659$, $P = .002$) with BMI, whereas no significant correlation with energy per volume tissue was established ($r = 0.267$, $P = .269$). No patient needed additional analgesic drugs after the therapy. During the treatment, one patient with a BMI of 34.4 kg/m^2 developed subcutaneous edema that persisted at 1 week and slowly disappeared during the subsequent period. Immediately after the HIFU session, mild skin redness was observed in one patient. At 1 week, it had persisted as a small rash area with red papules, and at 1 month it had disappeared. There were no serious adverse events such as dysphonia or tracheal or esophageal thermal injury.

Table 2

US Characteristics of Thyroid Nodules before and up to 6 Months after HIFU Ablation

Characteristic	Basal	1 Week	*P* Value	1 Month	*P* Value	3 Months	*P* Value	6 Months	*P* Value
Echogenicity			.004		.027		.060		.194
Isoechoic	13 (65)	3 (15)		5 (25)		6 (30)		6 (37.5)	
Hypoechoic	7 (35)	17 (85)		15 (75)		14 (70)		10 (62.5)	
Homogeneity			.006		.024		.072		.054
Homogeneous	8 (40)	0 (0)		1 (5)		2 (10)		1 (6.3)	
Heterogeneous	12 (60)	20 (100)		19 (95)		18 (90)		15 (93.7)	
Color flow Doppler pattern*			.002		.068		.050		.016
Type 0	0 (0)	10 (50)		6 (30)		6 (30)		6 (37.5)	
Type 1	11 (55)	7 (35)		8 (40)		6 (30)		5 (31.2)	
Type 2	7 (35)	3 (15)		5 (25)		7 (35)		5 (31.3)	
Type 3	2 (10)	0 (0)		1 (5)		1 (5)		0 (0)	

Note.—Data are number of nodules, with percentages in parenthesis. The *P* values were obtained with χ^2 tests.

* Type 0 = absence of flow, type 1 = presence of blood flow with patchy, uneven distribution, type 2 = clearly increased color flow Doppler signal intensity with patchy distribution, type 3 = marked increase in blood flow with diffuse homogeneous distribution (16).

Table 3

Demographic, US, and Treatment Characteristics with Respect to Thyroid Nodule Echogenicity and Change in Echogenicity after HIFU Ablation

	Basal Echogenicity			Echogenicity Change at 1 Week		
Characteristic	Isoechoic ($n = 13$)	Hypoechoic ($n = 7$)	*P* Value	Iso- to Hypoechoic ($n = 9$)	No Change ($n = 11$)	*P* Value
Age (y)	45.2 ± 12.0	43.0 ± 11.8	.696	50.7 ± 8.9	39.4 ± 11.6	.027
BMI (kg/m^2)	24.4 ± 4.2	25.5 ± 3.4	.553	25.1 ± 4.3	24.5 ± 1.5	.731
Depth (mm)	7.3 ± 2.7	8.8 ± 2.9	.265	8.2 ± 2.7	7.5 ± 3.0	.621
Basal volume (mL)	5.58 ± 2.91	3.80 ± 2.29	.181	5.3 ± 2.7	4.6 ± 2.9	.594
Energy per volume (kJ/mL)	3.3 ± 1.2	4.7 ± 1.6	.033	3.5 ± 1.4	4.0 ± 1.7	.492
Hyperechoic marks (%)	47.2 ± 16.0	42.4 ± 23.6	.607	46.6 ± 18.3	44.4 ± 19.9	.809
Volume reduction at 1 month (%)	31.6 ± 18.1	16.4 ± 8.6	.053	33.7 ± 19.7	20.3 ± 12.1	.076
Volume reduction at 3 months (%)	42.6 ± 23.0	30.8 ± 17.9	.255	48.0 ± 23.2	30.6 ± 17.6	.073
Volume reduction at 6 months (%)*	52.1 ± 27.7	41.2 ± 14.3	.427	57.3 ± 28.7	40.1 ± 16.6	.163

Note.—Data are means ± standard deviation. The *P* values were obtained by using the Student *t* test.

* Volume reduction was evaluated in 16 patients (11 isoechoic and five with hypoechoic basal echogenicity, eight with changed and eight with unchanged echogenicity at 1 week).

Discussion

The results of our study demonstrated that a single US-guided HIFU procedure induced significant volume reduction in benign thyroid nodules, with favorable cosmetic and safety outcomes. Up until now, various nonsurgical US-guided ablation methods for treatment of benign thyroid nodules have been applied. The results of using these methods have been comparable with our finding of 48.7% nodule reduction 6 months after a single HIFU procedure. Six months after a single laser ablation or radiofrequency ablation procedure, the nodule volume diminished 46%–64% (17,18) and 51%–80% (6), respectively. In a recent study of 15 patients treated with a single radiofrequency procedure, a 6-month volume reduction of 70.2% was demonstrated, but three patients with large nodules were retreated after 1 month of follow-up (15). Reduction of more than 90% was shown with radiofrequency and ethanol ablation of cystic thyroid nodules, when fluid was aspirated before the procedure (4). However, HIFU is not applicable in purely cystic nodules, because the acoustic energy is not absorbed by fluids, but it may be possible to treat mixed nodules with more than 30% cystic content after previous aspiration. All of these procedures are minimally invasive. Yet, in comparison with HIFU, these procedures include penetration of the treatment device into the nodule.

Similar to that of other nonsurgical techniques, heat generation is the main mechanism involved in HIFU ablation (7). Apparently, this is the reason all of these procedures cause similar US changes (eg, transient hyperechoic

areas as a marker of thermal effect) (6). In our patients, the proportion of hyperechoic marks showed no correlation with the amount of the applied energy per volume tissue and it was lower in patients with higher BMI. Most likely, the energy deposition in the prefocal subcutaneous fat tissue may affect the intensity of the HIFU beam and the treatment effect (19).

Changes in postablation nodule structure associated with the development of coagulative necrosis include lower echogenicity and a decrease in vascularization. Such changes were observed in our study and in studies of other nonsurgical techniques (6,20,21) and were similar to those described by Esnault et al (13). According to our results, initial echogenicity and vascularization may serve as a predictor of the effect of HIFU ablation. In comparison with the results of laser ablation (18,22), HIFU treatment induced greater initial volume reduction in isoechoic than in hypoechoic nodules, although less energy was applied. Our finding that highly vascularized nodules reduced to a lesser extent is concordant with observations in other HIFU-treated lesions and with the presumption that perfusion-mediated tissue cooling reduces the extent of thermal ablation (23,24). Because it proved to be an important factor for the success of ablation, the assessment of nodule vascularity might be further improved by using a measurement of peak systolic velocity instead of using a qualitative scale.

Compared with surgery or other nonsurgical methods, HIFU treatment resulted in fewer adverse effects in our patients. In unilateral and bilateral thyroid surgery, the total complication rates were 8% and 26%, respectively. In most patients, L-thyroxine substitution was obligatory (25). In radiofrequency or laser ablation, the most frequent complications were recurrent laryngeal nerve palsy or hematoma, whereas edema, skin burn, fever, or tracheal injury were rarely reported (6,26,27). In comparison with that of nonsurgical procedures, the duration of the overall HIFU treatment is longer. Yet, thanks to its noninvasive nature, it is not associated with risk of bleeding. The subcutaneous edema in one patient with high BMI and the positive correlation between reports of pain and BMI shown in our data might be explained by the increased prefocal heat deposition as a result of fat tissue attenuation. Patient selection for HIFU might be improved with a quantitative assessment of subcutaneous fat thickness (19).

Our study had limitations. First, the follow-up period was relatively short because of the recent introduction of this procedure. Long-term follow-up of patients treated with other ablative methods showed the possibility of thyroid nodule regrowth due to undertreated peripheral nodule portion (28,29). Second, the sample size was small, and our results might not be relevant for a larger population and for different types of thyroid nodules. In addition, four (20%) of the 20 patients were not included in the 6-month follow-up because three patients underwent repeated HIFU treatment and one patient did not return for follow-up. Finally, a single HIFU session enables treatment of one layer, and therefore, the results may not be satisfactory in nodules with a larger anteroposterior diameter. However, in patients with insufficient nodule volume reduction after the first HIFU session, the procedure may be repeated, or it may be followed by any other treatment (8,10).

To summarize, we have shown that US-guided HIFU ablation is an effective and safe noninvasive treatment method for benign solid thyroid nodules. The major limitation for this application is the technical accessibility of the nodule. However, larger clinical trials with longer follow-up should be undertaken to evaluate the long-term effectiveness and safety and to define the spectrum of thyroid abnormalities most suitable for this treatment.

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