



High-intensity focused ultrasound (HIFU) for benign thyroid nodules: 2-year follow-up results

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Abstract

Background High-intensity focused ultrasound (HIFU) is the last introduced thermal treatment of thyroid nodules. Here we evaluated the results at 24 months after HIFU.

Methods Since 2016, HIFU was considered as a therapeutic option at our institute in patients with benign thyroid nodules presenting local symptoms. We searched in our database all patients who had undergone thyroid HIFU and selected for the study only cases followed-up for at least 24 months after the treatment. Volume reduction rate (VRR) was evaluated. A reduction above 50% defined the success of HIFU.

Results Thirty-one nodules of 31 patients (24 females and 7 males, median age 67 years) with median major diameter from 17 to 34 mm and estimated nodule volume of 5.48 mL were included. HIFU was performed with median power of 42 W/site (interquartile range 25–45) and median energy of 263 J/site (interquartile range 225–273). Median duration of the procedure was 6 min (interquartile range 5–7). At 2 years after HIFU, nodule volume was significantly ($p < 0.0001$) lower (i.e., 3.40 mL) with VRR of 43.3%, and 26 (83.9%) lesions were reduced. A reduction by at least 50% was observed at 6, 12, and 24 months in 2 (6.4%), 5 (16.1%), and 7 (22.5%) nodules, respectively. Visual analog score showed a significant improvement ($p < 0.0001$). No complications were recorded.

Conclusions A reduction of benign thyroid nodule by more than 40% could be reached within 1 year by HIFU. Given the non-significant size increase of some lesions later, a larger study with a longer follow-up is necessary.

Keywords Thyroid · Thermal ablation · High-intensity focused ultrasound (HIFU)

Introduction

Thyroid nodule is a frequent condition being diagnosed in up to 70% of subjects who had undergone thyroid ultrasound (US) [1–3]. Fortunately, 90–95% of nodules turn out to be benign and, when they do not determine compressive symptomatology or esthetic problems, do not need specific therapy and are addressed to clinical follow-up. On the other hand, the surgical removal of thyroid nodule is traditionally offered to those patients with large goiter with compressive symptoms and, notably, thyroidectomy still

remains the standard of care of malignant tumors [4]. In order to avoid surgery and the related possible complications, non-invasive options treatments, such as laser, radiofrequency, microwaves, ethanol ablation, and high-intensity focused ultrasound (HIFU), have been diffusing [5]. In this context, a major document was published by Korean Society of Thyroid Radiology and another recent study was reported [6, 7].

HIFU is the most recently introduced non-surgical treatment of benign thyroid lesions. It presents some advantages and limitations that should be considered. HIFU does not include invasive tools, with patients being treated by a US beam [8–10]; this means that needle-related complications are completely avoided. Several studies have already examined the effectiveness of HIFU therapy in the reduction of benign thyroid nodule volume [11–16]. Furthermore, its reliability is good in those nodules with volume inferior to 3 mL or with diameter no larger than 4 cm [11, 12]. However, the cost of HIFU is not negligible and then its cost effectiveness should be lower than laser

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and radiofrequency, especially in patients with large size nodules. All these papers described series of patients followed-up after treatment for a brief period (i.e., 3 to 12 months) and this represents a significant weakness of literature. In fact, the true effectiveness of a thermal treatment of thyroid lesions should be evaluated over long periods [17]. To the best of our knowledge, only one paper on long-term follow-up after HIFU therapy has been published using high energy and general anesthesia [18]. As a consequence, whether the initial result of volume reduction rate (VRR) of nodules that had undergone HIFU is maintained over time is still unknown.

In our previous studies we showed findings on VRR at 6 to 12 months after HIFU [12, 14]. Therefore, the present study was undertaken to evaluate the trend of nodule volume at longer period to extend information of initial data. Accordingly, we retrospectively reviewed our series of HIFU therapy in benign nodules to select only those cases with adequate post-treatment clinical follow-up. To our knowledge, this is the first report of 2-year follow-up HIFU results using low energy without local anesthesia.

The aim of the present study was to evaluate the long-term (i.e., 2 years) efficacy of HIFU in reducing the volume of benign thyroid nodules. As main outcomes of the study, we included VRR and a volume reduction by at least 50% [19, 20].

Methods

Selection of patients

According to the study aim, here we searched in our database all patients who had undergone thyroid HIFU. Later we selected for the present study only those cases followed-up at our center for at least 24 months after the treatment. The informed consent was obtained from all patients. Local ethical committee approved this study.

Institutional management of HIFU

Since 2016, HIFU therapy was considered at our thyroid center as one option for those patients with cervical compressive symptoms in whom the latter concerns were directly caused by a benign thyroid nodule. However, nodules with large cystic composition, cystic area above 30% of the whole lesion, or macrocalcifications were not eligible for this therapy. In addition, nodules with a limited accessibility for US administration (i.e., nodule near to trachea, skin, vessels) were excluded. All lesion considered as eligible for HIFU needed a benign report from fine needle aspiration cytology (FNAC) and normal calcitonin value. Function laboratory tests (thyroid-stimulating

hormone, thyroid hormones, thyroid antibodies) were always performed.

The ultrasound therapies were conducted as previously described [12, 14]. Briefly, a HIFU machine with Beamo-motion system (Theraclion®, Paris, France) was used. Safety of the adjacent structures was ensured using a laser-based movement detector that enables power interruption if patient moves. Patient was placed in supine position with the hyperextended neck. The treatment head was placed on the skin and target nodule well identified. The margins of the target thyroid nodules as well as the other cervical structures (i.e., trachea, skin, carotid) were selected on the touch screen by a pen. The first HIFU pulse was performed at a fixed dose of 45 W/site; later, the power of the pulses was tailored according to the patient's tolerability. Importantly, no sedation or local/general anesthesia was performed.

Evaluation of response to HIFU therapy

The volumetric response to treatment was evaluated at 6, 12, and 24 months after therapy. Nodule volume was obtained using ellipsoid volume formula (i.e., longitudinal diameter \times transverse diameter \times anterior–posterior diameter \times 0.52). Also, visual analog scale (VAS) was used to evaluate the compressive symptoms in a 10-point scale at basal time and 24 months after treatment [18]. As main outcomes of the study, we included VRR and a volume reduction by at least 50% with respect to the baseline size [19, 20].

Statistical analysis

Nonparametric statistical analysis (Wilcoxon test for pairs and one-way analysis of variance) was used to compare the estimated nodules volume before and after HIFU. All data in the study was reported as median and interquartile ranges (IQR). Statistical analysis was performed by GraphPad Prism version 7 (GraphPad Software, Inc., La Jolla, CA 92037 USA).

Results

After using the above selection criteria, the final series included 31 nodules from 31 patients (24 females and 7 males) with median age of 67 years. These subjects had benign thyroid nodules with median major diameter ranging from 17 to 34 mm, and a median estimated nodule volume of 5.48 mL (IQR 3.98–7.14). The HIFU treatment was performed with a median power of 42 W/site (IQR 25–45). Median energy delivered was 263 J/site (IQR 225–273). Median effective duration of the procedure was 6 min (IQR 5–7).

At the final follow-up (24 months after HIFU therapy), 26/31 lesions showed a volume smaller than that recorded before HIFU and the remaining 5 (16.1%) had size larger than the baseline one. Median nodules' volume of whole group was 3.40 mL (IQR 2.60–4.19), this being significantly lower than the baseline one ($p < 0.0001$). Figure 1 illustrates the estimated nodule volume recorded in all cases before HIFU and over the follow-up. Median VRR at 24-month follow-up was 43.3% (IQR 17–50). Figure 2 shows the VRR over the 2-year follow-up. When we evaluated the trend of nodule size during the follow-up, we found a significant decrease over time ($p < 0.0001$); however, a significant reduction was present up to 12 months, while no further significant reduction was observed after the first

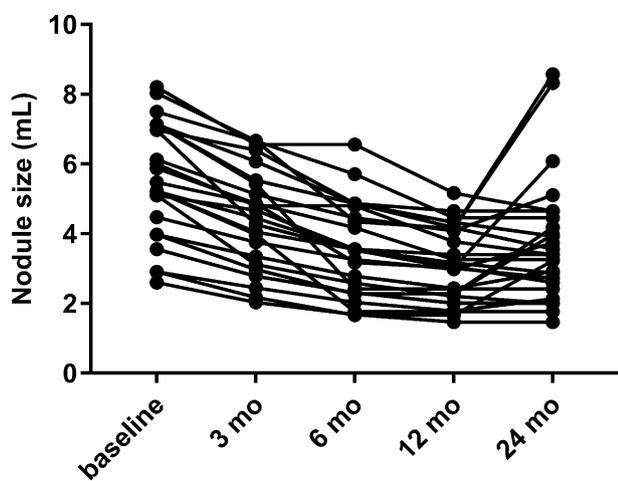


Fig. 1 Trend of volume of the 31 nodules treated by high-intensity focused ultrasound (HIFU). Each nodule is represented by a single line and point represents the examination at baseline, 3, 6, 12, and 24 months of follow-up

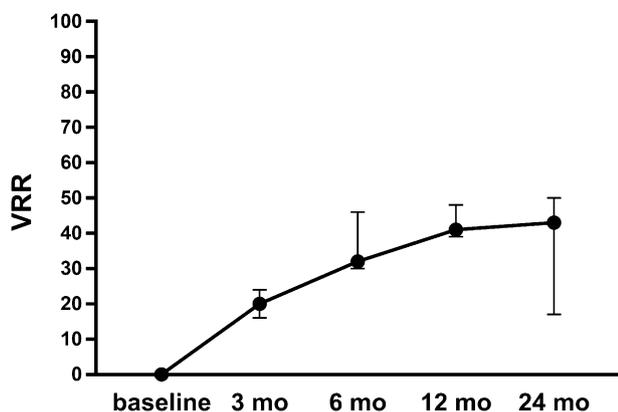


Fig. 2 Volume reduction rate (VRR) recorded after high-intensity focused ultrasound (HIFU). Each point indicates the median value recorded in the whole series of nodules, while bars indicate the interquartile range (IQR)

12 month of follow-up (Table 1). After 12 months to 24 months, there was slight increased size of the tumor with no significant difference. A reduction by at least 50% was observed at 6, 12, and 24 months in 2 (6.4%), 5 (16.1%), and 7 (22.5%) nodules, respectively. These 7 nodules responders at 2-year follow-up were solid in 6 cases, with no significant difference with respect to the non-responders which were solid in 14/24 ($p = 0.18$). Also, no significant difference was observed in vascularization between responders and non-responders. Moreover, as shown in Fig. 1, some lesions of our series showed a new increase of volume after the first 12 months and 5 of these had a size higher than the basal one. These lesions underwent a new FNAC and benignancy was confirmed in all cases.

Energy delivered was analyzed as a potential determinant of results. Considering the median VRR at 2-year follow-up, nodules with VRR above 43.3% received a median energy of 340 J/mL (IQR 266–457), while nodule with VRR below 43.3% received 278 J/mL (IQR 203–475) ($p = 0.24$); also, energy per site was 265 (IQR 217–280) and 264 (IQR 225–271) J/site ($p = 0.66$), respectively. Furthermore, there was no significant difference between nodules with a reduction above or below 50%, or between nodules with no reduction and the other ones.

Regarding the compressive symptoms, at baseline we recorded a median VAS of 5 (IQR 4–6), while at the end of the study median VAS was 4 (IQR 3–4), with these values being significantly different ($p < 0.0001$). No nodules showed increased size of more than 50% than the basal value. No complications were recorded.

Discussion

To avoid surgery in patients with benign goiter is a major challenge of our era. Then, several options for reducing size of benign thyroid lesions have been diffused during the last decade. The possibility to treat thyroid nodules by thermal ablation without needle, such as HIFU, was more recently reported and has represented a significantly appealing option. Due to its more recent introduction, the results of HIFU at a time longer than 1 year are poorly reported [18]. Thus, here we aimed to retrospectively analyze a series of patients whom we treated and followed-up for 2 years. Importantly, as we previously reported in our previous studies [12, 14], or sedation or local/general anesthesia was performed. Also, the institutional procedure included that the first energy pulse was performed at a fixed dose of 45 W, this being not very high, and the power of subsequent pulses was tailored according to the the patient's tolerability and comfort. This allowed us to have an optimal control of the patient's pain and compliance. Figure 3 illustrates one case with volume reduction at follow-up.

Table 1 Nodule volume recorded during the follow-up

	Baseline	3 Months	6 Months	12 Months	24 Months
Median	5.48	4.45	3.54	3.03	3.40
Min–Max	2.60–8.21	2.04–6.67	1.67–6.56	1.47–5.17	1.47–8.58
25–75 Percentile	3.98–7.14	3.12–5.54	2.31–4.80	2.28–4.15	2.60–4.19
<i>P</i> value	–	<0.0001	<0.0001	<0.0001	0.12

P expresses the difference between values recorded in one control and that recorded in the previous one

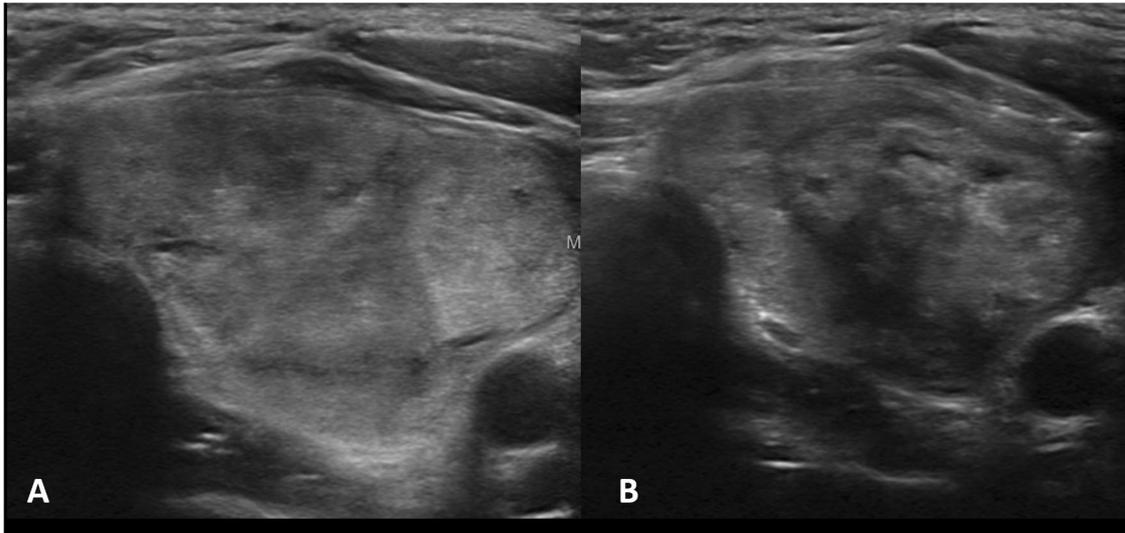


Fig. 3 A left lobe thyroid nodule treated by high-intensity focused ultrasound (HIFU). **a** Ultrasound before treatment (nodule's volume 10.5 mL). **b** Ultrasound after 6 months with nodule size reduction

(6.5 mL) and appearance of an area of major hypoechogenicity demonstrating the internal necrosis

As the main finding of our study, a significant nodule size decrease was reached 24 months after HIFU treatment. Also, 26/31 nodules had a volume smaller than the baseline one. Furthermore, VRR at last visit was 41.8%. However, our analysis showed that the reduction of nodule size was present up to 12 months after HIFU, while no further progression of volume decrease was observed. This nodule shrinkage allowed a decrease of compressive symptoms, as shown by VAS analysis. According to the most recent recommendations [19], the technical success of thyroid thermal treatments has to be defined as a reduction by at least 50% of baseline volume. Here we found 7 responders who had not significantly different echostructure from the non-responders. This should be not surprising considering that the selection of nodules for HIFU must include lesions with a solid component in at least 70%. We analyzed the energy delivered as a potential determinant of VRR and no significant correlation was observed between J per site or per mL and volume reduction. HIFU is a standardized procedure and this is a significant difference with respect to radiofrequency and laser treatment. Then, probably other variables, such as the compactness of a tissue, may determine a different absorption of ultrasounds.

As above mentioned, until now only one study [18] reported data on thyroid nodules treated by HIFU and followed-up for 24 months. There, a VRR of 70% was observed at 24-month follow-up, while a VRR of 62% was present yet at 6 months. Then, only mild further reduction was present after the first 6 months in the study by Lang et al. [18] similar to our study. No significant difference seems to be present between energy delivered for thermal ablation in that study (mean energy per pulse 299 J) with respect to that we used (median energy delivered per pulse 263 J). In the study of Lang et al. [18], a large number of nodules was enrolled and nodule volume (mean volume 13 mL) was higher than that of our series (median volume 5.5 mL). On one hand, we can explain the different outcomes of VRR on the basis on the different baseline values of the lesions. On the other hand, we can confirm in our series that the mean VRR recorded after the first period of follow-up is not further improved later. As a consequence of the volumetric results, as showed by evaluating VAS before HIFU and 24 months later, compressive symptoms were improved. Here we treated patients by a single-session HIFU, but a recent study reported that symptom score improved at 3 and 6 months after reapplication [21]. At the

end of the observation, five lesions had a size higher than the basal one. A slight median nodule size increase between 12 and 24 months was also found in the study by Lang et al. [18] where about one-fifth of nodules had a notable volume beyond 12 months. Both findings (by Lang et al. [18] and the present one), should indicate that a regrowth of nodule treated by HIFU may be possible after the first year. Thus, larger studies with longer follow-up period are essential to better define the efficacy of HIFU in thyroid nodule.

Larger information has been reported about the long-term follow-up of benign thyroid nodules treated by laser and radiofrequency with excellent results [22–24], while the performance of HIFU is yet to be proven [25]. Therefore, the present study extends the knowledge on this topic and shows that HIFU should be less effective than laser and radiofrequency.

HIFU allows the thermal tissue treatment by directing energy ultrasound beam inside the target nodule with neither needles nor other invasive instruments. To date, no major complications have been recorded and some minor transient adverse effects (i.e., local edema, skin redness, skin micro-blisters, vocal cord paresis) were observed [13]. Because HIFU uses ultrasounds and the treatment is monitored in a specific US display, anyone who is an expert in diagnostic US may be able to perform this thermal ablation after an initial training. On one hand, some disadvantages of HIFU with respect to laser and radiofrequency should be considered; firstly, higher costs and low efficacy in very large nodules. On the other hand, due to its manageability, HIFU might be useful in those patients with no significantly large lesions determining local symptoms in whom performing radiofrequency and laser might be difficult. Also, we would like to underline that our procedure did not include anesthesia or sedation [12–14], while current guidelines recommend local anesthesia for radiofrequency and laser [7]. The above study by Lang et al. [18] was conducted using narcosis, similar to other previous studies, and patients were discharged home 2–3 h after treatment. This setting looks like a surgical procedure performed in an operating room. While this could lead to different results, it effects significantly the overall cost of the procedure.

The strengths and limitations of this study can be discussed. First, this is the second study reporting data of HIFU therapy in thyroid nodules with follow-up at 2 years. Second, the sample size was not large, but the not parametric analysis should not be influenced by this aspect. Third, this was a retrospective study and this could introduce a bias in the selection of patients.

In conclusion, a reduction of benign thyroid nodule by more than 40% could be reached within 1 year by single-session HIFU treatment. Given the non-significant size increase after 1 year of some lesions, a larger study with a longer follow-up period is necessary.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Also, for this retrospective study, formal consent was not required.

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