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ORIGINAL SCIENTIFIC REPORT

The Efficacy and Safety of High-Intensity Focused Ultrasound (HIFU) Therapy for Benign Thyroid Nodules—A Single Center Experience from Singapore

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Abstract

Background High-intensity focused ultrasound (HIFU) is a recent noninvasive technique of treating thyroid nodules. Our study aims to investigate the efficacy and safety of HIFU in treating benign thyroid nodules.

Methods This is a retrospective analysis of consecutive patients who underwent HIFU of benign thyroid nodules at our institution from July 2017–2018. All procedures were performed by a single surgeon. Patients were evaluated immediately post-procedure, and at subsequent intervals of 1 week, 1 month, 3 months, and 6 months. The primary endpoint was thyroid nodule volume reduction at 6 months posttreatment. Secondary endpoints were post-procedure local complications.

Results Ten patients with 13 thyroid nodules were included. The median follow-up period was 426 days (range 238–573). Mean maximum diameter reduced from 2.6 cm (±0.8) pretreatment to 1.4 cm (±0.7, $P < 0.05$) 6 months posttreatment. Mean nodule volume reduced from 5.2 cm^3 (±4.2) pretreatment to 1.5 cm^3 (±1.3, $P = 0.01$) 6 months posttreatment. Mean volume reduction ratio (VRR) at 6 months posttreatment was 63.2% (±22.5, $P < 0.05$), with volume reduction of ≥50% in 10 of 13 (76.9%) nodules. Two nodules (15.4%) showed size increases from 4 months posttreatment. No patients experienced local skin burns or hematomas. Mean pain scores were 1.5 (±1.2) immediate post-procedure, 0.8 (±1.5) at 1 week, and 0.6 (±1.2) at 1 month post-procedure, respectively, with no reports of pain beyond 1 month. Only two (20.0%) patients had early, temporary posttreatment voice hoarseness.

Conclusion Our study shows HIFU ablation to be efficacious and safe—with significant thyroid nodule volume reductions, and no significant or prolonged local complications.

Introduction

Thyroid nodules are common, and although most are benign and remain static, some become large and symptomatic [1, 2]. The revised American Thyroid Association (ATA) guidelines recommend surgical resection for a benign solid or predominantly solid nodule that is either large (>4 cm in diameter) and/or causes compressive symptoms or clinical concern [3]. Cosmesis is another indication for treating benign thyroid nodules.

Surgery is still the mainstay of treatment, but it carries a risk of complications like bleeding, infection, and recurrent laryngeal nerve injury. General anesthetic risks due to patient comorbidities must also be factored in while considering surgery [1, 4, 5].

For these reasons, various nonsurgical techniques have now been introduced at specialized treatment centers [4, 6, 7]. Several thermal ablation techniques have been shown to be effective in treating predominantly solid or

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solid benign thyroid nodules [5]. It is well recognized that temperatures above 55 °C maintained for more than 1 s induce nonreversible enzymatic denaturation, leading to coagulative necrosis and cell death [4, 6].

High-intensity focused ultrasound (HIFU) is a relatively recent thermal ablative technique that directs energy inside the targeted nodule without invasive instruments [8, 9]. HIFU is gaining momentum as one of the most promising nonsurgical techniques for treating benign thyroid nodules due to its noninvasiveness with no scar formation, accuracy, and ease of use [10].

However, there is presently a lack of experiential studies on HIFU and this technique is yet to be well described in the literature. In a systematic review on HIFU by Lang et al. [3], only five studies fulfilled their inclusion criteria of any prospective or retrospective study involving human adults. But with the increasing use of HIFU by centers, there is gradually more literature that is now becoming available.

Thus, through this study on the efficacy and safety of HIFU in treating benign thyroid nodules in a Singaporean center, we hope to share our experience and expand on the current literature.

Materials and methods

This is an initial retrospective analysis of consecutive patients who underwent HIFU at a single tertiary surgical center from July 2017 to July 2018.

The data from this study were collected as part of a clinical safety evaluation of new devices approved by the hospital's New Surgical and Interventional Practice Committee (NSIPC) (New Device Ref No: 17/003). The HIFU device received Health Sciences Authority (HSA) regulatory approval for use in Singapore (HSA Ref No: DE0018298).

Inclusion criteria were patients with solid or predominantly solid thyroid nodules (cystic component <30% of nodule volume) with fine-needle aspiration (FNA)-proven benign cytology (Bethesda II), and which were between 1.5 and 3.0 cm in size, and more than 1 cm deep to the skin, as well as meeting one or more of the following: patients presenting with compressive symptoms (like dysphagia, or subjective dyspnea), who had cosmetic concerns, who declined or were medically unfit for surgery, and who had no limitations in extending their neck.

Patients who had thyroid nodules with cystic component >30% of the nodule volume (mixed solid and cystic, predominantly cystic, or cystic composition), nodules with coarse or microcalcifications, FNA results of Bethesda III and above, and patients with preexisting skin conditions on the neck anterior to the thyroid and/or limitations with neck extension were excluded.

Pretreatment

Prior to HIFU treatment, all patients had ultrasound imaging of their thyroid nodules with baseline nodule measurements (cm) in three dimensions obtained on transverse and longitudinal cross-sectional views. Nodule volume (mL) was calculated using the ellipsoid volume formula [Nodule Volume = Length × Breadth × Depth × (π/6)], where π was taken as 3.14159 [6]. All patients had baseline hematological thyroid function tests and thyroglobulin levels.

Intra-procedural

All HIFU treatments were performed as elective procedures by the same surgeon (N.K.Y).

All patients received intravenous analgesia using a combination of paracetamol or COX-II inhibitor (parecoxib) and/or an opioid agent like Fentanyl or Pethidine. The procedure was performed under conscious sedation with an intravenous benzodiazepine (midazolam) or propofol under monitored anesthesia care.

The HIFU system used in all patients was Echopulse® (Theraclion, Malakoff, France), with a frequency of 6 MHz, maximum ultrasound power of 70.2 mW, and maximum ultrasound intensity of 123.4 W/cm^2. Temperatures used and cooling were as per the thyroid nodule ablation protocol of the Echopulse® (Theraclion, Malakoff, France) manufacturers.

To ensure safety, nearby structures like the carotid artery and trachea were marked out on the treatment screen prior to starting treatment, shown in Fig. 1. There was continuous sonographic monitoring of the treatment area during the procedure for all patients. The Echopulse® (Theraclion, Malakoff, France) system had the facility to stop treatment at any time during the ablation.

Minute adjustments were constantly made by the operator to ensure optimal positioning of the target nodule to the intended point of ablation, while avoiding nearby critical structures. Immediate ultrasonographic ablation effects like cavitation artefacts were noted after each pulse.

HIFU treatment of each nodule was performed in a single session in one layer. For patients who had more than one nodule, the nodules were treated one after the other.

Posttreatment

All patients were evaluated immediate post-procedure, and at post-procedure intervals of 1 week, 1 month, 3 months, and 6 months in the outpatient setting.

Data including patient demographics, American Society of Anaesthesiologists (ASA) physical status scores, presenting symptoms, pretreatment nodule size and volume, intra-procedural parameters like duration, energy and

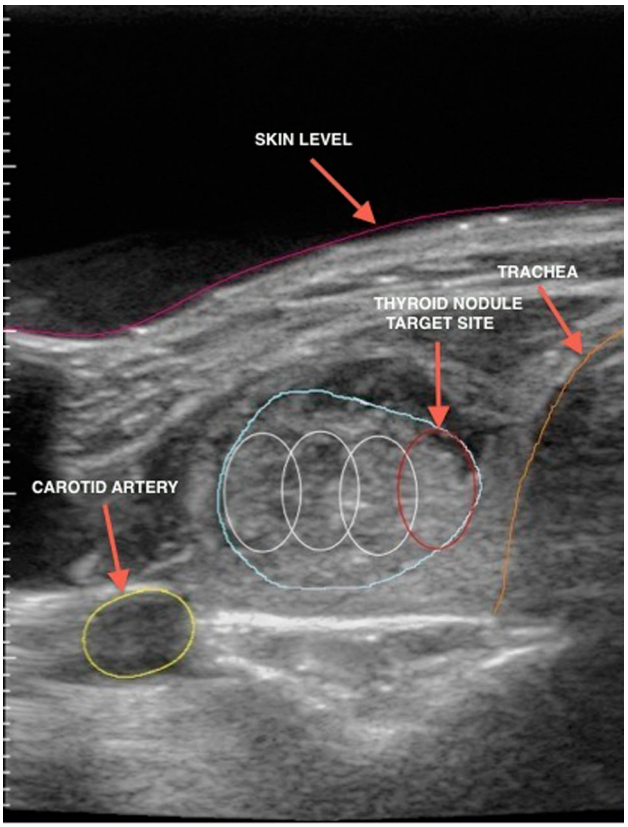

Fig. 1 Identification of critical structures on treatment screen prior to commencing HIFU treatment

power of treatment, posttreatment nodule size, and volume, and complications like local skin damage, pain, and voice hoarseness were collected.

The primary endpoint was volume reduction in thyroid nodules at 6 months posttreatment. Volume reduction ratio (VRR) was calculated as VRR = [(Baseline Volume − Volume at clinic visit)/Baseline Volume] × 100%. As cited in the literature, treatment success was defined as ≥50% volume reduction at 6 months from treatment [1]. This would answer our question on the efficacy of HIFU treatment in solid/predominantly solid benign thyroid nodules.

Secondary endpoints were post-procedure complications—local skin burns and hematomas, pain, and voice hoarseness. Pain scores were documented using a standard 10-cm visual analog scale (VAS). Post-procedure voice hoarseness was assessed as being temporary or permanent. This would address the safety of HIFU treatment in solid/predominantly solid benign thyroid nodules.

Statistical analysis

IBM® SPSS® Statistics 23 was used for statistical analysis. Continuous variables were expressed as mean and standard deviation (SD) and compared using an independent sample *T* test. Categorical variables were expressed as median and range. The Chi-square test was used to analyze dichotomous categorical variables. All results were presented as two-tailed values; results were considered to be statistically significant if $P < 0.05$.

Results

A total of ten patients with 13 thyroid nodules were included in the study. Three patients had bilateral nodules (one nodule each on the right and left), with each nodule being treated in a single layer one after the other.

Nine out of ten (90.0%) patients were females. The mean age was 52.1 years (±10.6), and the mean body mass index (BMI) was 23.9 kg/m^2 (±5.2). All (100.0%) patients were biochemically euthyroid at presentation.

The median ASA score was 2 (range: 1–2). All patients (100.0%) underwent HIFU treatment because they refused surgical intervention in spite of being indicated for it, as opposed to being unfit for surgery or general anesthesia. The patients provided reasons for refusing surgery such as fear of surgery, general anesthesia, and/or scar appearance.

IV Midazolam was used in nine out of ten (90.0%) patients, while one out of ten (10.0%) patients received IV Propofol.

The intra-procedural parameters are given in Table 1. The mean number of sites treated was 25.0 (±5.1), with a mean total duration of 27.4 min (±14.9) of treatment. The mean total energy delivered was 6.9 kJ (±4.0), and mean effective power per pulse was 37.9 W (±12.9).

Sonographically, central vacuolation and decreased blood flow on Doppler ultrasound were seen posttreatment.

All ten (100.0%) patients completed their planned HIFU treatments without any interim termination. Nine out of ten (90.0%) patients successfully had their HIFU treatments as day procedures, with a mean time from procedure to discharge of 5.1 h (±4.0). Only one (10.0%) patient was admitted for blood pressure monitoring due to post-procedure hypertension and was stably discharged 18 h post-procedure.

The median follow-up period was 426 days (range: 238–573).

Table 1 Intra-procedural parameters

	Mean	SD	Statistical significance
Duration of treatment (min)	27.4	14.9	$P < 0.05$
Total energy (kJ)	6.9	4.0	$P < 0.05$
Median effective power per pulse (W)	37.9	12.9	$P = 0.76$
Mean no. of sites of treatment	25.0	5.1	$P < 0.05$

Table 2 Pre- and Posttreatment nodule maximum diameter (cm)

Time interval post-procedure	Mean	SD	Statistical significance
Pretreatment	2.6	0.8	
Posttreatment			
1 week	2.3	0.6	$P = 0.27$
1 month	2.0	0.7	$P = 0.06$
3 months	1.7	0.7	$P < 0.05$
6 months	1.4	0.7	$P < 0.05$

Table 3 Pre- and Posttreatment nodule volume (cm^3)

Time interval post-procedure	Mean	SD	Statistical significance
Pretreatment	5.2	4.2	
Posttreatment			
1 week	4.0	3.0	$P = 0.42$
1 month	3.1	2.4	$P = 0.14$
3 months	2.0	1.6	$P = 0.02$
6 months	1.5	1.3	$P = 0.01$

Treatment efficacy

The pre- and posttreatment nodule maximum diameters and volumes at various time intervals are given in Tables 2 and 3.

The mean maximum diameter reduced from 2.6 cm (±0.8) pretreatment to 1.4 cm (±0.7) at 6 months post-treatment, and this was statistically significant ($P < 0.05$). Similarly, mean nodule volume reduced from 5.2 cm^3 (±4.2) pretreatment to 1.5 cm^3 (±1.3) 6 months post-treatment and was statistically significant ($P = 0.01$).

The mean volume reduction ratio (VRR) at 6 months posttreatment was calculated as 63.2% (±22.5). This result was also statistically significant ($P < 0.05$). Volume reduction of ≥ 50% was seen in 10 out of 13 (76.9%) thyroid nodules. The mean distance from the skin to the center of the nodule was 18.5 mm (±5.7). These results are displayed in Table 4.

Two out of 13 ablated nodules (15.4%) showed interval size increases from 4 months posttreatment. One was treated with aspiration of the liquefied central necrotic area of the ablated nodule with significant volume reduction. The second nodule had repeated HIFU at 12 months from initial ablation using the multilayer treatment protocol—this was the only patient treated with 2 layers.

Treatment safety

No patients in our study had posttreatment local skin burns or hematomas.

The mean post-procedure pain scores were 1.5 (±1.2) immediate post-procedure, 0.8 (±1.5) at 1 week, and 0.6 (±1.2) at 1 month post-procedure. All (100.0%) patients did not have pain beyond 1 month posttreatment. These results are given in Table 5.

Eight out of ten (80.0%) patients did not have post-treatment voice hoarseness, while the remaining two (20.0%) patients only had temporary posttreatment voice hoarseness that recovered as observed during clinic visits. Both patients with temporary voice hoarseness did not notice it immediately post-procedure. This only occurred on the second to third day post-procedure and persisted for up to 10 days.

Eight in ten (80.0%) patients experienced improvement in their compressive symptoms that originally prompted medical attention. Three (30.0%) patients reported that the thyroid nodule in question felt softer in consistency after HIFU treatment.

Discussion

Treatment efficacy

Treatment success was defined as ≥50% volume reduction at 6 months posttreatment [1]. Our study showed that HIFU treatment for benign thyroid nodules is efficacious, with a statistically significant mean VRR of 63.2% (±22.5) suggestive of a substantial reduction in thyroid nodule volumes. This result is likely explained by both patient and nodule factors.

Table 4 Volume reduction ratio (VRR) at 6 months posttreatment (%)

Nodule no.	Distance from skin to center of nodule (mm)	Pretreatment volume (cm^3)	Posttreatment volume at 6 months (cm^3)	Volume reduction ratio at 6 months posttreatment (%)
Nodule #1	19.0	10.9	4.8	55.9
Nodule #2	11.0	1.2	0.5	55.1
Nodule #3	12.0	2.6	1.0	61.4
Nodule #4	24.5	1.4	0.9	34.8
Nodule #5	26.0	3.5	2.7	24.9
Nodule #6	28.0	10.8	2.2	80.1
Nodule #7	16.0	1.9	0.4	79.4
Nodule #8	20.0	2.6	0.4	86.5
Nodule #9	18.0	6.2	2.7	57.0
Nodule #10	19.1	13.8	0.4	97.3
Nodule #11	22.0	6.4	1.6	74.5
Nodule #12	10.2	3.3	0.6	81.5
Nodule #13	14.0	2.3	1.6	32.3
Mean	18.5			63.2
SD	5.7			22.6
Statistical significance				$P < 0.05$

Table 5 Posttreatment pain scores (VAS)

Time interval post-procedure	Mean	SD	Statistical significance
Immediate post-procedure	1.5	1.2	$P = 0.51$
1 week	0.8	1.5	$P < 0.05$
1 month	0.6	1.2	$P < 0.05$
3 months	0.0	0.0	0.00
6 months	0.0	0.0	0.00

We postulate that these factors include the predominantly solid composition of nodules in our study, and the relatively smaller nodule diameters and volumes. One study previously found pre-ablation nodule volume to be an independent significant factor affecting treatment efficacy, whereby nodules ≤8.2 mL were almost two times more likely to have >50% nodule shrinkage at 12 months than nodules >8.2 mL [3]. Another study reported better results in smaller nodules with maximum diameter <4 cm [11].

Additionally, the mean BMI in our study falls within normal limits. Although we did not investigate a relationship between BMI and VRR, plausibly, the thickness of subcutaneous tissue attenuates the ultrasound energy traveling through and may affect the efficacy of nodule volume reduction.

Furthermore, adequate neck extension of patients in our study is a crucial factor that improved the accessibility of the thyroid nodule for HIFU treatment. This is important as it affects the tangential positioning of the HIFU treatment unit relative to the nodule (Fig. 2), as opposed to an oblique positioning of the treatment unit in order to reach nodules that might be slightly retroclavicular (Fig. 3). Indeed, the performing surgeon observed that oblique positioning of the treatment unit and higher treatment wattages were associated with more pain, particularly, back pain. This is presumed to be from the absorption of scattered ultrasound energy posteriorly by the vertebral column.

Overall, HIFU appears efficacious as a nonsurgical treatment option for reducing the volumes of benign solid/predominantly solid thyroid nodules, and its efficacy can be

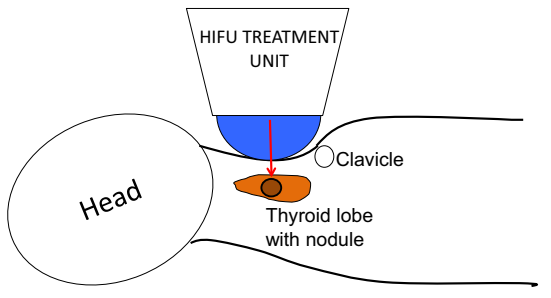

Fig. 2 Tangential positioning of HIFU treatment unit with adequate neck extension

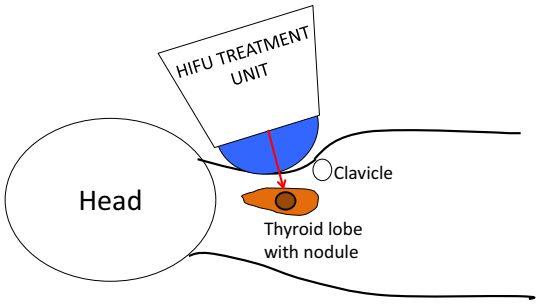

Fig. 3 Oblique positioning of HIFU treatment unit with inadequate neck extension

further optimized with appropriate nodule and patient selection.

Treatment safety

Our study results have shown no local skin complications, minimum and short-term posttreatment pain, and a low incidence of temporary but no permanent voice hoarseness. This aligns with results from other studies showing minor transient effects posttreatment [6], but no major complications [4].

Both our patients with temporary voice hoarseness did not report it immediately post-procedure, and there were no exact similarities in nodule or treatment characteristics between them. One patient had a left-sided nodule with pre-ablation size of 3.0 × 2.9 × 2.4 cm and underwent treatment for 45 min with 10.9 kJ of applied energy. The other patient had one nodule each on the right and left; the right-sided nodule had a pre-ablation size of 1.3 × 1.9 × 1.5 cm and was treated for 24 min with 5.3 kJ of energy, while the left-sided nodule had a pre-ablation size of 1.6 × 1.6 × 2.0 cm and was treated for 16 min with 4.5 kJ of energy.

This questions the underlying process accounting for the posttreatment voice hoarseness observed. Given its delayed manifestation, we suggest that the voice hoarseness may be due to local edema adjacent to the treated nodule rather than direct injury to the recurrent laryngeal nerve.

Limitations

This initial report of ten patients represents our early experience with HIFU, and these results may not hold true in a larger sample size. This is especially pertinent given that the efficacy of HIFU treatment remains highly unpredictable with some nodules showing good response, while others have less adequate response [11].

Despite the small observational cohort, we surmised that certain indications should be considered for optimal outcomes: adequate neck extension, use of Midazolam, and the size and depth of the lesion. We observed that with propofol, patient tended to move more compared to midazolam, despite adequate sedation and analgesia.

The follow-up period is short due to the recent introduction of HIFU treatment as a therapeutic option at our center. A longer follow-up period is required to reliably conclude on long-term outcomes. Experience from other types of thermal ablation, and from a 2-year follow-up of HIFU for thyroid nodule ablation by Lang et al. (2018), has shown that treated nodules tend to continually shrink over time, even for one or 2 years after initial treatment for some nodules [3, 12].

In our study, two ablated nodules demonstrated interval increase in size, both at 4 months posttreatment. A longer follow-up period will facilitate obtaining a more accurate incidence of interval size increase in nodules posttreatment, and thereby recurrence rate. Yet, it is worth noting that we are one of the first few studies to report data from a median follow-up period close to 6 months as opposed to 3 months.

Last but not least, our study is a retrospective analysis of existing records of ten consecutive patients who underwent HIFU ablative treatment at our center. We will continue to prospectively collect data and report our outcomes at a later date.

Conclusion

HIFU ablation of benign thyroid nodules is a noninvasive treatment and is also easy to use. Our study shows that HIFU ablation is both efficacious and safe in treating benign thyroid nodules. Further and large-scale studies are now required to compare HIFU ablation against other prevailing treatment methods to determine its superiority, equivalence, or non-inferiority in treating benign thyroid nodules.

Compliance with ethical standards

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

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