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ULTRASOUND

Combining high-intensity focused ultrasound (HIFU) ablation with percutaneous ethanol injection (PEI) in the treatment of benign thyroid nodules

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Abstract

Objective Assessing the 6-month efficacy of combined high-intensity focused ultrasound (HIFU) ablation with percutaneous ethanol injection (PEI) in benign thyroid nodules by comparing it with HIFU ablation alone.

Methods One hundred and eighty-one (55.2%) patients underwent HIFU alone (group I) while 147 (44.8%) underwent concomitant HIFU and PEI treatment for solid or predominantly solid nodules (group II). Intravenous sedation and analgesia were given before the start of treatment. Extent of nodule shrinkage (by volume reduction ratio (VRR)), pain scores (by 0–10 visual analogue scale) during and after ablation, and rate of vocal cord palsy (VCP), skin burn, and nausea/vomiting were compared between the two groups.

Results The mean amount of ethanol injected in group II was 1.3 ± 0.7 ml. The 3- and 6-month VRR were significantly greater in group II (60.41 ± 20.49% vs. 50.13 ± 21.06%, $p = 0.001$; and 71.08 ± 21.25% vs. 61.37 ± 22.76%, $p = 0.001$, respectively), and "on-beam" treatment time was significantly shorter in group II (26.55 min vs. 30.26 min, $p = 0.001$). Group II patients reported significantly lower pain score during treatment (2.24 ± 3.07 vs. 4.97 ± 3.21, $p < 0.001$) and 2 h after treatment (2.23 ± 2.50 vs. 2.97 ± 4.39, $p = 0.044$). Rates of VCP, skin burn, and nausea or vomiting were not significantly different ($p > 0.05$).

Conclusions The combined HIFU and PEI approach with improved administration of intravenous sedation and analgesia was associated with a significantly better 6-month efficacy than HIFU alone in benign thyroid nodules without compromising the safety and comfort of patients.

Key Points

- *Concomitant HIFU and PEI have a better treatment efficacy than HIFU alone.*
- *Concomitant HIFU and PEI have a comparable safety profile as HIFU alone.*

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

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Abbreviations

HIFU	High-intensity focused ultrasound
PEI	Percutaneous ethanol injection
Tg	Thyroglobulin
TSH	Thyroid-stimulating hormone
US	Ultrasonography
VCP	Vocal cord palsy
VRR	Volume reduction ratio

Introduction

Benign thyroid nodules are present in over 70% of the general population. Although most remain relatively static over time, some can grow and cause symptoms necessitating surgery

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[1–3]. However, surgery is not risk-free and needs a general anesthesia and hospital stay. As a result, there has been an increasing interest in developing non-invasive interventions in managing benign thyroid nodules [4–6]. For predominantly solid or solid nodules, non-invasive interventions such as laser, microwave, and radiofrequency ablation (RFA) have been shown to be an effective treatment [4–6]. High-intensity focused ultrasound (HIFU) is a relatively new ablation technique that has been shown to be effective in inducing physical nodule shrinkage and alleviating nodule-related symptoms [7–9].

However, relative to other ablation techniques, HIFU appears to be less efficacious in causing nodule shrinkage and generally takes longer to complete [10–12]. As a result, there is a real need to further improve the current technique in HIFU ablation for benign thyroid nodules [10]. Percutaneous ethanol injection (PEI) is a well-established, non-surgical treatment for cystic thyroid nodules. Although it is less frequently used in solid nodules because direct injection may cause seepage of ethanol into adjacent cervical tissues, it is clear that highly concentrated ethanol can result in areas of coagulative necrosis, and may lead to fibrosis and shrinkage of the target [13]. Some studies have shown when thermal ablation like RFA is combined with PEI, the ablation effects on solid tumors could be further enhanced [13–16]. Therefore, we hypothesized that combining HIFU with PEI may prove to be more effective than HIFU alone in causing shrinkage of solid benign thyroid nodules. Our study aimed to compare the 6-month nodule shrinkage (primary study endpoint) between combined HIFU/PEI and HIFU alone for solid or predominantly solid benign thyroid nodules.

Methods

This retrospective analysis was approved by the local institutional review board. All relevant clinical and treatment data were recorded prospectively after obtaining informed consent from patients. Consecutive patients who underwent HIFU ablation for a symptomatic, solid, or predominantly solid (< 30% cystic areas) single nodule (i.e., solitary nodular goiter) or a dominant nodule in a multinodular goiter from August 2015 to October 2019 were analyzed. To be eligible for ablation, the nodule had to be proven benign on fine needle aspiration cytology (Bethesda category II) with its center within 7–30 mm from the skin. Also, the nodule had to have all three orthogonal dimensions ≥ 20 mm but ≤ 50 mm on ultrasonography (US). For the purpose of the study, only patients who underwent treatment for a single nodule were analyzed. Patients who underwent ablation for more than one thyroid nodules, suffered thyrotoxicosis, received previous ablation, or had a follow-up < 6 months were not included. To evaluate the treatment efficacy of this combined HIFU and PEI approach, variables such as patient and nodule characteristics, treatment time (min), energy (KJ), energy per pulse (J), amount of sedation and analgesia used during treatment, the 3- and 6-month nodule shrinkage (%), rise in thyroglobulin (Tg) (%) shortly after treatment, severity of pain during and after treatment, and treatment-related complications were compared between those who underwent HIFU alone (group I or the reference group) and those who underwent the combined HIFU and PEI approach (group II).

Treatment selection

At the beginning of the study period, HIFU ablation alone (i.e., without the addition of PEI) was the approach of choice for a single solid or predominantly solid benign thyroid nodule. However, after November 2018, the combined HIFU and PEI approach became the preferred approach.

Combined HIFU and PEI approach

Like HIFU without PEI, the combined approach was carried out under intravenous sedation (see later). For this combined approach, PEI was given before HIFU ablation of the nodule. For PEI, up to 2 ml of 95% sterile ethanol was injected with a 21-gauge (21G) needle via the trans-isthmic approach into the middle of the target nodule under US guidance. The goal of the PEI was to inject up to 2 ml of 95% ethanol as evenly as possible throughout the entire target while avoiding any seepage of ethanol outside the target. In order to achieve this, the tip of the needle was first positioned in the deepest part of the nodule. Once positioned, a tiny amount of ethanol was infused while the tip of the needle was slowly being pulled out until the tip reached the inside wall of the thyroid capsule on the opposite side (Fig. 1). This technique was repeated in different areas of the nodule until intra-nodular echo-staining was seen throughout the entire nodule (Fig. 2). After that, the HIFU treatment was carried out in its usual matter (see later).

HIFU preparation and treatment

The preparation was the same for both approaches. All patients were instructed to be fasted overnight and to admit to the hospital in the morning where serum thyroid function tests (free T4 and thyroid-stimulating hormone (TSH) levels), thyroglobulin (Tg), and anti-thyroid autoantibodies were checked. All ablations (regardless of which approach) were performed by one person (B.H.L.) using the same commercially available US-guided HIFU device. Before 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). With greater experience, both drugs were given in larger doses with a longer interval as this was found to be more effective in controlling pain during

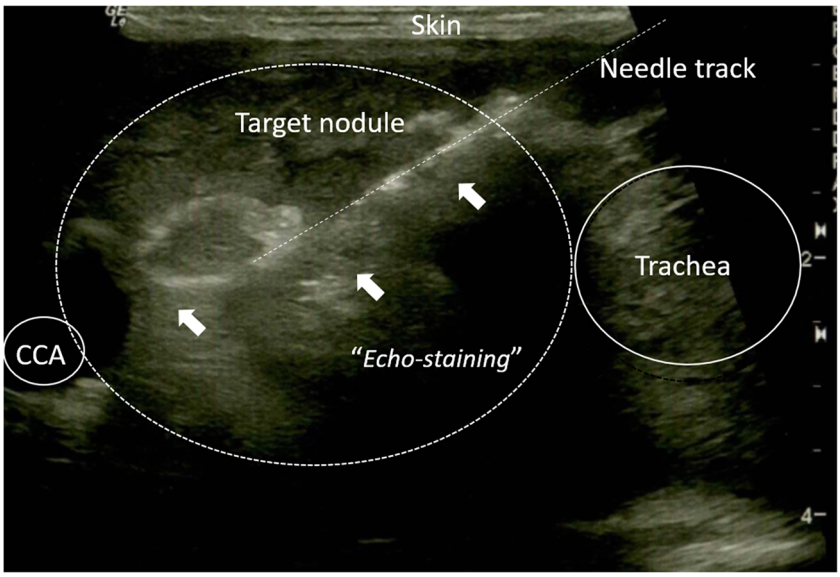

Fig. 1 An ultrasound image of the target taken immediately after the ethanol had been infused into the nodule

treatment. For predominantly solid nodules, any cystic components within the nodule were aspirated completely before the start of the ablation. Patients' heart rate, blood pressure, respiration rate, and peripheral oxygenation were monitored throughout. Patients were asked to show a hand sign if the pain became too severe. In that situation, either the energy was lowered or more medications were administrated.

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

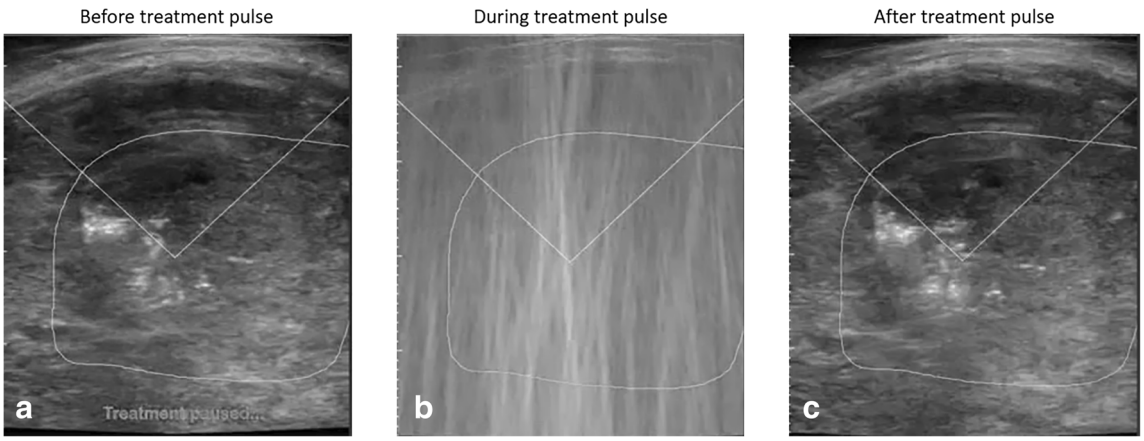

Fig. 2 The first one on the left (**a**) showed areas of echo-staining following PEI before HIFU ablation. The middle one (**b**) showed the appearance of the target during the 8-s treatment pulse. The third one on the right (**c**) showed the presence of hyperechoic marks immediately after the 8-s treatment pulse

discharged home a few hours after treatment. Afterwards, a transcutaneous laryngeal US was done to assess the mobility of both vocal cords as this was found to be a highly accurate alternative to laryngoscopy [17]. Vocal cord palsy (VCP) was defined as having an impaired or absent movement in one of the vocal cords corresponding to the ablated side. All patients were seen 4 days after treatment at the clinic where serum TSH, free T4, and Tg levels were checked again.

Pain assessment

Immediately after ablation, patients were asked to rate their overall pain experience during the treatment on a scale of 0 to 10 (0 = no pain and 10 = worse possible pain). They were asked again 2 h after treatment and on the following morning by phone. A dedicated person was involved in all the pain assessments.

Nausea and vomiting assessment

Patients were specifically asked about the feeling of nausea (which was defined as an unpleasant urge to vomit) 2 h after ablation. Any vomiting episodes were recorded prospectively. Anti-emetic medications were not prescribed over the study period.

Treatment efficacy

All nodule measurements by US on the day of treatment (baseline), 3 months, and 6 months were conducted by one independent person. Dimensions were done using the LOGIQ e (GE Healthcare) scanner equipped with a 10–14-MHz linear matrix transducer. Three orthogonal diameters of the index nodule (its longest diameter and two other perpendicular diameters) were measured. In general, the craniocaudal dimension (length) was the longest dimension while the mediolateral (width) and anteroposterior (depth) dimensions of the nodule were the shorter dimensions. US measurements were expressed to the nearest 0.01 cm. To estimate nodule volume, we used the following formula: volume (ml) = (width (in cm) × length (in cm) × depth (in cm)) × (π/6) where π was taken as 3.14159. The volume reduction ratio (VRR) was made according to the following formula: [Baseline volume − volume at visit]/[Baseline volume] * 100. Treatment success was defined as ≥ 50% VRR at 6 months from baseline.

Biochemistry/laboratory

All measurements of TSH, FT4, and anti-thyroid antibodies were carried out at our hospital's laboratory. The normal reference values for TSH were 0.35 to 4.78 mIU/l while T4 ranged from 12 to 23 pmol/l. Serum anti-Tg and anti-TPO antibodies were determined by radioimmunoassay (Bio Code) and any values > 99 IU/ml were considered positive.

Statistical analysis

The primary endpoint was the 6-month VRR. Continuous variables were generally expressed as mean ± SD. Continuous variables between groups were compared using the Mann-Whitney *U* test. Chi-square tests were used to compare categorical variables. 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

Three hundred and sixty-one patients underwent HIFU treatment during the study period. Of these, 26 (7.2%) patients underwent treatment for two thyroid nodules while 5 (1.4%) patients had a previous ablation and another 2 (0.6%) patients had < 6 months of follow-up. As a result, 328 (90.9%) were eligible for analysis. Among them, 181 (55.2%) complete HIFU treatment alone (group I) while 147 (44.8%) completed combined HIFU and PEI treatment (group II). The mean amount of 95% sterile ethanol used in group II was 1.3 ± 0.7 ml. Patients in both groups completed their treatment and were able to be discharged from hospital on the same day.

Patient baseline characteristics, treatment parameters, and amount of sedation and analgesia required were compared between groups I and II (Table 1). Baseline patient age, sex ratio, body weight, body height and body mass index, the longest nodule diameter (cm), nodule volume (ml), distance from skin to nodule center, thyroid function tests, and anti-thyroid auto-antibodies were comparable between the two groups. Interestingly, despite the similar nodule volume between the two groups, the "on-beam" treatment time was significantly shorter in group II than in group I (26.55 min vs. 30.26 min, $p = 0.001$). However, the amount of pethidine and diazepam used did not differ significantly between the two groups ($p = 0.965$ and $p = 0.225$, respectively).

Treatment efficacy and clinical outcomes were compared between groups I and II (Table 2). Both the 3- and 6-month VRR were significantly greater in group II than in group I (60.41 ± 20.49% vs. 50.13 ± 21.06%, $p = 0.001$; and 71.08 ± 21.25% vs. 61.37 ± 22.76%, $p = 0.001$, respectively). In group I, the mean baseline nodule volume decreased from 23.30 ± 13.58 to 12.60 ± 23.54 ml and 10.58 ± 18.38 ml at 3 and 6 months, respectively. In group II, the mean baseline nodule volume decreased from 22.45 ± 13.86 to 8.76 ± 10.38 ml and 6.51 ± 8.93 ml at 3 and 6 months, respectively.

However, the mean rise in the Tg level on day 4 was comparable between the two groups (524.79 ± 437.12% vs.

Table 1 A comparison of patient baseline characteristics, treatment parameters, and amount of sedation and analgesia required between those who underwent HIFU ablation alone (group I) and those who underwent HIFU ablation with ethanol infiltration (group II)

Variable	Group I ($n = 181$)	Group II ($n = 147$)	p value
Patient characteristics			
Age at treatment (years)	50.01 ± 11.61	48.02 ± 10.71	0.220
Sex (male:female)	24 (13.3):157 (86.7)	15 (10.2):132 (89.8)	0.385
Body weight (kg)	60.53 ± 10.66	58.57 ± 8.52	0.151
Body height (m)	1.62 ± 0.08	1.63 ± 0.07	0.245
Body mass index (kg/m^2)	23.20 ± 4.08	22.11 ± 2.91	0.181
Characteristics of the nodule			
Longest nodule diameter (cm)	4.02 ± 1.45	3.95 ± 1.17	0.816
Nodule volume at baseline* (ml)	23.30 ± 13.58	22.45 ± 13.86	0.937
Distance from the skin to nodule center (cm)$^+$	1.73 ± 0.41	1.73 ± 0.40	0.812
Baseline blood tests			
Serum TSH (mIU/l)	1.21 ± 0.95	1.40 ± 0.96	0.174
Serum free T4 (pmol/l)	16.36 ± 2.58	16.11 ± 2.00	0.961
Serum thyroglobulin$^\#$ (ng/ml)	342.80 ± 918.87	325.24 ± 808.67	0.334
Anti-Tg autoantibody (IU/ml)	145.82 ± 378.71	263.97 ± 653.00	0.290
< 99 (normal)	130 (71.8)	105 (71.4)	0.537
≥ 99	51 (28.2)	42 (28.6)	
Anti-TPO autoantibody (IU/ml)	474.11 ± 1651.96	346.82 ± 823.24	0.334
< 99 (normal)	129 (71.3)	107 (72.8)	0.731
≥ 99	52 (28.7)	40 (27.2)	
Treatment parameters			
Total energy delivered (KJ)	15.09 ± 6.18	13.87 ± 6.56	0.089
Total "on-beam" time (min)	30.26 ± 16.90	26.55 ± 11.35	*0.001*
Energy per each pulse (J)	308.30 ± 32.81	302.47 ± 30.40	0.217
Amount of sedation and analgesia required during ablation			
Intravenous pethidine (mg)	85.79 ± 25.48	86.34 ± 21.75	0.965
Intravenous diazepam (mg)	15.91 ± 6.64	16.53 ± 5.33	0.225

Values in italic signify statistical significance (or $p < 0.05$)

Continuous variables are expressed in mean ± standard deviation while categorical variables are expressed in number (percentage)

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

*nodule volume at baseline = (width x depth x length) x (π/6) where π was taken as 3.14159

$^+$ Measured from the transverse view of the pre-ablation ultrasonography

$^\#$ Normal reference for the thyroglobulin level is < 55 μg/l

413.94 ± 401.64%, $p = 0.453$). In group I, the serum Tg level increased from 317.12 ± 831.78 ng/ml at baseline to 1981.33 ± 1793.00 ng/ml on day 4 while in group II, the serum Tg level increased from 391.54 ± 903.03 ng/ml at baseline to 2012.30 ± 1688.11 ng/ml on day 4.

In terms of pain, patients in group II reported significantly lower pain score during treatment (2.24 ± 3.07 vs. 4.97 ± 3.21, $p < 0.001$) and 2 h after treatment (2.23 ± 2.50 vs. 2.97 ± 4.39, $p = 0.044$) but the pain score was not significantly different in the morning after treatment (1.10 ± 1.82 vs. 1.23 ± 1.63, $p = 0.309$). Rates of treatment-related VCP, skin burn, and nausea or vomiting were not significantly different between the two groups ($p > 0.05$).

Discussion

To our knowledge, this was the first study to evaluate the efficacy of combined HIFU and PEI approach as a treatment for solid or predominantly solid benign thyroid nodules. Consistent with the initial hypothesis, our data showed that this combined approach was associated with a more superior treatment outcome than HIFU alone. Both the 3- and 6-month VRR were significantly greater in the combined approach group than in the HIFU alone group (60.41% vs. 50.13%, $p = 0.001$; and 71.08% vs. 61.37%, $p = 0.001$). This was despite the fact that both groups had similar patient and nodule baseline characteristics. These findings were in concordance with those of previous studies which found that the presence of high concentration of ethanol within a target nodule was able to enhance and potentiate the thermal damage of thermal ablation by increasing the extent of tissue necrosis [13–16].

However, apart from better treatment efficacy in the combined approach, there were two other interesting findings worth highlighting. First, patients in the combined approach group reported less pain in the early post-ablation period than those in the HIFU alone group. Patients in the combined approach group reported significantly lower pain score during treatment (2.24 ± 3.07 vs. 4.97 ± 3.21, $p < 0.001$) and 2 h after treatment (2.23 ± 2.50 vs. 2.97 ± 4.39, $p = 0.044$). We believe

Table 2 A comparison of treatment efficacy and clinical outcomes between those who underwent single HIFU ablation alone (group I) and those who underwent HIFU ablation with ethanol infiltration (group II)

Variable	Group I ($n = 181$)	Group II ($n = 147$)	p value
Treatment efficacy (%)			
3-month VRR	50.13 ± 21.06	60.41 ± 20.49	*0.001*
6-month VRR	61.37 ± 22.76	71.08 ± 21.25	*0.001*
Rise in Tg 4 days after treatment (%)[#]	524.79 ± 437.12	413.94 ± 401.64	0.453
Severity of pain by VAS			
During treatment	4.97 ± 3.21	2.24 ± 3.07	*< 0.001*
2 h after treatment	2.97 ± 4.39	2.23 ± 2.50	*0.044*
The following morning (i.e., > 12 h after treatment)	1.23 ± 1.63	1.10 ± 1.82	0.309
Treatment-related complication			
Vocal cord palsy	2 (1.1)	1 (0.7)	1.000
Skin burn	0 (0.0)	0 (0.0)	-
Nausea or vomiting	1 (0.5)	2 (1.4)	0.585

Values in italic signify statistical significance (or $p < 0.05$)

Continuous variables are expressed in mean ± standard deviation

VRR, volume reduction ratio; *VAS*, visual analogue scale (0 = no pain; 10 = worst possible pain); *Tg*, thyroglobulin (normal < 55 μg/l)

[#] Based on the following formula: [Serum Tg on Day 4 − serum Tg at baseline]/[Serum Tg at baseline] * 100

this was related to the way the intravenous pethidine and diazepam were administered in the later part of the study period. Rather than giving small boluses in short intervals, in the later study period (when most of the combined approach were carried out), larger boluses in longer interval were given. This strategy led to better pain control and lower reported pain scores during and 2 h after treatment.

Second, the total "on-beam" treatment time was actually significantly shorter in the combined approach group than in the HIFU alone group (26.55 min vs. 30.26 min, $p = 0.001$). We believe this was a direct result of better pain control, leading to better patient compliance during treatment. That led to shorter treatment time in the combined approach group.

In terms of safety, our groups appeared to have similar rate of complications. The incidence of VCP, skin burn, and nausea/vomiting was not different between the two groups. Although PEI in solid nodules could potentially cause seepage of ethanol into surrounding cervical tissues, the relatively small amount of ethanol used made this possibility less likely. In fact, in our study, we did not observe any patients in the combined approach group complaining of direct or radiated pain during the PEI.

Relative to other ablation techniques like laser, microwave or RFA, the major benefits with HIFU are the lack of needle insertion into the target (i.e., a truly non-invasive approach) and the entire ablation process requires little inputs from the operator [4, 18]. Although the combined HIFU/PEI would diminish these benefits because PEI still requires the insertion of a small-bore needle into the target, the relatively small needle size (21G) and shorter time spent puncturing the skin should lower the chance of leaving permanent skin marks than other needle-dependent ablation techniques like RFA or laser ablation. Nevertheless, it remains unclear whether this combined technique has a clear advantage over more established techniques like RFA and laser ablation. The rate of major treatment-related complications was similar to other forms of ablation [19–21]. However, because HIFU energy has to propagate from the skin to the target, transfer of heat energy is less efficient and therefore, the treatment itself normally takes significantly longer to complete [9, 18]. And because it is a less established technique [10–12], it remains unclear which nodule characteristics and treatment-related factors may affect outcomes after HIFU. We believe the combined HIFU/PEI may prove to be an important technique in the future as it clearly enhances the short-term treatment efficacy.

Despite these, we should acknowledge several shortcomings. First, our study was not a large-scale study and so it was prone to type II errors. In other words, some of the non-significant findings could have been solely due to the lack of power. Second, we believe that the use of contrast-enhanced US after treatment may provide further insights into how nodules may response to the combined HIFU and PEI approach [22, 23]. Third, given the study design, it was not possible to know whether the more favorable outcomes from the combined approach were not solely due to the greater amount of experience accumulated towards the later part of the study period. Fourth, apart from nodule shrinkage, the present study was not able to evaluate other important clinical outcomes like relief of symptoms, quality of life, and cost/benefit ratio. Nevertheless, at least, our study showed that with appropriate

patient selection, this combined treatment was feasible and may produce superior efficacy with comparable safety and morbidity.

Conclusion

Our study showed that the combined concomitant HIFU and PEI approach with improved administration of intravenous sedation and analgesia was associated with more superior 3- and 6-month efficacy than the HIFU alone approach in the treatment of benign thyroid nodules. Furthermore, it did not appear to compromise the safety and comfort of patients.

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Authors' contribution BHH Lang, YC Woo, and KWH Chiu were involved in the review of literature, acquisition of data, and drafting and completing the manuscript. BHH Lang, YC Woo, and KWH Chiu were also involved in the review of literature and drafting the manuscript. BHH Lang, YC Woo, and KWH Chiu conceived the study, participated in the co-ordination and the acquisition of data, and helped to draft the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Guarantor The scientific guarantors of this publication are Professor Stephen Cheng (Head of Department) and Professor Brian Lang (first and corresponding author).

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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