NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of high-intensity focused ultrasound for symptomatic benign thyroid nodules

A thyroid nodule is a lump in the thyroid gland. Most are benign (not cancerous). This procedure uses heat generated by high-frequency sound waves to destroy tissue in the nodule. The aim is to make the nodule smaller, to relieve pressure symptoms and improve appearance.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety

and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2018 and updated in October 2018.

Procedure name

- High-intensity focused ultrasound for symptomatic benign thyroid nodules

Specialist societies

- Royal College of Surgeons
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow
- Royal college of radiologists
- British Association of Endocrine and Thyroid Surgeons
- British Thyroid Association
- British Society of Interventional Radiology
- ENT UK

Description of the procedure

Indications and current treatment

Thyroid nodules may be cystic, colloid, hyperplastic, adenomatous or cancerous. Most thyroid nodules are benign and are usually asymptomatic. There may be a single thyroid nodule (solitary nodule) or multiple thyroid nodules (multinodular goitre). Some thyroid nodules produce thyroxine or triiodothyronine and cause thyrotoxicosis. These are called hyperfunctioning or toxic thyroid nodules.

Treatment of benign thyroid nodules may be needed if they cause symptoms or cosmetic problems. Conventional treatment includes surgery. Other less invasive approaches than surgery include ethanol ablation, percutaneous laser ablation, radiofrequency ablation and microwave ablation.

What the procedure involves

High-intensity focused ultrasound is a minimally invasive technique that aims to reduce symptoms and improve cosmetic appearance, while preserving thyroid function, and with fewer complications than surgery.

High-intensity focused ultrasound for symptomatic benign thyroid nodules is usually done using sedation and systemic analgesia, in an outpatient setting. The patient is placed in the supine position with moderate neck extension. The focused ultrasound device is positioned on the patient's neck to deliver the treatment and allow for simultaneous imaging of the treatment area. The technology uses high-energy sound waves that pass through the tissues, generating local heat and inducing coagulative necrosis, protein denaturation and cellular destruction. A strong acute inflammatory response follows. The treatment duration depends on the nodule size.

Efficacy summary

Nodule volume reduction

In a systematic review of 88 patients, the overall nodule volume reduction after a single session of high-intensity focused ultrasound ablation ranged from 45% to 68%, depending on nodule size and length of follow-up (in the 4 studies reporting volume reduction outcomes with a follow-up of 3 to 12 months).[1]

In a case series of 108 patients, the mean volume reduction ratio was 51.32%±20.71% at 3 months, 68.66%±18.48% at 12 months and 70.41%±17.39% at 24 months. In the same study, the treatment success rates (defined as at least a 50% volume reduction from baseline) were 42% (42/108) at 3 months, 68% (73/108) at 12 months and 70% (76/108) at 24 months. Most nodules (58% [63/108]) had a further volume reduction (that is less than 4.5%) from 12 to 24 months, whereas 20% (22/108) of nodules had a volume increase of more than 4.5% from 12 to 24 months. None of the treated nodules fulfilled the criteria for nodule regrowth (that is less than 20% from lowest recorded volume) in the first 24 months of follow-up.[2]

In a study of 123 patients comparing 104 single high-intensity focused ultrasound treatments of a single nodule with 19 sequential high-intensity focused ultrasound treatments of 2 nodules in a multinodular goitre, there was no statistically significant difference between groups in the volume reduction ratio (VRR) of the index or first nodule at 3 and 6 months. At 3 months, the mean volume reduction ratio was 48.76%±20.73% in the patients who had a single high-intensity focused ultrasound treatment compared with 49.66%±18.20% in the patients who had sequential high-intensity focused ultrasound treatment. At 6 months, the mean VRRs were 61.77%±27.09% and 63.05%±16.29% respectively. The VRRs for

the second nodule in the patients who had sequential treatment were 58.08%±18.09% at 3 months and 64.81%±17.80% at 6 months.[3]

In a study of 146 patients comparing single-session high-intensity focused ultrasound treatment (n=43) with hemithyroidectomy (n=103), the mean volume of the index nodules decreased from 5.15 ml ±4.38 ml at baseline to 2.54 ml±2.28 ml at 6 months (52% volume reduction) in the high-intensity focused ultrasound group.[4]

In a case series of 136 patients, the mean nodule volume reduction was 50.29%±16.39% at 3 months and 55.80%±18.34% at 6 months. In the same study, treatment success rates were 54% (74/136) at 3 months and 64% at 6 months.[5]

In a case series of 26 patients, the mean nodule volume statistically significantly decreased from 2.81 ml±2.04 ml at baseline to 1.83 ml±1.63 ml at 6 months (40% volume reduction) and to 1.57 ml±1.47 ml (48% volume reduction) at 1 year ($p<0.0001$).[6]

In a study of 32 patients with hyperthyroidism because of a toxic nodule comparing high-intensity focused ultrasound (n=15) with radioiodine (n=17) treatments, the median toxic thyroid nodule volumes were similar at 1 year (0.79 ml compared with 0.73 ml).[7]

In a study of 94 patients comparing high-intensity focused ultrasound (n=14) with radiofrequency ablation (RFA, n=40) and microwave ablation (MWA, n=40), the median nodule volume reduction at 3 months was statistically significant compared with baseline in all the 3 groups (49%, 50% and 44% respectively) but there was no significant difference between the 3 groups.[8]

Improvement of nodule-related symptoms

In the case series of 108 patients, the mean obstructive symptom score (measured by visual analogue scale [VAS], range 0 to 10, 0=no obstructive symptoms; 10=most significant obstructive symptoms) improved from 4.12±1.22 at baseline to 2.57±1.35 at 6 months, 1.56±1.05 at 12 months and 1.27±1.04 at 24 months. At 24 months, 95% (103/108) of patients had a lower VAS score than at baseline and only 5% (5/108) had the same VAS score as baseline.[2]

In the comparative study of 146 patients, there was a statistically significantly higher proportion of patients in the high-intensity focused ultrasound group (67% [29/43]) who experienced a 'significant improvement' of symptoms compared with the hemithyroidectomy group (39% [40/103], p=0.009).[4]

In the case series of 26 patients, the proportion of patients with a reduction of local cervical compressive symptoms was 85% (22/26) at 1 year.[6]

Normalisation of serum thyrotropin (TSH)

In the comparative study of 32 patients with hyperthyroidism because of a toxic nodule, TSH levels were normal at 1 year in 27% (4/15) of patients after high-intensity focused ultrasound and in 82% (14/17) of patients who had treatment with radioiodine (p=0.0008).[7]

Patient comfort

In the case series of 26 patients, 73% (19/26) of patients reported good comfort during treatment and 100% (26/26) reported good comfort just after therapy.[6]

Tolerability of treatment

In the case series of 26 patients, the mean score for tolerability (on a scale from 1 [low] to 10 [high]) was 8.1±2.9.[6]

Safety summary

Pain

Pain during or after treatment was reported in 4 of the studies included in the systematic review of 88 patients.[1]

Mean pain scores measured by VAS during the procedure were 5.68±2.99 in the single high-intensity focused ultrasound treatment group compared with 6.34±2.14 in the sequential high-intensity focused ultrasound treatment group in the comparative study of 123 patients (no statistically significant difference between groups). The pain scores improved in both groups 2 hours after the procedure (2.54±2.78 in the single high-intensity focused ultrasound treatment group compared with 3.53±2.54 in the sequential high-intensity focused ultrasound treatment group, p=NS) and the following morning (1.15±1.65 in the single high-intensity focused ultrasound treatment group compared with 2.29±2.08 in the sequential high-intensity focused ultrasound treatment group, p=0.047).[3]

Mean pain scores were 3.5±4.0 during high-intensity focused ultrasound treatment, 1.0±1.0 immediately after high-intensity focused ultrasound treatment and 0.0±1.0 before hospital discharge in the comparative study of 146 patients. During the first week, 14% (3/43) of patients had mild residual discomfort.[4]

In the comparative study of 94 patients, all patients in the high-intensity focused ultrasound group experienced mild pain up to 2 days after treatment (median pain score of 7). In the RFA and MWA groups, all patients reported a mild or

rarely moderate pain radiating to the mandible, neck or shoulders (median pain score of 3 in the RFA group and of 4 in the MWA group). Patients also felt pressure when the ultrasound was applied to the nodule. The discomfort got worse if the nodules were superficial. Deep or large nodules barely caused discomfort.[8]

Skin burn or redness

Skin burn or skin redness was reported in 4 of the studies included in the systematic review of 88 patients.[1]

Vocal cord paresis

Unilateral vocal cord paresis was reported in 3% (3/108) of patients after the procedure in the case series of 108 patients. All patients recovered fully within 3 months of the procedure. [2]

Vocal cord palsy was reported in 2% (2/104) of patients who had single high-intensity focused ultrasound treatment and in none of the patients who had sequential high-intensity focused ultrasound treatment in the comparative study of 123 patients (p=NS).[3]

Vocal cord paresis was reported in 3% (4/136) of patients after the procedure in the case series of 136 patients. All patients recovered fully within 2 months of the procedure.[5]

Voice quality

There was no statistically significant difference in the voice handicap index (VHI) between the high-intensity focused ultrasound group (mean difference compared with baseline in VHI=4.8±19.5) and the hemithyroidectomy group (9.77±20.2) at 1 month in the comparative study of 146 patients.[4]

Laryngeal nerve injury

Laryngeal nerve injury was reported in 2% (1/43) of patients in the high-intensity focused ultrasound group and in 3% (3/103) of patients in the hemithyroidectomy group in the comparative study of 146 patients (p=NS). All patients fully recovered within 6 months of the procedures.[4]

Horner's syndrome

Horner's syndrome was reported in 1 patient after the procedure in the case series of 108 patients. The patient's ptosis improved gradually over a period of 6 months after the procedure.[2]

Oedema

A subcutaneous oedema and minor neck swelling were reported after the procedure in 2 of the studies included in the systematic review of 88 patients.[1]

Redness and swelling were reported in 30% (13/43) of patients treated by high-intensity focused ultrasound in the comparative study of 146 patients. They resolved within 1 week.[4]

Nausea or vomiting

Nausea or vomiting was reported in 1% (1/104) of patients who had single high-intensity focused ultrasound treatment and in 16% (3/19) of patients who had sequential high-intensity focused ultrasound treatment in the comparative study of 123 patients (p=0.012).[3]

Hypothyroidism

Subclinical hypothyroidism (defined as serum TSH exceeding 4.78 mIU/litre within the first 6 months following treatment) was reported in 2% (1/43) of patients treated by high-intensity focused ultrasound and in 20% (21/103) of patients treated by hemithyroidectomy in the comparative study of 146 patients (p=0.008).[4]

Cough

Cough was reported in 1 of the studies included in the systematic review of 88 patients.[1]

Blisters

Blisters were reported in 1 of the studies included in the systematic review of 88 patients.[1]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse event: patient discomfort during the procedure. They considered that the following were theoretical adverse events: tracheal burns, vascular injury and ineffective treatment of cancers (where incorrectly thought to be benign).

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to high-intensity focused ultrasound for symptomatic benign thyroid nodules. The following databases were searched, covering the period from their start to 30/10/2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with symptomatic benign thyroid nodules.
Intervention/test	High-intensity focused ultrasound.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 500 patients from 1 systematic review[1], 4 comparative studies[3,4,7,8] and 3 case series[2,5,6].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for symptomatic benign thyroid nodules

Study 1 Lang BHH (2017)a

Details

Study type	**Systematic review**
Country	Included studies: France (1), Germany (3), Bulgaria (1), China (1). Paper: China
Recruitment period	Search done on 27/10/2016
Study population and number	n= **88** patients with benign thyroid nodules
Age and sex	Not reported
Patient selection criteria	The search included all studies that evaluated the use of HIFU ablation as a treatment of benign thyroid nodules from Medline (PubMed) and Cochrane Library electronic databases using specific keywords. All titles identified by the search strategy were independently screened by 2 authors. Case reports, animal studies, editorials, expert opinions, reviews without original data and studies on pediatric population were excluded. Multiple reports of the same dataset were assessed and the most representative and updated report of a study was included.
Technique	HIFU treatment with the EchoPulse device (Theraclion).
Follow-up	**2 weeks to 12 months**
Conflict of interest/source of funding	None. The study was supported by the Health and Medical Research Fund, the Food and Health Bureau, the Government of the Hong Kong Special Administrative Region.

Analysis

Study design issues: The outcomes measured included treatment efficacy (i.e. extent of nodule shrinkage (%) within the first year from baseline), changes in symptoms and incidence of treatment-related complications.

Other issues: It is not clear whether 5 or 6 studies were included in this systematic review. It seems that the Korkusuz (2015) study of 9 nodules was excluded from the final analysis (probably because of an overlap of patients between studies) although it was included in the tables reported in the paper.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **88**

Inclusion and exclusion criteria of the included studies

First author (year)	Inclusion criteria	Exclusion criteria
Esnault (2011)	- At least two thyroid nodules, with at least one for surgery - Nodule targeted for HIFU located at least 3 mm from the trachea, oesophagus, recurrent nerve, carotid artery, skin - Selected nodule for HIFU treatment was different from the one indicated for surgery	- Suspicion of malignancy nodule, neck irradiation, previous surgery, previous radioactive iodine treatment - Any cystic components ≥ 20% or any large calcifications - Patient unable to maintain a stable position with hyperextended neck
Korkusuz (2014)	At least one benign thyroid nodule with associated thyrotoxicosis, neck pain, throat hoarseness, swallowing disorders, discomfort and/or cost concern.	- Malignant nodule - Close to heat-sensitive structures like the recurrent laryngeal nerve, trachea, oesophagus and carotid artery
Korkusuz (2015)	- Over 18 years old - At least one benign thyroid nodule with associated issues (neck pain, hoarseness, swallowing disorders, discomfort, cosmetic concerns and/or thyrotoxicosis - Refused surgery/RIT	- Malignant nodules - Target nodules close to sensible structures such as trachea, carotid arteries - Patients who showed any contraindication to HIFU
Korkusuz (2015)	- Patient with symptomatic nodule - Cosmetic concerns - Refused surgery or contraindicated	- Patients with asymptomatic nodules - Nodule volume ≥ 10 mL - Histological evidence for malignancy
Kovatcheva (2015)	- Over 18 years old - Presence of one or more thyroid nodules without signs of malignancy - A nodule measured on US ≥10 mm in three orthogonal dimensions - ≤30% of the targeted nodule is cystic - HIFU accessibility of the targeted nodule - Normal thyrotropin concentrations - Absence of vocal cord immobility at laryngoscopy	- Head and/or neck disease which prevents hyperextension of neck - Past medical history of thyroid cancer or other malignant tumours in the neck region - History of neck irradiation - Intra-nodular macro-calcifications which precludes treatment with HIFU - Nodules next to posterior margin of the thyroid lobe with anteroposterior diameter less than 15 mm - Pregnancy/lactation - Any contraindications related to intravenous moderate sedation

Safety

Complications

First author (year)	Complications
Esnault (2011)	Pain, skin burn, cough, blisters
Korkusuz (2014)	Pain
Korkusuz (2015)	Pain during treatment, reddening of skin
Korkusuz (2015)	None reported
Kovatcheva (2015)	Subcutaneous oedema, skin redness
Lang (2017)	Pain, skin redness, minor neck swelling

Lang (2017)	- Benign cytology and low to very low suspicion sonographic pattern - Nodule believed to be causing pressure symptoms - All 3 dimensions between 10 and 40 mm - Nodule ≥ 70% solidity - Nodule within 5–30 mm from skin - Normal thyroid function and calcitonin levels	- Age ≤ 18 years old - Pregnant or lactating women - Indeterminate or malignant nodules - Intra-nodular macro-calcifications - History of head and neck irradiation - History of non-medullary thyroid carcinoma - Pre-existing vocal cord palsy

Comparison of treatment and efficacy between the included studies

First author (year)	Number of nodules	Nodule volume (mL)	Total amount of DIAE to each nodule (KJ)	Treatment time (minutes)	Efficacy (% reduction from baseline)
Esnault (2011)	22	0.5–2.6	35–94 J/pulse	-	Feasibility study. Ablated nodules were examined on histology after 2 weeks Since these patients underwent thyroidectomy 2 weeks after ablation, the actual extent of nodule shrinkage following HIFU could not be assessed.
Korkusuz (2014)	10	Median: 3.19 (range: 0.8–7.67)	Median: 8.4 (range: 5.65–12.46)	-	Not reported
Korkusuz (2015)	9	Median: 3.5 (range: 0.8–7.7)	Median: 9.9 (range: 5.7–12.5)	Median: 62 (range: 42–96)	Median: 48.8 (range: 11.4–75.0) at 3-month
Korkusuz (2015)	12	Median: 3.4 (range: 0.6–5.0)	_	-	Median: 55 at 3-month

Kovatcheva (2015)	20	Mean: 4.96 ± 2.79 (range: 1.56–9.35)	Mean: 16.4 ± 7.7 (range: 5.5–31.7)	Mean: 86.8 ± 31.7 (range: 37–152)	Mean: 48.7 ± 24.3 at 6-month (after single ablation)	
Lang (2017)	22	Mean: 6.98 ± 4.04 (range: 1.68–16.76)	Mean: 15.17 ± 6.90 (range 5.88–28.35)	Mean: 75.71 ± 34.20 (range: 48.75 153.25)	Mean: 68.87 ± 15.27 at 12-month (following single ablation)	
The overall nodule volume reduction after single session of HIFU ablation ranged between 45 and 68%, depending on nodule size and length of follow-up.						
Abbreviations used: DIAE, depth-independent acoustic energy; HIFU, high-intensity focused ultrasound.						

Study 2 Lang BHH (2018)c

Details

Study type	**Retrospective case series**
Country	China (single centre)
Recruitment period	2015-16
Study population and number	n=**108** consecutive patients benign thyroid nodules
Age and sex	Mean 51 years; 86% (93/108) female
Patient selection criteria	Inclusion criteria: only patients who were indicated but refused thyroidectomy were considered for ablation. The nodule had to be proven benign on fine-needle aspiration cytology and to have a low or very low suspicion sonographic pattern together with its centre located within the treatable depth of 7–30 mm from the skin surface. Also, the swelling (which could either be a solitary nodule or a dominant nodule in a multinodular gland) had to be causing obstructive symptoms and the longest diameter of the nodule had to be ≥20 mm but ≤60 mm on ultrasonography. Exclusion criteria: any patients with incomplete or less than 24 months of follow-up or had received two or more treatments to the same nodule within 24 months were excluded.
Technique	All treatments were performed by one person using the same device (Theraclion). Patients were sedated with diazepam (10-15 mg) and pethidine (50–100 mg). Patients were asked to show a hand sign without moving the neck if the pain became too severe during treatment. In that situation, either the energy setting was lowered or more medications were administrated. Oral diet was resumed immediately afterwards and patients were allowed to go home 2-3 hours after treatment.
Follow-up	**2 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- A total of 136 patients underwent HIFU ablation of a symptomatic benign thyroid nodule during the study period. Of these, 4 (2.9%) patients were lost to follow-up within the first 24 months, while 24 (17.6%) patients either received two or more treatments in the same session or two or more treatments within 24 months. After excluding these 28 patients, 108 (79.4%) patients were eligible for analysis.

- At each visit (baseline and 3, 6, 12, 18 and 24 months), the three orthogonal dimensions of the index nodule were measured on US by an independent experienced sonographer.
- At each clinic visit, patients were also asked to rate their obstructive symptoms on a visual analogue scale (VAS).

Study design issues:

- After the procedure, a transcutaneous laryngeal ultrasound was done to assess the mobility of both vocal cords. Vocal cord palsy (VCP) was defined as having an impaired or absent movement in one of the vocal cords corresponding to the ablated side.

Study population issues: There is probably an overlap of patients with Study 3 (Lang 2018a), Study 4 (Lang 2017b) and Study 5 (Lang 2018b).

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 108

VRR and treatment success
<table>
<tr><th></th><th>3 months</th><th>6 months</th><th>12 months</th><th>18 months</th><th>24 months</th></tr>
<tr><td>Mean VRR (±SD)</td><td>51.32 ± 20.71%</td><td>62.99 ± 22.05%</td><td>68.66 ± 18.48%</td><td>69.76 ± 17.88%</td><td>70.41 ± 17.39%</td></tr>
<tr><td>Treatment success</td><td>42% (42/108)</td><td>61% (66/108)</td><td>68% (73/108)</td><td>69% (75/108)</td><td>70% (76/108)</td></tr>
</table>
• The VRR was calculated based on the formula: [Baseline volume–volume at visit] / [Baseline volume] * 100.
• Treatment success was defined as ≥ 50 % volume reduction from baseline.
• Only a change in nodule volume >4.5%between time-points was taken as an actual change.
• 58% (63/108) of nodules had a further volume reduction (i.e. > 4.5%) from 12 to 24 months, while 20% (22/108) of nodules had a volume increase of > 4.5% from 12 to 24 months.
• None of the treated nodules fulfilled the criteria for nodule regrowth (i.e. >20% from lowest recorded volume) in the first 24 months of follow-up.

Obstructive symptom score (measured by VAS, range 0 to 10, 0 = no obstructive symptoms; 10 = most significant obstructive symptoms)
<table>
<tr><th></th><th>Baseline</th><th>6 months</th><th>12 months</th><th>24 months</th></tr>
<tr><td>Mean VAS score(±SD)</td><td>4.12 ± 1.22 (median = 4.0; IQR = 2.0)</td><td>2.57 ± 1.35 (median = 2.0; IQR = 1.0)</td><td>1.56 ± 1.05 (median = 2.0; IQR = 1.0)</td><td>1.27 ± 1.04 (median = 1.0; IQR = 2.0)</td></tr>
</table>
At 24 months, 103 (95.4%) patients had a lower VAS score than that of baseline and only 5 (4.6%) patients had the same VAS score as baseline.

• Univariate analysis by logistic regression: The initial or pre-ablation nodule volume (OR = 0.945, 95% CI = 0.911–0.980, p = 0.003) and the total ‘’on-beam’’ time (OR = 0.972, 95% CI = 0.946–0.998, p = 0.035) were significant factors in the univariate analysis.
• In the multivariate analysis, none of the factors were significant after the step-down procedure.</td><td>Unilateral vocal cord paresis: 3% (3/108)
All patients had a full recovery within 3 months.

Horner’s syndrome: 1/108
The patient’s ptosis improved gradually over a period of 6 months.</td></tr>
<tr><td colspan="2">Abbreviations used: IQR, interquartile range; OR, odds ratio; SD, standard deviation; US, ultrasonography; VAS, visual analogue scale; VRR, volume reduction ratio.</td></tr>
</table>

Study 3 Lang BHH (2018)a

Details

Study type	**Comparative case series**
Country	China
Recruitment period	2015-17
Study population and number	n= **123 (104 single HIFU ablation of a single nodule versus 19 sequential ablation of 2 nodules in a MNG)** patients with benign thyroid nodules
Age and sex	Single ablation: Mean 50 years; 85% (88/104) female Sequential ablation: Mean 51 years; 89% (17/19) female
Patient selection criteria	Inclusion criteria: Consecutive patients who underwent HIFU ablation for a symptomatic, solid or predominantly solid (<30% cystic areas) benign thyroid nodule. Only patients who were indicated but refused thyroidectomy were considered for ablation. To be eligible for ablation, the nodule had to be proven benign on fine-needle aspiration cytology. Also, the nodule had to have all 3 orthogonal dimensions ≥20 mm but ≤50 mm on ultrasonography. Exclusion criteria: patients who had a previous ablation, a follow-up of less than 6 months or missing data on pain level after HIFU treatment. Single ablation was generally the preferred treatment for patients with a single nodule or a dominant nodule in a MNG. Sequential ablation (i.e. one ablation followed immediately by another within the same session) was preferred when a patient had 2 relatively dominant nodules (measuring at least 30 mm in their longest dimension). The reason for choosing a cut-off of 30 mm was because this was the general cut-off used for either ablation or surgical resection.
Technique	All single and sequential HIFU ablations were performed in a similar matter by one person, with the EchoPulse device (Theraclion). In general, for sequential treatment of 2 separate thyroid nodules, the larger of the 2 nodules was ablated first. Patients received Diazepam and Pethidine before treatment. 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.Oral diet was resumed immediately afterwards and patients were discharged home a few hours after treatment. Analgesics were not routinely prescribed after treatment.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis
Follow-up issues:

- After the procedure, a transcutaneous laryngeal ultrasound was done to assess the mobility of both vocal cords.
- All patients were seen 4 days after treatment at the clinic where serum TSH, free T4 and thyroglobulin levels were checked again.
- Two hours after treatment, patients were specifically asked about whether they had any feeling of nausea.
- Each nodule was measured by ultrasound on the day of treatment (baseline), then after 3 months and 6 months.

Study design issues:

- Retrospective analysis.
- The volume reduction ratio (VRR) was calculated based on the formula: (baseline volume – volume at visit) /(baseline volume) × 100.
- Treatment success was defined as ≥50% volume reduction from baseline.
- The primary endpoint was the 6-month VRR.

Study population issues:

- A total of 145 patients completed their treatment for a benign thyroid nodule. There were five (3.4%) patients who had a previous ablation, 6 (4.1%) patients with a <6-month follow-up and 11 (7.6%) patients with missing pain scores during or after treatment. As a result, 123 (84.8%) were eligible for analysis.

- In the sequential ablation group, 12 patients had treatment for bilateral disease, while the other seven patients had treatments for two nodules on the same side. All patients completed their sequential treatment within the same session and were able to be discharged home on the same day.

Other issues:

- Because of the longer treatment time, the amount of Pethidine and Diazepam were statistically significantly greater in the sequential ablation group than those in the single ablation group (87.50 ± 19.94 mg vs 72.64 ± 27.44 mg, p = 0.010 and 8.86 ± 2.05 mg vs 5.85 ± 2.80 mg, p = 0.002, respectively).
- There is probably an overlap of patients with Study 2 (Lang 2018c), Study 4 (Lang 2017b) and Study 5 (Lang 2018b).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **123 (104 single HIFU ablation versus 19 sequential ablation)**

Volume reduction ratio (mean±SD)

Variable	Single HIFU ablation	Sequential HIFU ablation	p value
Treatment efficacy of the index or first nodule			
3 – month VRR	48.76 ± 20.73	49.66 ± 18.20	0.959
6-month VRR	61.77 ± 27.09	63.05 ± 16.29	0.631
Treatment efficacy of the second nodule			
3 – month VRR	-	58.08 ± 18.09	0.167*
6-month VRR	-	64.81 ± 17.80	0.882*

*The index nodule in the single HIFU ablation group was compared with the second nodule in the sequential HIFU ablation group.

Safety

Severity of pain by VAS (from 0 to 10 [0 = no pain and 10 = worst possible pain])

	Single HIFU ablation	Sequential HIFU ablation	p value
During treatment	5.68 ± 2.99	6.34 ± 2.14	0.547
2 h after treatment	2.54 ± 2.78	3.53 ± 2.54	0.836
The following morning (>12 h after treatment)	1.15 ± 1.65	2.29 ± 2.08	**0.047**

Treatment-related complication

	Single HIFU ablation	Sequential HIFU ablation	p value
Vocal cord palsy	2% (2/104)	0	1.000
Skin burn	0	0	-
Nausea or vomiting	1% (1/104)	16% (3/19)	**0.012**

Rise in serum Thyroglobulin 4 days after treatment (%)[a] (mean±SD)

Variable	Single HIFU ablation	Sequential HIFU ablation	p value
Rise in serum Tg 4 days after treatment (%)	1,319.49 ± 1,898.63	1,992.03 ± 1,596.70	0.179

[a] Based on the formula: (serum Tg on day 4 – serum Tg at baseline) / (serum Tg at baseline) × 100

Abbreviations used: HIFU, high-intensity focused ultrasound; MNG, multinodular goitre; SD, standard deviation; Tg, thyroglobulin; VAS, visual analogue scale; VRR, volume reduction ratio.

Study 4 Lang BHH (2017)b

Details

Study type	**Retrospective comparative study**
Country	China
Recruitment period	2015-16
Study population and number	n= **146 (43 single-session HIFU ablation versus 103 hemithyroidectomy)** consecutive patients with benign thyroid nodules
Age and sex	HIFU: Mean 48 years; 95% (41/43) female Hemithyroidectomy: Mean 51 years; 73% (75/103) female
Patient selection criteria	HIFU ablation was only indicated when the patient did not wish to have surgery.
Technique	HIFU: all treatments were done by 1 person with more than 2 years of experience using the Echopulse (Theraclion) device. Patients were sedated with diazepam and pethidine. Oral diet was resumed immediately afterwards and patients could go home 2 hours after the procedure. Hemithyroidectomy: all procedures were done by 1 surgical team. All patients needed at least 1 overnight stay.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Each nodule was graded by ultrasound measurement at the day of treatment (baseline), 1 month and at 6 months. All patients completed these assessments.
- At 6 months, patients in the HIFU group had their nodule assessed clinically using the WHO grading system and were asked to rate how much their obstructive or local pressure symptoms had improved from baseline. Patients' serum TSH and FT4 were also checked.
- Voice quality was assessed by a computerised multi-dimensional voice programme (MVDP) and a voice handicap index-30 (VHI-30) questionnaire 1 month after treatment. VHI-30 is a self-administered questionnaire to measure the impact of a voice disorder on a person's vocal functions, vocal physical ability and emotion. It produces a total single score (0-120) by adding the score of 30 questions with each having a response option from 0 (never) to 4 (always).
- In the HIFU group, 1 patient had an apparent unilateral vocal cord paralysis after the procedure and 2 patients did not complete the 1-month MVDP testing; in the surgery group, 3 patients had an apparent unilateral VCP after the procedure. Therefore, only 40 patients in the HIFU group and 100 patients in the surgery group were included for the voice quality analysis.

Study design issues:

- The volume reduction ratio (VRR) was calculated based on the formula: (baseline volume – volume at visit) /(baseline volume) × 100.
- Safety was defined by the absence of major complications such as recurrent laryngeal nerve injury and skin burn.

Study population issues:

- Age at treatment, sex ratio, size and volume of the dominant nodule were statistically significantly different between the 2 groups ($p<0.05$).
- The baseline mean and maximum fundamental frequency (F_0) were also statistically significantly higher in the HIFU group (probably related to the fact that there were more female patients in the HIFU group).

Other issues: There is probably an overlap of patients with Study 2 (Lang 2018c), Study 3 (Lang 2018a) and Study 5 (Lang 2018b).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **146 (43 single-session HIFU ablation versus 103 hemithyroidectomy)**

Comparison of treatment efficacy between HIFU and hemithyroidectomy

	HIFU (n=43)	Hemithyroidectomy (n=103)	p value
Hospital stay (days)	0.3±0.2	1.0±0.0	**<0.001**
Size/ volume of index nodule (ml)			
Baseline	5.15±4.38	10.23±9.97	**<0.001**
1 week	5.31±4.46	-	-
1 month	4.23±3.58	-	-
6 months	2.54±2.28	-	-
Volume reduction from baseline (%)			
1 week	-3.05±4.63	-	
1 month	17.84±5.56	-	
6 months	51.71±16.04	-	
WHO nodule grade at 6 months (no pre-procedure data available)			
Grade 1a (palpable but not visible when neck is extended)	67% (29/43)	-	
Grade 1b (palpable and visible when neck is extended)	26% (11/43)	-	
Grade 2 (visible when neck is in the normal position)	7% (3/43)	-	
Grade 3 (visible from distance)	0	-	
Symptom improvement score at 6 months			**0.009**

Safety

Comparison of treatment safety between HIFU and hemithyroidectomy

	HIFU (n=43)	Hemithyroidectomy (n=103)	p value
Pain scores (VAS)			
During treatment	3.5±4.0	-	-
Immediately after treatment	1.0±.1.0	-	-
Before hospital discharge	0.0±1.0	-	-
Skin burn	0	-	-
Recurrent laryngeal nerve injury*	2% (1/43)	3% (3/103)	1.000
Subclinical hypothyroidism[a]	2% (1/43)	20% (21/103)	**0.008**
Hypothyroidism (FT4<12pmol/L)	0	0	-

*Transient. There was a complete recovery within 6 months of the procedure in all patients.

[a]Defined as serum TSH exceeding 4.78 mIU/L within the first 6 months following treatment.

-For HIFU ablation, 14% (3/43) of patients had mild residual **discomfort** during the first week.

-For HIFU, **redness and swelling** were reported in 30% (13/43) of patients. They resolved within the first week.

Voice handicap index

	HIFU (n=42)		Surgery (n=100)		Linear regression (unadjusted)		
	Baseline	1 month	Baseline	1 month	Coeff	95% CI	p
Total VHI-30 score	6.0±7.9	10.8±18.0	6.6±11.9	16.0±20.1			
Difference in total VHI-30	4.8±19.5		9.77±20.2		-4.65	-12.08 to 2.78	0.218
Mean VHI-30 score per item	0.2±0.3	0.4±0.6	0.2±0.4	0.5±0.7			
Difference in mean VHI	0.16±0.65		0.32±0.69		-0.16	-0.41 to	0.228

0 (no improvement)	7% (3/43)	10% (10/103)			score per item				0.10		
1 (slight improvement)	5% (2/43)	21% (22/103)			The 1-month pitch in the hemithyroidectomy group was lower than baseline. In the HIFU group, pitch was not significantly affected.						
2 (moderate improvement)	19% (8/43)	30% (31/103)									
3 (significant improvement)	67% (29/43)	39% (40/103)									

Abbreviations used: CI, confidence interval; HIFU, high-intensity focused ultrasound; TSH, thyroid-stimulating hormone; VAS, visual analogue scale; VHI, voice handicap index; WHO, world health organisation.

Study 5 Lang BHH (2018)b

Details

Study type	**Retrospective case series**
Country	China (single centre)
Recruitment period	2015-17
Study population and number	n= **136** patients benign thyroid nodules
Age and sex	Mean 47 years; 85% (116/136) female
Patient selection criteria	Inclusion criteria: only patients who were indicated but refused thyroidectomy were considered for ablation. Only nodules proven to be benign on fine needle aspiration cytology with their centre measured within 5–30 mm from the skin were eligible for HIFU ablation. The index nodule had to have all three orthogonal dimensions ≥ 10 mm but ≤ 50 mm on ultrasonography. Only patients who had single treatment were considered for analysis.
Technique	All treatments were performed by one person using the same device (Theraclion). Patients were sedated with diazepam (5–10mg) and pethidine (50–100 mg). Oral diet was resumed immediately afterwards and patients were allowed to go home 2 hours after treatment.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- 154 consecutive patients had HIFU ablation for a benign thyroid nodule during the study period. 18 patients were excluded from the analysis because they had had 2 sequential HIFU treatments in the same session.

Study design issues:

- Each nodule was measured by ultrasonography on the day of treatment (baseline) and at 3 months and 6 months.

Study population issues: There is probably an overlap of patients with Study 2 (Lang 2018c), Study 3 (Lang 2018a) and Study 4 (Lang 2017b).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 136

VRR and treatment success
<table>
<tr><th></th><th>3 months</th><th>6 months</th></tr>
<tr><td>Mean VRR</td><td>50.29 ± 16.39% (median = 52.20 %; IQR = 26.57 %)</td><td>55.80 ± 18.34 % (median = 58.00 %; IQR = 30.00 %)</td></tr>
<tr><td>Treatment success</td><td>54% (74/136)</td><td>64% (87/136)</td></tr>
</table>
The VRR was calculated based on the formula: [Baseline volume–volume at visit] / [Baseline volume] * 100.
Treatment success was defined as ≥ 50 % volume reduction from baseline.

• In univariate analysis, older age (OR = 1.046, 95 % CI =1.011–1.081, p=0.009), larger nodule size (OR = 1.200, 95 % CI = 1.126–1.282, p<0.001), higher total energy delivered (OR = 1.208, 95%CI = 1.105–1.319, p<0.001), higher power per pulse (OR = 1.032, 95 % CI = 1.015–1.049, p<0.001), longer treatment time (OR = 1.041, 95 % CI = 1.016–1.065, p=0.001) and appearance of HEMs (OR = 100.02, 95 % CI = 83.33–10,027.56, p=0.001) were statistically significantly associated with treatment success at 6 months.
• Given that baseline nodule volume was statistically significantly associated with total energy delivered (ρ=0.333, p<0.001) and total ‘on-beam’ treatment time (ρ=0.193, p=0.035), only baseline nodule volume was entered in final regression models.
• After adjusting for age and energy per pulse, only smaller nodule volume at baseline (OR = 1.143, 95 % CI = 1.038–1.256, p=0.006) and the appearance of HEMs (OR = 275.44, 95 % CI = 26.63– 2848.98, p<0.001) were independent factors for treatment success.
• In a second model, only proportion of HEMs was entered instead of the appearance of HEMs. None of the four variables turned out to be independent factors for treatment success.</td><td>Vocal cord paresis: 3% (4/136)
All patients had a full recovery within 2 months.</td></tr>
<tr><td colspan="2">Abbreviations used: HEMs, hyperechoic marks; HIFU, high-intensity focused ultrasound; IQR, interquartile range; OR, odds ratio; VRR, volume reduction ratio.</td></tr>
</table>

Study 6 Trimboli P (2018)

Details

Study type	**Retrospective case series**
Country	Switzerland (single centre)
Recruitment period	From 2016
Study population and number	n= **26** patients with benign thyroid nodules
Age and sex	Mean 62 years; 81% (21/26) female
Patient selection criteria	Inclusion criteria: normal thyroid laboratory and local compressive symptoms specifically due to solid benign thyroid nodules with major diameter no larger than 4 cm. Patients with neck symptoms or cosmetic concerns specifically determined by thyroid nodule. Exclusion criteria: Nodules with cystic changes (i.e. >30% of the targeted nodule), micro- and macrocalcifications, and difficult HIFU accessibility, patients with vocal cord disease or significant alterations of the skin anterior to thyroid.
Technique	HIFU treatment using the EchoPulse system (Theraclion). In all patients, the first HIFU pulse was performed at a fixed dose of 45 W/site. This power was maintained for the next pulses only when patient had good comfort. In case of patient's discomfort, the power of the subsequent pulses was tailored according to the patient's tolerability, with a range from 19 to 35 W/site. No anaesthesia was administrated for the therapy, and no specific method for pain control was necessary.
Follow-up	**1 year**
Conflict of interest/source of funding	None

Analysis
Study design issues:

- Nodule size and thyroid function were evaluated before HIFU and 6 and 12 months later. Complications to therapy were also recorded.
- Data of patient's comfort with and tolerability of HIFU, and reduction of local compressive symptoms, were systematically collected by a specific questionnaire. Ten minutes after HIFU treatment, each patient was asked to answer to the following multiple choice three questions:
    - 1. how was your comfort during HIFU also considering the complete absence of anaesthesia (good or not)
    - 2. how was your comfort 10 min after HIFU (good or not)
    - 3. how was your tolerability of HIFU therapy in a scale from 1 (low) to 10 (high).
- At 1 year follow-up, patients were also asked if they experienced a reduction of symptoms correlated to the presence of nodule treated by HIFU (patients could answer yes or no).

Other issues:

- The mean energy used during the HIFU procedures in this study seemed to be lower than in other published studies.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 26

Procedure outcomes
Mean power of HIFU treatment: 33.3 ± 10.3 W/site
Mean energy delivered: 2.1 ± 1.1 kJ
Duration of the procedure: 9 ± 4 min (ranging from 3 to 18).

Nodule volume
<table>
<tr><th></th><th>Baseline</th><th>6 months</th><th>1 year</th></tr>
<tr><td>Mean nodule volume</td><td>2.81 ± 2.04 mL</td><td>1.83 ± 1.63 mL</td><td>1.57 ± 1.47 mL</td></tr>
<tr><td>% of nodule volume reduction from baseline</td><td></td><td>40%</td><td>48%</td></tr>
</table>
Nodules volume was statistically significantly reduced at 6 and 12 months ($p < 0.0001$).

Patient’s comfort with HIFU
<table>
<tr><th></th><th>Good comfort during treatment</th><th>Good comfort just after therapy</th></tr>
<tr><td>% patients</td><td>73% (19/26)</td><td>100% (26/26)</td></tr>
</table>
Mean result of tolerability scale assessment (scale of 1 to 10): 8.1 ± 2.9

Proportion of patients with a reduction of local cervical compressive symptoms at 1 year: 85% (22/26)

No significant difference was recorded in thyroid laboratory before and after HIFU treatment.</td><td>No complications were reported.</td></tr>
<tr><td colspan="2">Abbreviations used: HIFU, high-intensity focused ultrasound</td></tr>
</table>

Study 7 Giovanella L (2018)

Details

Study type	**Retrospective comparative study**
Country	Switzerland (single centre)
Recruitment period	From 2016
Study population and number	n= **32 (15 HIFU versus 17 radioiodine)** patients with toxic thyroid nodules
Age and sex	HIFU: Mean 62 years; 80% (12/15) female RAI: Mean 63 years; 76% (13/17) female
Patient selection criteria	Inclusion criteria: sex and age-matched patients >18 years old with a unifocal toxic thyroid nodule for which (i) the indication to the RAI as first-line treatment had been placed and (ii) eligibility criteria for HIFU treatment had been fulfilled (patients carrying unifocal toxic thyroid nodules with a maximum diameter of 40 mm and (if present) a cystic component <30% of the nodules' volume). Exclusion criteria: patients with toxic thyroid nodules close to skin, trachea and carotid; vocal cord disease or significant alterations of the skin anterior to thyroid were excluded from the HIFU treatment.
Technique	HIFU treatment using the EchoPulse system (Theraclion). The first HIFU pulse was performed at a fixed dose of 45 W/site. In case of patient's discomfort, the power of the subsequent pulses was tailored according to the patient's tolerability to avoid anaesthesia or sedation. Intravenous paracetamol was administrated intravenously (1 g in 15 minutes) if needed.
Follow-up	**1 year**
Conflict of interest/source of funding	None

Analysis

Study design issues: Normalisation of serum thyrotropin (TSH) 1 year after treatment was the primary end-point; concurrent changes in nodules' volume and scintigraphic pattern were also evaluated as secondary end-points.

Study population issues:

- No significant difference was found at baseline in demographic variables, TSH, fT3, fT4 levels and toxic thyroid nodules' volume in patients treated with RAI or HIFU, respectively.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 32 (15 HIFU versus 17 RAI)

Procedure outcomes
RAI-treated patients received a median activity of 370 (range 200-780) MBq of I-131.
HIFU-treated patients received a median energy of 2.29 (range 1.56-3.53) kJ/mL.

Efficacy outcomes at 1 year
<table>
<tr><th></th><th>HIFU</th><th>RAI</th><th>p</th></tr>
<tr><td>Normal TSH</td><td>27% (4/15)</td><td>82% (14/17)</td><td>0.0008</td></tr>
<tr><td>Toxic thyroid nodule’s volume (mL, median [range])</td><td>0.79 (0.24-3.25)</td><td>0.73 (0.12-2.52)</td><td>0.61</td></tr>
<tr><td>Toxic thyroid nodule’s largest diameter (mm, median [range])</td><td>18 (6-26)</td><td>16 (5-28)</td><td>0.51</td></tr>
<tr><td>^{99m}Tc-pertechnetate Thyroid Scintigraphy responders*</td><td>53% (8/15)</td><td>94% (16/17)</td><td>0.024</td></tr>
</table>
* Toxic thyroid nodules with isofunctioning or hypofunctioning scintigraphic pattern after treatment were rated as responders while persistently hyperfunctionig toxic thyroid nodules were rated as non-responders.

None of patients developed hypothyroidism at the last follow-up..</td><td>No safety events reported.</td></tr>
<tr><td colspan="2">Abbreviations used: fT3, free-tri- iodo- thyronine; fT4, free-thyroxine; HIFU, high-intensity focused ultrasound; RAI, radioiodine; TSH, serum thyrotropin</td></tr>
</table>

Study 8 Korkusuz Y (2018)

Details

Study type	**Retrospective comparative study**
Country	Germany (single centre)
Recruitment period	Not reported
Study population and number	n= **94 (14 HIFU versus 40 RFA versus 40 MWA)** patients with benign, symptomatic thyroid nodules (118 nodules in total)
Age and sex	Median 47 years; 59% (55/94) female
Patient selection criteria	• HIFU was limited to patients with small nodules who were able to lie flat with reclined head for over 30 minutes without moving too much. • RFA and MWA were practicable for all patients who met the inclusion criteria. • All patients had symptoms, which were indications for surgery, but refused this intervention because of contraindications, a high risk of postoperative mortality or a high risk of complications. Exclusion criteria: malignancy and an unsafe position of the nodule nearby important structures such as trachea, oesophagus, large vessels and nerves.
Technique	• HIFU was done with the Theraclion device with a probe that emitted pulses at 3MHz and a maximum power of 125W. The device was used without beamotion. • Bipolar RFA was conducted with a generator (POWER System) and cooled 15 gauge electrodes or un-cooled 18 gauge electrodes made by Olympus Hamburg. • MWA was done with a generator made by MedWaves Incorporated and cooled or un-cooled 14 to 16 gauge electrodes.
Follow-up	**3 months**
Conflict of interest/source of funding	None

Analysis
Study design issues:

- The patients were asked to describe the pain intensity with a score between 0 and 10 where '0' means 'no pain' and '10' means 'intolerable pain'.
- The pre-ablative and post-ablative volumes were measured by ultrasound.
- There is no mention in the material and methods about power calculation and allocation of patients to each treatment option.

Study population issues: The median volume of the nodules before the procedure was different between groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **94 (14 HIFU versus 40 RFA versus 40 MWA)**

Efficacy outcomes at 3 months

	HIFU	RFA	MWA	p value
Pre-ablation nodule volume (median [range])	2.8 ml (0.6 ml to 7.6 ml)	6.5 ml (0.3 ml to 90 ml)	19 ml (1.3 ml to 82 ml)	
Nodule volume at 3 months (median [range])	1.6 ml (0.1 ml to 3.5 ml)	2.1 ml (0.2 ml to 49.2 ml)	8.9 ml (0.3 ml to 76 ml)	
Median volume reduction (range)	49% (12 % to 77 %)	50% (8.3 % to 89 %)	44 % (0.3 % to 82 %)	NS*
p value for the median volume reduction	**<0.05**	**<0.05**	**<0.05**	
Median application energy	9.2 kJ per 30 minutes	14 kJ in 7.8 minutes divided up into 6.2 shots	12 kJ in 10 minutes divided up into 2.6 shots	

*The difference in median volume reduction was not statistically significant between groups.

Safety

Safety outcomes within 3 months of the procedure

	HIFU	RFA	MWA
Haematoma	None	A mild haematoma occurred in 65% (26/40) of patients	A mild haematoma after treatment occurred in 53% (21/40) patients
Pain	All patients experienced **mild pain** up to 2 days after treatment	All patients reported a mild or rarely moderate pain radiating to the mandible, neck or shoulders. They also felt pressure during energy submission into the nodule. The discomfort got worse if the nodules were superficial. Deep or large nodules barely caused discomfort.	
Skin burn	None	Uncooled systems often caused slight first-degree skin burn	

Pain score during the procedure

	HIFU	RFA	MWA
Median pain score (range)	7 (3 to 8)	3 (1 to 6)	4 (1 to 7)

Abbreviations used: HIFU, high intensity focused ultrasound; MWA, microwave ablation; NS, not statistically significant; RFA, radiofrequency ablation

Validity and generalisability of the studies

- There were no RCTs included in the overview.
- 1 systematic review of 88 patients was included (study 1).
- There was a probable overlap of patients between studies 2, 3, 4 and 5.
- The longest follow-up was 2 years (study 2) and the biggest case series included 136 patients (study 5).
- 3 comparative studies with small sample sizes compared HIFU with hemithyroidectomy (study 4), radioiodine (study 7), radiofrequency ablation or microwave ablation (study 8).
- 1 comparative study compared single and sequential nodule ablation (study 3).
- The same HIFU device was used in all the studies (Echopulse from Theraclion).
- The studies were from China, France, Germany, Switzerland or Bulgaria.
- It seems that local anaesthesia was not usually used. In some studies no conscious sedation or pain control were used.

Existing assessments of this procedure

- Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules were published by the American Association of Clinical Endocrinologists, the American College of Endocrinology, and the Associazione Medici Endocrinologi in May 2016[9]. They stated:

  7.2.5. Image-guided thermal ablation for benign nodules
  • Consider laser or radiofrequency ablation for the treatment of solid or complex thyroid nodules that progressively enlarge, are symptomatic, or cause cosmetic concern.
  • Repeat FNA for cytologic confirmation before thermal ablation treatment.
  • Discuss alternative therapy options and their efficacy, limitations, and adverse effects with the patient.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

Condition-related

- Ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules. NICE interventional procedures guidance 562 (2016). Available from http://www.nice.org.uk/guidance/ipg562
- Minimally invasive video-assisted thyroidectomy. NICE interventional procedures guidance 499 (2014). Available from http://www.nice.org.uk/guidance/ipg499
- Intraoperative nerve monitoring during thyroid surgery. NICE interventional procedures guidance 255 (2008). Available from http://www.nice.org.uk/guidance/ipg255

Procedure-related

- High-intensity focused ultrasound for symptomatic breast fibroadenoma. NICE interventional procedures guidance 592 (2017). Available from http://www.nice.org.uk/guidance/ipg592
- Focal therapy using high-intensity focused ultrasound for localised prostate cancer. NICE interventional procedures guidance 424 (2012). Available from http://www.nice.org.uk/guidance/ipg424
- High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery. NICE interventional procedures guidance 184 (2006). Available from http://www.nice.org.uk/guidance/ipg184
- High-intensity focused ultrasound for prostate cancer. NICE interventional procedures guidance 118 (2005). Available from http://www.nice.org.uk/guidance/ipg118

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for high-intensity focused ultrasound for symptomatic benign thyroid nodules were submitted and can be found on the NICE website and http://www.nice.org.uk/guidance/ipg643/evidence

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

NCT02491502 Treatment of Benign Thyroid Nodules With FastScan HIFU. Bulgaria. Actual enrolment: 36 patients. Case series. Estimated study completion date: July 2020.

NCT03331172 HIFU Reapplication in Benign Nodules. China. Estimated enrolment: 20 patients. Case series. Estimated study completion date: September 2018.

References

1. Lang B H, and Wu A L. H (2017) High intensity focused ultrasound (HIFU) ablation of benign thyroid nodules - a systematic review. Journal of Therapeutic Ultrasound 5, 11
2. Lang B H. H, Woo Y C, and Chiu K W (2018) Two-year efficacy of single-session high-intensity focused ultrasound (HIFU) ablation of benign thyroid nodules. European Radiology 19, 19
3. Lang B H. H, Woo Y C, and Chiu K W (2018) Sequential high intensity focused ultrasound (HIFU) ablation in the treatment of benign multinodular goitre: an observational retrospective study. European Radiology 19, 19
4. Lang B H. H, Wong C K. H, and Ma E P. M (2017) Single-session high intensity focussed ablation (HIFU) versus open cervical hemithyroidectomy for benign thyroid nodule: analysis on early efficacy, safety and voice quality. International Journal of Hyperthermia 33(8), 868-874
5. Lang B H. H, Woo Y C, and Chiu K W (2018) Significance of hyperechoic marks observed during high-intensity focused ultrasound (HIFU) ablation of benign thyroid nodules. European Radiology 28(6), 2675-2681
6. Trimboli P, Bini F, Marinozzi F et al. (2018) High-intensity focused ultrasound (HIFU) therapy for benign thyroid nodules without anesthesia or sedation. Endocrine 16, 16
7. Giovanella L, Piccardo A, Pezzoli C et al. (2018) Comparison of high intensity focused ultrasound and radioiodine for treating toxic thyroid nodules. Clinical Endocrinology 09, 09
8. Korkusuz Y, Groner D, Raczynski N et al. (2018) Thermal ablation of thyroid nodules: are radiofrequency ablation, microwave ablation and high intensity focused ultrasound equally safe and effective methods?. European Radiology 28(3), 929-935
9. Gharib H, Papini E, Garber J R et al. on behalf of the AACE/ ACE/ AME Task Force on Thyroid nodules (2016) American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules--2016 Update. Endocrine Practice 22(5), 622-39

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/10/2018	2018, Issue 10
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/10/2018	2018, Issue 10
HTA database (CRD website)	30/10/2018	-
MEDLINE (Ovid)	30/10/2018	1946 to October 29, 2018
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	30/10/2108	October 29, 2018
EMBASE (Ovid)	30/10/2018	1974 to 2018 Week 44

Trial sources searched 17th April 2018

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 17th April 2018

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Thyroid Nodule/
2 exp Thyroid Diseases/
3 (Thyroid* adj4 (nodul* or adenom* or cyst* or diseas* or lump* or tumor* or tumour*)).tw.
4 AFTN.tw.
5 exp Goiter/
6 Goit*.tw.
7 Hyperthyroidism/

8 hyperthyroidis*.tw.
9 exp THYROIDECTOMY/
10 Thyroidectom*.tw.
11 or/1-10
12 High-Intensity Focused Ultrasound Ablation/
13 (HIFU or HIFU-F or MRgHIFU or MR-HIFU or MRgFUS).tw.
14 (high adj4 frequen* adj4 ultrasound*).tw.
15 (high* adj4 inten* adj4 focus* adj4 ultrasound*).tw.
16 exp Ultrasonic Therapy/
17 (ultrasonic* adj4 therap*).tw.
18 hemi-ablat*.tw.
19 (thermal adj4 ablat*).tw.
20 or/12-19
21 11 and 20
22 Animals/ not Humans/
23 21 not 22
24 Echopulse.tw.
25 23 or 24

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bandeira-Echtler E, Bergerhoff K, Richter B. Levothyroxine or minimally invasive therapies for benign thyroid nodules. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD004098. DOI: 10.1002/14651858.CD004098.pub	Search up to April 2014 n=31 RCTs (2952 patients) on LT4, PEI, LP and RF ablation therapy but none on HIFU.	None of the interventions investigated death from any cause, the development of thyroid cancer or health-related quality of life. Nodule volume reductions were achieved by all therapies; however, the clinical relevance of this outcome is doubtful. Minimally invasive treatments resulted in improvements in pressure symptoms and cosmetic complaints. Some side effects such as light-to-moderate pain were observed after minimally invasive procedures.	No RCTs on HIFU were identified.
Esnault O, Franc B, Menegaux F et al. (2011) High-intensity focused ultrasound ablation of thyroid nodules: first human feasibility study. Thyroid 21(9), 965-73	Case series n=22 FU=2 weeks	This study showed the potential efficacy of HIFU for human thyroid nodule ablation. Lesions were clearly visible by histology and ultrasound after high energy treatments, and safety and tolerability were good. We identified a power threshold for optimal necrosis of the target thyroid tissue. Further studies are ongoing to assess nodule changes at longer follow-up times.	This study is included in the Lang 2017a systematic review which is included in Table 2.
Esnault O, Rouxel A, Le Nestour et al. (2010) Minimally invasive ablation of a toxic thyroid nodule by high-intensity focused ultrasound. Ajnr: American Journal of Neuroradiology 31(10), 1967-8	Single case report FU=18 months	This case report describes the first successful ablation of a toxic TN with HIFU. TSH and radioiodine scan normalization were achieved without complications and maintained for 18 months.	Single case report
Korkusuz H, Sennert M, Fehre N et al. (2015) Localized Thyroid Tissue Ablation by High Intensity Focused Ultrasound: Volume Reduction, Effects on Thyroid Function and Immune Response. RoFo Fortschritte auf dem Gebiet der	Case series n=12 FU=3 months	HIFU is a safe and effective alternative for treating benign thyroid nodules, while preserving thyroid function. Further investigations with multiple treatments should be conducted to evaluate whether additional treatments can achieve greater volume reduction.	Larger studies or studies with longer follow-up are already included in table 2.

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Korkusuz H, Fehre N, Sennert M et al. (2015) Volume reduction of benign thyroid nodules 3 months after a single treatment with high-intensity focused ultrasound (HIFU). Journal of Therapeutic Ultrasound 3, 4	Case series n=9 FU=3 months	HIFU treatment of benign predominantly solid TNs appears to be safe and effective for inducing nodular shrinkage. Despite potential for improvement, a single treatment session with HIFU is already a viable alternative to more standard methods. The feasibility of multiple HIFU treatments requires further investigation. Due to the small sample size, the findings of this analysis need conformation by larger studies.	This study is included in the Lang 2017a systematic review which is included in Table 2.
Korkusuz H, Fehre N, Sennert M et al. (2014) Early assessment of high-intensity focused ultrasound treatment of benign thyroid nodules by scintigraphic means. Journal of Therapeutic Ultrasound 2:18	Case series n=10 nodules FU=post treatment	HIFU appears to be safe and is an easy to perform means of thermal ablation. This study shows that HIFU treatment in thyroidal nodules can be evaluated by scintigraphic means shortly after the intervention. Due to small sample size, the exact magnitude of HIFU ablation efficiency in thyroidal nodules remains a value to be assessed in a larger study.	This study is included in the Lang 2017a systematic review which is included in Table 2.
Korkusuz H, Sennert M, Fehre N et al. (2014) Local thyroid tissue ablation by high-intensity focused ultrasound: effects on thyroid function and first human feasibility study with hot and cold thyroid nodules. International Journal of Hyperthermia 30(7), 480-5	Case series n=10 FU=1 day	HIFU is a safe and effective method to treat benign, solid, complex, hot and cold thyroid nodules preserving thyroid function. Further developments of the system are needed to gain suitability for daily use.	Larger studies or studies with longer follow-up are already included in table 2.
Kovatcheva R D, Vlahov J D, Stoinov J I et al. (2015) Benign Solid Thyroid Nodules: US-guided High-Intensity Focused Ultrasound Ablation-Initial Clinical Outcomes. Radiology 276(2), 597-605	Case series n=20 FU=6 months	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.	This study is included in the Lang 2017a systematic review which is included in Table 2.
Lang B H-H, Woo Y-C, and Chiu K W-H (2018) Role of second high-intensity focused ultrasound (HIFU) treatment for unsatisfactory benign	Case series n=28 FU=6 months after 2nd HIFU treatment	Although subjective obstructive symptoms continued to improve after the second treatment, the actual extent of nodule shrinkage was small. Larger-volume nodules tended to shrink more significantly than smaller-	Larger studies or studies with longer follow-up are already included in table 2.

thyroid nodules after first treatment. European radiology. https://doi.org/10.1007/s00330-018-5671-0		volume nodules in the second treatment.	
Lang B H. H, Woo Y-C, and Chiu K W-H (2018) Changes in serum thyroglobulin and antithyroglobulin shortly following high-intensity focused ablation of benign thyroid nodules in patients with positive antithyroglobulin status. nternational journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, and North American Hyperthermia Group , 1-7	Case series n=85 FU=6 months	Given the fact that the percentage anti-Tg drop correlated significantly with 6-month nodule shrinkage in group I, monitoring early anti-Tg change may help to predict the 6-month nodule shrinkage in patients with positive anti-Tg.	The main objective of this study was to describe changes in serum thyroglobulin (Tg) and anti-Tg after HIFU ablation of benign thyroid nodules in patients with positive anti-Tg status by comparing them with patients with negative anti-Tg and to correlate them with 6-month nodule shrinkage and treatment success. Moreover, these patients are probably included in one of the Lang studies already included in Table 2.
Lang B H. H, Woo Y C, and Chiu K W (2018) Evaluation of pain during high-intensity focused ultrasound ablation of benign thyroid nodules. European Radiology 28(6), 2620-2627	Case series (subgroup analysis) n=128 FU=6 months	A moderate to severe amount of pain was reported during ablation of benign thyroid nodules in over 50 % of patients. Patients' BMI and length of nodule diameter were independent variables for pain during HIFU ablation.	This is a subgroup analysis of the Lang 2018c and 2018b studies which are already included in Table 2.
Lang B H, and Wu A L. H (2018) The efficacy and safety of high-intensity focused ultrasound ablation of benign thyroid nodules. Ultrasonography 37(2), 89-97	Review	The extent of nodule shrinkage following treatment ranged from 48.8% to 68.8%. Like other forms of ablation, the shrinkage rate was greatest in the first 3-6 months, and the best responders were patients with small (<=10 mL) nodules. Complications were uncommon, but temporary vocal cord palsy occurred in 3%-4% of patients, and was related to the distance between the HIFU beam and the recurrent laryngeal nerve. Despite being safe and efficacious, a larger-scale prospective trial is required.	All the studies included in this review are included in Table 2.
Lang B H, Woo Y C, and Chiu K W (2017) Single-Session High-Intensity Focused Ultrasound Treatment	Case series n=73	Single-session HIFU ablation was highly effective in causing shrinkage of benign thyroid nodules at six months, but the extent of shrinkage for larger-sized nodules (>30mL) was noticeably	The patients included in this study are likely to be already included

in Large-Sized Benign Thyroid Nodules. Thyroid 27(5), 714-721	FU=6 months	less than that of smaller-sized nodules. Both pre-ablation nodule volume and total energy per nodule volume were significant determinants of ablation success. For larger-sized nodules, additional HIFU treatment three to six months after initial treatment might be preferred over sequential treatment within the same session.	in the Lang 2018c and 2018b studies.
Lang B H. H, Woo Y C, and Chiu K W. H (2017) The percentage of serum thyroglobulin rise in the first-week did not predict the eventual success of high-intensity focussed ablation (HIFU) for benign thyroid nodules. International Journal of Hyperthermia 33(8), 882-887	Case series n=105 FU=6 months	There was an almost seven-fold increase in the mean Tg level 4d after HIFU ablation. The % of Tg rise in the first week did not appear to correlate with the 6-month nodule shrinkage or treatment success.	The patients included in this study are likely to be already included in the Lang 2018c and 2018b studies
Lang B H, Woo Y C, and Wong C K. H (2017) High-Intensity Focused Ultrasound for Treatment of Symptomatic Benign Thyroid Nodules: A Prospective Study. Radiology 284(3), 897-906	Prospective case series n=22 FU=1 year	HIFU ablation of symptomatic benign thyroid nodules not only induced significant shrinkage but also improved pressure symptom scores and HRQOL throughout a 12-month period.	This study is included in the Lang 2017a systematic review which is included in Table 2.
Lang B H. H, Woo Y C, and Chiu K W (2017) Vocal cord paresis following single-session high intensity focused ablation (HIFU) treatment of benign thyroid nodules: incidence and risk factors. International Journal of Hyperthermia 33(8), 888-894	Retrospective case series n=103 FU= 6 months	The incidence of VCP was 3.9% (4/103) and they completely recovered within 6 weeks. The distance between the FP and the TEG was the only related factor for VCP. The safe distance between FP and TEG should be >=1.1cm.	The patients included in this study are likely to be already included in the Lang 2018c and 2018b studies.
Lang B H. H, Woo Y C, and Chiu K W (2017) High-intensity focused ablation (HIFU) of single benign thyroid nodule rarely alters underlying thyroid function. International Journal of	Retrospective case series n=83 FU=6 months	Hypothyroidism following single HIFU ablation occurred rarely (1.4%) and resulted in little clinical relevance. Given that only one patient developed hypothyroidism following single HIFU ablation, it remains unclear how patients with different amount of parenchyma and relative extent of ablation may affect subsequent thyroid function.	The patients included in this study are likely to be already included in the Lang 2018c and 2018b studies.

Hyperthermia 33(8), 875-881			
Sennert M, Happel C, Korkusuz Y et al. (2018) Further Investigation on High-intensity Focused Ultrasound (HIFU) Treatment for Thyroid Nodules: Effectiveness Related to Baseline Volumes. Academic Radiology 25(1), 88-94	Retrospective case series n=15 patients (19 nodules) FU= 3 months	HIFU of benign thyroid nodules can be carried out as an alternative therapy for nodules <=3mL if patients are refusing surgery or radioiodine therapy.	Larger studies or studies with longer follow-up are already included in table 2.