NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules

Thyroid nodules are lumps in the thyroid gland. The majority are benign (not cancerous) and this must be determined using appropriate diagnostic tests. In this procedure, a small probe is inserted through the skin into a benign nodule in the neck and an electrical current is used to heat and destroy the nodule.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 IP overview was prepared in November 2015 and updated in April 2016.

Procedure name

- Ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules

Specialist societies

- British Association of Endocrine and Thyroid Surgeons
- British Thyroid Association
- British Society of Interventional Radiology.

Description

Indications and current treatment

Thyroid nodules may be cystic, colloid, hyperplastic, adenomatous or cancerous. The majority of thyroid nodules are benign and they are often asymptomatic. There may be a single thyroid nodule (solitary nodule) or multiple thyroid nodules (multinodular goitre). Thyroid nodules can cause an overactive thyroid, which affects the normal production of thyroxine or triiodothyronine.

Treatment of benign thyroid nodules may be necessary if they are symptomatic or causing cosmetic problems. Conventional treatment includes suppressive levothyroxine therapy or surgery. More recently, other approaches that are less invasive than conventional surgery have been introduced, such as ethanol ablation and percutaneous laser ablation.

What the procedure involves

Radiofrequency ablation is a minimally invasive technique that aims to reduce symptoms and improve cosmetic appearance, while preserving thyroid function, and with fewer complications than surgery.

Before treatment, the thyroid nodule is confirmed as benign, typically by the use of 2 fine-needle aspiration biopsies. Ultrasound-guided percutaneous radiofrequency ablation for thyroid nodules is usually done using local anaesthesia in an outpatient setting. The patient is placed in the supine position with moderate neck extension. A radiofrequency electrode is inserted into the nodule using ultrasound guidance to visualise the electrode during the procedure. Once in position, the radiofrequency electrode is activated to heat and destroy the tissue.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ultrasound-guided percutaneous radiofrequency ablation for thyroid nodules. The following databases were searched, covering the period from their start to 24 February 2016: 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 appendix C for details of 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 benign thyroid nodules.
Intervention/test	Ultrasound-guided percutaneous radiofrequency ablation.
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 approximately 2500 patients from 1 systematic review (including 1 randomised controlled trial of 50 patients that has been summarised in more detail in table 2), 2 additional randomised controlled trials, 1 non-randomised comparative studies, and 3 case series[1–8].

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

Table 2 Summary of key efficacy and safety findings on ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules

Study 1 Fuller CW (2014)

Details

Study type	**Systematic review and meta-analysis**
Country	Studies were based in Korea and Italy
Recruitment period	Search date: April 2013
Study population and number	**n=284 patients** (292 nodules; 306 treatments) Adults with benign thyroid nodules 9 studies were included (3 observational studies on radiofrequency ablation [RFA] alone, 2 observational studies on RFA before or after percutaneous ethanol injection [PEI], 2 RCTs using observation as the control, 1 RCT comparing 1 RFA treatment with 2 RFA treatments, 1 RCT comparing RFA to PEI).
Age and sex	Not reported
Patient selection criteria	Any prospective study evaluating the efficacy of radiofrequency ablation (RFA) for the treatment of thyroid nodules in adults was included if it assessed at least 1 outcome measure, such as nodule volume, symptom score, cosmetic score, or medication use. Included studies had to specify the use of tests to exclude patients with nodules of increased malignant potential. Studies were excluded in they assessed 2 or more treatments simultaneously or if they did RFA within a month of another treatment modality.
Technique	Not reported
Follow-up	**1–12 months (varied between studies)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: When multiple follow-up data points were available, the longest follow-up data were used. Final follow-up time varied between the studies. 98% of patients (277/284) were followed up.

Study design issues: The primary outcomes of interest included change in nodule volume, symptom score, cosmetic score, and methimazole use. The meta-analysis used a pre-treatment (baseline) to post-treatment comparison, with all patients serving as their own controls. For all instances of missing or incomplete data, attempts were made to obtain additional details from the authors. Both the fixed-effects model and the random-effects model were used in the study. Adverse events of treatment were tallied and grouped as either serious or non-serious. Serious adverse events were defined as any adverse event that was fatal, life threatening, resulted in significant or persistent disability or incapacity, or resulted in hospitalisation, or any event categorised as a serious adverse event by the original study authors. There was a high level of heterogeneity between the studies.

Study population issues: 3 studies included both hot and cold nodules; the remaining 6 studies included cold nodules only. Radioactive iodine scanning was only routinely done on euthyroid patients to confirm that nodules were cold in 2 studies.

Other issues: There was some overlap in authorship between the studies; 7 of the 9 included studies derived from 1 of 2 author groups.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **284 patients** (292 nodules) **Nodule volume** Change in nodule volume after RFA treatment=−9.77 ml (95% CI −13.83 to −5.72; 9 studies, n=284 nodules; I^2=98%) Change in nodule volume for autonomously functioning thyroid ('hot') nodules=−16.14 ml (95% CI −24.28 to −7.99; 2 studies, n=51 nodules; I^2=75%) Change in nodule volume for 'cold' nodules=−9.67 ml (95% CI −15.04 to −4.30; 8 studies, n=213 nodules; I^2=97%) **Symptom and cosmetic score** Change in mean symptom score on 10-point visual analogue scale (0–10) after RFA treatment ('cold' nodules only)=−2.89 (95% CI −2.51 to −3.28; 4 studies, n=85 patients; I^2=56%) Change in mean cosmetic score (scored by physician from 1 to 4) after RFA treatment ('cold' nodules only)=−2.02 (95% CI −1.69 to −2.35; 5 studies, n=114; I^2=78%) Change in combined symptom and cosmetic score (scale 0–6) after RFA treatment=-2.96 (95% CI −2.66 to −3.25; 2 studies, n=114, I^2=94%) **Withdrawal from antihyperthyroid medication** Before RFA treatment, 60 patients with 'hot' nodules were given methimazole at doses sufficient to maintain thyroid-stimulating hormone within the normal range; 29 patients continued to need some dose of this medication after RFA to maintain euthyroidism based on thyroid-stimulating hormone measurements and symptoms (odds ratio 40.34, 95% CI 7.78 to 209.09; 3 studies, n=60; I^2=2%).	**Serious adverse events (n=2)** • 1 diffuse glandular haemorrhage resulting in interruption of procedure. The patient was given oral analgesics for pain relief for 3 days. • 1 ipsilateral vocal fold palsy at 1-month follow-up. The patient was subsequently lost to follow-up. **Non-serious adverse events (n=10)** • Fever, n=5 (resolved spontaneously within 1 day) • Postoperative oedema, n=3 (all patients were treated with betamethasone medication) • First-degree burn, n=1 • Haematoma, n=1
Abbreviations used: CI, confidence interval; RFA, radiofrequency ablation	

Study 2 Cesareo R (2015)

Details

Study type	**Randomised controlled trial**
Country	Italy
Recruitment period	2011–13
Study population and number	**n=84 (42 RFA versus 42 control [no treatment])** Adults with benign solid thyroid nodules
Age and sex	Mean 54 years; 61% (51/84) female
Patient selection criteria	Age >18 years; thyroid nodules with cosmetic or compressive symptoms or nodules >5 ml or with maximum diameter >2 cm; benign thyroid solid nodule (solid portion>70%) at repeat ultrasound-guided fine-needle aspiration cytological examinations; cold nodule at 99mTc-pertechnetate scinitigraphy; serum thyroid hormone thyrotropin and calcitonin levels within normal limits; no history of radioiodine therapy or thermal ablation; no previous neck or trunk external beam radiotherapy; refusal or ineligibility for surgery. Exclusion criteria: pregnancy, malignant or suspicious thyroid nodules, or nodules that were confluent in a compressive lobar mass.
Technique	A radiofrequency generator (Cool-tip, E-series; Covidien) and a 17-gauge, 15 cm electrode with a 1 cm active tip were used. All procedures were done by the same operator under ultrasonography control with the same scanner used for the initial diagnostic evaluation. The patients were given prednisone before RFA of large nodules to reduce postoperative oedema. A transisthmic approach along the short axis of the nodule was used, with a 'moving-shot' technique. All patients treated by RFA had a single session of treatment.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Patients were randomised to RFA or no treatment using a computer-based number generator. The main aims of the study were to evaluate the effectiveness and safety of RFA on debulking benign thyroid nodules, the relationship between RFA and baseline nodule volume, and the relationship between the baseline sonographic characteristics of thyroid nodular disease and RFA. All patients were asked to rate pressure symptoms on a 10-cm visual analogue scale at enrolment and follow-up. A cosmetic score of 1–4 was used (1=no palpable mass, 2=no cosmetic problems but palpable mass, 3=a cosmetic problem on swallowing only, 4=easily visible mass). Photographs were taken of all patients at baseline and at 1- and 6-month follow-up.

Study population issues: There were no statistically significant differences between the 2 groups in main characteristics and clinical data at baseline.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **84 (42 versus 42)**

Thyroid nodule volume (ml), mean±standard deviation (sd)

Follow-up	RFA, n=42	Control, n=42	p value
Baseline	24.5±19.6	27.5±22.1	Not significant
1 month	17.5±34.7	27.6±22.1	<0.001
6 months	8.6±9.5	27.8±22.1	<0.001
p value	<0.001	Not significant	

The mean percentage decrease after RFA was 49.7±14.5% at 1 month and 68.5±13.5% at 6 months.

Thyroid nodule volume after RFA, stratified by volume at baseline (ml), mean±sd (mean percentage decrease in volume±sd)

Follow-up	Small nodules n=10	Medium nodules n=21	Large nodules n=11
Baseline	7.4±2.7	18.1±4.4	52.3±17.5
1 month	3±1.2 (57.5±8.6%)	9.3±3 (47±15%)	27.8±13.7 (47.7±16.3%)
6 months	1.6±1 (78.2±10.7%)	5.9±2.5 (67±12.2%)	20.1±12.1 (62.8±14.8%)
p value	<0.01	<0.001	≤0.05 (1 month) and <0.01 (6 months)

Hormonal evaluation

All patients were euthyroid at baseline and there were no hormonal changes seen in either group at follow-up.

Pressure symptom score (0–10 VAS, lower scores better), mean±sd

Follow-up	RFA, n=42	Control, n=42	p value
Baseline	2.8±3.3	2.7±3	Not significant
1 month	1.4±1.7	2.7±3	Not significant
6 months	0.4±0.8	2.9±3.2	Not reported
p value	<0.001 (6 months)	0.01 (6 months)	

46.4% (39/84) of patients had pressure symptoms at baseline. In the RFA group, 19 patients had pressure symptoms before treatment and 10 patients had pressure symptoms at the 6-month follow-up.

The pressure symptom score improved significantly in the medium and large nodule subgroups but the difference was not statistically significant in the small nodule subgroup.

Cosmetic score (scale, 1–4, lower scores better), mean±sd

Follow-up	RFA, n=42	Control, n=42	p value
Baseline	2.6±0.9	2.6±1.0	Not significant
1 month	2±0.6	2.6±1.0	Not reported
6 months	1.7±0.7	2.6±1.0	Not reported
p value	<0.001 (6 months)	Not significant	

The cosmetic score improved significantly in all nodule subgroups.

Treatment time by nodule size (minutes), mean±sd (minimum-maximum):

- All nodules=37±17.4 (17–85)
- Small=20.7±2.8 (17–25)
- Medium=31.9±6.7 (24–45)
- Large=61.6±12.5 (48–85)

The rate of thyroid nodule volume reduction was not statistically significantly different between solid and predominantly solid nodules.

Safety

No major complications were observed and no patient needed to be hospitalised after treatment.

Complications

- Local pain=21.4% (8/42) The pain occasionally radiated to the ear, jaw, or chest but it was limited and resolved quickly after the power was switched off. In 1 patient, the procedure was stopped because of severe chest pain.
- Voice change immediately after the procedure=4.7% (2/42) resolved completely within 3 hours of the procedure
- Permanent right paramedian vocal cord palsy with inspiratory stridor without dysphonia=2.4% (1/42)

Abbreviations used: RFA, radiofrequency ablation; sd, standard deviation

Study 3 Deandrea M (2015)

Details

Study type	**Randomised controlled trial**
Country	Italy and Korea
Recruitment period	2010–12
Study population and number	**n=80 (40 RFA versus 40 control [no treatment])** Adults with solid, compressive, non-functioning benign thyroid nodules
Age and sex	Mean 39.5 years (RFA) versus 52.2 years (control) in Korea and 54.3 years (RFA) versus 62.5 years (control) in Italy (p=0.05 for comparison between Korean and Italian RFA groups). 90% (72/80) female
Patient selection criteria	Age>18 years; presence of a solid thyroid nodule (solid portion >70%) with a volume between 10–20 ml; presence of pressure symptoms or cosmetic problems for which patients specifically requested treatment; confirmation of benign findings in at least 2 separate ultrasound-guided core needle or fine-needle aspiration biopsies; normal serum levels of thyroid hormones, thyrotropin and calcitonin. Exclusion criteria: nodules showing ultrasound features suggestive of malignancy; treatments for the thyroid nodule in the 6 months prior to enrolment in this study.
Technique	A transisthmic approach with an 18-gauge needle was used, with a 'moving-shot' technique. All patients treated by RFA had a single session of treatment. The treatment method differed between the 2 study centres: the mean ablation time was significantly longer in Italy than Korea (819.5 versus 435.8 seconds, p=0.0001) but the mean radiofrequency power was higher in Korea than Italy (75.3 versus 49.7 Watt, p=0.0001). The same energy per ml of nodule volume was applied in both countries.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Patients were randomly assigned to RFA or no treatment using a random allocation sequence. The outcomes were assessed by investigators who were blinded to the group allocation. The primary end points of the study were the quantitative volume reduction of thyroid nodule between RFA and control at 6 months after the procedure and the comparison of the volume reduction ratio of the patients at 2 centres after RFA. The Korean centre had an experience of about 3000 procedures and the Italian centre had treated 50 patients with the moving-shot technique, after instruction by a Korean radiologist. The secondary endpoints included the therapeutic success rate, in terms of improvement in symptoms and cosmetic problems, and the number of major complications. Symptoms were rated by patients on a 10 cm visual analogue scale. Cosmetic scores were recorded by the investigator, on a scale of 1–4 (1=no palpable mass, 2=no cosmetic problem but a palpable mass, 3=cosmetic problem only on swallowing, 4=readily detected cosmetic problem).

Study population issues: The patients from Korea were younger than the patients treated in Italy. The symptom scores and cosmetic scores in the RFA groups were statistically significantly different between the 2 study centres, with higher symptom scores and lower cosmetic scores in Italy compared with Korea. The baseline nodule volume was also larger in the Italian patients (p=0.009).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **80 (40 versus 40)**

Baseline demographic data, mean±standard deviation (sd), (range)

	Korea		Italy		
	RFA	**Control**	**RFA**	**Control**	**p value***
Nodule largest diameter (cm)	4.0±0.5 (3.1–4.9)	2.8±0.3 (2.2–3.2)	4.0±0.4 (3.4–4.6)	3.9±0.5 (3.0–5.2)	0.95
Nodule volume (ml)	13.9±3.1 (10–19.7)	13.7±3.2 (10–19.8)	16.4±3.4 (12.6–25.1)	15.0±3.2 (9.4–20.2)	0.009
Symptom score (scale 0–10)	3.4±0.9 (2–5)	3.1±0.8 (2–5)	4.0±2.7 (0–8)	3.9±2.1 (0–7)	0.001
Cosmetic score (scale 1–4)	4.0±0	4.0±0	3.2±0.7 (2–4)	2.8±0.7 (1–4)	0.001

* comparison between Korean and Italian RFA groups

Comparison of clinical characteristics between RFA and control groups at 6-month follow-up, mean±sd

Outcome	**RFA n=40**	**Control group n=40**	**p value**
% volume reduction (median)	71	−3	0.0001
Symptom score (scale 0–10)	0.4±0.7	3.3±1.7	0.0001
Cosmetic score (scale 1–4)	1.7±0.8	3.5±0.7	0.0001
TSH (µIU/ml)	0.9±0.8	1.0±0.9	0.190
fT4 (pg/ml)	10.8±2.9	11.9±2.0	0.05
Thyroglobulin (ng/ml)	31.5±38	13.6±22	0.02

In the RFA group, the compressive score decreased from 3.6±1.9 at baseline to 0.4±0.7 at 6-month follow-up ($p<0.0001$). The cosmetic score decreased from 3.6±0.5 at baseline to 1.7±0.84 at 6-month follow-up ($p<0.0001$). The results were similar in both Korea and Italy. There were no significant changes in the control group.

95% (38/40) of treated nodules showed shrinkage of more than 50%.

All the patients were euthyroid at baseline, with normal calcitonin levels. Thyroid function did not change after treatment.

Safety

No significant side effects were observed and no patient needed to be hospitalised after the procedure.

After the procedure, no local oedema, pain or other adverse effects were detected.

Abbreviations used: fT4, free thyroxine; RFA, radiofrequency ablation; sd, standard deviation; TSH, thyrotropin

Study 4 Sung JY (2013) – also included in Fuller CW et al. (2014)

Details

Study type	**Randomised controlled trial**
Country	Korea
Recruitment period	2010–11
Study population and number	**n=50 (25 RFA versus 25 ethanol ablation)** Patients with a single benign cystic thyroid nodule
Age and sex	Mean 45 years; 90% (45/50) female
Patient selection criteria	Cystic thyroid nodule (cystic portion >90%); reports of pressure symptoms or cosmetic problems; cytological confirmation of benign findings in at least 2 separate ultrasound-guided fine needle aspiration biopsies; serum levels of thyroid hormone, thyrotropin, and calcitonin within normal limits. Exclusion criteria: nodules showing malignant features at ultrasound; previous treatment for thyroid nodules (including medication) within 6 months before enrolment to study.
Technique	A transisthmic approach was used for both procedures. For RFA, patients were asked to fast for at least 6 hours before the procedure. RFA was done using a generator (Cool-Tip RF system, Radionics, USA) and internally cooled electrodes (Well-Point RF Electrodes, Taewoong Medical, Korea). As much fluid as possible was aspirated from the nodule before ablation. During ablation, the electrode was fixed in the central portion of the cystic nodule. Ethanol ablation: a 16- or 18-gauge needle was inserted into the nodule through an isthmus and as much fluid was aspirated as possible. Ethanol was then slowly injected into the cystic space and removed after 10 minutes.
Follow-up	**6 months**
Conflict of interest/source of funding	One of the authors is a patent holder for a unidirectional ablation electrode but has not yet received any money from the company. The study centre has received a research grant from Dongkook Pharmaceutical and from GE Healthcare.

Analysis

Follow-up issues: Four patients (16%) in each group were lost to follow-up. These patients were excluded from the analysis.

Study design issues: Single-centre, randomised, non-inferiority trial. The method of randomisation is not described. The outcome assessors were blinded to the treatment allocation. The primary end point of the study was the quantitative volume reduction ratio of a thyroid nodule at 6 months after treatment. Secondary end points included the therapeutic success rate, defined as the proportion of patients with >50% reduction in nodule volume, improvement of symptoms and cosmetic problems, and the number of major complications. Symptoms were assessed on a 0–10 cm visual analogue scale, reported by patients. Cosmetic scores were recorded by the physicians (1=no palpable mass, 2=no cosmetic problem but a palpable mass, 3=cosmetic problem on swallowing only, 4=readily detected cosmetic problem at all times). 3 patients (2 in the RFA group and 1 in the ethanol ablation group) had incomplete improvement after their initial treatment and requested additional treatments. These patients were included in the intention-to-treat analysis but not in the per-protocol analysis.

Study population issues: The baseline clinical and demographic parameters were similar between the 2 treatment groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **50 (25 versus 25)**

Baseline demographic data, mean±standard deviation (sd), (range)

	RFA n=25	Ethanol ablation n=25	p value
Nodule diameter (cm)	3.0±1.2 (1.8–6.2)	3.4±1.0 (1.7–5.7)	0.068
Nodule volume (ml)	9.3±11.7 (1.8–54.0)	12.2±11.0 (1.9–39.0)	0.105
Symptom score (scale 0–10)	3.5±2.2 (1–8)	3.4±2.0 (1–8)	0.847
Cosmetic score (scale 1–4)	3.6±0.6 (2–4)	3.6±0.6 (2–4)	0.783

Comparison of clinical characteristics between RFA and ethanol ablation at 6-month follow-up, intention-to-treat analysis, mean±sd

Outcome	RFA n=21	Ethanol ablation n=21	p value
% volume reduction (median)	93.3±5.4 (73.6–98.5)	96.9±4.1 (81.7–100.0)	Not reported
Symptom score (scale 0–10)	0.5±0.8 (0–3)	0.5±0.7 (0–2)	0.806
Cosmetic score (scale 1–4)	1.1±0.4 (1–2)	1.2±0.4 (1–2)	0.682
Therapeutic success (%)	100	100	>0.99

Comparison of clinical characteristics between RFA and ethanol ablation at 6-month follow-up, per-protocol analysis, mean±sd

Outcome	RFA n=19	Ethanol ablation n=20	p value
% volume reduction (median)	93.5±5.3 (73.6–98.5)	97.7±2.2 (92.2–100.0)	Not reported
Symptom score (scale 0–10)	0.4±0.6 (0–2)	0.5±0.6 (0–2)	0.856
Cosmetic score (scale 1–4)	1.1±0.3 (1–2)	1.2±0.4 (1–2)	0.680
Therapeutic success (%)	100	100	>0.99

Safety

There were no major complications.

Abbreviations used: fT4, free thyroxine; RFA, radiofrequency ablation; sd, standard deviation; TSH, thyrotropin

Study 5 Che Y (2015)

Details

Study type	**Non-randomised comparative study**
Country	Korea
Recruitment period	2012–13
Study population and number	**n=400 (200 RFA versus 200 surgery)** Patients with nodular goitre.
Age and sex	Mean 44 years (RFA) versus 52 years (surgery) (p=0.76); 80% (319/400) female
Patient selection criteria	Patients with nodular goitre (diagnosed by surgical pathology in the surgical group and cytologically by 2 preoperative fine-needle aspirates in the RFA group). All the enrolled patients fulfilled the following criteria according to the RFA recommendations of the Korean Society of Thyroid Radiology: cosmetic problem, nodule-related symptoms, hyperfunctioning nodules related to thyrotoxicosis, refusal of surgery (for RFA group).
Technique	Ultrasound-guided RFA was done using a transisthmic approach and a 'moving-shot' technique. An internally cooled RFA system (VIVA RF generator; STARmed, Korea) with an 18-gauge internally cooled electrode (VIVA; STARmed, Korea) was used. Patients were treated by RFA under local anaesthesia. Patients in the surgery group were treated under general anaesthesia; surgery included total thyroidectomy and lobectomy.
Follow-up	**12 months**
Conflict of interest/source of funding	Not reported.

Analysis

Follow-up issues: Patients without complete surgical or follow-up information were excluded from the study.

Study design issues: Retrospective study. There was no randomisation; patients who refused surgery were treated by RFA.

Study population issues: There were no significant differences between the 2 groups before treatment, with regard to age, sex, nodule size and the number of nodules.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **400 (200 versus 200)**

Changes in nodule volume after RFA

Follow-up period	Number of nodules	Mean volume (ml)	% volume reduction*	p value
Baseline	375	5.4±7.1		
1 month	375	3.1±4.4	37.5±43.4	0.030
3 months	301	2.1±3.0	61.3±37.6	0.025
6 months	247	1.2±1.9	74.6±23.3	0.009
12 months	194	0.4±0.7	84.8±17.1	0.002

***** the proportion of residual volume compared with the index nodule volume

Residual rate (defined as a certain part of single or multiple nodules that is not completely inactivated – calculated as the rate of the number of people who had residual goitre divided by the total number):

- RFA=2.9%
- Surgery=11.9%, p=0.004

Recurrence (defined as the regrowth of thyroid tissue after treatment):

- RFA=0.05%
- Surgery=2.5%, p=0.100

Postoperative medication for hypothyroidism:

- RFA=0%
- Surgery=71.5%, p=0.002

In the RFA group, 93% of patients had normal levels of T3, T4 and thyroid-stimulating hormone. 7% of patients had a decreased thyroid-stimulating hormone without an elevation in T3 or T4 while also having no hyperthyroid symptoms. This had spontaneously resolved by the 1-month follow-up.

Mean length of hospital stay (days):

- RFA=2.1±0.9
- Surgery=6.6±1.6, p<0.001

Safety

Complication rate:

- RFA=1%
- Surgery=6%, p=0.002

Complications observed after RFA and surgery – number of patients (%)

Complication	RFA n=200	Surgery n=200
Transient hoarseness	1 (0.5)	3 (1.5)
Permanent hoarseness	0 (0)	2 (1.0)
Transient hypoparathyroidism	0 (0)	6 (3.0)
Haematoma	0 (0)	1 (0.5)
Nodule rupture	1 (0.5)	0 (0)
Total	2 (1.0)	12 (6.0)

Abbreviations used: RFA, radiofrequency ablation

Study 6 Lim HK (2013)

Details

Study type	**Case series**
Country	Korea
Recruitment period	2002–07
Study population and number	n=**111 patients (126 nodules)** Patients with benign non-functioning thyroid nodules (45 nodules had ≤50% solidity and 81 had >50% solidity).
Age and sex	Mean 38 years; 84% (101/121) female
Patient selection criteria	Reported cosmetic or symptomatic problems; largest diameter of nodule greater than 2 cm; cytologically confirmed benign nodule on 2 separate ultrasound-guided fine-needle aspirate biopsies; ultrasound imaging finding without suspicious malignant features; serum thyroid hormone and thyrotropin levels within normal ranges; refusal or ineligible for surgery.
Technique	RFA was done using an RF generator (Cool-Tip RF system, Covidien; SSP-2000, Taewoong Medical) and a 17- or 18-gauge internally cooled electrode. Local anaesthesia was used, with a transisthmic approach and a 'moving shot' technique. The mean number of treatment sessions was 2.2.
Follow-up	**Mean 49.4±13.6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: A total of 505 patients were treated at the study centre during the study period. Only patients who were followed up for more than 3 years were enrolled into the study.

Study design issues: Retrospective, single centre study. Patients were asked to rate pressure symptoms on a 10 cm visual analogue scale (0–10 cm) and cosmetic grading was assessed by the physician. Additional treatment was allowed if follow-up ultrasound showed a remaining viable portion of the nodule or if a patient complained of incompletely resolved clinical problems.

Other issues: The authors noted that 91 of the 111 patients in this study were also included in previous published studies. Although this particular study was not included in the meta-analysis by Fuller et al. (2014), it is likely that there is some patient overlap with other studies that were included in the systematic review.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 111

Nodule characteristics at baseline and at last follow-up after RFA treatment, mean±sd (range) or number of nodules
<table>
<tr><th>Characteristic</th><th>Baseline</th><th>Last follow-up</th><th>p value</th></tr>
<tr><td>Largest diameter (cm)</td><td>3.3±1.0 (2–6)</td><td>1.1±0.8</td><td><0.001</td></tr>
<tr><td>Volume (ml)</td><td>9.8±8.5 (2–43)</td><td>0.9±3.3</td><td><0.001</td></tr>
<tr><td>Vascularity</td><td>1.7±0.7 (1–4)</td><td>1.1±0.4</td><td><0.001</td></tr>
<tr><td>Cosmetic score</td><td>3.2±0.8 (1–4)</td><td>1.3±0.6</td><td><0.001</td></tr>
<tr><td>Symptom score</td><td>4.3±1.6 (0–10)</td><td>0.8±0.9</td><td><0.001</td></tr>
</table>
Mean volume reduction, ±sd (range) by follow-up:
• 6 months=70.3±17.2% (30–98%)
• 1 year=89.9±10.2% (51–100%)
• 2 years=90.1±10.1% (51–100%)
• 3 years=90.7±15.8% (17–100%)
• Last follow-up=93.5±11.7% (17–100%)

At last follow-up, the therapeutic success rate was 98.4% (124/126) and the complete disappearance rate was 18.3% (28/126).

The mean volume reduction was greater for nodules of ≤50% solidity than those of >50% solidity (96.0% versus 92% at last follow-up, p=0.002).

Larger nodules needed more treatment sessions than smaller nodules to achieve similar reductions in volume.

Overall recurrence rate (defined as increases in nodule volume >50% compared with previous ultrasound images)=5.6% (7/126). All nodules were benign on repeat fine-needle aspirate biopsy. Four of the recurrent nodules decreased in size after repeat RFA, 2 were treated with repeat RFA without further follow-up and 1 patient chose not to receive further treatment and was lost to follow-up.

At the last follow-up, no nodule was larger than its initial size.</td><td>Overall complication rate=3.6% (4/111)

Major complications
• Voice change, n=1
• Brachial plexus injury, n=1

Minor complications
• Haematoma, n=1
• Vomiting, n=1

In addition, 2 patients had local pain.

All of these patients recovered without sequelae. No patient experienced a life-threatening or delayed complication during follow-up.</td></tr>
<tr><td colspan="2">Abbreviations used: RFA, radiofrequency ablation; sd, standard deviation</td></tr>
</table>

Study 7 Baek JH (2012)

Details

Study type	Case series (retrospective)
Country	Korea (13 centres)
Recruitment period	2002–09
Study population and number	**n=1459 patients (1543 nodules)** Patients with benign thyroid nodules.
Age and sex	Mean 41 years; 87% (1269/1459) female
Patient selection criteria	Pressure symptoms or cosmetic problems; benign nodules greater than 2 cm in diameter, as confirmed at 2 ultrasound-guided fine needle aspirations and no malignant ultrasound findings according to the guidelines of the Korean Society of Thyroid Radiology; serum thyroid hormone levels within normal limits; refusal of or ineligible for surgery.
Technique	RFA was done with a radiofrequency generator (Cool-Tip, Covidien, USA; SSP-2000, Taewoong Medical, Korea) and an internally cooled electrode (Cool-Tip, Well-Point, and Big-Tip). All procedures were done with percutaneous ultrasound guidance and the electrode was placed using a transisthmic approach. A 'moving shot' technique was used. The total number of treatment sessions was 2197.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: The total number of patients who were lost to follow-up is not stated.

Study design issues: Questionnaires were sent to each enrolled hospital to assess the total number of patients who had radiofrequency ablation and the number and type of complications. A major complication was defined as life-threatening (if left untreated), leading to substantial morbidity or disability or resulting in a lengthened hospital stay. All other complications were considered to be minor. Side effects were defined as 'untoward consequences that did not require therapy or prescription medications'.

Study population issues: The mean largest diameter of the treated nodule was 3.8±1.4 cm (range 2–20 cm).

Other issues: This study is cited in the Fuller et al. (2014) systematic review but it is not included in the analysis. However, other studies with the same authorship are included. There is likely to be considerable overlap in patients between this case series and the systematic review.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 1459

The study was designed to assess the number and type of complications: no efficacy data were reported.</td><td>Total complication rate=3.3% (48/1459)
Major complications (n=20)
<table>
<tr><th>Complication</th><th>No. (%)</th><th>Time of detection (days)</th><th>Time to recovery (days)</th><th>Further details</th></tr>
<tr><td>Voice change</td><td>15 (1.02)</td><td>1–2</td><td>1–90</td><td>All patients recovered completely, except for 2 who were lost to follow-up.</td></tr>
<tr><td>Nodule rupture</td><td>2 (0.14)</td><td>22–30</td><td><30</td><td>Symptoms included sudden neck bulging and pain: 1 patient recovered without treatment, 1 patient was admitted to hospital and treated with antibiotics and analgesics.</td></tr>
<tr><td>Nodule rupture with abscess formation*</td><td>1 (0.07)</td><td>50</td><td>None</td><td>The patient was treated by left thyroidectomy because of nodule rupture.</td></tr>
<tr><td>Permanent Hypothyroidism*</td><td>1 (0.07)</td><td>180</td><td>None</td><td>The patient had gradual neck bulging, ultrasound showed diffuse enlargement of the thyroid gland without a thyroid nodule.</td></tr>
<tr><td>Brachial plexus injury</td><td>1 (0.07)</td><td>1</td><td>60</td><td>The patient had numbness and decreased sensation in the fourth and fifth fingers of her left hand; she gradually recovered during the next 2 months.</td></tr>
</table>
* complications with remaining sequelae.
Minor complications (n=28)
<table>
<tr><th>Complication</th><th>No. (%)</th><th>Time of detection (days)</th><th>Time to recovery (days)</th><th>Further details</th></tr>
<tr><td>Haematoma</td><td>15 (1.02)</td><td>1</td><td><30</td><td>Located in the perithyroidal, supcapsular, and intranodular locations and caused by mechanical injury due to the electrode. Most haematomas completely disappeared within 1–2 weeks.</td></tr>
<tr><td>Vomiting</td><td>9 (0.62)</td><td>1–2</td><td>1–2</td><td>Treatment with anti-emetics resulted in improvement within 1–2 days.</td></tr>
<tr><td>Skin burn</td><td>4 (0.27)</td><td>1</td><td><7</td><td>All were at the puncture sites and were first-degree burns. All patients recovered from pain and skin colour changes within 7 days without sequelae.</td></tr>
</table>
Side effects (n=46)
<table>
<tr><th>Complication</th><th>No. (%)</th><th>Time of detection (days)</th><th>Time to recovery (days)</th><th>Further details</th></tr>
<tr><td>Pain</td><td>38 (2.6)</td><td>1</td><td>1–2</td><td>Excludes patients with tolerable pain immediately after the procedure.</td></tr>
<tr><td>Vasovagal reaction</td><td>5 (0.34)</td><td>1</td><td>1</td><td>Included sweating, difficulty breathing and hesitation. Treated by elevation of the patient’s legs and stopping the ablation.</td></tr>
<tr><td>Mild fever (up to 38°C)</td><td>4 (0.27)</td><td>Not reported</td><td>Not reported</td><td>-</td></tr>
<tr><td>Coughing</td><td>3 (0.21)</td><td>1</td><td>1</td><td>Treated by stopping the ablation.</td></tr>
</table></td></tr>
</table>

Study 8 Valcavi R (2015)

Details

Study type	**Case series (retrospective)**
Country	Italy
Recruitment period	2012–14
Study population and number	**n=40 patients** Patients with benign thyroid nodules (cold solitary nodules or a dominant nodule within a normofunctioning multinodular goitre).
Age and sex	Mean 55 years (range 18–84); 88% (35/40) female
Patient selection criteria	Single nodule or a dominant, well-circumscribed nodule within a multinodular goitre; solid nodule or mixed nodule with a fluid component <20% of the total volume; nodule size 5–90 ml; cold nodule on technetium 99m scintigraphy scan; normal thyroid-stimulating hormone (TSH) levels; normal free thyroxine and free triiodothyronine levels; anti-TSH-receptor antibody negative; benign cytology at least 2 times on 2 to 3 nodule areas at each fine needle aspiration, the second cytology done <6 months before radiofrequency ablation (RFA); normal calcitonin levels; absence of ultrasound features suggesting malignancy; absence of family history of thyroid cancer; no history of previous radiation neck therapy; normal platelet count and blood coagulation tests; no repeat RFA sessions; 2-year follow-up. The patients had refused surgery or had poor surgical indications because of previous thyroid surgery, age, or cardiovascular risk.
Technique	A VIVA RF generator and star RF electrodes (STARmed, Republic of Korea) were used, with a transisthmic approach and a 'moving shot' technique. Conscious sedation and local anaesthesia were used. All patients received methylprednisolone immediately after the procedure and for the subsequent 12 days. Oral proton pump inhibitors were given for 12 days after the procedure. All patients had a single session of RFA.
Follow-up	**2 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: All patients were followed up for 2 years.

Study design issues: Retrospective, single centre study. Health related quality of life was assessed using the SF-12 Health Survey, which covers 8 health domains: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Higher scores indicate better health status. The results were summarised as a physical component summary (PCS-12) and a mental component summary (MCS-12). Compressive symptoms and cosmetic signs were evaluated on a 0–10 cm visual analogue scale completed by the patients. Pain was measured on a 0–10 cm visual analogue scale 2 hours after the procedure. A score of >5 was considered to be intense pain.

Other issues: The files of 225 patients treated by RFA at the study centre were reviewed and 40 patients met the inclusion criteria.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **40**

Nodule volume, health related quality of life, symptom score, and cosmetic score after radiofrequency ablation (mean±sd)

	Follow-up			
	Baseline	**6 months**	**1 year**	**2 years**
Nodule volume (ml)	30.0±18.2	15.5±14.7*	11.2±11.8*	7.9±9.8*
Volume change (%)		−55.1±18.5*	−67.7±17.3*	−80.1±16.1*
SF-12 PCS	50.4±8.9		54.6±5.2*	54.5±5.3*
SF-12 MCS	36.0±13.3		49.7±7.0*	50.3±6.3*
Symptom score (VAS, 0–10)	5.6±3.1		2.1±1.3*	1.9±1.3*
Cosmetic score (VAS, 0–10)	5.7±3.2		2.0±1.7*	1.9±1.5*

*p<0.0001

Serum thyroid stimulating hormone, free triiodothyronine, and free thyroxine levels remained stable during follow-up.

2 patients became anti-thyroglobulin antibody-positive during follow-up.

Safety

Complications and side effects

	n (%)
Intraoperative	
Intense pain (VAS>5) (local or radiating to the jaw, teeth, chest or back)	7 (17.5)
Intranodular bleeding (blocked by swift needle-electrode insertion and heat administration)	3 (7.5)
Pericapsular bleeding (asymptomatic other than extensive neck bruising 5–10 days later)	1 (2.5)
Vasovagal reaction (bradycardia, hypotension, vomiting and defecation–the bed was tilted and ablation was stopped; the patient recovered within a few minutes and had a subsequent RFA session 3 weeks later.)	1 (2.5)
Cough	2 (5.0)
Immediate postoperative period (within 24 hours)	
Swelling (lasting 4–7 days)	4 (10.0)
Periprocedural (within 30 days)	
Bruise	1 (2.5)
Fever (38.5°C) – no treatment needed	1 (2.5)
Pseudocystic transformation – the patient had a painful sudden swelling 3 weeks after RFA; treated with oral corticosteroids.	1 (2.5)
Nodule rupture – 26 days after RFA; treated with anti-inflammatory medication.	1 (2.5)

When patients reported intense pain, the radiofrequency generator was turned off, the electrode needle was repositioned in a more central area of the nodule and ablation was completed.

Abbreviations used: RFA, radiofrequency ablation; sd, standard deviation

Study 9 Baek JH (2015)

Details

Study type	**Randomised controlled trial**
Country	Korea
Recruitment period	2013
Study population and number	**n=50 patients (25 radiofrequency ablation versus 25 ethanol ablation)** Patients with predominantly cystic benign thyroid nodules.
Age and sex	Mean 50 years (range 23–82); 74% (37/50) female
Patient selection criteria	Predominantly cystic thyroid nodules (proportion of cystic component, less than 90% and greater than 50% of the nodule); reports of pressure symptoms or cosmetic problems caused by thyroid nodules; benign cytological confirmation in at least 2 separate ultrasound-guided fine-needle aspiration or core needle biopsies; normal serum levels of thyroid hormone, thyrotropin, and calcitonin. Exclusion criteria: nodules showing malignant features on ultrasound, lack of informed consent, younger than 20 years old, pregnant women.
Technique	A VIVA RF generator (STARmed, Republic of Korea) was used, with a 'moving shot' technique. All procedures were done in an outpatient setting.
Follow-up	**6 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 4 patients were lost to follow-up (1 assigned to ethanol ablation and 3 assigned to radiofrequency ablation).

Study design issues: Single-blind (outcome assessor blinded) randomised trial. Method of randomisation was not described. The primary outcome was the tumour volume reduction ratio at 6-month follow-up. The clinically relevant difference in the primary outcome was set at 13%, corresponding to an estimated mean volume reduction ratio of 80% and 67% for radiofrequency and ethanol ablation respectively. An intention-to-treat and per-protocol analysis was done. Symptoms were rated by patients on a 10-cm visual analogue scale. Cosmetic scores were recorded by the physician (1=no palpable mass, 2=no cosmetic problem but a palpable mass, 3=cosmetic problem on swallowing only, 4=cosmetic problem at all times). The therapeutic success rate was defined as the proportion of patients with volume reduction greater than 50%.

Population issues: The mean tumour diameter and volume were significantly larger in the ethanol ablation group. The symptom score was statistically significantly lower for patients in the radiofrequency ablation group (2.9 versus 4.0, p=0.02).

Other issues: 1 patient refused radiofrequency ablation and had to be enrolled in the ethanol ablation group.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **50 (25 versus 25)**

Outcomes of radiofrequency ablation and ethanol ablation at 6-month follow-up (intention-to-treat analysis)

Outcome	Radiofrequency ablation	Ethanol ablation	p value
Volume reduction (%)	87.5±11.5 (63.1–99.5)	82.4±28.6 (-35.7–99.2)	0.710
Symptom score	0.2±0.4 (0–1)	0.7±1.3 (1–4)	0.205
Cosmetic score	1.5±0.5 (1–2)	1.7±1.0 (1–4)	0.710
Therapeutic success	100 (22/22)	91.7 (22/24)	0.490

means±standard deviations (with ranges)

Outcomes of radiofrequency ablation and ethanol ablation at 6-month follow-up (per-protocol analysis)

Outcome	Radiofrequency ablation	Ethanol ablation	p value
Volume reduction (%)	87.1±11.6 (63.1–99.5)	83.1±28.7 (-35.7–99.2)	0.904
Symptom score	0.2±0.4 (0–1)	0.7±1.3 (0–6)	0.280
Cosmetic score	1.5±0.5 (1–2)	1.6±0.9 (1–4)	0.901
Therapeutic success	100 (21/21)	92 (23/25)	0.493

means±standard deviations (with ranges)

Safety

Major complications:

- Radiofrequency ablation=0% (0/22)
- Ethanol ablation=4.2% (1/24)

1 patient complained of a voice change immediately after ethanol ablation but the issue was resolved by the 2-month follow-up without treatment.

Patients in the radiofrequency ablation group had a greater tendency to experience pain during and after the procedure.

Abbreviations used: RFA, radiofrequency ablation; sd, standard deviation

Study 10 Bernardi S (2016)

Details

Study type	**Case report**
Country	Italy
Recruitment period	Not reported
Study population and number	**n=1** Patient with a benign thyroid nodule.
Age and sex	34-year old woman
Patient selection criteria	Not applicable
Technique	The procedure was done under conscious sedation and local anaesthesia. A RF AMICA_PROBE monopolar electrode was inserted into the thyroid nodule under ultrasound guidance. It was inserted directly from above instead of using a transisthmic approach.
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Key efficacy and safety findings

Case report: Full-thickness skin burn

During the procedure, the active needle tip must have come into close proximity to the skin with the power delivery possibly not switched off. The lesion was noticed by the operator and the procedure was stopped, leaving most of the nodule untreated. The lesion appeared as a full-thickness burn that surrounded the electrode puncture site, with a maximum diameter of 1.5 cm and a charred white necrotic core. Treatment involved topical gentamicin sulphate and hyaluronic acid for the first week, followed by an activated charcoal cloth with silver for a week. The wound was surgically debrided and then treated with a collagen wound dressing for another 2 weeks. After more than 1 month, the final appearance looked almost like the normal skin.

Efficacy

Nodule volume

A systematic review of 284 patients with benign thyroid nodules reported a reduction in the mean nodule volume of 9.8 ml (95% CI −13.83 to −5.72; 9 studies, n=284 nodules; I^2=98%) after radiofrequency ablation (RFA)[1]. A randomised controlled trial (RCT) of 84 patients with benign solid thyroid nodules reported that the mean thyroid nodule volume reduced from 24.5±19.6 ml at baseline to 8.6±9.5 ml at 6-month follow-up (p<0.001) in patients treated by RFA compared with no volume reduction in the group of patients randomised to no treatment (27.5±22.1 ml at baseline and 27.8±22.1 ml at 6-month follow-up)[2]. An RCT of 80 patients with solid, compressive, non-functioning benign thyroid nodules treated by RFA or no treatment reported a median percentage volume reduction of 71% and −3% respectively (p=0.0001)[3]. A non-randomised comparative study of 400 patients with nodular goitre treated by RFA or surgery reported a mean percentage volume reduction of 85% after RFA at 12-month follow-up (p=0.002)[5]. A case series of 111 patients with benign, non-functioning thyroid nodules reported a mean volume reduction of 91% after RFA at 3-year follow-up[6]. An RCT of 50 patients with a single benign cystic thyroid nodule treated by RFA or ethanol ablation (also included in the systematic review) reported a median percentage volume reduction of 93% and 97% respectively (p value not reported)[4]. A second RCT of 50 patients with predominantly cystic thyroid nodules treated by RFA or ethanol ablation reported mean volume reductions of 87.5% and 82.4% respectively (p=0.710)[9].

Pressure symptoms

The systematic review of 284 patients with benign thyroid nodules reported a reduction in the mean symptom score (measured on a 10-point visual analogue scale) of 2.89 (95% CI −2.51 to −3.28; 4 studies [‘cold’ nodules only], n=85; I^2=56%) after radiofrequency ablation (RFA)[1]. The RCT of 84 patients with benign solid thyroid nodules reported that the mean pressure symptom score (measured on a 10-point visual analogue scale) reduced from 2.8 at baseline to 0.4 at 6-month follow-up (p<0.001) in patients treated by RFA compared with no reduction in the group of patients randomised to no treatment (2.7 at baseline and 2.9 at 6-month follow-up)[2]. The RCT of 80 patients with solid, compressive, non-functioning benign thyroid nodules treated by RFA or no treatment reported symptom scores (on a scale of 0–10) of 0.4 and 3.3 respectively (p=0.0001) at 6-month follow-up[3]. The case series of 111 patients with benign, non-functioning thyroid nodules reported that the symptom score (scale 0–10) reduced from 4.3 at baseline to 0.8 at last follow-up (mean follow-up 49 months, p<0.001)[6]. The RCT of 50 patients with a single benign cystic thyroid nodule treated by RFA or ethanol ablation (also included in the systematic review) reported symptom scores (scale 0–10) of 0.4 and 0.5 respectively at 6-month follow-up (p=0.856)[4].

Cosmesis

The systematic review of 284 patients with benign thyroid nodules reported a reduction in the mean cosmetic score (scored by a physician from 1–4) of 2.02 (95% CI −1.69 to −2.35; 5 studies ['cold' nodules only], n=114; I^2=78%) after radiofrequency ablation (RFA)[1]. The RCT of 84 patients with benign solid thyroid nodules reported that the mean cosmetic score (scale 1–4, lower scores better) reduced from 2.6 at baseline to 1.7 at 6-month follow-up (p<0.001) in patients treated by RFA compared with no reduction in the group of patients randomised to no treatment (2.6 at baseline and at 6-month follow-up)[2]. The RCT of 80 patients with solid, compressive, non-functioning benign thyroid nodules treated by RFA or no treatment reported cosmetic scores (on a scale of 1–4) of 1.7 and 3.5 respectively (p=0.0001) at 6-month follow-up[3]. The case series of 111 patients with benign, non-functioning thyroid nodules reported that the cosmetic score (scale 1–4) reduced from 3.2 at baseline to 1.3 at last follow-up (mean follow-up 49 months, p<0.001)[6]. The RCT of 50 patients with a single benign cystic thyroid nodule treated by RFA or ethanol ablation (also included in the systematic review) reported cosmetic scores (scale 1–4) of 1.1 and 1.2 respectively at 6-month follow-up (p=0.680)[4].

Postoperative medication

The systematic review of 284 patients with benign thyroid nodules reported that 60 patients with 'hot' nodules were given methimazole at doses sufficient to maintain thyroid-stimulating hormone within the normal range before RFA treatment. After RFA treatment, 29 patients continued to need some dose of this medication to maintain euthyroidism based on thyroid-stimulating hormone measurements and symptoms (odds ratio 40.34, 95% CI 7.78 to 209.1; 3 studies, n=60; I^2=2%). The non-randomised comparative study of 400 patients with nodular goitre treated by RFA or surgery reported that no patients treated by RFA needed medication for hypothyroidism compared with 71.5% of patients treated by surgery (p=0.002)[5].

Recurrence

The case series of 111 patients reported an overall recurrence rate (defined as increases in nodule volume >50% compared with previous ultrasound images) of 6% (7/126). All nodules were benign on repeat fine-needle aspirate biopsy. Four of the recurrent nodules decreased in size after repeat RFA, 2 were treated with repeat RFA without further follow-up and 1 patient chose not to receive further treatment and was lost to follow-up.

Safety

Nodule rupture

Nodule rupture was reported in 1 patient treated by RFA in a non-randomised study of 400 patients[5]. Nodule rupture was reported in <1% (2/1459) of patients in a case series of 1459 patients: 1 patient recovered without treatment and 1 patient was admitted to hospital and treated with antibiotics and analgesics[7]. In the same study, 1 patient had nodule rupture with abscess formation: the patient was treated by left thyroidectomy. Nodule rupture was reported in 1 patient in a case series of 40 patients: this occurred 26 days after RFA and was treated with anti-inflammatory medication[8].

Vocal fold palsy and voice change

Vocal fold palsy was reported in 1 patient in a systematic review of 284 patients. This was diagnosed at the 1-month follow-up but the patient was subsequently lost to follow-up[1]. Permanent vocal cord palsy with inspiratory stridor without dysphonia was reported in 1 patient treated by RFA in an RCT of 84 patients[2].

Voice change immediately after the procedure was reported in 5% (2/42) of patients treated by RFA in the RCT of 84 patients; this resolved completely within 3 hours of the procedure[2]. Transient hoarseness was reported in 0.5% (1/200) of patients treated by RFA and 1.5% (3/200) of patients treated by surgery in a non-randomised comparative study[5]. Voice change was reported in 1% (15/1459) of patients in the case series of 1459 patients; all patients recovered completely, except for 2 who were lost to follow-up[7].

Brachial plexus injury

Brachial plexus injury was reported in 1 patient in the case series of 1459 patients[7]. The patient had numbness and decreased sensation in the fourth and fifth fingers of her left hand; she gradually recovered during the next 2 months.

Haemorrhage/haematoma

Diffuse glandular haemorrhage was reported in 1 patient in a systematic review of 284 patients. This resulted in interruption of the procedure. The patient was given oral analgesics for pain relief for 3 days[1]. Intranodular bleeding was reported in 8% (3/40) of patients in the case series of 40 patients: this was stopped by swift needle-electrode insertion and heat administration[8]. In the same study, pericapsular bleeding was reported in 1 patient, who had extensive neck bruising 5–10 days after the procedure. Haematoma was reported in 1 patient in the systematic review of 284 patients[1]. Haematoma was reported in 1% (15/1459) of patients in the case series of 1459 patients: most completely disappeared within 1–2 weeks[7].

Oedema

Postoperative oedema was reported in 1% (3/284) of patients in the systematic review of 284 patients. This was treated with betamethasone medication[1].

Burn

A full-thickness burn was described in a case report[10]. The burn took more than 1 month to heal but its final appearance looked almost like the normal skin. First-degree skin burns at the puncture sites were reported in <1% (4/1459) of patients in the case series of 1459 patients: all patients recovered from pain and skin colour changes within 7 days without sequelae[7].

Pain

Local pain was reported in 21% (8/42) of patients treated by RFA in an RCT of 84 patients[2]. The pain was described as limited and resolved quickly after the power was switched off. The procedure was stopped in 1 patient because of severe chest pain. Intense pain (visual analogue score >5) that was local or radiated to the jaw, teeth, chest or back was reported in 18% (7/40) of patients in a case series of 40 patients[8]. Pain (other than tolerable pain immediately after the procedure) was reported in 3% (38/1459) of patients in the case series of 1459 patients; this resolved within 1–2 days[7].

Vomiting

Vomiting was reported in <1% (9/1459) of patients in the case series of 1459 patients: this improved within 1–2 days after treatment with anti-emetics[7].

Vasovagal reaction

Vasovagal reaction was reported in <1% of patients in the case series of 1459 patients. This included sweating, difficulty breathing and hesitation; it was treated by elevation of the patient's legs and stopping the ablation[7]. Vasovagal reaction was reported in 1 patient in the case series of 40 patients. The patient had bradycardia, hypotension, vomiting and defaecation – the bed was tilted and ablation was stopped; the patient recovered within a few minutes and had a subsequent RFA session 3 weeks later[8].

Pseudocystic transformation

Pseudocystic transformation was reported in 1 patient in the case series of 40 patients: the patient had a painful sudden swelling 3 weeks after RFA, which was treated with oral corticosteroids[8].

Permanent hypothyroidism

Permanent hypothyroidism was reported in 1 patient in the case series of 1459 patients: the patient had gradual neck bulging and ultrasound showed diffuse enlargement of the thyroid gland without a thyroid nodule.

Validity and generalisability of the studies

- Most of the studies were reported from Korea or Italy.
- There is likely to be some patient overlap between the studies.
- The patient population was heterogenous; some studies only included solid nodules, some included cystic nodules and there was also variation with regard to whether the nodules were 'cold' or 'hot'.
- One of the RCTs compared RFA with ethanol ablation, whereas the other 2 compared it with no treatment.

Existing assessments of this procedure

A Cochrane review of 'Levothyroxine or minimally invasive therapies for benign thyroid nodules' was published in 2014. Two studies on radiofrequency ablation were included. The review concluded that:

'No study evaluated all-cause mortality, health-related quality of life or provided systematic data on the development of thyroid cancer. Longest follow-up was five years and median follow-up was 12 months. Nodule volume reductions were achieved by PEI [percutaneous ethanol injection], LP [laser photocoagulation] and RF [radiofrequency], and to a lesser extent, by LT4 [levothyroxine]. However, the clinical relevance of this outcome measure is doubtful. PEI, LP and RF led to improvements in pressure symptoms and cosmetic complaints. Adverse events such as light-to-moderate periprocedural pain were seen after PEI, LP and RF. Future studies should focus on patient-important outcome measures, especially health-related quality of life, and compare minimally invasive procedures with surgery. RCTs with follow-up periods of several years and good-quality observational studies are needed to provide evidence on the development of thyroid cancer, all-cause mortality and long-term adverse events.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Minimally invasive video-assisted thyroidectomy. NICE interventional procedure guidance 499 (2014). Available from http://www.nice.org.uk/guidance/ipg499

- Intraoperative nerve monitoring during thyroid surgery. NICE interventional procedure guidance 255 (2008). Available from http://www.nice.org.uk/guidance/ipg255

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 ultrasound-guided percutaneous radiofrequency ablation for thyroid nodules were submitted and can be found on the NICE website.

Patient commentators' opinions

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

Issues for consideration by IPAC

None other than those described above.

References

1. Fuller CW, Nguyen SA, Lohia S et al. (2014) Radiofrequency ablation for treatment of benign thyroid nodules: systematic review. Laryngoscope 124: 346-353
2. Cesareo R, Pasqualini V, Simeoni C et al. (2015) Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules. Journal of Clinical Endocrinology & Metabolism 100: 460-466
3. Deandrea M, Sung JY, Limone P et al. (2015) Efficacy and Safety of Radiofrequency Ablation Versus Observation for Nonfunctioning Benign Thyroid Nodules: A Randomized Controlled International Collaborative Trial. Thyroid 25: 890-896
4. Sung JY, Baek JH, Kim KS et al. (2013) Single-session treatment of benign cystic thyroid nodules with ethanol versus radiofrequency ablation: a prospective randomized study. Radiology 269: 293-300
5. Che Y, Jin S, Shi C et al. (2015) Treatment of Benign Thyroid Nodules: Comparison of Surgery with Radiofrequency Ablation. American Journal of Neuroradiology 36: 1321-1325
6. Lim HK, Lee JH, Ha EJ et al. (2013) Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. European Radiology 23: 1044-1049
7. Baek JH, Lee JH, Sung JY et al. (2012) Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology 262: 335-342
8. Valcavi R, Tsamatropoulos P (2015) Health-related quality of life after percutaneous radiofrequency ablation of cold, solid, benign thyroid nodules: A 2-year follow-up study in 40 patients. Endocrine Practice 21: 887-896
9. Baek JH, Ha EJ, Choi YJ et al. (2015) Radiofrequency versus ethanol ablation for treating predominantly cystic thyroid nodules: a randomized clinical trial. Korean Journal of Radiology 16: 1332–40
10. Bernardi S, Lanzilotti V, Papa G et al. (2016) Full-thickness skin burn caused by radiofrequency ablation of a benign thyroid nodule. Thyroid 26: 183–4

Appendix A: Additional papers on ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules

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
Baek JH, Moon WJ, Kim YS et al. (2009) Radiofrequency ablation for the treatment of autonomously functioning thyroid nodules. World Journal of Surgery 33: 1971-1977	**Autonomously functioning thyroid nodules** Case series n=9 FU=6 months	After ablation, four patients became a cold or normal scan and five remained as a hot nodule. The mean symptom and cosmetic grading score was reduced from 2.4 +/- 1.7 to 0.6 +/- 0.7 (p = 0.011) and from 3.1 +/- 1.2 to 1.4 +/- 1.0 (p = 0.017), respectively. No major complications were encountered.	Small case series.
Baek JH, Kim YS, Lee D et al. (2010) Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. American Journal of Roentgenology 1137-1142	**Benign, solid or predominantly solid, nodules** RCT n=30 (15 RFA vs 15 observation) FU=6 months	The control group had no resolution of symptoms or cosmetic problems. The mean nodule volume increased slightly after 6 months but without statistical significance (p=0.46). In the RFA group, the mean symptom score and cosmetic grade (p = 0.001) improved significantly (p=0.001 for both). Mean nodule volume decreased significantly from 7.5 +/- 4.9 ml to 1.3 +/- 0.8 ml at 6 month follow-up (p=0.001). There were no major complications of ablation.	Included in Fuller CW (2014) systematic review.
Bernardi S, Dobrinja C, Fabris B et al. (2014) Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. International Journal of Endocrinology 934595-2014.	**Benign nodules** Non-randomised comparative study n=111 FU=12 months	RFA reduced nodular volume by 70% after 12 months and it was an effective method for treating nodule-related clinical problems, but it was not as effective as surgery for the treatment of hot nodules. RFA and surgery were both safe, although RFA had less complications and pain was rare. RFA, however, did not allow for any pathologic analysis of the nodules, which, in 6 patients who had undergone surgery (8%), revealed that the nodules harboured malignant cells.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Deandrea M (2008) US-Guided Percutaneous Radiofrequency Thermal Ablation for the Treatment of Solid Benign Hyperfunctioning or Compressive Thyroid Nodules. Ultrasound in medicine & biology. 34: 784-791	**Benign solid nodules** n=31 FU=6 months	Improvement in compressive symptoms was reported in 42% (13/31) of patients, with reduction in severity from 6.1 to 2.2 ($p<0.0001$). Volume significantly decreased during follow-up. Hyperfunction was fully controlled in 24% of patients and partially reduced in the others.	Included in Fuller CW (2014) systematic review.
Dobrinja C, Bernardi S, Fabris B et al. (2015) Surgical and Pathological Changes after Radiofrequency Ablation of Thyroid Nodules. International Journal of Endocrinology 576576-2015.	**Benign nodules and follicular lesions/neoplasms** Case series n=64	RFA is effective for the treatment of Thy2 (benign) nodules, but it should not be recommended as first-line therapy for the treatment of Thy3 (follicular lesions/neoplasms) nodules (irrespective of their mutational status), as it delays surgery in case of malignancy. Moreover, it is unknown whether RFA might promote residual tumour progression or neoplastic progression of Thy3 lesions. Nevertheless, here we show for the first time that one session of RFA does not affect subsequent thyroid surgery and/or histological diagnosis.	Small case series.
Faggiano A, Ramundo V, Assanti AP et al. (2012) Thyroid nodules treated with percutaneous radiofrequency thermal ablation: a comparative study. Journal of Clinical Endocrinology & Metabolism 97: 4439-4445	**Benign, solid or predominantly solid, nodules** RCT n=40 (10 RFA vs 20 observation) FU=12 months	Thyroid nodule volume significantly decreased in RFA group (1.8 +/- 0.3 ml at 12 months vs 13.3 +/- 1.8 ml at baseline; $p<0.0001$) and remained stable in control group (11.7 +/- 1.5 ml at 12 months vs 11.2 +/- 1.5 ml at baseline; p=not significant (NS). At 3-, 6-, and 12-months, thyroid nodule volume was significantly lower in RFA group than in control group ($p<0.005$). At the end of the follow-up, pressure symptoms were improved in all patients in RFA group but persisted unchanged in control group. In RFA group, hyperthyroidism completely recovered in 40% and improved in 40% of patients with toxic nodules, whereas it persisted in all patients with toxic nodules in the control group. RFA was safe and well tolerated in all patients.	Included in Fuller CW (2014) systematic review.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ha EJ, Baek JH, Kim KW et al. (2015) Comparative efficacy of radiofrequency and laser ablation for the treatment of benign thyroid nodules: systematic review including traditional pooling and bayesian network meta-analysis. Journal of Clinical Endocrinology & Metabolism 100 (5) 1903-1911	**Systematic review n=184 (65 RFA)**	Based on the traditional frequentist approach, the pooled percentage mean changes (95% confidence interval) of RFA and laser ablation (LA) were 76% (70-82) and 50% (41-59), respectively, and the pooled absolute mean changes (95% confidence interval) were 8.9 mL (6.6-11.2) and 5.2 ml (4.3-6.1), respectively. Based on the Bayesian network meta-analysis, RFA achieved a larger pooled percentage mean change (95% credible interval) and absolute mean change (95% credible interval) compared to LA [77.8% (67.7-88.0) vs 49.5% (26.7-72.4), and 9.2 ml (5.8-11.9) vs 5.3 ml (2.1-8.5), respectively]. The RFA group has the highest probability of having the most efficacious treatment (99%). There were no major complications.	The review includes 1 RCT comparing 1 RFA session against 2 RFA sessions, and 2 RCTs comparing RFA against observation: these were all included in the Fuller CW (2014) systematic review.
Ha EJ, Baek JH, Lee JH et al. (2013) Radiofrequency ablation of benign thyroid nodules does not affect thyroid function in patients with previous lobectomy. Thyroid 23: 289-293	**Benign, predominantly solid nodules** Case series n=11 FU=44 months	Mean volume reduction=87%. The mean symptom score (p=0.003) and cosmetic score (p=0.003) were both significantly decreased at the last follow-up. Levels of TSH, free thyroxine, and triiodothyronine were not significantly different prior to treatment and at the last follow-up (p>0.05), and remained normal in all patients.	Small case series.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Huh JY, Baek JH, Choi H et al. (2012) Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session--prospective randomized study. Radiology 263: 909-916	**Benign, solid or predominantly solid, nodules** RCT (1 RFA session vs 2 sessions) n=30 FU=6 months	Single-session RFA showed significant volume reduction and satisfactory clinical response in most patients. Therefore, additional RFA should be limited to patients with a large nodule (>20 ml) or unresolved clinical problems.	Included in Fuller CW (2014) systematic review.
Jang SW, Baek JH, Kim JK et al. (2012) How to manage the patients with unsatisfactory results after ethanol ablation for thyroid nodules: role of radiofrequency ablation. European Journal of Radiology 81: 905-910	**Benign, cystic or predominantly cystic, nodules** Case series n=20 FU=6 months	RFA after a single session of ethanol ablation was effective in reducing mean symptom score from 4.8 to 1.1 ($p<0.001$), mean cosmetic score from 3.5 to 1.4 ($p<0.001$) and mean nodule volume from 11.3 to 0.9 ml ($p<0.001$). The only independent factor related to volume reduction after ethanol ablation was the presence of a solid component ($p<0.001$), and ethanol ablation was less effective in nodules when solid component >20% ($p=0.001$).	Included in Fuller CW (2014) systematic review.
Jeong WK, Baek JH, Rhim H et al. (2008) Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. European Radiology 18: 1244-1250	**Benign nodules** Case series n=236 FU = 1–41 months	The mean volume of index nodules decreased to 1.12+/-2.92 ml and the volume reduction ratio (VRR) was 12.5-100% (mean 84.1+/-14.9%) at the last follow-up. A VRR greater than 50% was observed in 91.06% of nodules, and 27.81% of index nodules disappeared. The complications were pain, hematoma and transient voice changes.	Non-comparative studies with more patients or longer follow-up are included.
Ji Hong M, Baek JH, Choi YJ et al. (2015) Radiofrequency ablation is a thyroid function-preserving treatment for patients with bilateral benign thyroid nodules. Journal of Vascular & Interventional Radiology 26: 55-61	**Bilateral benign nodules** Case series n=18 FU=6–12 months	RF ablation improves cosmetic problems and symptoms and preserves thyroid function in patients with bilateral thyroid nodules.	Small case series

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Kim DW (2012) Sonography-guided ethanol ablation of a remnant solid component after radio-frequency ablation of benign solid thyroid nodules: a preliminary study. American Journal of Neuroradiology 33: 1139-1143	**Benign solid nodules** Case series n=17 FU=3-6 months	Of 18 post-RFA nodules, 8 nodules were subsequently treated with ethanol ablation because of incomplete ablation, as defined by the presence of peripherally located vascularised solid components. No serious complications were observed during or after RFA or ethanol ablation, with the exception of 1 patient who experienced diffuse glandular haemorrhage during these procedures.	Small case series focusing on ethanol ablation after RFA. Included in Fuller CW (2014) systematic review.
Kim Y-S, Rhim H, Tae K et al. (2006) Radiofrequency ablation of benign cold thyroid nodules: Initial clinical experience. Thyroid 16: 361-367	**Benign nodules (cystic and solid)** Case series n=30 FU=1–9 months	Mean volume of the nodules before ablation=6.3 ml. The residual volume was 54% of original at 1-3 months (n=32), 36% at 3-6 months (n=20), 31% at 6-9 months (n=15), and 12% at 9-18.5 months (n=13). Mixed/mainly cystic nodules showed a significantly better response than mainly solid nodules ($p<0.05$). Thyroid function after the procedure was maintained as normal in all patients. 88% of patients reported an improvement of their symptoms. There was no major complication other than vocal cord palsy in one patient (3%).	Included in Fuller CW (2014) systematic review.
Lee JH, Kim YS, Lee D et al. (2010) Radiofrequency ablation (RFA) of benign thyroid nodules in patients with incompletely resolved clinical problems after ethanol ablation (EA). World Journal of Surgery 34: 1488-1493	**Benign nodules** Case series n=27 FU=21 months	RFA is an effective and safe method for treating benign thyroid nodules in patients with incompletely resolved clinical problems following ethanol ablation.	Small case series.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Li XL, Xu HX, Lu F et al. (2016) Treatment efficacy and safety of ultrasound-guided percutaneous bipolar radiofrequency ablation for benign thyroid nodules. British Journal of Radiology: 89 (1059) 20150858-2016	**Non-randomised comparative study** n=70 (35 RFA vs 35 untreated controls) Follow-up= 6 months	The procedures were tolerated well in all the patients without causing any major complications. At follow-up, all of the nodule volume decreased significantly (from 8.8+/-8.7 to 1.6+/-1.6ml, p<0.001) in Group A (RFA), whereas the nodule volume increased from 6.9+/-3.8 to 7.9+/-3.95ml in Group B (untreated) (p<0.001). All 35 nodules in Group A had volume reduction ratios (VRRs) of >50%, among which 3 (8.6%) had VRRs >90%. In Group A, the clinical symptoms of the patients who had symptoms before RFA disappeared, whereas in Group B, the patients had no resolution of clinical symptoms at the 6-month follow-up.	Larger studies are included.
Shin JH, Jung SL, Baek JH et al. (2011) Rupture of benign thyroid tumors after radio-frequency ablation. Ajnr: American Journal of Neuroradiology 32: 2165-2169	**Benign nodules** Case reports n=6	Nodule rupture was reported after 0.2% (6/2616) of RFA procedures at 4 centres. All patients presented with abrupt neck swelling and pain between 9–60 days after RFA. Imaging and clinical findings of the ruptured tumours were anterior subcapsular location, mixed composition, large size, and repeated ablations. Conservative treatment was sufficient in 3 patients, whereas surgical management was needed in 3.	Safety outcome of nodule rupture is already included in table 2.
Shin JH, Baek JH, Oh Y et al. (2013) Combination therapy of temporary tracheal stenting and radiofrequency ablation for multinodular thyroid goiter with airway compression. Korean Journal of Radiology 14: 805-809	**Thyroid goitre** Case report n=1	Combination therapy of temporary airway stenting and RF ablation for the treatment of thyroid goitre has 2 advantages, i.e., immediate reliefs of dyspnoea with airway stenting and reductions of the thyroid volume with RF ablation, and thus, allowing symptom relief even after the stent removals.	Case report.

Article	Number of patients/		Article
Sung JY, Kim YS, Choi H et al. (2011) Optimum first-line treatment technique for benign cystic thyroid nodules: ethanol ablation or radiofrequency ablation? AJR American: W210-W214	**Benign cystic nodules** Non-randomised comparative study n=57	Both ethanol ablation and RFA resulted in significant decreases in nodule volume ($p<0.001$), symptom score ($p<0.001$), and cosmetic score ($p<0.001$). There were no between-group differences in mean volume reduction ($p=0.15$), decreases in symptoms ($p=0.53$), cosmetic scores ($p=0.69$), or therapeutic success rate ($p=0.61$). However, the mean number of treatment sessions was significantly lower in the ethanol ablation than in the RFA group ($p=0.026$). No serious complications were encountered in either group.	Larger studies are included.
Sung JY, Baek JH, Jung SL et al. (2015) Radiofrequency ablation for autonomously functioning thyroid nodules: a multicenter study. Thyroid 25: 112-117	**Toxic or pretoxic nodules** Case series n=44 FU=20 months	Significant improvement of triiodothyronine, free thyroxine, and thyrotropin was observed at the last follow-up. Regarding scintigraphy, 35 hot nodules became cold or were normal when scanned and 9 decreased uptake, although they remained hot nodules. The mean symptom and cosmetic scores were significantly reduced at the last follow-up. No major complications were encountered.	Small case series.
Turtulici G, Orlandi D, Corazza A et al. (2014) Percutaneous radiofrequency ablation of benign thyroid nodules assisted by a virtual needle tracking system. Ultrasound in Medicine & Biology 40: 1447-1452	**Benign non-functioning nodules** Case series n=45 FU=6 months	The overall mean volume reduction and complication rate were 72.6 +/- 11.3% and 2.5%, respectively. Overall satisfaction at the 6-mo follow-up was rated by patients as positive in 42 cases (93%).	Small case series.
Ugurlu MU, Uprak K, Akpinar IN et al. (2015) Radiofrequency ablation of benign symptomatic thyroid nodules: prospective safety and efficacy study. World Journal of Surgery 39: 961-968	**Benign nodules** Case series n=33 FU=6 months	The volume reduction was 74% at 6 months following the RFA ($p=0.005$). 8 patients had autonomously functioning nodules in the pre-treatment period, 4 became euthyroid at the 6th month after RFA. There were no complaints other than pain (12%).	Small case series.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Yoon HM, Baek JH, Lee JH et al. (2014) Combination therapy consisting of ethanol and radiofrequency ablation for predominantly cystic thyroid nodules. Ajnr: American Journal of Neuroradiology 35: 582-586	**Predominantly cystic nodules** Case series n=11	Ethanol ablation and radiofrequency ablation combination therapy is a feasible and safe technique for treating predominantly cystic thyroid nodules that exhibit internal bleeding during preparatory aspiration	Small case series.

Appendix B: Related NICE guidance for ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules

Guidance	Recommendations
Interventional procedures	**Minimally invasive video-assisted thyroidectomy. NICE interventional procedure guidance 499 (2014).** 1.1 Current evidence on the efficacy and safety of minimally invasive video‑assisted thyroidectomy is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection is very important and, along with treatment, should only be done in units specialising in thyroid surgery. 1.3 Minimally invasive video‑assisted thyroidectomy should only be done by clinicians with specific training and a regular practice in the procedure. **Intraoperative nerve monitoring during thyroid surgery. NICE interventional procedure guidance 255 (2008).** 1.1 The evidence on intraoperative nerve monitoring (IONM) during thyroid surgery raises no major safety concerns. In terms of efficacy, some surgeons find IONM helpful in performing more complex operations such as reoperative surgery and operations on large thyroid glands. Therefore, it may be used with normal arrangements for consent, audit and clinical governance.

Appendix C: Literature search for ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	24/02/2016	Issue 2, 2016
Cochrane Central Database of Controlled Trials - CENTRAL	24/02/2016	Issue 2, 2016
HTA database (Cochrane)	24/02/2016	Issue 2, 2016
MEDLINE (Ovid)	24/02/2016	1946 to February Week 2 2016
MEDLINE In-Process (Ovid)	24/02/2016	February 23, 2016
EMBASE (Ovid)	24/02/2016	1974 to 2016 Week 08
PubMed	24/02/2016	-
JournalTOCS [for update searches only]	24/02/2016	-

Trial sources searched on 29 September 2015

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

Websites searched on 29 September 2015

- 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 Thyroid Diseases/

3	(Thyroid* adj4 (Nodul* or adenom* or cyst* or diseas* or lump* or tumour* or tumor*)).tw.
4	AFTN.tw.

5	Goiter/
6	goit*.tw.
7	Hyperthyroidism/
8	hyperthyroidis*.tw.
9	or/1-8
10	Catheter Ablation/
11	(catheter adj4 ablat*).tw.
12	((needle* or electrode* or heat* or termal*) adj4 ablat*).tw.
13	(radiofrequen* adj4 ablat*).tw.
14	(radio frequen* adj4 ablat*).tw.
15	(radio-frequen* adj4 ablat*).tw.
16	(rf adj4 ablat*).tw.
17	rfa.tw.
18	*Ultrasonography, Interventional/
19	(ultrasound* adj2 guid*).tw.
20	US guid*.tw.
21	*Laser Therapy/
22	(Laser* adj2 (therapy or therapies or treat* or surg* or procedur*)).tw.
23	or/10-22
24	9 and 23
25	(Amica or "RF medical").tw.

26	24 or 25
27	Animals/ not Humans/
28	26 not 27