NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

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

A thyroid nodule is a lump in the thyroid gland. Most are benign (not cancerous). In this procedure, a thin wire is inserted into the nodule under local anaesthetic and guided into position using ultrasound. Microwaves from the wire heat the nodule to destroy it (ablation). The aim is to make the nodule smaller, relieve symptoms and improve appearance.

Contents

Abbreviations

Word or phrase	Abbreviation
Benign thyroid nodule	BTN
Confidence interval	CI
Cooled microwave ablation	cMWA
Laser ablation	LA
Microwave ablation	MWA
Quality of life	QoL
Radiofrequency ablation	RFA
Standard mean difference	SMD
Uncooled microwave ablation	uMWA
Volume reduction ratio	VRR

Introduction

The National Institute for Health and Care Excellence (NICE) has 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 IP overview was prepared in January 2022 and updated in September 2022.

Procedure name

- Percutaneous ultrasound-guided microwave ablation for symptomatic benign thyroid nodules

Specialist societies

- 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 are benign and often asymptomatic. They may be single (solitary nodule) or multiple (multinodular goitre). Some thyroid nodules produce thyroxine or triiodothyronine and cause thyrotoxicosis. These are called hyperfunctioning or toxic thyroid nodules.

NICE's guideline on the assessment and management of thyroid disease describes current treatment options. Benign thyroid nodules may need treatment if they are symptomatic or causing cosmetic problems. Conventional treatment includes surgery. Less invasive alternatives to surgery include ethanol ablation, percutaneous laser ablation, high intensity focused ultrasound ablation and radiofrequency ablation.

What the procedure involves

Ultrasound-guided percutaneous microwave ablation for symptomatic benign thyroid nodules is a minimally invasive procedure done in an outpatient setting using local anaesthesia. The patient is placed in the supine position with moderate neck extension.

A microwave antenna is inserted into the nodule using ultrasound guidance to visualise the electrode during the procedure. Once in position, the microwave antenna is activated to heat and destroy the tissue by coagulative necrosis. The antenna may be repositioned to ensure that most of the nodule is ablated.

The aim of the procedure is to reduce symptoms and improve cosmetic appearance by making the nodule smaller while preserving thyroid function and with fewer complications than surgery.

Efficacy summary

Nodule volume reduction

A systematic review of 1,461 people with benign thyroid nodules reported a pooled reduction in mean nodule volume of 89% (95% CI 85% to 92%), n=1,845 nodules, I^2=93%) 12 months after MWA from an initial mean nodule volume of 15.0 ml after MWA (Zheng 2018).

A systematic review of 1,146 people with BTNs or papillary thyroid microcarcinomas reported that in benign nodule subgroup analysis, the VRR after MWA treatment (follow-up range 3 to 12 months) was 75% (SMD: 0.99, 95% CI 0.91 to 1.08; 5 studies, n=1,159 nodules; I^2=0%; Cui 2019).

A systematic review of 1,768 patients reported that after 12-month follow up, the VRR in people who had MWA was 80% (95% CI 77% to 83%; 3 studies, n=938 nodules; I^2=74%; Guo 2021).

A non-randomised comparative study of 267 people reported that after 15 months of follow up, the mean VRR was 93±1.8% and the mean nodule area decreased to 0.16±0.07 cm^2 from a baseline of 5.28±3.63 cm^2. When split by nodule type, the VRR was 92%±2.4% and the mean nodule area decreased to 0.18±0.06 cm^2 from a baseline of 4.7±3.51 cm^2 in nodular goitres, and in thyroid cystadenomas the VRR was 94%±1% and the mean nodule area decreased to 0.22±0.09 cm^2 from a baseline of 5.87±3.75 cm^2 (Honglei 2021).

A non-randomised comparative study of 578 propensity matched people reported that after 18 months of follow up, the mean VRR in people who had MWA was 92% (range 89% to 95%; Jin 2021).

A case series of 171 people reported that after 3 years of follow up, the mean VRR was 93.2%. When split by nodule diameter, the mean VRR was 85%±13% for nodules ≤10 ml, 86%±15% for nodules 10 ml to 30 ml, and 87%±15% for nodules ≥30 ml at 12-month follow-up. When split by nodule component, the mean VRR was 83%±16% for solid nodules, 87%±14 % for predominantly solid nodules, and 89%±10% for cystic nodules at 12-month follow up (Luo 2021).

A non-randomised comparative study of 318 people reported a VRR at last follow up (mean 14.3±6.5 months) of 83%±32% across all nodules (Shi 2019).

A non-randomised comparative study of 212 people reported a decrease in nodule volume from a baseline volume of 2.5 cm^3 to 0.51 cm^3 after 12-month follow up, and a VRR of 80%±10% after 12 months (Jin 2018).

A case series of 115 people reported a decrease in nodule volume from a baseline mean volume of 5.30±8.56 ml to 0.58±1.32 ml after 12-month follow up, and a VRR of 91%±10% after 12 months (Fu 2021).

A case series of 173 people reported a decrease in nodule volume from a median volume of 4.23 ml (IQR 2.27 ml to 9.0 ml) at baseline to 0 ml (IQR 0 to 0.2 ml) at 36 months ($p<0.01$), and a mean VRR of 97% at 36 month follow up (Liu 2022).

A case series of 40 people reported a decrease in nodule volume from 21.1 ± 15.3 ml at baseline to 4.2 ± 3.5 ml at 12 month follow up, and mean % VRR of 79% ± 9% at 12 months ($p<0.0001$; Yildirim 2022).

Pressure symptoms

A systematic review of 1,146 people with BTNs or papillary thyroid microcarcinomas reported that across 2 studies looking at benign nodules, the pooled changes in symptom score gave an SMD of 1.51 (95% CI -0.40 to 3.42; 2 studies, n=766 nodules; I^2=100%) at 12-month follow up (Cui 2019).

A systematic review of 1,768 people reported that after 12-month follow up, there was a decrease in symptom score with an SMD of 1.45 (95% CI 0.34 to 2.56; 3 studies, n=866 nodules; I^2=98%; Guo 2021).

A non-randomised comparative study of 318 people reported a decrease in symptom score (scored 1 to 10 with 10 being the most severe) from a mean value of 5.8±2.5 to 3.5±1.6 at last follow up (mean 14.3 ±6.5 months; Shi 2019).

A case series of 40 people reported a decrease in symptom score (scored 1 to 10 with 10 being the most severe) from a mean of 6.25 ± 0.74 at baseline to 0.95 ± 0.74 at 12 month follow up ($p<0.0001$; Yildirim 2022).

Cosmetic appearance

A systematic review of 1,146 people with BTNs or papillary thyroid microcarcinomas reported that across 3 studies looking at benign nodules, the pooled changes in cosmetic score gave an SMD of 1.20 (95% CI 0.87 to 1.52; 3 studies, n=876 nodules; I^2=83%; Cui 2019).

A systematic review of 1,768 people reported that after 12-month follow up, there was a decrease in cosmetic score with an SMD of 1.15 (95% CI 0.83 to 1.47; 3 studies, n=866 nodules; I^2=81%; Guo 2021).

A non-randomised comparative study of 318 people reported a decrease in cosmetic score (scored 1 to 4 with 4 being the most severe) from a mean value of 3.0±0.8 to 1.5±0.8 at last follow up (mean 14.3±6.5 months; Shi 2019).

A case series of 173 people reported a decrease in cosmetic score (scored 1 to 4 with 4 being the most severe) from a median value of 2 (IQR 2 to 3) to a value of 1 at 36 month follow up ($p<0.01$; Liu 2022).

A case series of 40 people reported a decrease in cosmetic score (scored 1 to 4 with 4 being the most severe) from a mean of 3.52 ± 0.5 at baseline to 1.92 ± 0.88 at 12-month follow up ($p<0.0001$; Yildirim 2022).

Thyroid function

A non-randomised comparative study of 267 people reported that all thyroid function tests at baseline and post-ablation showed no statistically significant difference in thyroid function following MWA (Honglei 2021).

A case series of 40 people reported that levels of free thyroxine increased slightly from 1.07 ± 0.21 nanograms/dl at baseline to 1.14 ± 0.21 nanograms/dl at 12-month follow up ($p=0.007$). All other thyroid function tests showed no statistically significant difference in thyroid function following MWA (Yildirim 2022).

Quality of life

A non-randomised comparative study of 578 propensity matched people reported that after 18-month follow up, quality of life (scored from 0 to 410) increased from an average of 271/410 to 373/410 (range 360 to 386; Jin 2021).

Safety summary

Nodule rupture

Nodule rupture was reported in <1% (4/1461) of people who had MWA in a systematic review of 1,461 patients (Zheng 2018). Nodule rupture was reported in <1% (6/1226) of nodules in people who had MWA in a systematic review of 1,146 people with BTNs or papillary thyroid microcarcinomas (Cui 2019).

Nodule rupture was reported in <1% (4/869) of people who had MWA in a systematic review of 1,768 people (Guo 2021).

Nodule rupture was reported in 2% (3/171) of patients in a case series of 171 people, with symptoms improving within 1 to 2 weeks after treatment with non-steroidal anti-inflammatory drugs (Luo 2021).

Voice change and vocal cord palsy

Transient voice change was reported in 4% (54/1461) of people who had MWA, and transient hoarseness was reported in <1% (3/1461) of people who had MWA in a systematic review of 1,461 people. In the same study, 1 person experienced ipsilateral vocal cord palsy (Zheng 2018).

Transient or permanent voice change was reported in 5% (58/1146) people who had MWA in a systematic review of 1,146 people with BTNs or papillary thyroid microcarcinomas (Cui 2019).

Transient voice change was reported in 5% (44/869) of people who had MWA in a systematic review of 1,768 people (Guo 2021). Transient voice change was reported in <1% (2/267) of people who had MWA in a non-randomised comparative study of 267 people (Honglei 2021).

Hoarseness was reported in 1 person in the MWA group in a non-randomised comparative study of 578 propensity matched people (Jin 2021).

Hoarseness was reported in 2% (4/171) of people in a case series of 171 people, with all patients recovering within 1 month (Luo 2021).

Voice change was reported in 1% (2/160) of people who had MWA in a non-randomised comparative study of 318 people (Shi 2019).

Vocal cord paralysis was reported in 1 person who had MWA in a non-randomised comparative study of 212 people. The patient recovered from this complication within 3 months of the procedure (Jin 2018).

Hoarseness was reported in 3% (4/115) of people in a case series of 115 people. Three of these resolved within 1 day of the procedure and 1 resolved 3 months after procedure (Fu 2021).

Hoarseness was reported in 1% (2/173) of people in a case series of 173 people (Liu 2022).

Haemorrhage or haematoma

Haemorrhage was reported in 2% (27/1461) of people who had MWA in a systematic review of 1,461 people. In the same study haematomas were reported

in <1% (2/1461) of people. Superficial haematomas were also reported across 'almost all patients' in 1 included study of 30 people within the systematic review but the exact number was not specified (Zheng 2018).

Haematoma was reported in 4% (46/1146) of people who had MWA in a systematic review of 1,146 people with BTNs or papillary thyroid microcarcinomas (Cui 2019).

Haemorrhage, haematoma, or both, were reported in 4% (33/869) of people who had MWA in a systematic review of 1,768 people (Guo 2021). In a non-randomised comparative study of 578 propensity matched people, haemorrhage and haematoma was reported in 1 patient (Jin 2021).

Haematoma was reported in 3% (5/160) of nodules in people who had MWA in a non-randomised comparative study of 318 patients (Shi 2019).

Haematoma was reported in 3% (4/115) of people in a case series of 115 people; this resolved 2 to 7 days after the procedure in all people affected (Fu 2021).

Nerve injury

Horner's syndrome was reported in <1% (2/1461) of people who had MWA in a systematic review of 1,461 people, and sympathetic nerve injury was reported in 1 person in the same study (Zheng 2018).

Sympathetic nerve injury was reported in <1% (2/869) of people in a systematic review of 1,768 people (Guo 2021).

Thyroid dysfunction

Thyroid dysfunction was reported in <1% (6/1461) of people who had MWA in a systematic review of 1,461 people. In the same study, hyperthyroidism was reported in <1% (2/1461) of people and Graves' disease was reported in 1 person (Zheng 2018).

Hyperthyroidism was reported in 1 people who had MWA in a systematic review of 1,768 people (Guo 2021).

Burns

First-degree burn was reported in 2% (25/1461) of people who had MWA in a systematic review of 1,461 people, and in the same study skin burn was reported in <1% (3/1,461) of people (Zheng 2018).

Skin burns were reported in 1 person who had MWA in a systematic review of 1,146 people with BTNs or papillary thyroid microcarcinomas (Cui 2019).

Skin burns were reported in 1 person who had MWA in a systematic review of 1,768 people (Guo 2021).

Skin burns were reported in 1% (4/267) of people who had MWA in a comparative study of 267 people (Honglei 2021).

Skin burns were reported in <1% (2/289) of people who had MWA in a non-randomised comparative study of 578 propensity matched people (Jin 2021).

Skin burns were reported in 1 person who had MWA in a non-randomised comparative study of 212 propensity matched people (Jin 2018).

Skin burn was reported in 1 person and oesophageal burn was reported in 1 person in a case series of 115 people (Fu 2021).

First degree skin burn was reported in 1 person in a case series of 40 people who had uncooled MWA; this later resolved spontaneously (Yildirim 2022).

Pain and swelling

Pain was reported in 9% (130/1461) of people who had MWA in a systematic review of 1,461 people (Zheng 2018).

Unbearable pain was reported in 2% (28/1146) of people who had MWA in a systematic review of 1,146 people with BTNs and papillary thyroid microcarcinomas (Cui 2019).

Slight pain at the site of ablation was reported by most patients on the first day after MWA (exact numbers unspecified) in a case series of 171 people (Luo 2021).

Pain was reported in 13% (20/160) of people who had MWA in a comparative study of 318 people (Shi 2019).

Neck pain was reported in 10% (11/115) of people in a case series of 115 people, which resolved within 5 days of procedure (Fu 2021).

Pain was reported in 3% (5/173) of people who had MWA in a case series of 173 people (Liu 2022).

Fever

Fever was reported in <1% (13/1461) of people who had MWA in a systematic review of 1,461 people (Zheng 2018).

Fever was reported in 2% (2/115) of people in a case series of 115 people, and in all cases was resolved 3 days after the procedure (Fu 2021).

Vomiting or nausea

Vomiting was reported in 1 person in a systematic review of 1,461 patients (Zheng 2018), and in 1 person in a systematic review of 1,768 patients (Guo 2021).

In a comparative study of 267 people, nausea was reported in 2% (5/267) of people and vomiting was reported in <1% (2/267) of people who had MWA (Honglei 2021).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts 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, the professional expert did not list any adverse events that had not been described in the literature.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous ultrasound-guided microwave ablation for symptomatic benign thyroid nodules. The following databases were searched, covering the period from their start to 30 November 2021: 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 inclusion criteria were applied to the abstracts identified by the literature search. When selection criteria could not be determined from the abstracts the full paper was retrieved.

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 when 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	People with benign thyroid nodules.
Intervention/test	Ultrasound-guided percutaneous microwave 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 around 4,900 people from 3 systematic reviews, 4 non-randomised comparative studies and 4 case series. There is some overlap of studies across the systematic reviews.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the Appendix.

Summary of key evidence on percutaneous ultrasound-guided microwave ablation for symptomatic benign thyroid nodules

Study 1 Zheng (2018)

Study details

Study type	**Systematic review and meta-analysis**
Country	China (n=6), Germany (n=3)
Recruitment period	Search period: inception to June 2018
Study population and number	n=1,461 patients with 1,845 BTNs across 9 studies (cooled MWA: n=1,408 patients with 1,784 BTNs, uncooled MWA n=53 with 61 BTNs)
Age and sex	Mean age 42 to 66 years, 50% to 91% female
Patient selection criteria	Inclusion criteria: Human studies published in English language demonstrating the clinical value of MWA for BTNs, studies reporting results of volume reduction at 3-, 6- or 12-month follow up, or complications. Exclusion criteria: Overlapping studies, case reports, case series with fewer than 8 patients, review articles, editorials, letters, comments, conference proceedings.
Technique	6 studies used cooled MWA carried out at 2450 MHz and 4 studies used uncooled MWA carried out at 902-928 MHz (1 study used both cooled and uncooled MWA). 5 studies used a moving-shot technique, 5 studies used a hydrodissection approach and 3 studies used a transisthmic approach.
Follow up	3 to 24 months – meta-analysis done up to 12 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Reported follow up was short; 1/9 studies reported a follow up of greater than 12 months and maximum follow up for uncooled microwave ablation (uMWA) was 6 months. The majority of efficacy outcomes are reported only at 3 months.

Study design issues: Relevant studies were identified using MEDLINE, EMBASE and the Cochrane Library, and to identify other suitable articles, the bibliographies of the returned articles were also screened. Two independent reviewers extracted relevant study data and assessed the quality of the included studies using the Methodological Index for Non-Randomised Studies (MINORS) evaluation tool. Disagreements were resolved by consensus with a third reviewer.

The primary efficacy outcome was mean % VRR. Mean VRR % and SDs from studies where this was not reported were estimated from medians and interquartile ranges as outlined in Hozo (2005).

Meta-analytic pooling of VRR and proportions of complications was done using the inverse-variance method for calculating weights. Pooled VRR and pooled proportions of complications were summarised using a fixed-effect model in the case of zero or non-significant heterogeneity. In the case of significant heterogeneity, a random-effects model was used. Heterogeneity among studies was assessed by using chi-square testing and I^2 statistics (in which 0–40%, is defined as not significant; 30–60%, may represent moderate heterogeneity; 50–90% - may represent substantial heterogeneity; 75–100% - may represent considerable heterogeneity).

Publication bias was visually assessed by funnel plots, and statistical significance was evaluated by Egger's test (with statistical significant set at p=0.05).

Study population issues: The mean initial nodule volume was 15.0 ml (range 2.1–102.1 ml) across all studies, but the mean initial nodule volume of cooled microwave ablation (cMWA) (11.3 ml; range, 2.1–99.0 ml) was lower than that of uMWA (47.8 mL; range, 19.8–102.1 ml; p <0.01).

Significant publication bias was noted at 3-month follow up (p<0.01) for % VRR and for cMWA group in subgroup analysis. (p = 0.03). Significant heterogeneity was noted for complications in cMWA and across all MWA, as well as in percentage VRR for overall VRR and both cMWA and uMWA in subgroup analysis.

Other issues: 1 study included in this systematic review is also included in the Cui (2019) systematic review (Study 2) and the Guo (2021) systematic review (Study 3).

Key efficacy findings

Number of patients analysed: 1,461 (9 studies, cMWA: n=1,408 patients, uMWA n=53)

Overall reduction in nodule volume

Length of follow up	VRR of BTNs at 3-month follow up (95% CI)	I^2 value	P value (publication bias)
3 months	54.3% (45.3% – 63.3%)	97.6%	<0.01
6 months	73.5% (66.7% – 80.3%)	94.9%	0.14
12 months	88.6% (84.9% – 92.4%)	92.7%	0.72

Overall reduction in nodule volume by MWA type:

Type of MWA	Pooled VRR of BTNs at 3-month follow up (95% CI)	I^2 value	P value (publication bias)
cMWA	58.4% (49.3% - 67.4%)	97.0%	0.03
uMWA	45.3% (29.5% - 61.1%)	92.7%	0.07

There was no statistically significant difference between cMWA and uMWA in pooled VRR (P = 0.07).

Key safety findings

262 complications of MWA were reported among 1,845 thyroid nodules in 1,461 patients (72 major complications and 190 minor complications).

Overall incidence of complications

Type of MWA	Pooled proportion (95% CI) (number of cases)	I^2 value	P value for publication bias
cMWA	29.7% (18.8% - 40.5%)	97.4%	0.40
uMWA	97.8% (94.0% - 100%)	0%	0.11
All MWA	52.4% (29.8% - 74.9%)	99.5%	0.08

There was a statistically significant difference between cMWA and uMWA in overall incidence of complications (P <0.01).

Incidence of major complications

Type of MWA	Pooled proportion (95% CI) (number of cases)	I^2 value	P value for publication bias
cMWA	4.9% (2.4% - 7.4%)	69.9%	0.58
uMWA	5.0% (0% - 10.8%)	0%	0.07
All MWA	4.8% (2.7% - 7.0%)	55.9%	0.42

There was no statistically significant difference between cMWA and uMWA in incidence of major complications (P = 0.49)

Incidence of minor complications

Type of MWA	Pooled proportion (95% CI) (number of cases)	I^2 value	P value for publication bias
cMWA	21.0% (13.2% - 28.8%)	98.0%	0.45
uMWA	97.8% (94.0% - 100%)	0%	0.11

All MWA	48.3% (31.2% - 65.4%)	99.7%	0.09

There was a statistically significant difference between cMWA and uMWA in incidence of minor complications (P <0.01).

List of major complications

Major complication	Percentage incidence (cMWA) (n=1,408)	Percentage incidence (uMWA) (n=53)	Percentage incidence (overall) (n=1,461)
Transient voice change	3.7% (54/1408)	0% (0/53)	3.7% (54/1461)
Transient hoarseness	0.21% (3/1408)	0% (0/53)	0.21% (3/1461)
Ipsilateral vocal cord palsy	0.07% (1/1408)	0% (0/53)	0.07% (1/1461)
Horner's syndrome	0.07% (1/1408)	1.9% (1/53)	0.1% (2/1461)
Thyroid dysfunction	0.41% (6/1408)	0% (0/53)	0.41% (6/1461)
Nodule rupture	0.27% (4/1408)	0% (0/53)	0.27% (4/1461)
Sympathetic nerve injury	0.07% (1/1408)	0% (0/53)	0.07% (1/1461)
Graves' disease	0% (0/1408)	1.9% (1/53)	0.07% (1/1461)

List of minor complications

Minor complication	Percentage incidence (cMWA) (n=1,408)	Percentage incidence (uMWA) (n=53)	Percentage incidence (overall) (n=1,461)
Pain	5.4% (77/1408)	100% (53/53)	8.9% (130/1461)
Skin burn	0.21% (3/1408)	0% (0/53)	0.21% (3/1461)
Haemorrhage	1.9% (27/1408)	0% (0/53)	1.8% (27/1461)
Vomiting	0.07% (1/1408)	0% (0/53)	0.07% (1/1461)
First-degree burn	0% (0/1408)	47.2% (25/53)	1.7% (25/1461)
Hyperthyroidism	0.07% (1/1408)	1.9% (1/53)	0.1% (2/1461)
Haematoma	0% (0/1408)	3.7% (2/53)	0.1% (2/1461)

List of side effects

Side effect	Percentage incidence (cMWA)	Percentage incidence (uMWA)	Percentage incidence (overall)
Heat sensation	0.57% (8/1408)	0% (0/53)	0.55% (8/1461)
Superficial haematomas	0.64% (9/1408)	Exact number not reported*	Unknown*

Coughing	0.07% (1/1408)	0% (0/53)	0.07% (1/1461)
Choking and coughing	0.85% (12/1408)	0% (0/53)	0.82% (12/1461)
Mild bleeding	0.28% (4/1408)	0% (0/53)	0.27% (4/1461)
Fever	0.92% (13/1408)	0% (0/53)	0.89% (13/1461)

*Paper states “almost all patients” in 1 study of 30 patients

Study 2 Cui (2019)

Study details

Study type	**Systematic review and meta-analysis**
Country	China (n=6), Germany (n=1)
Recruitment period	Search date: not reported
Study population and number	n=1,146 patients with BTNs or papillary thyroid microcarcinoma (BTNs: n=1,085 patients with 1,159 nodules across 5 studies, papillary thyroid microcarcinoma: n = 61 patients with 67 nodules across 2 studies)
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: Human studies published in English language demonstrating the clinical value of MWA for benign thyroid nodules and papillary thyroid microcarcinoma; studies in which clinical outcomes for nodules treated with US-guided MWA were reported (such as nodule volume, symptom score, cosmetic score); follow up of at least 3 months. Exclusion criteria: Abstracts, case reports, case series, in vitro studies, animal studies. In the case of multiple articles by the same author being returned, articles that were not the most up to date or reported incomplete data were excluded.
Technique	Of the 7 selected articles, 2 studies used multiple rounds of MWA, while a single round of MWA was used in the other studies.
Follow up	3-12 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up length varied between studies. 6/7 studies had a follow up of greater than 12 months, while 1 study had a follow up of 3 months.

Study design issues: Relevant studies were identified using PubMed, EMBASE, Cochrane, and Web of Science. Some additional studies were found through a manual search that included references from other studies, and any duplicate publications were excluded. One reviewer extracted relevant study data and 2 further reviewers verified the accuracy of the extracted data.

The primary efficacy outcomes of this study included changes in nodule volume, symptom scores, and cosmetic scores. The included articles estimated nodule volumes using the formula for the volume of an ellipsoid: $V=\pi/6*(abc)$ where a, b, and c are the largest diameters in the x-, y-, and z-dimensions. The primary safety outcome was the rate of major and minor complications as defined by the Society of Interventional Radiology. Major complications included transient or permanent voice change, hypoparathyroidism, oesophageal injury, dysphagia, infection, and nodule rupture, while minor complications included unbearable pain (severe pain that need medication to relieve it), skin burns, haematoma, and vomiting.

For the continuous data, the SMD was calculated for all outcomes as all of the analysed outcomes used the same unit scale. A 95% CI was calculated for each SMD. The odds ratio (OR) and 95% CI were calculated for one dichotomous outcome. P values were considered significant if less than 0.05. When possible, subgroup analyses were done for all outcomes for “benign thyroid nodules” and “papillary thyroid microcarcinomas”.

Meta-analysis was done using the Cochrane Review Manager (RevMan) Version 5.3 and used a pre-treatment to post-treatment comparison, with all subjects serving as their own controls. Each treatment outcome was assessed and recorded as an absolute value or change from the baseline using the last available timepoint. Efficacy and safety outcomes included in the meta-analysis were summarised using a fixed-effect model in the case of zero or non-significant heterogeneity. In the case of significant heterogeneity ($p \leq 0.05$), a random-effects model was used. Heterogeneity within studies was assessed using the I^2 statistic (in which a value of 25% illustrates low heterogeneity; 50% illustrates moderate heterogeneity and 75% illustrates high heterogeneity).

The quality of the included studies in terms of risk of bias was assessed using the Cochrane Collaboration’s tool. 3/7 studies had high levels of selection bias and 2/7 studies had issues with blinding participants and personnel (performance bias).

Other issues: 1 study included in this systematic review is also included in the Guo (2021) systematic review, and a second study is included in both the Guo (2021) systematic review (Study 3) and the Zheng (2018) systematic review (Study 1).

Key efficacy findings

Number of patients analysed: 1,146 (1,226 nodules)

Reduction in nodule volume (benign nodule subgroup analysis)

% VRR after MWA treatment = 75% (SMD: 0.99, 95% CI 0.91-1.08; 5 studies, n=1,159 nodules; I^2=0%, p<0.00001)

Symptom score change

Symptom score after MWA treatment = SMD: 1.51 (95% CI -0.40-3.42; 2 studies, n=766 nodules; I^2=100%, p<0.12)

All studies reporting symptom score contained patients with benign nodules only.

Cosmetic score change

Cosmetic score after MWA treatment = SMD: 1.20 (95% CI 0.87-1.52; 3 studies, n=876 nodules; I^2=83%, p<0.00001)

All studies reporting cosmetic score contained patients with benign nodules only.

Key safety findings

Incidence of major complications

Complication	% incidence (number of nodules)	Incidence as % of patients*
Transient or permanent voice change	4.6 (58/1226)	5.1 (58/1146)
Nodule rupture	0.5 (6/1226)	0.5 (6/1146)
Unbearable pain	2.2 (28/1226)	2.4 (28/1146)
Skin burns	0.08 (1/1226)	0.08 (1/1146)

*Calculated values

Incidence of minor complications

Complication	% incidence (number of nodules)	Incidence as % of patients*
Haematoma	3.8 (46/1226)	4.0 (46/1146)

*Calculated values

Study 3 Guo (2021)

Study details

Study type	**Systematic review and meta-analysis**
Country	China (n=3), Germany (n=2)
Recruitment period	Search period: inception to September 2020
Study population and number	n=1,768 patients with 1,894 BTNs across 5 studies (MWA: 869 patients with 938 BTNs, RFA: 899 patients with 956 BTNs)
Age and sex	MWA: Mean age 47.1 to 57.0 years, 53% to 78% female RFA: Mean age 46.3 to 54 years, 55% to 78% female
Patient selection criteria	Inclusion criteria: Human studies published in English language comparing the clinical results of RFA and MWA in treatment of BTNs, studies reporting results of volume reduction at 3-, 6- or 12-month follow up and complications. Exclusion criteria: Overlapping/duplicated studies, review articles, conference abstracts, case reports, letters, animal studies, studies with insufficient data to calculate VRR.
Technique	Not reported
Follow up	3 to 14 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Reported follow up was short; meta-analysis was done up to 12 months (with 1/5 studies reporting a follow up of greater than 12 months and 2/5 studies only reporting a follow up of 3 months).

Study design issues: Relevant studies were identified using MEDLINE, EMBASE and the Cochrane Library, and data was extracted by 2 independent reviewers. The quality of the included studies was assessed by using the Cochrane Collaboration's tool in RevMan 5.3. Most of the studies showed unclear risks in blinding of participants and personnel (performance bias), and blinding of outcome assessment (detection bias).

The primary efficacy outcome was mean percentage VRR. Mean VRR and SDs from studies where this was not reported were estimated from medians and interquartile ranges as outlined in Wan (2014). Ablation-related major and minor complications were as defined by the Society of Interventional Radiology.

The pooled VRRs were calculated using an inverse-variance weighting model. Standard mean differences (SMD) with 95% CIs were used to analyse symptomatic and cosmetic scores; risk difference (RD) with 95% CI was utilised to analyse complications.

Heterogeneity within the studies was estimated using the chi-square test, with $p < 0.05$ suggesting significant heterogeneity, and the I^2 statistic (with 0%–40% suggesting mild heterogeneity, 30%–60% suggesting moderate heterogeneity, 50%–90% suggesting substantial heterogeneity, and 75%–100% suggesting considerable heterogeneity). Meta-analyses were using a fixed-effect model in the case of zero or non-significant heterogeneity. In the case of significant heterogeneity, a random-effects model was used.

Study population issues: The preoperative mean nodule volume did not significantly differ between RFA (9.0 ml, 95% CI: 2.1-15.9 ml) and MWA (8.5 ml, 95%CI: 2.2–14.9 ml; p=0.923).

Other issues: 1 study included in this systematic review is also included in the Cui (2019) systematic review, and a second study is included in both the Cui (2019) systematic review (Study 2) and the Zheng (2018) systematic review (Study 1).

Key efficacy findings

Number of patients analysed: 1,768 (MWA: 869 patients with 938 BTNs, RFA: 899 patients with 956 BTNs)

Overall reduction in nodule volume (n=number of nodules):

Follow up	VRR % of BTNs (95% CI) for MWA (n=938 at 3 months, n=866 at 6/12 months)	VRR % of BTNs (95% CI) for RFA (n=956 at 3 months, n=861 at 6/12 months)	P value for significant difference
3 months (5 studies)	54% (48- 60%) I^2 = 93%, p<0.01	56% (49-63%) I^2 = 98%, p<0.01	0.668
6 months (3 studies)	75% (70-80%) I^2 = 89%, p<0.01	81% (77-85%) I^2 = 92%, p<0.01	0.08
12 months (3 studies)	80% (77-83%) I^2 = 74%, p<0.01	86% (82-91%) I^2 = 95%, p<0.01	0.036

Symptom improvement (n=number of nodules):

Follow up	SMD (95% CI) for MWA (n=866)	SMD (95% CI) for RFA (n=861)	P value for significant difference
6 months (3 studies)	1.12 (0.38-1.87) I^2=97%, p<0.01	1.17 (0.36-1.98) I^2=97%, p<0.01	0.93
12 months (3 studies)	1.45 (0.34-2.56) I^2=98%, p<0.01	1.46 (0.29-2.62) I^2=98%, p<0.01	0.93

Cosmetic improvement (n=number of nodules):

Follow up	SMD (95% CI) for MWA (n=866)	SMD (95% CI) for RFA (n=861)	P value for significant diff.
6 months (3 studies)	0.94 (0.84-1.04) I^2 = 0%, p=0.38	0.87 (0.77-0.97) I^2 = 0%, p=0.46	0.334
12 months (3 studies)	1.15 (0.83-1.47) I^2 = 81%, p<0.01	1.21 (0.66-1.76) I^2 = 87%, p<0.01	0.872

Key safety findings

Major complications

Risk difference between RFA and MWA across all studies (major complications) = -0.02 (95% CI 0.04 to 0.00, I^2=0%, p=0.107)

Study	Major complications (RFA)	Major complications (MWA)
Cheng, 2017	Transient voice change (29/649) Nodule rupture (2/649)	Transient voice change (35/603) Nodule rupture (4/603) Sympathetic nerve injury (1/603)
Hu, 2019	Transient voice change (2/72)	Transient voice change (4/100)
Korkusuz, 2018	None	None
Vorländer, 2018	None	Sympathetic nerve injury (1/24)
Yue, 2016	Transient voice change (4/102)	Transient voice change (5/102)
All	Transient voice change (35/899) Nodule rupture (2/899) **Total major complications: 37/899**	Transient voice change (44/869) Nodule rupture (4/869) Sympathetic nerve injury (2/869) **Total major complications: 40/869**

Minor complications

Risk difference between RFA and MWA across all studies (minor complications) = 0.00 (95% CI -0.01 to 0.02, I^2=0%, p=0.661)

Study	Minor complications (RFA)	Minor complications (MWA)
Cheng, 2017	Haemorrhage/haematoma (13/649)	Haemorrhage/haematoma (12/603) Skin burn (1/603) Vomiting (1/603) Hyperthyroidism (1/603)
Hu, 2019	Haemorrhage (1/72)	None
Korkusuz, 2018	Haematoma (26/40)	Haematoma (21/40)
Vorländer, 2018	None	None
Yue, 2016	None	None

All	Haemorrhage/haematoma (40/899) **Total minor complications: 40/899**	Haemorrhage/haematoma (33/869) Skin burn (1/869) Vomiting (1/869) Hyperthyroidism (1/869) **Total minor complications: 36/869**

Study 4 Honglei (2021)

Study details

Study type	**Non-randomised comparative study**
Country	China
Recruitment period	2017-2019
Study population and number	n=267 patients with 1,075 BTNs (132 patients with 530 thyroid cystadenoma, 134 patients with 543 nodular goitre, 1 patient with both thyroid cystadenoma and nodular goitre)
Age and sex	Mean age 50.1±11.7 years, 80% female
Patient selection criteria	Inclusion criteria: BTNs associated with symptoms (neck discomfort due to lump; general examination found thyroid lump causing psychological discomfort; and dysphagia), nodules classified as TIR1-TIR3 on fine-needle aspiration, growing nodule size as confirmed by follow up. Exclusion criteria: Irradiation and/or surgery on the head and neck, malignant nodules, pregnancy, lactation, non-adherent patients.
Technique	Patients were placed in a dorsal decubitus position with the arms extended to the side of the body, and the neck in hyperextension. A 2450 MHz MWA system (KY-2000, Kangyou Medical, China) MWA system and accompanying microwave antennas (KY-2450A-1, Kangyou Medical, China) were used with a continuous output of 40W. Ablation time depended on the size and number of nodules.
Follow up	Mean 23 months (outcomes reported to 15 months)
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Thyroid function tests, antibodies against Tg, thyrotropin receptors, and thyroid peroxidase were measured 24 hours after MWA, as well as every 3 months for a year. Follow up using ultrasound was carried out every 3 months for at least 1 year.

Study design issues: This non-randomised, single-centre, retrospective study assessed safety and efficacy of MWA using ultrasound guidance for BTNs (specifically thyroid cystadenoma and nodular goitre). The primary efficacy outcomes measured were nodule area and % VRR, and the primary safety outcome measured was the rate of complications.

Study population issues: The baseline nodule area did not statistically significantly differ between patients with nodular goitre (mean area 4.7±3.51 cm^2) and thyroid cystadenoma (mean area 5.87±3.75 cm^2; p = 0.48). The mean nodule area across all patients was 5.28±3.63 cm^2.

Key efficacy findings

Number of patients analysed: 267

Changes in nodule volume (number of nodules)

	Nodular goitre (n=133)	Thyroid cystadenoma	Total	P value
Baseline nodule area (cm^2)	4.7±3.51	5.87±3.75	5.28±3.63	0.4842
Mean nodule area (cm^2) – 3 months	2.34±2.52	2.44±2.26	2.39±2.35	0.2450
% VRR – 3 months	50.22±27.7	59.29±22.3	54.74±24.9	-
Mean nodule area (cm^2) – 6 months	0.82±0.30	1.14±1.27	0.98±1.14	<0.05
% VRR – 6 months	82.56±16.5	84.31±14.2	81.44±17.1	-
Mean nodule area (cm^2) – 9 months	0.57±0.15	0.79±0.19	0.68±0.27	<0.05
% VRR – 9 months	90.3±4.4	91.4±3.2	89.8±6.9	-
Mean nodule area (cm^2) – 12 months	0.20±0.08	0.21±0.10	0.20±0.10	<0.05
% VRR – 12 months	91.2±3.5	93.5±1.3	92.9±2.0	-
Mean nodule area (cm^2) – 15 months	0.18±0.06	0.22±0.09	0.16±0.07	<0.05
% VRR – 15 months	92.0±2.4	93.8±1.0	93.3±1.8	-

Thyroid function tests

Follow up	TSH uIU/ml	FT3 pmol/l	FT4 pmol/L	T.abs	P value
Baseline	1.92±0.64	4.66±0.61	11.40±3.1	Negative	-
3 months	2±0.9	4.78±1.1	13.37±1.2	Negative	Not significant
6 months	1.77±0.7	4.1±0.4	12.40±1.1	Negative	Not significant

9 months	1.8±0.99	4.18±1.20	14.40±2.1	Negative	Not significant
1 year	1.88±1.0	3.89±0.21	12.40±0.9	Negative	Not significant

FT3=free triiodothyronine, FT4=free thyroxine, T.abs=thyroid antibodies test, TSH=thyroid-stimulating hormone

All thyroid function tests at baseline and post-ablation showed no statistically significant difference in thyroid function following MWA.

Key safety findings

Rate of complications

Complication	**Number of cases (% of patients)**
Nausea	5/267 (1.85)
Skin burn	4/267 (1.48)
Cough	3/267 (1.11)
Vomiting	2/267 (0.74)
Local oedema	2/267 (0.74)
Transient voice change	2/267 (0.74)
All complications	**18/267 (6.69) (95% CI 0.039 – 0.095)**

Study 5 Jin (2021)

Study details

Study type	Non-randomised comparative study
Country	China
Recruitment period	2018-2019
Study population and number	n=943 patients with BTNs (n=532 MWA, n=411 RFA); 578 matched patients n=289 MWA, n=289 RFA
Age and sex	MWA: Median age 48 years (range 35 to 88 years), sex not reported RFA: Median age 52 years (range 39 to 91 years), sex not reported
Patient selection criteria	Inclusion criteria: Patients aged 18 to 80 years inclusive, 2 sets of fine-needle aspiration cytology (FNAC) results confirming benign nature of nodules, maximum diameter of BTNs ≥ 2 cm. Exclusion criteria: Basic function disorders (including disorders in respiratory, circulatory, or metabolic systems), abnormal coagulation functions, abnormal liver or kidney function, allergy to local anaesthetic, BTNs less than 2 mm from thyroid capsule, more than 5 BTNs, addiction to smoking or drinking, non-completion of QoL questionnaire at baseline or follow up.
Technique	MWA: A 2450 MHz MWA system (MTI-5DT, Changcheng Co. Ltd. Nanjing, Jiangsu Province, China) was applied to BTNs. RFA: An RFA system (S-1500, Maide Co.Ltd. Shanghai, China) was applied to BTNs, with different active tips (5, 7, 10 mm) applied according to diameter of nodules.
Follow up	18 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients returned to hospital for ultrasound examination at the 1st, 3rd, 6th, 12th, and 18th postoperative month, and also filled out QoL questionnaires at the same time points.

Study design issues: This was a retrospective non-randomised comparative study. To balance group characteristics (including age, gender, number of BTNs, average volume of BTNs, Body mass index (BMI), and preoperative QoL scores,) a 1:1 propensity score matching was done. After 1:1 propensity score matching, 289 pairs of patients were matched.

The primary efficacy outcomes were mean VRR and QoL, and the primary safety outcome was the rate of complications. To calculate effect size for QoL-related parameters, ordinal logistic regression and binary logistic regression were used to calculate odds ratios. The Mann–Whitney U test was used to compare continuous variables and Fischer's exact test to compare small percentages.

The QoL questionnaire that patients filled out was made by the Korean Thyroid Association and translated into Chinese by the researchers. The QoL questionnaire was composed of 41 items divided into 4 parts, evaluating

the spiritual wellbeing, psychological wellbeing, social wellbeing, and physical wellbeing. Each item was scored between 1 and 10, resulting in a possible score range between 0 and 410.

Study population issues: Following propensity score matching, baseline characteristics did not significantly differ between MWA and RFA. The preoperative median nodule volume was 9.2 ml for both groups (range 5.6-18.9 ml) and the median preoperative quality of life as measured by the QoL questionnaire provided was 271/410 (range 181 to 410). However, baseline characteristics are given for all patients eligible for the study (n=532 in the MWA group and n=411 in the RFA group) instead of the paired patients (n=289 in each group) in whom outcomes are reported.

Key efficacy findings

Number of patients analysed: 578 (n=289 MWA, n=289 RFA)

Reduction in nodule volume

Follow up	Mean VRR % (min, max) MWA (n=289)	Mean VRR % (min, max) RFA (n=289)	P value
1 month	15.3 (8.2, 22.4)	15.4 (8.2, 22.6)	0.32
3 months	47.9 (37.7, 58.1)	48.2 (36.9, 59.5)	0.72
6 months	67.8 (59.9, 75.7)	68.1 (60.0, 76.2)	0.91
12 months	79.3 (76.1, 82.5)	80.1 (78.3, 81.9)	0.56
18 months	91.7 (88.5, 94.9)	89.2 (84.4, 94.0)	0.58

Cases of BTN recurrence

There was 1 BTN recurrence in a patient with a preliminary BTN volume of 10.28 ml (treatment group not stated). The patient had a secondary ablation treatment. After 6 months, VRR of this BTN reached 67.2% and no recurrence was found.

Quality of life

Postoperative QoL measure	Mean value for MWA (n=289) (min, max)	Mean value for RFA (n=289) (min, max)	Adjusted effect size (95% CI)	P value
Postoperative QoL score across all time points (min, max)	341.57 (334.25, 348.89)	343.91 (335.20, 352.62)	1.02 (0.78 to 1.52)	0.32

QoL (1 month postoperative)	291.38 (284.1, 298.66)	293.46 (286.65, 300.27)	0.81 (0.72 to 1.03)	0.59
QoL (3 months postoperative)	310.59 (301.83, 319.35)	312.49 (304.93, 320.05)	0.71 (0.56 to 0.91)	0.68
QoL (6 months postoperative)	337.86 (329.93, 345.79)	341.58 (332.67, 350.46)	1.09 (0.71 to 1.25)	0.81
QoL (12 months postoperative)	352.19 (340.27, 364.11)	353.78 (340.96, 366.59)	0.82 (0.56 to 1.26)	0.38
QoL (18 months postoperative)	372.89 (360.08, 385.70)	373.19 (360.68, 385.70)	0.32 (0.13 to 0.58)	0.67
Overall QoL score*: Total physical wellbeing	93.2 (85.88, 100.52)	92.9 (86.32, 99.48)	1.52 (1.32 to 1.89)	0.78
Overall QoL score*: Total psychological wellbeing	91.7 (81.92, 101.48)	93.9 (83.34, 104.46)	1.38 (1.09 to 3.56)	0.39
Overall QoL score*: Total spiritual wellbeing	91.32 (79.4, 103.04)	92.97 (79.78, 106.16)	1.52 (1.32 to 1.86)	0.38
Overall QoL score*: Total social wellbeing	72.56 (63.44, 81.68)	73.91 (62.34, 85.48)	1.08 (1.03 to 1.95)	0.24

*Max score in each category not reported (but overall max 410)

QoL parameter	**% MWA (n=289) (number of patients)**	**% RFA (n=289) (number of patients)**	**Adjusted effect size**	**P value**
Proportion of QoL scores >400	59 (170/289)	58 (167/289)	0.38 (0.31 to 0.49)	0.38
Proportion of QoL scores =410	12 (34/289)	13 (38/289)	0.59 (0.21 to 0.89)	0.42
Proportion of QoL scores 300-400	20 (58/289)	19 (55/289)	0.41 (0.18 to 0.97)	0.50
Proportion of QoL scores 200-300	12 (35/289)	13 (38/289)	0.95 (0.52 to 1.39)	0.41
Proportion of QoL scores <200	9 (26/289)	10 (29/289)	0.28 (0.11 to 0.59)	0.17

Key safety findings

Rate of complications

Complication	MWA group (n=289) % rate (number of patients)	RFA group (n=289) % rate (number of patients)	P value
Haemorrhage and haematoma	0.34 (1/289)	0	0.12
Skin burn and pain (all)	0.69 (2/289)	1.03 (3/289)	0.37
Skin burn and pain (mild)	0.35 (1/289)	0.35 (1/289)	-
Skin burn and pain (moderate)	0.35 (1/289)	0.35 (1/289)	-
Skin burn and pain (severe)	0	0.35 (1/289)	-
Hoarseness	0.35 (1/289)	0.69 (2/289)	0.72
Cough after drinking	0.35 (1/289)	0.35 (1/289)	0.49
All complications	1.73 (5/289)	2.06 (6/289)	0.73

Study 6 Luo (2021)

Study details

Study type	Case series
Country	China
Recruitment period	2014-2017
Study population and number	n=171 patients with BTNs
Age and sex	Mean age 47.0±14.2 years
Patient selection criteria	Patients with BTNs confirmed via core-needle (18-gauge) biopsy; nodules with a largest diameter larger than 3 cm; BTNs with a fluid component <80% as seen with an ultrasound assessment; normal serum free thyroxine (FT4) level and a corresponding normal or low thyrotropin (TSH) level; no vocal cord immobility, as confirmed via a laryngoscope.
Technique	A 2450 MHz MWA system (KY-2000, Kangyou Medical, Nanjing, China) was applied to BTNs with power output from 20-30W.The hydrodissection technique was applied to prevent damage to critical adjacent structures, and MWA was done using the moving-shot technique. For nodules with a diameter ≤5 cm, MWA was done in one session, while for nodules with a diameter >5 cm, MWA was done in 2 or 3 sessions.
Follow up	3 years
Conflict of interest/source of funding	No conflict of interest. Funding supported by various grants.

Analysis

Follow-up issues: Ultrasound examination was done in all patients at the time of the 1-, 3-, 6-, 12-, 24, and 36-month follow-up examinations by 2 radiologists. Upon ultrasound examination, changes in nodule volume, therapeutic success rate, and improvement of symptomatic and cosmetic problems were checked.

20/171 (11.6%) patients were lost to follow up at 24 months and 31/171 (18.1%) patients were lost to follow up after 36 months.

Study design issues: This was a retrospective case series aiming to evaluate efficacy of MWA by nodule composition.

Therapeutic success was defined as a VRR > 50% at the 12-month follow up. Technical efficiency was defined as a VRR ≥50% of the initial nodule volume at each follow-up time point. Recurrence was defined as a nodule volume increase >50% over the smallest recorded volume.

In statistical analyses, groups were compared using the Mann–Whitney U test and chi-square tests were used to compare categorical variables (where p values less than or equal to 0.05 were considered to indicate a statistically significant difference).

Study population issues: The mean diameter of these nodules was 4.3±1.3 cm, and the mean volume was 21.2±18.9 ml. Of the nodules, 58 (32.2%), 85 (47.2%), and 37 (20.6%) had volumes ≤10, 10.0–30, and ≥ 30 ml, respectively.

For the fluid component assessment, 87 (48.3%) were solid (≤10% fluid component), 74 (41.1%) were predominantly solid (11%–50% fluid component), and 19 (10.6%) were predominantly cystic nodules (51%–90% fluid component); none of the nodules were cystic (>90% fluid component).

Key efficacy findings

Number of patients analysed = 171 (151 at 24 months, 140 at 36 months)

Overall effect of procedure (n=number of nodules)

Technical success (n=number of nodules)

	All nodules (n=180)
Mean duration of ablation (min)	14.7±8.2
Technical success	97.8% (176/180)
Total energy (kJ)	19.9±12.1

Median nodule volume (n=number of nodules)

Follow up	**Median nodule volume in ml (n=180)**
Baseline	21.2±18.9
1 month	10.6±9.5*
3 months	6.2±6.0*#
6 months	3.9±5.1*♦
12 months	2.4±3.2*#♦^

* = p < 0.001 versus baseline values respectively,
# = p < 0.001 versus 1-month values respectively,
♦ = p < 0.001 versus 3-month values respectively,
^ = p < 0.05 versus 6-month values respectively.

Mean VRR % (n=number of nodules)

	Mean VRR % (n=180)

1 month	47.1±20.2
3 months	68.2±18.1
6 months	79.7±15.9
12 months	87.4±12.3
24 months (n=151 patients)	90.1
36 months (n=140 patients)	93.2

Efficacy by nodule diameter (n=number of nodules)

Technical success by nodule diameter

	Initial nodule diameter ≤10 ml (n=58)	**Initial nodule diameter 10–30 ml (n=85)**	**Initial nodule diameter ≥30 ml (n=37)**
Mean duration of ablation (min)	14.9±6.5	15.3±9.0	15.8±9.5
Technical success	96.6% (56/58)	97.6% (83/85)	100% (37/37)
Total energy (kJ)	20.2±9.0	21.5±14.5	17.4±9.5

Median nodule volume by initial nodule diameter (n=number of nodules)

Follow up	**Median nodule volume (ml) for nodules with initial diameter ≤10 ml (n=58)**	**Median nodule volume (ml) for nodules with initial diameter 10–30 ml (n=85)**	**Median nodule volume (ml) for nodules with initial diameter ≥30 ml (n=37)**
Baseline	11.5±4.7	15.1±8.5	22.8±8.2
1 month	7.5±1.9*	11.4±8.1*	27.9±13.1*
3 months	4.5±1.7*#	6.7±5.6*#	14.8±10.9*#
6 months	3.0±1.6*#♦	4.1±3.8*#♦	10.1±12.4*#♦
12 months	1.2±1.1*#♦^	2.5±3.0*#♦^	5.6±6.3*#♦^

* = p < 0.001 versus baseline values respectively,
# = p < 0.001 versus 1-month values respectively,

♦ = p < 0.001 versus 3-month values respectively,
^ = p < 0.05 versus 6-month values respectively.

Mean VRR % by initial nodule diameter (n=number of nodules)

Follow up	**Mean VRR % for nodules with initial diameter ≤10 ml (n=58)**	**Mean VRR % for nodules with initial diameter 10–30 ml (n=85)**	**Mean VRR % for nodules with initial diameter ≥30 ml (n=37)**
1 month	40.6±23.2	45.9±20.9	42.2±24.5
3 months	61.1±20.8†††	62.6±22.0†††	58.8±32.9†††
6 months	74.6±19.1†††	77.2±17.5†††	74.0±32.9†††
12 months	84.7±13.0†††	85.7±15.3†††	86.6±14.7†††

††† = p < 0.001 versus VRR(%) at 1-month follow up after ablation, respectively

Technical efficacy by nodule composition (n=number of nodules)

	Solid nodules (n=87)	**Predominantly solid nodules (n=74)**	**Predominantly cystic nodules (n=19)**
Mean duration of ablation (min)	14.8±7.7	15.2±8.5	10.7±7.4
Technical success	96.6% (84/87)	98.6% (73/74)	100% (19/19)
Total energy (kJ)	20.2±11.4	20.5±12.9	14.2±12.5

Median nodule volume by nodule composition (n=number of nodules)

Follow up	**Median nodule volume (ml), solid nodules (n=87)**	**Median nodule volume (ml), predominantly solid nodules (n=74)**	**Median nodule volume (ml), predominantly cystic nodules (n=19)**
Baseline	17.3±15.2	24.4±20.5	26.5±2.4
1 month	9.7±7.9*	11.8±10.7*	9.7±9.6*
3 months	5.8±5.0*#	6.8±5.5*#	5.5±5.3*#
6 months	3.6±2.6*#♦	4.4±3.3*#♦	3.7±4.6*#♦

12 months	2.2±2.1*#♦^	2.5±3.1*#♦^	2.8±3.9*#♦^

* = p < 0.001 versus baseline values respectively,
# = p < 0.001 versus 1-month values respectively,
♦ = p < 0.001 versus 3-month values respectively,
^ = p < 0.05 versus 6-month values respectively.

Mean VRR % by nodule composition (n=number of nodules)

Follow-up	Mean VRR %, solid nodules (n=87)	Mean VRR %, predominantly solid nodules (n=74)	Mean VRR %, predominantly cystic nodules (n=19)
1 month	31.1±26.9	38.5±31.8	35.0±34.3
3 months	56.4±22.2†††	65.2±22.6†††	73.3±17.3†††
6 months	72.6±19.6†††	78.3±20.6†††	83.9±10.8†††
12 months	83.3±15.8†††	87.4±13.5†††	88.9±10.1†††

††† = p < 0.001 versus VRR(%) at 1-month follow up after ablation, respectively

Key safety findings

Rate of complications

Complication	Number (%)	Comments
Nodule rupture	3/171 (1.7%)	Symptoms improved within 1–2 weeks after treatment with nonsteroidal anti-inflammatory drugs such as ibuprofen for 1 or 2 weeks. Lesions gradually regressed without further treatment
Hoarseness	4/171	All patients recovered within 1 month

Slight pain at the ablative site was also reported by most patients on the first day after MWA.

Study 7 Shi (2019)

Study details

Study type	Non-randomised comparative study
Country	China
Recruitment period	2015-2018
Study population and number	n=318 patients with 328 treated benign thyroid nodules; 320 matched nodules (n=160 nodules treated with MWA and n=160 nodules treated with laser ablation (LA))
Age and sex	MWA: Mean age 42.9±17.7 years, 70.6% female LA: Mean age 44.5±21.4 years, 75.0% female
Patient selection criteria	Inclusion criteria: Patients with nodules >50% solid and benign, confirmed by cytologic examination or histopathological biopsy; neck symptoms, cosmetic problems, or refused surgery or clinical observations, requirement for minimally invasive interventional therapy with absolute informed consent; serum levels of thyrotropin and thyroid hormone within normal limits. Exclusion criteria: Medication or additional treatment for thyroid nodules; incomplete data; follow up shorter than 6 months.
Technique	MWA was done with a KY-2000 2450 MHz microwave system (KY-2000, Kangyou Medical, Nanjing, China), equipped with a 16-gauge, Teflon-coated, internal-cooled microwave antenna with a 3-mm active tip and a 10-cm shaft. The power output was 30W. LA was done with an ultrasonic laser integrated system produced by Italian Esaote Medical, and Echolaser X4 laser treatment system. The device comprised a 1,064-μm diode laser unit with a maximum of 4 laser sources, each with an individual energy emission setting and independent activation, 0.3-mm optic fibre, 21-gauge Chiba needle, and a foot pedal. Power output used was 3W. Patients were positioned supine with the neck fully exposed. The target nodule location and its adjacent structures were evaluated under ultrasound and the puncture route was pre-designed. All procedures were done under aseptic conditions and local anaesthesia with 1% lidocaine. When the nodule was located at the upper or lower pole of the thyroid or adjacent to important structures such as the vagus nerve, trachea, or oesophagus, hydrodissection was chosen to prevent accidental injury.
Follow up	MWA: 14.3±6.5 months LA: 14.1±6.2 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Volume of the ablated nodules, symptom scores, cosmetic score and thyroid function were all measured 3, 6, and 12 months during the first year of follow up, and every 6 months thereafter.

Study design issues: This retrospective, non-randomised comparative study aimed to examine efficacy and safety of percutaneous ultrasound-guided microwave and laser ablation. Prior to ablation, the nodules were classified as either large or small (nodular volume ≥13 or <13 ml, respectively).

1:1 propensity score matching was done to balance baseline characteristics of the MWA and LA groups.

After the 1:1 match, qualitative variables were analysed using the chi-squared test or Fisher's exact test. Quantitative variables were analysed by Student's t-test. A p value of <0.05 was considered statistically significant.

The main efficacy outcomes were % VRR, symptom score reduction and cosmetic score reduction. Symptom scores ranged from 0 (none) to 10 (most severe) and were self-assessed based on pain or discomfort, foreign body sensation, and compression. The cosmetic scores were evaluated by an experienced physician and ranged from 1 to 4 as follows: 1, no palpable mass; 2, palpable mass but no cosmetic problems; 3, cosmetic problem on swallowing only or detected by an experienced physician; and 4, a readily detected cosmetic problem.

Complications associated with the MWA and LA ablations were in accordance with the report standard of the Society of Interventional Radiology. Major complications were considered voice changes, sympathetic nerve injury, and nodule rupture with or without infection. Minor complications included haemorrhage or hematoma, vomiting, skin burns, and thyroid function changes. Side effects included pain, coughing, and mild fever during the perioperative and follow-up periods.

Patient population issues: The baseline mean nodule volume was 12.7±5.1 ml in the MWA group and 13.1±4.7 ml in the LA group (p=0.466), the baseline symptom score was 5.8±2.5 in the MWA group and 6.0±1.9 in the LA group (p=0.421), and cosmetic score was 3.0±0.8 in the MWA group and 2.9±0.9 in the LA group (p=0.294). Baseline values by nodule size were not reported.

Key efficacy findings

Number of patients analysed = 320 (n=160 MWA, n=160 LA)

Nodule volume reduction (all nodules)

Follow up	% VRR for MWA (n=160)	% VRR for LA (n=160)	P value
3 months	54±40	56±28	0.605
6 months	70±22	75±26	0.064
12 months	75 ± 30	79±33	0.257
Last follow up	83±32	88±25	0.120

Nodule volume reduction by nodule size (n=number of nodules)

Follow up	% VRR, MWA - large nodules (n=85)	% VRR, LA - large nodules (n=75)	P value	% VRR, MWA - small nodules (n=85)	% VRR, LA - small nodules (n=75)	P value
3 months	55±37	57±31	0.703	53 ±41	55±27	0.725
6 months	68±24	77±31	0.036	72±21	73±26	0.796
12 months	72±25	81±30	0.035	77±24	76±33	0.832
Last follow-up	79±26	87±25	0.042	85 ± 25	89±28	0.358

Symptom and cosmetic score, all nodules (n=number of nodules)

Follow up	Symptom score for MWA (n=160)	Symptom score for LA (n=160)	Cosmetic score for MWA (n=160)	Cosmetic score for LA (n=160)
3 months	5.5±1.8	5.8±2.0	2.8±1.1	2.8±1.0
6 months	4.6±2.2	4.7±2.1	2.2±0.9	2.3±1.1
12 months	4.2±1.8	4.1±1.9	1.8±1.2	1.9±1.0
Last follow up	3.5±1.6	3.6±1.9	1.5±0.8	1.6±0.7

Symptom score by nodule size (n=number of nodules)

Follow up	Symptom score, MWA - large nodules (n=85)	Symptom score, LA - large nodules (n=75)	Symptom score, MWA - small nodules (n=85)	Symptom score, LA - small nodules (n=75)
3 months	5.8±1.9	6.2±2.0	5.1±1.7	5.2±1.8
6 months	5.0±2.2	5.2±1.9	4.4±2.0	4.3±2.3
12 months	4.5±1.6	4.7±1.7	4.0±1.8	3.8±2.0
Last follow-up	3.9±1.9	4.0±1.8	3.2±1.5	3.2±1.8

Cosmetic score by nodule size (n=number of nodules)

Follow up	Cosmetic score, MWA - large nodules (n=85)	Cosmetic score, LA - large nodules (n=75)	Cosmetic score, MWA - small nodules (n=85)	Cosmetic score, LA - small nodules (n=75)
3 months	3.0±0.8	3.0±1.0	2.5±1.2	2.6±1.1
6 months	2.4±1.1	2.5±1.2	2.0±0.9	2.0±1.3
12 months	2.0±1.3	2.2±0.9	1.7 ± 0.7	1.7±0.8
Last follow-up	1.6±1.0	1.8±0.8	1.4±0.7	1.4±0.5

Key safety findings

Complications observed after MWA and LA – number of nodules (%)

Complication	MWA (n=160)	LA (n=160)	P value
Voice change	2 (1.3)	3 (1.88)	0.937
Haematoma	5 (3.1)	2 (1.3)	0.813
Pain	20 (12.5)	39 (24.4)	0.135

Complications by nodule size

	MWA, large nodules (n=85)	LA, large nodules (n=75)	P value, large nodules	MWA, small nodules (n=85)	LA, small nodules (n=75)	P value, small nodules
Voice change	2 (2.4)	1	0.914	0	2	0.818
Haematoma	3	1	0.829	2 (2.4)	1	0.908
Pain	10	23	0.162	10	16	0.491

Study 8 Jin (2018)

Study details

Study type	Non-randomised comparative study
Country	China
Recruitment period	2015-2017
Study population and number	n=212 patients with BTNs (n=106 treated with MWA and n=106 treated by conventional thyroidectomy)
Age and sex	MWA: Mean age 39.6±9.3 years, 74% female Thyroidectomy: Mean age 45.4±11.2 years, 74% female
Patient selection criteria	Inclusion criteria: Patients with nodules over 2 mm apart from the thyroid capsule; maximum diameter of the TN ≥ 2 cm; existence of cosmetic problems or compressive symptoms; cytological conformation of the benign nature of the nodule through US-guided fine-needle aspiration cytology; serum levels of thyrotropine and thyroid hormone within normal levels. Exclusion criteria: Whole or a large part of the TN is located behind the sternum; abnormal function of the vocal cords on the opposite side of the TN; serious coagulation disorders; serious cardiopulmonary diseases; history of chemotherapy or radiotherapy.
Technique	Patients were placed in a supine position with their necks fully exposed. MWA was done with a MTI-5DT microwave system (Changcheng Medical Instruments Cooperation, Nanjing, China). For conventional thyroidectomy, a 4–6 cm incision was made on the superior border of the sternum. The thyroid goitre was dissected with an ultrasound knife (Johnson & Johnson Inc., New Brunswick, NJ, USA).
Follow up	MWA: Mean 12.8 ± 5.1 months Thyroidectomy: Mean 12.7 ± 2.8 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Serum concentrations of thyrotropine, triiodothyronine, free thyroxine, thyroglobulin, IL-6, TNF-a and CRP were detected at 12 h after the operation. US assessments were done at 1, 3, 6 and 12 months after treatment.

Study design issues: This retrospective, non-randomised comparative study aimed to compare ultrasound (US)-guided percutaneous MWA and conventional thyroidectomy in benign thyroid nodules treatment.

280 patients were initially selected for study, and 106 pairs matched after 1:1 propensity score matching was done. After the 1:1 match, qualitative variables were analysed using the chi-squared test. One-way analysis of

variance was used to compare the normal distribution quantitatively. A p value of < 0.05 was considered statistically significant.

The main efficacy outcomes were % VRR and nodule volume where TN volume = ¼ p*a*b*c/6 (where a is the largest diameter, b and c are the other 2 perpendicular diameters) and VRR(%) = ¼ [(baseline volume - final volume)*100]/baseline volume.

Patient population issues: The baseline median nodule volume was 5.7 ml (IQR 3.8-10.3) in the MWA group and 5.5 ml (IQR 3.5-9.6) in the thyroidectomy group (p=0.531). The baseline median nodule diameter was 28.6 mm (IQR 24.1–35.3) in the MWA group and 28.2 mm (IQR 23–35.9) in the thyroidectomy group (p=0.56).

Key efficacy findings

Number of patients analysed = 212 (n=106 MWA, n=106 thyroidectomy)

Nodule volume reduction for MWA group (n=106)

Follow up	Volume cm^3	% VRR
Baseline	2.50 (0.30–5.00)	-
1 month	2.12 (1.21–2.79)	15.2±2.3
3 months	1.31 (0.89–1.91)	47.6±3.6%
6 months	0.82 (0.32–1.21)	67.2±6.8%
12 months	0.51 (0.00–1.00)	79.6±10.2%

Key safety findings

Percentage incidence of complications

Complication	Incidence in MWA (n=106)	Thyroidectomy (n=106)
Vocal cord paralysis	0.94% (1/106)	6.6% (7/106)
Skin burn	0.94% (1/106)	0

All patients recovered from complications within 3 months of their procedure.

Study 9 Fu (2021)

Study details

Study type	Case series
Country	China
Recruitment period	2018-2020
Study population and number	n=115 patients with 115 BTNs
Age and sex	Mean age 44.3±9.3 years for males (range 30-74), mean age 43.8±10.8 years for females (range 19-68 years), 85% female
Patient selection criteria	Inclusion criteria: Patients with BTNs confirmed twice by cytological diagnosis; no suspicion of malignancy; compression symptoms, foreign body sensation or neck discomfort; patient request to undergo thermal ablation due to anxiety about condition; patients refusing traditional surgery or patients unable to undergo surgery. Exclusion criteria: Previous ablation of thyroid nodules; severe cardiac or pulmonary disease or coagulation dysfunction; severe adhesions between the nodules and oesophagus, trachea, and large blood vessels that could not be effectively separated; abnormally high calcitonin; incomplete medical follow up; unilateral multiple nodules
Technique	Patients were placed in the supine position with hyper-extended neck. A 2450 MHz MWA system (KY-2000, Kangyou Medical, China) MWA system was used with a continuous output of 30W, and the procedure was done using the moving-shot technique.
Follow up	12 months
Conflict of interest/source of funding	No conflict of interest reported. Funded by National Natural Science Foundation of China.

Analysis

Follow-up issues: Ultrasonography was done 1, 3, 6, and 12 months after the procedure, and thyroid function was re-examined 1 month after the procedure.

Study design issues: This single-centre, retrospective study assessed safety and efficacy of MWA using ultrasound guidance for BTNs and examined factors linked to efficacy.

The primary efficacy outcomes measured were nodule volume and % VRR, and the primary safety outcome measured was the rate of complications. “Cured” patients were defined as a VRR of >90% after 12-month follow up.

Study population issues: A total of 171 patients (with 247 nodules) were selected in this research, with 115 patients meeting the criteria. The baseline nodule volume in the cohort of 115 patients was 5.30±8.56 ml.

Key efficacy findings

Number of patients analysed: 115

Follow up	Mean nodule volume in ml (±SD)*	Mean % VRR (±SD)*
Baseline	5.30±8.56	-
1 month	2.62±4.45	41.96±21.66
3 months	1.48±2.42	68.64±18.85
6 months	0.89±1.70	83.56±14.05
12 months	0.58±1.32	91.43±10.35

*Both mean nodule volume and % VRR were statistically significant ($p<0.05$) at all time points.

Differences in thyroid function before and after treatment was not statistically significant ($p > 0.05$).

In a univariate analysis of parameters, there were statistically significant ($p<0.05$) differences in maximum BTN diameter, preoperative volume, echo, internal composition, blood flow distribution, enhancement mode, and immediate volume after ablation between cured (VRR >90%) and non-cured (VRR ≤90%) nodules. Multivariate logistic regression analysis showed that internal composition of the BTNs, enhancement mode, and the immediate volume after ablation were statistically significant in the determination of the ablation efficacy ($p<0.05$).

Key safety findings

Rate of complications

Side effect/complication	% incidence (no. of patients)	Comments on resolution
Neck pain	9.56 (11/115)	Resolved within 5 days of procedure
Hoarseness (short-term)	2.61 (3/115)	Resolved within 1 day of procedure
Hoarseness (long term)	0.87 (1/115)	Resolved 3 months after procedure
Haematoma	3.48 (4/115)	Resolved 2-7 days after procedure
Fever	1.74 (2/115)	Resolved 3 days after procedure
Skin burn	0.87 (1/115)	-
Oesophageal burn	0.87 (1/115)	-

Study 10 Liu (2022)

Study details

Study type	Case series
Country	China
Recruitment period	2016-2018
Study population and number	n=173 patients with BTNs
Age and sex	Mean age 54 years (range 45 to 63), 74% female
Patient selection criteria	Inclusion criteria: People who had ultrasound-guided MWA with confirmation of the benign nature of the nodule (Bethesda Class II) based on fine-needle aspiration cytology (FNAC); serum thyroid hormone and thyrotropin levels that were within normal ranges. Exclusion criteria: Confirmation of follicular lesion/atypia of 'undetermined significance' and 'follicular neoplasm'; patients with follow-up time <36 months.
Technique	Patients were placed in a supine position with their necks fully exposed. MWA was done with a 2450 MHz MWA system (KY-2000, Kangyou Medical, China) MWA was done using the moving-shot technique.
Follow up	3 years
Conflict of interest/source of funding	No conflict of interest. Study funded by Shandong Province Natural Science Foundation (item numbers: ZR2017LH054) and the Shandong Province Science and Technology Development projects (item numbers: 2011YD18028).

Analysis

Follow-up issues: Ultrasound examinations, clinical symptom evaluations, and laboratory examinations were carried out on the second day after ablation. Thyroid ultrasonography was performed one month, 6 months, and 12 months after the ablation, and then subsequently every 12 months.

Study design issues: Case series with long-term follow up. The main efficacy outcomes were % VRR and cosmetic score reduction. The cosmetic scores were evaluated by an experienced physician and ranged from 1 to 4 as follows: 1, no palpable mass; 2, palpable mass but no cosmetic problems; 3, cosmetic problem on swallowing only or detected by an experienced physician; and 4, a readily detected cosmetic problem. Therapeutic success was defined as a reduction of more than 50% in nodule volume after 6 month follow up.

Statistical differences in continuous variables were evaluated using the Wilcoxon test for coupled samples. A p value <.05 was considered statistically significant.

Patient population issues: The baseline median nodule volume was 4.23 ml (IQR 2.27 to 9 ml), and ±11.42 ml, the baseline symptom score was 4.93±2.16, and median cosmetic score was 2.00 (IQR 2.00 to 3.00).

Key efficacy findings

Number of patients analysed: 173

Reduction in nodule volume and cosmetic score

Follow up	Median nodule volume in ml (IQR)	Mean % VRR	Median cosmetic score (IQR)
Baseline (n=173)	4.23 (2.27 to 9.00)	-	2.00 (2.00 to 3.00)
1 month (n=173)	3.54 (1.62 to 7.55)*	18%	2.00 (1.00 to 3.00)*
6 months (n=170)	0.79 (0.33 to 1.91)*	78.7%	1.00 (1.00 to 2.00)*
12 months (n=164)	0.35 (0.07 to 0.90)*	89%	1.00 (1.00 to 1.00)*
24 months (n=100)	0.08 (0.00 to 0.48)*	94.5%	1.00 (1.00 to 1.00)*
36 months (n=87)	0.00 (0.00 to 0.20)*	97.1%	1.00 (1.00 to 1.00)*

*p<0.01.

Key safety findings

Rate of complications

Side effect/complication	% incidence (no. of patients)
Pain	2.9 (5/173)
Hoarseness	1.2 (2/173)

Study 11 Yildirim (2022)

Study details

Study type	Case series
Country	Turkey
Recruitment period	2019-2020
Study population and number	n=40 patients with BTNs
Age and sex	Mean age 44.1±10.1 years, 40% female
Patient selection criteria	Inclusion criteria: Presence of benign diagnosis on two independent Ultrasound (US)-guided fine needle aspiration biopsies (FNAB); solid or mainly solid nodules with solid component >80% on US study; clinical compressive symptoms or cosmetic concerns; normal thyroid functions. Exclusion criteria: Retrosternal excessive growth; presence of US findings indicating malignant nodule in spite of benign results of biopsies.
Technique	MWA was done with a 2450 MHz TATO microwave generator (Terumo, Italy) and an uncooled type 18 G, thyroid dedicated probe antenna. The MWA antenna was placed into the nodule along its short axis with the trans-isthmic approach and 15W power applied for a duration of 10 to 20 minutes depending on the size of nodules.
Follow up	12 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Ultrasound examination, laboratory, symptomatic and clinical data were evaluated at 3rd, 6th and 12th month. The US examination was performed to assess the nodule with size, volume and echogenicity.

Study design issues: This retrospective case series aimed to evaluate the long-term efficacy and safety of uncooled MWA for the treatment of benign thyroid nodules and its long-term effect on thyroid functions. The primary efficacy outcome was % VRR, and secondary outcome was preservation of thyroid function.

Laboratory studies included complete blood count, coagulation tests, and complete thyroid function tests (triiodothyronine [T3], free thyroxine [fT4], and thyroid stimulating hormone [TSH] levels). In addition, anti-thyroid peroxidase antibody (anti-TPO) and anti-thyroglobulin (anti-TG) antibody levels were also measured to exclude autoimmune thyroid disease. The reference value ranges accepted as normal in the laboratory are as follows: Anti-TPO: 0 to 34 IU/ml, Anti-TG: 0 to 115 IU/ml, TSH: 0.27 to 4.2 uIU/ml, fT4: 0.93–1.7 nanograms/dl, T3: 2.04 to 4.4 pg/ml.

Clinical symptoms were scored by using a visual analogue scale of 0-10 cm (with higher score indicating worse symptoms) and, a four-point subjective scale was used for cosmetic scoring. According to this scale (I) no

palpable mass, (II): an invisible but palpable mass; (III), a visible mass during neck extension or swallowing; and (IV), an easily visible mass.

Statistical analyses were performed with IBM SPSS Statistics (version 22, IBM, USA). Data were described using descriptive statistical methods. Continuous variables were reported as the mean ± standard deviation (SD) with range and categorical variables were reported as frequency and percentage.

Statistical differences were evaluated using the Wilcoxon test for coupled samples. A p value of <0.05 was considered statistically significant.

Patient population issues: The baseline mean nodule diameter at its widest point was 39.3±11.3 mm, and the mean nodule volume was volume was 19.04±16.98 ml. The mean symptom score was 6±0.73 and the mean cosmetic score was 3.6±0.49.

Key efficacy findings

Number of patients analysed = 40

Nodule volume reduction

Parameter (mean±SD)	Baseline	3 months	6 months	12 months
Longest diameter (mm)	39.35 ± 11.32	33.00 ± 9.02*	29.85 ± 9.14*	25.8 ± 8.54*
Nodule volume (ml)	21.08 ± 15.29	10.63 ± 9.58*	7.20 ± 7.19*	4.16 ± 3.45*
% VRR	-	49.88 ± 12.49*	65.3 ± 11.78*	79.06 ± 8.65*
Symptom score	6.25 ± 0.74	2.42 ± 1.19*	1.47 ± 0.96*	0.95 ± 0.74*
Cosmetic score	3.52 ± 0.50	2.45 ± 0.84*	2.15 ± 0.83*	1.92 ± 0.88*

* p<0.0001

Preservation of thyroid function

Parameter (mean± SD)	Baseline	3 months (p value)	6 months (p value)	12 months (p value)
TSH (uIU/ml)	1.30 ± 0.53	1.46 ± 0.84 (p=0.199)	1.45 ± 0.89 (p=0.538)	1.46 ± 0.72 (p=0.065)
fT4 (nanograms/dl)	1.07 ± 0.21	1.06 ± 0.20 (p=0.928)	1.16 ± 0.23 (p=0.05)*	1.14 ± 0.21 (p=0.007)*
T3 (pg/ml)	3.23 ± 0.37	3.27 ± 0.40 (p=0.086)	3.26 ± 0.37 (p=0.398)	3.17 ± 0.38 (p=0.732)
Anti-thyroglobulin (IU/ml)	6 ± 7	7.29 ± 14.01 (p=0.652)	5.19 ± 5.23 (p=0.138)	6.96 ± 9.01 (p=0.192)

Anti-thyroid peroxidase antibody (IU/ml)	6.05 ± 6.20	6.03 ± 5.92 (p=0.893)	6.56 ± 5.94 (p=0.139)	7.12 ± 5.72 (p=0.41)

* p<0.05

Key safety findings

1/40 patients experienced first-degree skin burn which resolved spontaneously.

Validity and generalisability of the studies

- The majority of the studies were carried out in China, with a few studies from Germany included in the 3 systematic reviews.
- There is some overlap between the studies that have been included in the systematic reviews.
- The longest follow up was 3 years but the majority of the studies included in the overview have a 12-month follow up or shorter.
- The studies included in the key evidence used both cooled and uncooled MWA devices; most of the studies looked at cooled microwave ablation.
- The comparative studies included in the summary of evidence compare MWA with RFA, traditional thyroidectomy and laser ablation.

Existing assessments of this procedure

A consensus statement on non-surgical and non-radioiodine techniques for BTN ablation (including but not limited to microwave ablation) from the Thyroid Section (German Society for Endocrinology), the Thyroid Working Committee (German Society for Nuclear Medicine), and the German Association of Endocrine Surgeons (CAEK) for the German Society of General and Visceral Surgery (DGAV) was published in 2020 (Feldkamp 2020). They stated:

- If treatment of a thyroid nodule is planned with surgical/non-radioiodine ablation therapy, fine-needle aspiration cytology is required prior to treatment in the following situations and must show benign cytology (according to Bethesda class I, II) with reliable/sufficient diagnostic value (at least 6 groups of follicular cells with 10–15 cells each).
- In nodules with low risk of malignancy (completely cystic, mixed cystic and solid isoechoic, spongiform, isoechoic appearance, nodule with smooth margins) a single fine-needle biopsy is required.

- In nodules with higher probability of malignancy (intermediate risk according to TIRADS, EU-TIRADS), 2 fine-needle biopsies are necessary. In contrast, autonomously functioning nodules do not require a fine-needle biopsy.
- Pre-and post-interventional, all patients who are planned for a local-ablative procedure must be examined as accurately as patients who undergo surgery. Calcitonin-screening is mandatory as is laryngoscopy prior to and after the procedure.
- The performing institution must be able to treat complications (bleeding, infection) in case of Radiofrequency ablation (RFA), Percutaneous Microwave Ablation (PMWA), and Laser Thermal Ablation (LTA).

A second consensus statement on thermal ablation (including but not limited to microwave ablation) from the Italian MIT Thyroid Group was published in 2019 (Papini 2019). They stated:

- In symptomatic predominantly cystic thyroid nodules, image-guided thermal ablation should be considered as an option when local symptoms persist after ethanol ablation.
- A double cytological confirmation of benignity should be obtained prior to image-guided thermal ablation of thyroid nodules.
- Thermal ablation may be proposed as a first-line treatment for solid non-functioning thyroid nodules that are benign at cytology when they become symptomatic.
- Thermal ablation may be proposed as a treatment for non-functioning benign multinodular goitre only in patients who refuse or who cannot undergo surgery.
- Thyroid nodules treated with thermal ablation should be routinely followed-up with clinical and US examination.
- In case of incomplete symptom resolution, symptom relapse, or nodule regrowth, a re-treatment with thermal ablation may be considered.

- Thermal ablation may be proposed as a treatment option for AFTN in patients who refuse or cannot undergo traditional treatments with radioiodine or surgery.
- Small size AFTN can be treated with thermal ablation when the preservation of normal thyroid tissue function is a priority and it is reasonable to expect at least 80% nodule volume ablation.

Related NICE guidance

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

Interventional procedures

- High-intensity focused ultrasound for symptomatic benign thyroid nodules. Interventional procedures guidance 643 (2019). Available from https://www.nice.org.uk/guidance/ipg643
- Ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules. Interventional procedures guidance 562 (2016). Available from https://www.nice.org.uk/guidance/ipg562
- Minimally invasive video-assisted thyroidectomy. Interventional procedures guidance 499 (2014). Available from https://www.nice.org.uk/guidance/ipg499

NICE guidelines

- Thyroid disease: assessment and management. NICE guideline 145 (2019). Available from Thyroid disease: assessment and management

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional 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 professional experts, 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 professional expert questionnaires for percutaneous ultrasound-guided microwave ablation for symptomatic benign thyroid nodules were submitted and can be found on the NICE website.

Patient organisation opinions

One patient organisation submission for percutaneous ultrasound-guided microwave ablation for symptomatic benign thyroid nodules was received and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 2 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 3 companies 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

- Several non-English language studies carried out in China may contribute further to the evidence base but have not been included in this overview.

References

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2. Cui T, Jin C, Jiao D et al. (2019) Safety and efficacy of microwave ablation for benign thyroid nodules and papillary thyroid microcarcinomas: A systematic review and meta-analysis. European Journal of Radiology 118: 58–64.
3. Guo DM, Chen Z, Zhai YX et al. (2021) Comparison of radiofrequency ablation and microwave ablation for benign thyroid nodules: A systematic review and meta-analysis. Clinical Endocrinology 95(1): 187–96.
4. Honglei G, Shahbaz M, Farhaj Z et al. (2021) Ultrasound guided microwave ablation of thyroid nodular goiter and cystadenoma: A single center, large cohort study. Medicine 100(34): e26943.
5. Jin H, Fan J, Lu L et al. (2021) A Propensity Score Matching Study Between Microwave Ablation and Radiofrequency Ablation in Terms of Safety and Efficacy for Benign Thyroid Nodules Treatment. Frontiers in Endocrinology 12: 584972.
6. Luo F, Huang L, Gong X et al. (2021) Microwave ablation of benign thyroid nodules: 3-year follow-up outcomes. Head & Neck 43(11): 3437–47.
7. Shi YF, Zhou P, Zhao YF et al. (2019) Microwave Ablation Compared With Laser Ablation for Treating Benign Thyroid Nodules in a Propensity-Score Matching Study. Frontiers in Endocrinology 10: 874.
8. Jin H, Fan J, Liao K et al. (2018) A propensity score matching study between ultrasound-guided percutaneous microwave ablation and conventional thyroidectomy for benign thyroid nodules treatment. International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 35(1): 232–8.
9. Fu QQ, Kang S, Wu CP et al. (2021) A study on the efficacy of microwave ablation for benign thyroid nodules and related influencing factors. International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 38(1): 1469–75.
10. Liu LH, Yang BB, Liu Y et al. (2022). Factors related to the absorption rate of benign thyroid nodules after image-guided microwave ablation: a 3-year follow-up. International Journal of Hyperthermia 39(1): 8–14.

11. Yildirim G, Karakas HM. (2022). Uncooled Microwave Ablation as a Treatment Option to Preserve Thyroid Function in Patients with Benign Thyroid Nodules. Journal of the Belgian Society of Radiology 106(1): 50, 1-7.
12. Zhao J, Qian L, Liu Y et al. (2021) A long-term retrospective study of ultrasound-guided microwave ablation of thyroid benign solid nodules. International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 38(1): 1566–70.
13. Feldkamp J, Grunwald F, Luster M et al. (2020) Non-Surgical and Non-Radioiodine Techniques for Ablation of Benign Thyroid Nodules: Consensus Statement and Recommendation. Experimental and Clinical Endocrinology & Diabetes, 128(10): 687–92.
14. Papini E, Pacella CM, Sollini M et al. (2019) Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT) group. International Journal of Hyperthermia, 36(1): 376–82.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	22/12/2021	Issue 12 of 12, December 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	22/12/2021	Issue 12 of 12, December 2021
International HTA database (INAHTA)	22/12/2021	-
MEDLINE (Ovid)	22/12/2021	1946 to December 21, 2021
MEDLINE In-Process (Ovid)	22/12/2021	1946 to December 21, 2021
MEDLINE Epubs ahead of print (Ovid)	22/12/2021	1946 to December 21, 2021
EMBASE (Ovid)	22/12/2021	1974 to 2021 December 21
EMBASE Conference (Ovid)	22/12/2021	1974 to 2021 December 21

Trial sources searched

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

Websites searched

- 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)
- 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.

Literature search strategy

Number	Search term

1	Thyroid Nodule/
2	Thyroid Diseases/
3	(Thyroid* adj4 (nodul* or adenom* or cyst* or diseas* or lump* or tumor* or tumour*)).tw.
4	AFTN.tw.
5	BTNs.tw.
6	exp Goiter/
7	(goitre* or goiter*).tw.
8	or/1-7
9	(benign or benignant or harmless or non-malignant or non-cancerous).tw.
10	8 and 9
11	Radiofrequency Ablation/
12	Catheter Ablation/
13	((radiofrequen* or radio-frequen* or radio frequen* or rf) adj4 ablat*).tw.
14	(Radio* adj4 frequen* adj4 ablat*).tw.
15	RFA.tw.
16	((catheter* or needle* or electrode* or heat* or (transvenous adj1 electric*)) adj4 ablat*).tw.

17	Ablation Techniques/
18	(percutan* adj4 ablat*).tw.
19	Microwaves/
20	MWA.tw.
21	(Microwave* adj4 ablat*).tw.
22	ultrasound guided.tw.
23	or/11-22
24	10 and 23
25	TATO.tw.
26	Thermal Ablation Treatments for Oncology.tw.
27	25 or 26
28	24 or 27
29	animals/ not humans/
30	28 not 29

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Aydenizoz D, Selcuk OT, Cetinkaya EA et al. (2021) A case of vocal cord paralysis after thyroid nodule microwave ablation. International Medicine 2(6): 362–5.	**Benign nodule** Case report n=1	The risk of nerve damage is very low in the microwave ablation technique. In the case of recurrent nerve paralysis, it is important to perform a laryngoscopic examination by the otolaryngologist and to call the patient for monthly outpatient clinic controls to check for temporary or permanent paralysis.	Case report.
Bo XW et al. (2022) Comparison of efficacy, safety, and patient satisfaction between thermal ablation, conventional/open thyroidectomy, and endoscopic thyroidectomy for symptomatic benign thyroid nodules. International Journal of Hyperthermia 39(1): 379–89.	Non-randomised comparative study N=505 (n=320 conventional thyroidectomy, n=56 endoscopic thyroidectomy, n=88 MWA, n=41 RFA) Follow up = median 19 months	Compared to conventional thyroidectomy and endoscopic thyroidectomy, thermal ablation has comparable efficacy, safety, and patient satisfaction and exhibits greater protection of thyroid function for the treatment of symptomatic BTNs.	Outcomes for MWA not reported separately.
Cao J et al. (2022) Application of contrast-enhanced ultrasound in minimally invasive ablation of benign thyroid nodules. Journal of	Non - randomised	The mean nodular volume reduction rate (VRR) at 1, 6, and 12 months follow-up demonstrated no significant difference between the two ablation groups (microwave ablation versus radiofrequency ablation).	Study mainly focuses on imaging outcomes.

Interventional Medicine 5(1): 32–6.	comparative study N=62 (n=43 MWA versus n=19 RFA) Follow up = 12 months	Twelve months after ablation, the mean (SD) VRR of all BTNs was 60.3±10.3%. CEUS helped guide treatment decisions for BTNs before ablation treatment. Moreover, it could also be used to accurately and noninvasively evaluate treatment efficacy.	
Chen X, Wu W, Gong X et al. (2017) Ultrasound-Guided Percutaneous Microwave Ablation for Solid Benign Thyroid Nodules: Comparison of MWA versus Control Group. International Journal of Endocrinology, 2017: 9724090.	**Benign solid nodules** Non-randomised comparative study n=115 (75 MWA vs 40 untreated controls) Follow up = 12 months	Volume of all 90 benign thyroid nodules obviously decreased after microwave ablation at 3-, 6-, 9-, and 12-month follow-ups ($p < 0.01$), while that of the control group increased at the follow-up of 12 months ($p < 0.01$). The volume reduction rate (VRR) at 3-, 6-, 9-, and 12-month follow-ups was 55.98%, 69.31%, 76.65%, and 84.67% in the MWA group, respectively. The cosmetic problems and clinical symptoms were also improved in the MWA group. All the patients are well tolerated to the procedure. Hoarseness occurred in 2 cases (2.7%) and Horner syndrome in 1 case (1.3%), and 1 patient (1.3%) developed slight burn on cervical skin.	Studies with more patients or longer follow-up are included.
Cheng Z, Che Y, Yu S et al. (2017) US-Guided Percutaneous Radiofrequency versus Microwave Ablation for Benign Thyroid Nodules: A Prospective Multicenter Study. Scientific Reports 7(1): 9554.	**Benign nodules** Non-randomised comparative study n= 1252 (603 MWA vs 649 RFA) Follow up = Mean 13.9 months (MWA)	The results for the nodular MDRR and VRR in the RFA group were significantly better than those in the MWA group at 6 months and later follow-up, and the major complication rates of 4.78% and 6.63% in RFA and MWA groups showed no statistically significant differences.	Included in Zheng (2018) and Guo (2021) systematic reviews

Cui R, Yu J, Han Z et al. (2019) Ultrasound-Guided Percutaneous Microwave Ablation for Substernal Goiter: Initial Experience. Journal of Ultrasound in Medicine 38(11): 2883–91.	**Substernal goitre** Case series n=10 Follow up = 3 months	The nodule volume was significantly reduced at the 3-month follow-up (17.5 ± 9.5 mL; P < .05). The mean 3-month VRR of the index nodule was 66.7% ± 7.1%. A higher ablated portion-to-nodule ratio 1 day after MWA predicted a higher 3-month VRR (Spearman r = 0.646; P = .044). The mean symptom score (from 4.5 ± 1.7 to 1.5 ± 1.0; P = .005) and cosmetic grade (from 3.3 ± 0.5 to 2.2 ± 0.4; P = .004) declined significantly 3 months after the procedure. No complications or unexpected side effects were observed.	Studies with more patients or longer follow-up are included.
Dong P, Wu X-L, Sui G-Q et al. (2021) The efficacy and safety of microwave ablation versus lobectomy for the treatment of benign thyroid nodules greater than 4 cm. Endocrine 71(1): 113–21.	**Benign nodules** Non-randomised comparative study n=101 (48 MWA vs 53 lobectomy) Follow up = Mean 13.9 months (MWA)	During the 12-month follow-up, the mean nodule volume in the MWA group was reduced from 36.1 +/- 23.1 to 4.0 +/- 4.1 ml, and the mean VRR of the nodules was 90 +/- 5% in the MWA group, which was comparable with that in the surgery group. MWA is safe and effective for the treatment of benign thyroid nodules > 4 cm. Moreover, MWA is associated with a faster recovery, fewer complications, better protection of thyroid function, and superior aesthetic results relative to thyroid lobectomy.	Studies with more patients or longer follow-up are included.
Erturk MS, Cekic B, Celik M (2020) Microwave Ablation of Benign Thyroid Nodules: Effects on Systemic Inflammatory Response. Journal of the College of Physicians and	**Benign nodules** Case series n=35 patients Follow up = 6 months	The nodule volume decreased from 23.89 ±15.44 cc to 11.57 ±8.65 cc at two months and to 7.79 ±5.74 cc at six months. The VRR% increased from 38.65 ±16.82 to 63.16 ±14.19 at three months and to 68.29 ±11.80 at six months. The mean value of NLR decreased from 2.28 ±0.86 to 1.78 ±0.54.	Studies with more patients or longer follow-up are included.

Surgeons Pakistan 30(7): 694–700.			
Erturk MS, Cekic B, Celik M et al. (2021) Microwave ablation of symptomatic benign thyroid nodules: Short- and long-term effects on thyroid function tests, thyroglobulin and thyroid autoantibodies. Clinical Endocrinology 94(4): 677–83.	**Benign nodules** Case series n= 46 Follow up = 6 months	The difference between all thyroid hormone levels at pre MWA and 24 h after MWA was statistically significant (p <.001). FT3 (4.62) pmol/L and FT4 (10.81) pmol/L median levels increased significantly (p <.001), while thyrotropin (TSH) levels decreased at 24 h after MWA (p <.001). Thyroid antibodies levels were not statistically different at 6-month (p >.05), whereas Tg levels decreased (p <.001) compared to pre MWA. While no significant effect was observed at 6 month, the effect of MWA on thyroid function tests was prominent at 24 h.	Studies with more patients or longer follow-up are included.
Fei Y, Xing Z, Li Z et al. (2020) Effects of energy-based ablation on thyroid function in treating benign thyroid nodules: a systematic review and meta-analysis. International Journal of Hyperthermia 37(1): 1090–1102.	**Benign nodules** Systematic review n=6380 (42 studies)	Energy-based ablation was more likely to have negative effects on thyroid function and antibodies and led to transient increase in Tg level in the short term. However, most of the patients would not develop any thyroid dysfunction in the long-term follow-up.	Mixed interventions
Feng B, Liang P, Cheng Z et al. (2012) Ultrasound-guided percutaneous microwave ablation of benign thyroid nodules: experimental and clinical studies. European Journal of Endocrinology 166(6): 1031–7.	**Benign nodules** Case series n=11 Follow up = 9 months	At the last follow- up, the largest diameter decreased from 2.9±1.0 (range 1.6–4.1) to 1.9±0.7 (range 0.4–3.0) cm (P<0.01), and the volume decreased from 5.30±4.88 (range,0.89–14.81) to 2.40±2.06 (range, 0.02–6.35) ml (P<0.01). The volume reduction ratio was 45.99±29.90 (range, 10.56–98.15) %. The cosmetic grading score was reduced	Included in Zheng (2018) systematic review

		from 3.20±0.79 to 2.30±0.95 (P<0.05). One patient experienced temporary nerve palsy and was recovered within 2 months after treatment.	
Guan SH, Wang H, Teng DK (2020) Comparison of ultrasound-guided thermal ablation and conventional thyroidectomy for benign thyroid nodules: a systematic review and meta-analysis. International Journal of Hyperthermia 37(1): 442–9.	**Benign nodules** Systematic review n=1289 (7 studies)	The incidences of hoarseness [odds ratio (OR) 0.33, 95% confidence interval (95% CI; 0.14, 0.79)], hypothyroidism [risk difference (RD) -0.31, 95% CI -0.34,-0.28)] and postoperative pain [OR 0.35, 95% CI (0.25,0.49)] were lower, and the hospitalization time was shorter [standard mean difference (SMD) -4.01, 95% CI -4.22, -3.81)], in the thermal ablation group than in the conventional thyroidectomy group, and postoperative cosmetic effects were better [relative risk (RR) ratio 1.12, 95% CI (1.01, 1.24)] (p < 0.05).	Mixed interventions
Wang B, Han ZY, Yu J et al. (2017) Factors related to recurrence of the benign non-functioning thyroid nodules after percutaneous microwave ablation. International Journal of Hyperthermia, 33(4): 459–64.	**Benign non-functioning solid nodules** Case series n=110 Follow up = 12 months	The US-guided MWA results in a satisfactory long-term outcome of the patients with a benign solitary thyroid nodule. We identified three risk factors for recurrence: initial volume, vascularity, and the energy per 1 ml reduction in nodular volume.	Included in Cui (2019) systematic review
Happel C, Korkusuz H, Koch DA et al. (2015) Combination of ultrasound guided percutaneous microwave ablation and radioiodine therapy in benign	**Nodular goitre** Case series n=10 Follow up = not reported	Depending on ablated volume by MWA, RIT monotherapy requires on average 31.2% more 131I-activity than the combined therapy. The combined therapy remarkably decreases 131I-dose and hospitalization time. The combined MWA and RIT	Combined interventions

thyroid diseases. A suitable method to reduce the 131I activity and hospitalization time?. Nuklearmedizin 54(3): 118–24.		therapy is a considerable, effective and safer alternative to surgery for the treatment of very large benign nodular goitres.	
Heck K, Korkusuz Y, Happel C et al. (2016) Percutaneous microwave ablation of thyroid nodules: Efficacy evaluation with 99m Tc-pertechnetate and 99m Tc-MIBI functional imaging. International Journal of Radiation Research 14(2): 91–8.	**Benign nodules** Case series n=30 Follow up = 3 months	The determined results show the effectiveness of MWA as a treatment option for benign thyroid nodules. With functional scintigraphy a significant activity decrease could be detected in the ablation zone; hence a verification of affectivity was possible after a short period of time.	Functional imaging study
Heck K, Happel C, Grunwald F et al. (2015) Percutaneous microwave ablation of thyroid nodules: effects on thyroid function and antibodies. International Journal of Hyperthermia 31(5): 560–7.	**Benign nodules** Case series n=30 Follow up = 6 months	Serum TSH, T4, T3 and Tg levels did not change significantly at the 3-month or 6-month follow-up ($p<0.05$); thyroid function was not affected by MWA. Antibody levels did not change significantly either; however, two patients developed antibodies after treatment. A volume reduction of 51.4% or 7.85 mL could be demonstrated after 3 months and a reduction of 55.8% or 14.0 mL after 6 months. Slight complications such as mild pain during the ablation or superficial haematomas emerged. The development of Graves' disease and mild Horner's syndrome were observed as more severe side effects.	Studies with more patients or longer follow-up are included.

Hu K, Wu J, Dong Y et al. (2019) Comparison between ultrasound-guided percutaneous radiofrequency and microwave ablation in benign thyroid nodules. Journal of Cancer Research and Therapeutics 15(7): 1535–40.	**Benign nodules** Case series n=30 Follow up = 6 months	The mean VRRs of the RFA group vs. the MWA group at 1, 3, 6, and 12 months were 22.7±13.4% vs. 24.0±16.1% (P = 0.681), 56.1±19.5% vs. 54.8±22.8% (P = 0.788), 77.9±21.0% vs. 68.7±19.1% (P = 0.038), and 85.4±18.9% vs. 75.8±19.4% (P = 0.029), respectively. There was no significant difference in the VRRs between the two treatments at 1 and 3 months and the RFA group achieved higher VRRs than MWA group at 6 and 12 months. Moreover, the symptom and cosmetic scores decreased significantly in both groups and all patients succeeded in preserving thyroid function. Of the total patients, 2.8% in the RFA group and 4% in the MWA group experienced voice changes after undergoing thyroid ablation, and one patient in the RFA group had intraoperative haemorrhage of about 10 ml.	Studies with more patients or longer follow-up are included.
Javadov M, Karatay E, Ugurlu MU (2021) Clinical and functional results of radiofrequency ablation and microwave ablation in patients with benign thyroid nodules. Saudi Medical Journal 42(8): 838–46.	**Benign nodules** Case series n=100 Follow up = 6 months	There were statistically significant differences in pain scores, dysphagia scores, and foreign body sensation scores at 1, 3, and 6 months after therapy in both ablation groups (p=0.0006, p=00004, p=0.0005). At the same time, there were statistically significant reductions in size and volume of the nodules for RFA and MWA (p=0.0004, p=0.0003). There was no significant difference between the RFA and MWA groups' cosmetic scoring and volume changes (p=0.68, p=0.43).	Studies with more patients or longer follow-up are included.

Jin H, Lin W, Lu L et al. (2021) Conventional thyroidectomy vs thyroid thermal ablation on postoperative quality of life and satisfaction for patients with benign thyroid nodules. European Journal of Endocrinology 184(1): 131–41.	**Benign nodules** RCT n=450 (225 thermal ablation vs 225 thyroidectomy) Follow up = 15 months	At the 15th month after randomisation, more patients in the thyroid thermal ablation group were satisfied with the treatment effects compared to those in the conventional thyroidectomy group. More patients in the thyroid thermal ablation group have a QoL score of 410 (QOL scores ranges from 0 to 410) than patients in conventional thyroidectomy. Eight (4%) of the 209 patients in conventional thyroidectomy group and 6 (3%) of the 208 patients in thyroid thermal ablation group had at least one severe postoperative complication. The time to achieve volume reduction was longer in the thermal ablation group.	Mixed interventions
Khanh HQ, Hung NQ, Vinh VH et al. (2020) Efficacy of Microwave Ablation in the Treatment of Large (>=3 cm) Benign Thyroid Nodules. World Journal of Surgery 44(7): 2272–9.	**Benign nodules** Case series n=40 Follow up = median 12 months	The medians of largest diameter and volume of the nodules were 40 mm and 22 ml. Four (10%) minor complications were observed. The mean VRR was 75.1, 85.2, and 96.4% after 3, 6, and 12 months. The mean symptom and cosmetic scores dropped from 8.0 and 3.8 (before treatment) to 2.8 and 2.3 (at 12 months), respectively. Thirteen nodules (31%) required two MWA sessions.	Studies with more patients or longer follow-up are included.
Korkusuz H, Happel C, Heck K et al. (2014) Percutaneous thermal microwave ablation of thyroid nodules. Preparation, feasibility, efficiency.	**Benign nodules** Case series n=11 Follow up = 3 months	The treatment was well tolerated and no severe complications were observed. The preliminary data suggests that MWA is an effective method to treat benign thyroid nodules.	Functional imaging study

Nuklearmedizin 53(4): 123–30.			
Korkusuz H, Happel C, Koch DA et al. (2016) Combination of Ultrasound-Guided Percutaneous Microwave Ablation and Radioiodine Therapy in Benign Thyroid Disease: A 3-Month Follow-Up Study. Fortschr Röntgenstr 188(1): 60–8.	**Nodular goitre, Graves' disease** Case series n=15 Follow up = 3 months	TSH, T4, T3 and Tg did not change at 3MFU, except for in two patients in whom the initial TSH levels improved to normal thyroid functioning levels at follow-up. One of the patients developed a high TRAb-level that receded back into the normal range. At 3MFU, the combined therapy showed a mean thyroid volume reduction of 26.4ml ± 7.9 ml (30.5 % ± 4.6 % ($p < 0.05$)).	Combined intervention s
Korkusuz H, Nimsdorf F, Happel C et al. (2015) Percutaneous microwave ablation of benign thyroid nodules. Functional imaging in comparison to nodular volume reduction at a 3-month follow-up. Nuklearmedizin 54(1): 13–9.	**Benign nodules** Case series n=14 Follow up = 3 months	Mean relative nodular volume reduction after three months was 55.4 ± 17.9% ($p < 0.05$). MWA can be considered as an efficient, low-risk and convenient new approach to the treatment of benign thyroid nodules.	Functional imaging study
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): 929–35.	**Benign nodules** Non-randomised comparative study n=94 (14 HIFU vs 40 MWA vs 40 RFA) Follow up = 3 months	RFA showed a significant volume reduction of nodules of 50 % ($p<0.05$), MWA of 44 % ($p<0.05$) and HIFU of 48 % ($p<0.05$) three months after ablation. None of the examined ablation techniques caused serious or permanent complications.	Studies with more patients or longer follow-up are included.
Korkusuz Y, Mader OM, Kromen W et	**Benign nodules,**	All patients tolerated cMWA well. Median pain intensity	Studies with more

al. (2016) Cooled microwave ablation of thyroid nodules: Initial experience. European Journal of Radiology 85(11): 2127–32.	**thyroid carcinoma** Case series n=9 Follow up = 3 months	averaged 2.1 ± 0.8 (range: 1–3). Post ablative hematoma was observed in all cases. cMWA led to a significant decrease of blood circulation, nodule echogenicity and a significant increase of elasticity (Δ= 1.1 ± 0.33; 0.8 ± 0.4 and 1.1 ± 0.6 points)($p < 0.05$). An average increase of 4495 ng/ml Tg was measured ($p < 0.05$). cMWA is an effective and secure method for treatment of thyroid nodules.	patients or longer follow-up are included.
Li S, Yang M, Guo H et al. (2021) Microwave Ablation Vs Traditional Thyroidectomy for Benign Thyroid Nodules: A Prospective, Non-Randomized Cohort Study. Academic Radiology.	**Benign nodules** Non-randomised comparative study n=84 (56 MWA vs 28 thyroidectomy) Follow up = 12 months	The VRR was 80.70 ± 18.60%, and TSR was 91.70% at 6-months. Furthermore, the VRR increased to 90.45 ± 11.51%, and TSR increased to 100% at 12-months. C-reactive protein levels were significantly higher in group B on the first postoperative day (POD) (3.89 ± 0.86 mg/mL vs 3.39 ± 0.56 mg/mL, p = 0.002). Visual analogue scale scores were significantly lower in group A on the first and second POD. Thyroid stimulating hormone levels were significantly lower in group A at three (1.71 ± 1.12uIU/mL vs 2.37 ± 1.24uIU/mL, p = 0.013) and 6-months (1.34 ± 0.70uIU/mL vs 1.97 ± 0.94uIU/mL, p = 0.002). There were no significant between-group differences in QOL and complication rates. Microwave ablation shows acceptable and promising efficacy. Compared with thyroidectomy, MWA was associated with less trauma and comparable complication rates.	Studies with more patients or longer follow-up are included.

Liu SY, Guo WH, Yang B et al. (2019) Comparison of stress response following microwave ablation and surgical resection of benign thyroid nodules. Endocrine 65(1): 138–43.	**Benign nodules** Non-randomised comparative study n=144 (72 MWA vs 72 surgical resection) Follow up = 6 months	The effects of MWA are more tolerable than those of surgical resection and the physiological function of the thyroid is preserved, which has high clinical value.	Studies with more patients or longer follow-up are included.
Liu YJ, Qian LX, Liu D et al. (2017) Ultrasound-guided microwave ablation in the treatment of benign thyroid nodules in 435 patients. Experimental Biology and Medicine 242(15): 1515–23.	**Benign nodules** Case series n=435 Follow up = 12 months	The volume of all thyroid nodules significantly decreased after ultrasound-guided microwave ablation. The average volume was 13.07±0.95 ml before treatment, and 1.14±0.26 ml at 12-months follow-up. The mean volume reduction rate was 90% and the final volume reduction rate was 94%. The volume reduction rate of mainly cystic nodules was significantly higher than that of simple solid and mainly solid nodules (all $P < 0.05$). The retreatment volume of nodules was positively correlated with the final volume reduction rate at final follow up ($P = 0.004$). No serious complications were observed after treatment.	Included in Zheng (2018) systematic review
Mader OM, Tanha NF, Mader A et al. (2017) Comparative study evaluating the efficiency of cooled and uncooled single-treatment MWA in thyroid nodules after a 3-month follow up. European Journal of Radiology Open 4: 4–8.	**Benign nodules** Case series n=10 Follow up = 3 months	Cooled MWA was better tolerated than uncooled MWA. A significant reduction of thyroid nodule volume was observed in all cases. The reduction after cMWA was higher (40%) than after uMWA (29%). Pain intensity during cMWA was significantly lower than after uMWA. CMWA and uMWA led to a significant decrease of nodule blood circulation and echogenicity and to a significant increase of	Studies with more patients or longer follow-up are included.

		nodule elasticity. Thyroid function remained intact in all cases. cMWA leads to a slightly higher but statistically not significant nodule volume reduction than uMWA. Patient comfort during cMWA is higher than during uMWA. The risk of unintended side effects is less in cMWA. A single treatment provides sufficient results.	
Mo HS, Wei L, Ye H et al. (2022) Microwave Ablation of Visible Benign Thyroid Nodules with Different Internal Characteristics: A Comparative Study with Follow-up Results. Journal of Investigative Surgery 35(2): 347-53.	**Benign nodules** Case series n=51 Follow up = 18 months	The average volume of the nodules was 11.68 ± 10.16 ml, the volume reduction rates (VRR) at 1st, 3rd, 6th, 12th, and 18th months after ablation were 0.29 ± 0.27, 0.46 ± 0.25, 0.67 ± 0.19, 0.83 ± 0.10, and 0.92 ± 0.10, respectively. The VRR was significantly different among the three categories of lesions ($p < 0.05$). The symptoms of all patients were improved. Thyroid function indicators were fluctuated in normal range. There were no serious complications during and after the procedure. MWA of visible BTN is safe and effective, and the short-time ablation effect is significantly different due to the internal characteristics of the nodule.	Studies with more patients or longer follow-up are included.
Su C, Liu YJ, Qian LX (2021) Modified percutaneous ethanol injection method combined with microwave ablation for the treatment of symptomatic, predominantly cystic, benign	**Benign cystic nodules** Case series n=201 Follow up = mean 13 months	No major complications were observed during or after the treatment. Ten patients (4.8%) experienced temporary voice change, which resolved within 3 months. Of 200 (97.6%) out of 205 nodules showed significant volume reduction at the final follow-up. Recurrence occurred for only 5 (2.4%) nodules. The mean thyroid	Combined interventions

thyroid nodules: a retrospective study of 201 cases. International Journal of Hyperthermia 38(1): 995–1001.		nodule volume decreased from 17.40 ± 3.21 mL at baseline to 1.17 ± 0.37 mL at 12 months. The greatest VRR was observed within the first 3 months after treatment.	
Vorlander C, David Kohlhase K, Korkusuz Y et al. (2018) Comparison between microwave ablation and bipolar radiofrequency ablation in benign thyroid nodules: differences in energy transmission, duration of application and applied shots. International Journal of Hyperthermia 35(1): 216–25.	**Benign nodules** Non-randomised comparative study n=60 (24 MWA vs 36 RFA) Follow-up = 3 months	Mean initial volume (MWA: 23.90 ± 17.35 ml; RFA: 29.44 ± 30.09 ml), energy transmission (MWA: 13.56 ± 10.17 kJ; RFA: 15.12 ± 13.45 kJ), energy transmission per ml (MWA: 0.85 ± 1.01 kJ/ml; RFA: 0.65 ± 0.32 kJ/ml), power (MWA: 22.69 ± 12.32 J/s; RFA: 20.97 ± 7.86 J/s) and duration of ablation (MWA: 618 ± 304 s; RFA: 695 ± 463 s) were not statistically different (p >.05). MWA required significantly less shots (MWA: 3 ± 1; RFA: 6 ± 3) than RFA (p <.05). At three-months follow-up a significant mean nodular volume reduction of 53.54 ± 15.40% after MWA and 51.21 ± 16.58% after RFA (p <.05) was measured. However, mean nodular volume reduction was not significantly different between both systems (p >.05). One patient treated by MWA reported a transient Horner's syndrome, which recovered without any further treatment.	Studies with more patients or longer follow-up are included.
Wei Y, Qian L, Liu JB et al. (2018) Sonographic measurement of thyroid nodule changes after microwave ablation: relationship	**Benign nodules** Case series n=236 Follow up = 1 to 36 months	All of the thyroid nodules underwent a significant decrease in size after MWA. The mean decrease in the volume of the thyroid nodules was from 17.40 ± 22.52 mL to 1.31 ± 2.71 mL, with a mean percent decrease of 0.90 ± 0.15% after 12 months. Index	Included in Cui (2019) systematic review

between multiple parameters. International Journal of Hyperthermia 34(5) : 660–8.		R increased over time from 2.55 ± 1.08 to 8.10 ± 5.01, which increased the effectiveness of shape parameterisation between the follow-up periods after the three-month time point, regardless of the initial volume size. For the nodules with a baseline Dmax ≤ 3.4 cm, the V, VRR and index R demonstrated similar capabilities in the evaluation of efficiency before the six-month follow-up visit.	
Wu W, Gong X, Zhou Q et al. (2017) US-guided percutaneous microwave ablation for the treatment of benign thyroid nodules. Endocrine Journal 64(11): 1079–85.	**Benign nodules** Case series n=100 Follow up = 12 months	Microwave ablation was associated with a significant decrease in nodule volume {1.05±1.05mL (0.08~4.33mL) vs 8.56±4.21mL(4.05~22.66mL), p<0.001} at 12-month follow-up. The largest diameter was also decreased {1.36±0.53cm(0.60~3.73cm) vs 2.94±0.55cm(2.00~4.40cm), p<0.001}. The symptom score and cosmetic score were decreased significantly after the procedure(1.71±0.68 vs 3.31±1.13, p<0.001; 1.16±0.37 vs 2.37±0.94, p<0.001). The VRR was 57.66±22.95%,.70.23±20.07% , 85.97±14.04% at 3-, 6- and 12-month follow-up after ablation, respectively. Two patients(2.0%) experienced hoarseness and recovered within 2 months. Two patients(2.0%) developed slight burn on cervical skin. One case(1%) developed Horner Syndrome, recovered within 2 months..	Studies with more patients or longer follow-up are included.
Xia B, Yu B, Wang X et al. (2021)	**Benign nodules**	The VRR at 1 month, 3 months, 6 months and 12	Included in Zheng

Conspicuousness and recurrence related factors of ultrasound-guided microwave ablation in the treatment of benign thyroid nodules. BMC Surgery 21(1): 317.	Case series n=214 Follow up = 12 months	months were 40.79%, 60.37%, 74.59% and 85.60%, respectively. In addition, MWA had a better ablation effect for small nodules (initial volume≤10 mL). In recurrent studies, we found that the energy volume ratio was an independent risk factor for benign thyroid nodules (P<0.05).	(2018) systematic review
Yildirim G, Karakas H. (2022) Artery-first microwave ablation in the treatment of benign thyroid nodules. Advances in Clinical and Experimental Medicine 31(10)	Non-randomised comparative study N=40 (n=19 artery first MWA versus n=21 standard MWA) Follow up = 6 months	The artery-first MWA technique can be used in the treatment of benign thyroid nodules as a method of increasing the effectiveness of MWA.	Studies with more patients or longer follow-up are included.
Yue WW, Wang SR, Lu F et al. (2017) Radiofrequency ablation vs. microwave ablation for patients with benign thyroid nodules: a propensity score matching study. Endocrine 55(2): 485-95.	**Benign nodules** Non-randomised comparative study n=260 (158 MWA vs 102 RFA) Follow up = 12 months	Between the well-matched groups, no significant differences were found in all nodule volume-related endpoints at 6 months (volume reduction ratio: 79.4 vs. 77.2 %, P = 0.108; symptom score: 2.1 vs. 1.9, P = 0.456; cosmetic score: 2.1 vs. 2.3, P = 0.119; therapeutic success rate: 99 vs. 97 %, P = 0.621) and 12 months (volume reduction ratio: 83.6 vs. 81.6 %, P = 0.144; symptom score: 1.5 vs. 1.5, P = 0.869; cosmetic score: 1.6 vs. 1.7, P = 0.409; therapeutic success rate: 100 vs. 100 %, P > 0.99) after treatment. No major complications occurred in either group (P > 0.99).	Included in Guo (2021) systematic review
Yue W, Wang S, Wang B et al. (2013) Ultrasound guided	**Benign nodules** Case series	All thyroid nodules significantly decreased in size after microwave ablation. A 6-month follow-up	Included in Zheng (2018)

percutaneous microwave ablation of benign thyroid nodules: safety and imaging follow-up in 222 patients. European Journal of Radiology 82(1): e11-6.	n=222 Follow up = 12 months	was achieved in 254 of 477 nodules, and the mean decrease in the volume of thyroid nodules was from 2.13 ± 4.42 ml to 0.45 ± 0.90 ml, with a mean percent decrease of 0.65 ± 0.65. A volume-reduction ratio greater than 50% was observed in 82.3% (209/254) of index nodules, and 30.7% (78/254) of index nodules disappeared 6-month after the ablation. The treatment was well tolerated and no major complications were observed except pain and transient voice changes.	systematic review
Zhao J, Qian L, Liu Y et al. (2021) A long-term retrospective study of ultrasound-guided microwave ablation of thyroid benign solid nodules. International Journal of Hyperthermia : The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 38(1): 1566–70	**Benign nodules** Case series n=40 Follow up = 3 years	MWA is an effective and safe approach for reducing nodule volume and symptoms in patients with benign thyroid solid nodules.	Studies with more patients or longer follow-up are included.
Zhi X, Zhao N, Liu Y et al. (2018) Microwave ablation compared to thyroidectomy to treat benign thyroid nodules. International Journal of	**Benign nodules** RCT n=52 (28 MWA vs 24 thyroidectomy) Follow up = 12 months	MWA reduced mean nodule volume by 72.3% at 3 months, 84.5% at 6 months and 92.4% at 12 months as effective as surgery in inactivating nodules, and thyroid dysfunction did not occur during 12-month follow-up for those receiving MWA. Although both MWA and	Studies with more patients or longer follow-up are included.

Hyperthermia 34(5): 644–52.		surgery were safe, patients undergoing MWA had fewer cases of complications and rarely reported pain. The MWA group was superior to the surgery group in length of stay, postoperative scar length and the operation time. Compared to patients who underwent surgery, those who underwent MWA had better general health and mental health scores at 6 months and 12 months.	
Zhou B, Yan X, Wang X et al. (2018) Clinical study of ultrasonic guided percutaneous microwave ablation in the treatment of benign thyroid nodules with a one-year follow-up. International Journal of Clinical and Experimental Medicine, 11(10): 10903–9.	**Benign nodules** Case series n=65 Follow up = 12 months	Thyroid nodules were significantly decreased in size after MWA. Preoperative maximum diameter of the nodules was 2.95 ± 0.54 cm and the volume was 5.32 ± 2.08 cm3. Values were 1.47 ± 0.61 cm and 1.12 ± 0.67 cm3 twelve months after the operation ($P < 0.01$, respectively). At postoperative 1, 3, 6, and 12 months, VRRs were 11.85%, 29.07%, 60.23%, and 78.86% ($P < 0.01$). Thyroid function status was normal at postoperative 1, 3, and 6 months ($P > 0.05$).	Studies with more patients or longer follow-up are included.