SAHLGRENSKA UNIVERSITETSSJUKHUSET VGR

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Radiofrequency or microwave ablation versus surgery for treatment of benign non-toxic or toxic nodules, and toxic diffuse autoimmune hyperthyroidism (Graves' disease)

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[Ablation med radiofrekvens eller mikrovågor jämfört med kirurgi för behandling av benigna icke-toxiska eller toxiska noduli och toxisk diffus autoimmun hypertyreos (Graves' sjukdom)]

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1 Abstract

Background Benign thyroid nodules occur in up to 60% of the general population and the vast majority of such nodules are non-toxic, i.e. not producing excess thyroid hormone. Non-toxic nodules are usually asymptomatic but may give symptoms such as difficulty swallowing. Management for non-toxic nodules is usually observation although surgery (usually hemi- or subtotal/total thyroidectomy), or hormone therapy may be needed in some cases. Toxic nodules need treatment, usually radioactive iodine therapy, anti-thyroid medication or surgery. Graves' disease, an autoimmune disorder with excess thyroid hormone production, is managed with antithyroid medications, radioactive iodine, or thyroidectomy. Thermal ablation (TA), a minimally invasive technique using heat induced by radiofrequency, microwave or laser, has emerged as an alternative to surgery for benign thyroid nodules or Graves' disease.

Question at issue Is radiofrequency ablation (RFA) or microwave frequency ablation (MWA) an effective and patient safe alternative, compared with thyroid surgery, for treatment of adult patients with benign non-toxic or toxic nodules, and toxic diffuse autoimmune hyperthyroidism (Graves' disease).

Methods After definition of PICO, systematic literature searches were conducted in Medline (OvidSP), Embase (OvidSP), and Web of Science Core Collection, and websites of Scandinavian HTA-organisations. Two authors screened the obtained abstracts and made a first selection of full-text reports which were then read by at least two authors, and it was finally decided in consensus which reports should be included. Included studies were critically appraised using checklists. Data was extracted by at least two authors, summarised for each outcome and when possible, pooled in a meta-analysis. The certainty of evidence for each outcome was assessed using the GRADE approach. Summary of the results per outcome and the associated certainty of evidence were presented in a Summary-of-findings table.

Results Twenty-five reports (four RCTs, 14 cohort studies and seven case series) were included in the assessment. All comparisons are RFA or MWA compared with surgery in adults

Benign non-toxic (P1) and toxic thyroid (P2) nodules if not otherwise stated
Critical outcomes were all assessed as very low certainty of evidence (GRADE ⊕OOO). Thus, it is uncertain whether there is any difference for TA versus surgery regarding mortality (reported in one RCT with zero events), health-related quality of life (two RCTs and four cohort studies), symptom change (one RCT and three cohort studies), complications (four RCTs, and 13 cohort studies), relapse (three cohort studies) and re-intervention (four cohort studies). The frequency of malignancy was reported in two cohort studies with zero detected events by ultrasound and fine needle biopsy in the TA group, while 9% malignancies were detected in the specimens resected in the surgery group. There were no specimens for microscopy in the TA group, and thus the true frequency of malignancy is unknown.

Important outcomes: Operation time was reported in three RCTs, and in ten cohort studies. Data from two RCTs were pooled in a meta-analysis with reduced operation time for TA compared with surgery, MD: -77.64 (95%CI: -93.40 to –61.88) min., p<00001, and from eight cohort studies, MD: -52.15 (95% CI: -62.06 to –42.23) min., p<0.00001. *Conclusion*: Operation time is probably reduced with TA compared with surgery (GRADE ⊕⊕⊕O). Volume reduction was reported in two RCTs, and twelve cohort studies. For the RCTs, the mean volume reduction at 12 months for TA was 79.79 (95% CI: 79.02; 80.55) % while it was 82.59 (95% CI: 77.06; 90.10) % for seven cohort studies. Volume reduction for

surgery was not reported but is supposedly usually 100% (hemithyroidectomy). Conclusion: Nodule volume reduction after TA at 12 months of follow-up is approximately 80%.

Biochemical response in terms of TSH (Thyroid stimulating hormone) levels was reported in four cohort studies, three of which could be pooled in a meta-analysis with MD: -0.38 (95% CI: -0.98 to 0.22) µU/L, n.s. *Conclusion*: It is uncertain whether there is any difference in biochemical response with TA compared with surgery (GRADE ⊕OOO). Need of postinterventional hormonal treatment was reported in one RCT, Zhi et al. (2018) (n=52) with 0/28 events in the TA and 1/24, in the surgery group, n.s., and in seven cohort studies with a Peto OR of 0.11 for P1 (5 cohorts) and 0.05 for P1 + P2 (2 cohorts). *Conclusion*: TA may reduce the need of hormone replacement compared with surgery (GRADE ⊕⊕OO). Hospital stay was reported in two RCTs and data were pooled in a meta-analysis, with MD: -3.14 (95% CI: -4.80 to -1.48) days, p=0.0002. Results from eight of the cohort studies could be pooled with MD: -3.59 (95% CI: -4.46 to -2.71) days, p=0.00001. *Conclusion*: The length of hospital stay may be reduced with TA compared with surgery (GRADE ⊕⊕OO).

Graves' Disease in adults (P3) No controlled studies were identified for TA compared with surgery. One of three case series reported complications in 10/50 (20%) patients.

Economical aspects From societal and healthcare system perspectives, the cost per ablation patient amounts to 32.6% and 37.8%, respectively, of the cost per surgical patient. However, critical evidence gaps preclude a definitive assessment of the cost-effectiveness and value-for-money of each treatment modality.

Ethical aspects Since TA is available as a treatment option in other regions, introduction in Region Västra Götaland could be considered from an equality perspective. From a risk-benefit perspective, the present report suggests that TA offers a less invasive outpatient alternative to surgical intervention. However, the effectiveness and safety of TA is uncertain. A significant limitation with the technique is that histopathological evaluation of the treated tissue is not possible.

From a cost-effective perspective, the current report suggest that TA may have a potential to be a more economically favourable option, if effectiveness and safety compared with surgery can be shown in future studies.

Conclusions Twenty-five studies mainly from Asia, four small RCTs, 14 non-randomised controlled studies and seven case series were identified evaluating RFA or MWA compared with conventional surgery. For all critical outcomes, the available evidence does not allow any conclusions about effectiveness and safety for TA compared with surgery. Regarding outcomes important for decision making, operation time and the need of hormonal replacement are probably reduced, while hospital stay may be reduced when comparing TA with surgery. Complications with TA are not infrequent and may be severe, as also for surgery, and the incidence and impact of missed malignancies after TA are poorly known. There is an absence of high-quality well-designed large RCTs evaluating critical outcomes for TA compared with surgery.

2 Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Fråga: Är värmeablation med radio- eller mikrovågor effektivt och patientsäkert jämfört med kirurgi för behandling av vuxna patienter med godartade icke-toxiska eller toxiska sköldkörtelknutor, eller med diffus giftstruma (Graves sjukdom)?

Konklusion: Denna systematiska översikt inkluderande 25 studier främst från Asien: fyra små randomiserade kontrollerade studier (RCT), 14 icke-randomiserade kontrollerade studier och sju fallserier, har utvärderat värmeablation med radio- eller mikrovågor jämfört med konventionell kirurgi för behandling av icke-toxiska eller toxiska sköldkörtelknutor samt diffus giftstruma. För samtliga utfall som är kritiska för beslutsfattande gick det inte att bedöma eventuella skillnader i resultat för värmeablation jämfört med kirurgi. Bland utfall som är viktiga för beslutsfattande är operationstid och behov av hormonbehandling efter ingreppet troligen reducerade, och vårdtiden kan vara kortare vid värmeablation jämfört med kirurgi. Komplikationer efter värmeablation är inte ovanliga och kan vara allvarliga, liksom för kirurgi. Frekvensen och konsekvenserna av att elakartade sköldkörtelknutor kan missas är dåligt kända. Sammanfattningsvis saknas högkvalitativa stora RCT som utvärderar kritiska utfall för värmeablation jämfört med kirurgi.

Bakgrund: Godartade sköldkörtelknutor förekommer hos upp till 60% av befolkningen och det stora flertalet av sådana knutor är icke-toxiska, det vill säga inte förknippade med förhöjd ämnesomsättning. Icke-toxiska knutor är vanligen asymtomatiska, men kan ge symtom såsom sväljningssvårigheter. Icke-toxiska knutor handläggs oftast med observation, men kan ibland behöva behandlas med kirurgi (borttagande av halva, eller nästan hela/hela sköldkörteln) eller hormonbehandling. Toxiska knutor kräver behandling, vanligen med läkemedel som hämmar sköldkörtelns hormonproduktion, radioaktivt jod som förstör överaktiva sköldkörtelceller eller med kirurgi. Graves sjukdom (diffus giftstruma), en autoimmun sjukdom med förhöjd ämnesomsättning, behandlas med läkemedel som hämmar sköldkörtelns hormonproduktion, radioaktivt jod eller med kirurgiskt borttagande av hela sköldkörteln. Som ett alternativ till kirurgi har värmeablation, en minimalinvasiv teknik som använder värme från radio- eller mikrovågor eller laser för att bränna bort knutor, tagits fram för behandling av godartade sköldkörtelknutor eller Graves sjukdom.

Metod: Efter definition av PICO genomfördes systematiska litteratursökningar i Medline (OvidSP), Embase (OvidSP), Web of Science Core Collection, och hemsidor hos skandinaviska HTA-organisationer. Två författare granskade sammanfattningar av de funna artiklarna och gjorde ett första urval av artiklar som lästes i fulltext av minst två författare och samtliga författare avgjorde sedan i konsensus vilka artiklar som skulle inkluderas. Inkluderade studier granskades kritiskt med hjälp av checklistor av minst tre författare. Data extraherades av minst två författare, sammanställdes per utfall och sammanvägdes om möjligt i en metaanalys. Vår tilltro till resultatet för varje utfall bedömdes enligt GRADE och presenteras tillsammans med resultaten i en sammanfattande tabell.

Resultat: Fyra RCT, 14 kohortstudier med kontroller och sju fallserier inkluderades. Resultaten avser värmeablation jämfört med kirurgi hos vuxna med icke-toxiska knutor *om ej annat anges. Kritiska utfall:* För samtliga kritiska utfall bedömdes vår tilltro till resultaten vara mycket låg (GRADE ⊕OOO). Det går således inte att bedöma om det finns någon skillnad mellan värmeablation och kirurgi vad gäller mortalitet (1 RCT, med noll händelser), hälsorelaterad livskvalitet (2 RCT och 4 kohortstudier),

symtomförändring (1 RCT och 3 kohortstudier), komplikationer (4 RCT och 13 kohortstudier), återfall (3 kohortstudier) och re-intervention (4 kohortstudier). Frekvensen av elakartade förändringar i knutan bedömt med ultraljud och cellprov från finnålspunktion rapporterades i två kohortstudier med noll fall i ablationsgruppen, mot 9 % elakartade förändringar vid mikroskopisk undersökning av bortopererade preparat i kirurgigruppen. Ingen mikroskopisk undersökning gjordes i värmeablationsgruppen, så den sanna frekvensen av elakartade knutor är okänd i den gruppen.

Viktiga utfall: Operationstid rapporterades i tre RCT och tio kohortstudier. Data från två RCT och åtta kohortstudier sammanfördes separat i två metaanalyser som visade minskad operationstid för värmeablation jämfört med kirurgi, medelskillnad i RCT: -77,64 (95% konfidensintervall: -93,40; -61,88) minuter, p<0,00001 och i kohortstudierna: -52,15 (95% konfidensintervall: -62,06; -42,23) minuter, p<0,00001. Slutsats: Operationstiden är troligen kortare vid värmeablation jämfört med kirurgi (GRADE ⊕⊕⊕O). Volymminskning av knutan rapporterades i två RCT och tolv kohortstudier. I två RCT var den genomsnittliga volymminskningen efter 12 månader 79,8 % (95% konfidensintervall: 79,0; 80,6) och i sju kohortstudier: 82,6 % (95% CI: 77,1; 90,1). Volymminskning vid kirurgi rapporterades inte men är vanligen 100 % efter bortoperation av halva sköldkörteln. Slutsats: Volymminskningen av sköldkörtelknutor efter värmeablation vid 12 månaders uppföljning är cirka 80 %. Nivå för sköldkörtelstimulerande hormonet rapporterades i fyra kohortstudier, tre kunde sammanföras i metaanalys med medelskillnad: -0,38 µU/L (95% konfidensintervall: -0,98; 0,22), icke signifikant. Slutsats: Det är osäkert om det finns någon skillnad för sköldkörtelstimulerande hormonnivån efter värmeablation jämfört med kirurgi (GRADE ⊕OOO). Behov av sköldkörtelhormonbehandling efter ingreppet rapporterades i en RCT med 0/28 fall i ablations- och 1/24 i kirurgigruppen, ej signifikant. Sju kohortstudier rapporterade ett lägre behov av hormonbehandling efter värmeablation (oddskvot 0,11 för icke-toxiska i 5 kohorter och *0,05 för blandat icke-toxiska och toxiska knutor i 2 kohorter*). Slutsats: Värmeablation kan minska behovet av hormonbehandling jämfört med kirurgi (GRADE ⊕⊕OO). Vårdtid: metaanalys visade en medelskillnad i två RCT på -3,14 dagar (95% konfidens-intervall: -4,80; -1,48), p=0,0002 och -3,59 dagar (95% konfidensintervall: -4,46; -2,71), p=0,00001 i åtta kohortstudier. Vårdtiden efter kirurgi var mycket längre är normalt för Sverige. Slutsats: Vårdtiden kan vara reducerad med värmeablation jämfört kirurgi (GRADE ⊕⊕OO).

För Graves sjukdom hos vuxna fanns tre fallserier men inga kontrollerade studier för värmeablation jämfört med kirurgi. En fallserie rapporterade komplikationer, vilket förekom hos 10/50 (20 %) patienter.

Ekonomiska aspekter: Kostnaden för ablation uppgår till cirka 1/3 av kostnaden för kirurgi för godartade sköldkörtelknutor. Då kunskapsläget för kritisk patientnytta och säkerhet för värmeablation jämfört med kirurgi ej kan bedömas går det i nuläget inte att bedöma de totala kostnaderna för respektive teknik.

Etiska aspekter: Ur ett jämlikhetsperspektiv skulle introduktion av värmeablation kunna övervägas eftersom tekniken erbjuds i andra regioner. Ur ett risk-nytta-perspektiv talar denna rapport för att värmeablation erbjuder ett mindre invasivt alternativ jämfört med kirurgi. Det måste dock beaktas att effektivitet och säkerhet med värmeablation jämfört med kirurgi är osäker. En särskild begränsning med tekniken är att mikroskopisk undersökning av knutan inte kan genomföras. Ur ett kostnadseffektivitetsperspektiv skulle värmeablation kunna ha potentialen att vara ett mer gynnsamt alternativ än kirurgi, men detta förutsätter att framtida forskning styrker teknikens effektivitet och säkerhet i jämförelse med kirurgi.

The above summaries were written by representatives from HTA-centrum. The HTA report was approved by the regional board for quality assurance of activity-based HTA.

Ylva Carlsson
Head of HTA-centrum of Region Västra Götaland, Sweden, 2025-06-30

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
RN Registered Nurse
RNRM Registered Nurse Registered Midwifery

3 Summary of findings

Outcomes	Study design (Number of studies)	Relative effect (95% CI)	Absolute effect Mean (SD) unless otherwise stated	Certainty of evidence* Grade
P1 & P2: Thermal ablation (TA) of benign non-toxic, toxic nodules in adults				
Health related quality of life	2 RCT (n=378) 4 cohort studies (n=618)	TQoL AOR§:0.34 (0.21 to 0.45), p<0.0001	SF-36 Physical general health TA: 75, surgery: 70, n.s. Mental health: TA: 75, surgery 70, n.s. QoL EORTC QLQ C30 MD: -0.24 (95% CI: -8.30 to 7.82), n.s. SF-36 HRQoL RFA: 68.5, surgery: 66.7, p=0.029 Vitality RFA: 71.3, surgery: 67.5, p<0.001 Mental health RFA: 80.9, surgery: 75.3, p=0.02.	Very low (⊕OOO) [1]
Symptoms change	1 RCT (n=52) 3 cohort studies (n=491)	Symptom remission RR: 0.74 (0.27 to 2.05), n.s.	Symptom scores (%) TA: 10/28 (35.7%), Surgery: 11/24 (45.8%), n.s. Symptom remission TA baseline: 4.5 (0.9), 12 months: 0.7 (0.7), surgery baseline: 4.5 (0.9), 12 months: 0.8 (0.7), n.s.	Very low (⊕OOO) [1]
Major complications	4 RCT (n=592) 13 cohort studies (n=2,279) 5 case series (n=13,022)	Peto OR: 0.63 (0.25 to 1.63), n.s. Peto OR: 0.39 (0.23 to 0.65), p=0.0004)		Very low (⊕OOO) [2]
Relapse	3 cohort studies (n=645)	Not estimable#	Not estimable#	Very low (⊕OOO) [3]
Malignancy	2 cohort studies (n=279)	Peto OR: 0.15 (0.05 to 0.43), p=0.0004	Event rate in total (%) TA: 0/121 (0%) surgery: 15/159 (9.4%)	No GRADE [4]
Re-intervention	4 cohort studies (n=1,121)	Peto OR: 1.49 (0.40 to 5.46), n.s	Event rate in total (%) TA: 5/436 (11,5%) surgery: 5/685 (7.3%)	Very low (⊕OOO) [5]
Mortality	1 RCT (n=52)		Not estimable (zero events)	Very low (⊕OOO) [6]
Operation time	3 RCT (n=512)		MD: -77.64 (95%CI: -93.40 to –61.88) min., p<00001	Moderate (⊕⊕⊕O) [7]

	10 cohort studies (n=1,453)		MD: -52.15 (95% CI: -62.06 to –42.23) min., p<0.00001	
Volume reduction	2 RCT (n=478) 12 cohort studies (n=2,005)		Mean volume reduction for TA at 12 months: 79.79 (95% CI: 79.02 to 80.55) % Mean volume reduction for TA at 12 months: 82.59 (95% CI: 77.06 to 90.10) %	No GRADE [8]
Biochemical response	4 cohort studies (n=399)		MD: -0.38 (95% CI: -0.98 to 0.22) µU/L, n.s.	Very low (⊕OOO) [9]
Need of hormone replacement therapy	1 RCT (n=52) 7 cohort studies (n=1,241)	P1 (benign noduli) Peto OR: 0.11 (0.06 to 0.20), p<0.00001 P1+P2 (benign, non-toxic or toxic noduli) Peto OR: 0.05 (0.04 to 0.08), p<0.00001	Event rate (%) 0/28 (0%) 1/24 (4.2%), n.s.	Low (⊕⊕OO) [7]
Hospital stay	2 RCT (n=160) 11 cohort studies (n=2,240)		MD: -3.14 (95% CI: -4.80 to -1.48) days, p=0.0002 MD: -3.59 (95% CI: -4.46 to -2.71) days, p=0.00001	Low (⊕⊕OO) [10]
P3: TA in Graves' Disease in adults				
Complications	3 case-series (n=95)		Observed complication rate: 12/50 (24%)	No GRADE [11]

§ QoL was coded as an ordinal variance with four categories, since this outcome was extremely skewed in follow-up, and adjusted for relevant baseline scores.
# In one study, the number of patients with relapse was not estimable (each patient had either single- or multiple nodules at baseline). In two studies there were zero events.
[1] Downgraded one step for some study limitations (selection, no blinding) and some indirectness, another step for inconsistency, and one step for serious imprecision (no 95% CI reported, unclear power).
[2] Downgraded one step for serious indirectness (RCTs with many asymptomatic patients with cosmetic treatment), two steps for very serious imprecision (very few events).
[3] Downgraded two steps for very serious imprecision (number of patients with relapse not reported in one study, and two studies with zero events).
[4] No GRADE since there were no specimens for microscopy in the TA group.
[5] Downgraded two steps for very serious imprecision (very few events), also problems with study limitations (selection bias), and very serious inconsistency.
[6] Downgraded two steps for very serious imprecision (one RCT with zero events).
[7] Downgraded one step for some study limitations (RCT, baseline differences, blinding) and some indirectness (RCT, recruitment, many asymptomatic patients), one step for serious inconsistency, and upgraded one step (cohort studies for large effect).
[8] No GRADE due to data solely based on volume reduction rates for TA.
[9] Downgraded one step for some study limitations (selection) and some indirectness (recruitment, indication).

[10] Downgraded one step for serious inconsistency.
[11] No GRADE, due to no controlled studies.

[*] Certainty of evidence
High certainty ⊕⊕⊕⊕: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty ⊕⊕⊕O: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different to the estimate of the effect.

Low certainty ⊕⊕OO: Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty ⊕OOO: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

4 Abbreviations and acronyms

EA = Ethanol ablation

FNA = Fine-needle aspiration biopsy

HRQoL = Health-related quality of life

LA = Laser ablation

MWA = Microwave ablation

RAI = Radioactive iodine

RCT = Randomised controlled trial

RFA = Radiofrequency ablation

TA = Thermal ablation

TSH = Thyroid-stimulating hormone

VGR = Region Västra Götaland [Västra Götalandsregionen]

5 Background

Benign non-toxic or toxic thyroid nodules

Benign thyroid nodules can be either toxic or non-toxic. Toxic thyroid nodules are associated with hyperthyroidism due to autonomously functioning thyroid tissue and can cause symptoms such as weight loss, palpitations, and tremors due to excessive thyroid hormone production (Doubleday and Sippel, 2020). Treatment options for toxic nodules include antithyroid medications, radioactive iodine (RAI) therapy or surgery. Non-toxic benign thyroid nodules are more common than toxic nodules and can lead to symptoms such as difficulty swallowing, neck pain, or cosmetic concerns due to their size (Durante et al., 2018). Traditionally, non-toxic nodules are managed through observation, surgery, or hormone therapy.

Graves' Disease

Toxic diffuse autoimmune hyperthyroidism or Graves' disease is an autoimmune disorder characterised by hyperthyroidism and is traditionally managed with an initial period with antithyroid medications to normalise thyroid hormone levels. Definitive treatment is then provided by RAI or thyroidectomy (Ross et al., 2016). In this HTA the biochemical response is therefore only defined as an important outcome.

Disease/disorder of interest and its degree of severity

Symptomatic benign non-toxic thyroid nodules, toxic thyroid nodules and toxic diffuse autoimmune hyperthyroidism (Graves' disease). These diagnoses are associated with an increased risk of permanent illness or damage (reduced bone density/osteoporosis, cardiac arrythmias) and reduced quality of life.

Prevalence and incidence

Up to 60% of adults in the general population harbour one or more thyroid nodules (Durante et al., 2023). In surveys of unselected subjects using ultrasonography, 20 to 76% of women had at least one thyroid nodule (Ezzat et al., 1994). The incidence of a toxic thyroid nodule and Graves' disease in Sweden is approximately 450 and 2,100 new cases/year, respectively (Berg et al., 2007).

Fortunately, only 5-6% of nodules are cancerous. The likelihood of malignancy is an overriding concern, but the actual prevalence of cancer in unselected thyroid nodule populations generally ranges from 1 to 5%, with variation related to selection criteria and the population under evaluation (Grussendorf et al., 2022). Thus, most lesions are benign, asymptomatic, and do not warrant treatment. In the case of cancer diagnosis, most are small, intrathyroidal and indolent neoplasms (up to 53.6%, as shown in one contemporary large-scale study, in an unselected population) that can safely be managed conservatively (Grani et al., 2020).

Present treatment

In Sweden today, patients with benign non-toxic thyroid nodules, toxic thyroid nodules or Graves' disease are treated with surgery, RAI or antithyroid medications, respectively. Thyroid surgery is usually hemithyroidectomy, subtotal or total thyroidectomy, performed by endocrine surgeons and head and neck surgeons in 34 hospitals throughout the country. Treatment with RAI or antithyroid medications are given by nuclear medicine specialists and endocrinologists. TA for thyroid disorders is at present not provided in Region Västra Götaland.

The currently used interventions are frequently associated with loss of thyroid function and subsequent need for life-long levothyroxine supplementation. In addition, thyroid surgery, although performed by experienced surgeons, can be associated with increased risk of major complications including permanent recurrent laryngeal nerve palsy and/or hypoparathyroidism.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

Following diagnosis at the primary health care centre, patients are referred to one of the five regional hospitals in Region Västra Götaland (VGR) for surgical or medical treatment. The treatment of these patients in Sweden is today associated with significant waiting time to intervention (mean: 230 days).

Number of patients per year who undergo current treatment regimen

In 2024, 61 patients at Sahlgrenska University Hospital underwent hemithyroidectomy due to compression symptoms from benign non-toxic goitre (P1). Corresponding numbers for toxic adenoma (P2) was 8 and for Graves' disease (P3) 57, respectively.

In 2024, 75 patients underwent hemithyroidectomy and 40 patients underwent total thyroidectomy at Northern Älvsborg County Hospital. Ten of these surgeries were performed at a day-care centre.

Present recommendations from medical societies or health authorities

There are yet no recommendations from the Swedish National Board of Health and Welfare (Socialstyrelsen) or other Swedish societies regarding the use of TA. Internationally, there are several guidelines on the ablation of benign thyroid nodules from South Korea, Europe, USA and China (Kim et al., 2018; Papini et al., 2020; Sinclair et al., 2023; Han et al., 2025)

According to the 2023 European Thyroid Association Clinical Practice Guidelines for thyroid nodule management, TA can be considered for treatment of solid benign thyroid nodules that cause local symptoms, as an alternative to surgery, and for cystic lesions that relapse after ethanol ablation (Durante et al., 2023).

6 Health Technology at issue

Thermal ablation

TA is a minimally invasive procedure increasingly used in the management of thyroid diseases, including benign non-toxic thyroid nodules, toxic thyroid nodules (Noel et al., 2023), and Graves' disease (Cai et al., 2024). TA techniques include LA, RFA, and MWA (Baldwin et al., 2022). All techniques use heat to target the nodule, with MWA offering the advantage of larger tissue coverage due to its ability to generate more heat in a shorter period (Ahmed et al., 2011). According to the American Thyroid Association, thyroid ablative procedures provide valid alternative treatment strategies to conventional surgical management for a subset of patients with symptomatic benign thyroid nodules (Sinclair et al., 2023).

The TA procedure is performed under local anaesthesia, and a needle electrode is inserted into the nodule. High-frequency energy is then applied to the tissue, causing localised heating and necrosis of the nodule. Most patients report a significant improvement in symptoms, such as pain or cosmetic concerns. TA for toxic nodules aims to reduce the size of the hyperfunctioning nodule, thereby decreasing the production of thyroid hormones and is suggested to be specifically beneficial for patients with a solitary toxic nodule. Some reports have also suggested that TA may offer an alternative for patients with Graves' disease who are not responsive to medical therapies or wish to avoid RAI and thyroidectomy. Studies have shown that TA can reduce thyroid volume and improve thyroid function in patients with Graves' disease (Cai et al., 2024).

Potential early complications after TA of the thyroid include local pain, skin burns, voice changes, haematoma, and damage to surrounding structures, such as the recurrent laryngeal nerve or parathyroid glands (Liang et al., 2024). Post-procedure monitoring is crucial to ensure proper healing and to identify any complications early. Patients typically experience a mild recovery period, with many returning to their normal activities within a few days. Another important topic is the need for retreatment with surgery and histopathological evaluation due to nodule regrowth after initial TA. Regarding post-ablation surgery there is growing evidence of increased surgical complexity due to adhesions.

Even though TA techniques offer advantages they do not permit histopathological evaluation of the treated tissue and thus a risk for missed malignancies. Ablation-induced tissue alterations can also complicate histological assessment and pathological diagnosis (Kuo et al., 2024).

This HTA analysis will include evaluation of the two most used techniques, RFA and MWA. Laser ablation (LA) is not yet commonly used and is therefore not included in this evaluation.

7 Focused question

The question at issue	
Is radiofrequency or microwave ablation an efficient and patient safe alternative, compared with thyroid surgery, for treatment of adult patients with benign non-toxic, toxic nodules, and toxic diffuse autoimmune hyperthyroidism (Graves' disease).	
PICO	
P	P1: Adult patients with benign non-toxic nodules (as defined by authors) P2: Adult patients with toxic nodules P1+P2 if not reported separately (5% inclusion of P1 or P2 accepted in each group above) P3: Adult patients with toxic diffuse autoimmune hyperthyroidism (Graves' disease), suitable for surgery
I	Thermal ablation using radiofrequency or microwaves
C	Surgery (open or endoscopic) – Excluding local excision
O	*Critical for decision making* Health-related quality of life (measured with validated scales) Symptoms change (measured with validated scales) Complications (post-intervention, and late) Relapse (re-growth of treated nodule during follow-up period) Malignancy (pathology report indicative of malignancy following surgery due to relapse after initial thermal ablation) Re-intervention (repeated thermal ablation due to regrowth of treated nodule) Mortality *Important for decision making* Operation time (time of surgery) Volume reduction Biochemical response Need of hormonal treatment Hospital stay
Study design	
RCT	

Non-randomised controlled studies, >20 patients per group	
Case series for complications, >1,000 patients Case series P3 – no limitation regarding number of patients	
SR (commented upon)	
Publication year	Language
2005-	English
SR 2023-	

8 Method

Systematic literature search (Appendix 1)

In January 2025 two of the authors; two medical librarians with several years' experience in systematic review searching (TS, IS), performed systematic searches in Medline (OvidSP), Embase (OvidSP), and Web of Science Core Collection. Websites of Scandinavian national and regional HTA-organisations were visited. Reference lists of relevant reports were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, and independently of one another screened the obtained abstracts to decide eligibility for full-text retrieval. All abstracts were screened using the Rayyan tool/Covidence systematic review software (Ouzzani et al., 2016). Any disagreements were resolved in consensus. All full-text reports were read by at least two authors, independently of one another, and it was finally decided in a consensus meeting which reports should be included in the assessment.

The HTA was registered in PROSPERO (CRD 1010690), 2025-03-24, prior to data extraction.

Critical appraisal and certainty of evidence

Included studies were critically appraised using checklists, modified from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), for assessment of RCTs and for assessment of non-randomised controlled studies.

Data was extracted by at least two authors and summarised for each outcome in Appendix 4.

When possible, data was pooled in meta-analysis (Review Manager 5.4, or Stata) using random and fixed effects models, and risk ratios (RR), or mean differences (MD), and in

case of zero events in one study arm, Peto odds ratio (OR), as point estimates with 95% CI. RCTs and cohort studies were handled separately in meta-analyses. If comparisons in an individual study were available for both an MWA group, and for an RFA group, against a single surgery group (hemi- or total thyroidectomy), the RFA group was chosen for the meta-analysis.

The certainty of evidence for each outcome was assessed using the GRADE approach combining RCTs and cohort studies (Atkins et al., 2004; GRADE Working group). Summary of the results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (Chapter 3).

The outcome complications were deemed as major or minor as defined by Scappaticcio et al. (2025). Major complications: permanent dysphagia, permanent hoarseness / dysphonia / voice change, transient hoarseness /dysphonia / voice change (If not transient), vocal cord paralysis, transient / permanent, nodule rupture, permanent hypocalcaemia, skin burns/necrosis, wound infection, fistula formation, arrythmia, Horner syndrome, thyrotoxicosis / hyperthyroidism, hypothyroidism, oesophageal injury, and tracheal injury. Minor complications: transient dysphagia, hematoma / haemorrhage, neck swelling, hypocalcaemia, skin burns, pain, local enema, fever, skin numbness, paraesthesia, and cough.

Ongoing research

A search in Clinicaltrials.gov (19 March 2025) using the search terms: Other terms: (thermoablation OR thermoablative OR ablation OR ablative OR MWA OR RFA) AND (nodule OR nodules OR AFTN OR "thyroid adenoma" OR "thyroid tumor" OR "thyroid tumor" OR graves OR basedow OR ((autoimmune OR auto-immune) AND (hyperthyroid OR hyper-thyroid)) OR goiter OR goitre) identified 207 records.

9 Results

Search results and study selection (Appendix 1)

The literature search identified 2,075 records after removal of duplicates. DedupEndNote (Lobbestael, 2023) was used for deduplication. After reading the abstracts 1,971 records were excluded. One report could not be retrieved, and 78 reports were excluded after full-text reading. 25 reports (four RCTs, 14 cohort studies and seven case series) were finally included in the assessment (Appendix 2).

Included studies

Four RCTs, 14 cohort studies, and seven case series (for complications only), were included (Appendix 2). The RCTs had some problems related to risk of bias (e.g. selection and blinding), indirectness (e.g. unclear recruitment, many asymptomatic patients), and imprecision (e.g. sample size, few events for some outcomes), and the cohort studies had issues related to risk of bias (e.g. selection, directness (e.g. unclear recruitment, different health care setting), and precision (e.g. few events for some outcomes).

Results per outcome

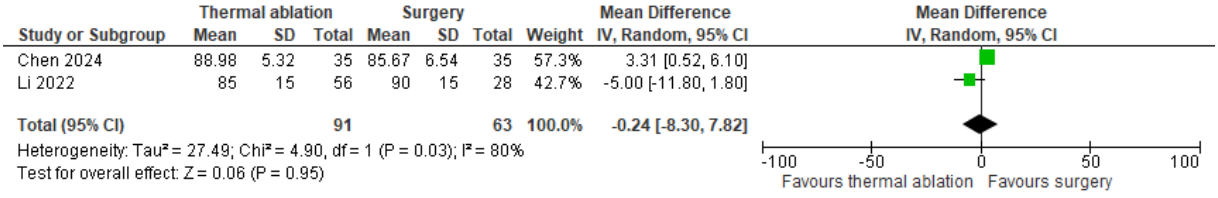
Thermal ablation of benign non-toxic and toxic thyroid nodules in adults (P1 and P2)

Health-related quality of life (Appendix 4:1)

Health-related quality of life (HRQoL), (measured with validated scales) was studied in two RCTs, (n=387), and in four cohort studies (n=1,018). One RCT compared MWA (n=89) and RFA (n=112) with surgery (n=225) and showed an improvement in Thyroid specific Quality-of-Life Questionnaire Scale with adjusted odds ratio (AOR): 0.34 (95%CI: 0.21 to 0.45), p<0.0001, at 15 months. The other RCT, compared MWA (n=28) with surgery (n=24), resulted in no significant differences in patient reported HRQoL, measured with Short form survey (SF-36) components, Physical general health (MWA 75 vs. surgery 70), and Mental health (MWA 75 vs. surgery 70).

SF-36 was also reported by Yue et al. (2016) with RFA mean, HRQoL: 68.5, compared with surgery: 66.7, p=0.029. Two of the cohort studies reported EORTC Core Quality of Life questionnaire (QoL EORTC QLQ C30) scores, at 6 months, and were pooled together in a meta-analysis with MD: -0.24 (95% CI: -8.30 to 7.82), n.s. (Figure 1).

Figure 1. HRQoL measured with QoL EORTC QLQ C30 in cohort studies

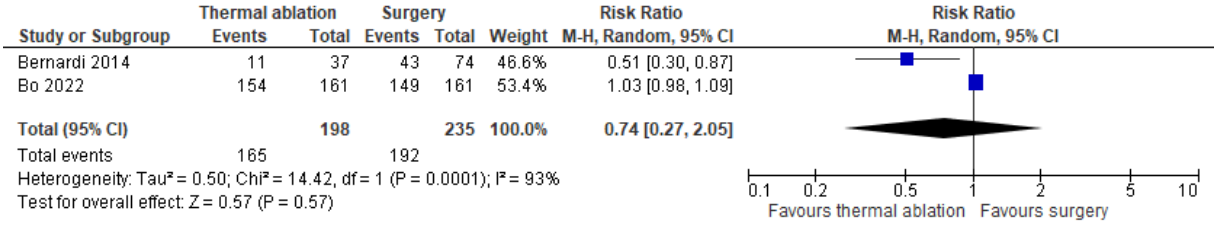


Conclusion: It is uncertain whether TA results in any difference in HRQoL compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Very low certainty of evidence (GRADE ⊕OOO).

Symptom change (Appendix 4:2)

Symptom change was studied in one RCT (n=52), and in three cohort studies (n=491). In the RCT, no significant difference in symptom relief was seen between MWA, 10/28 (35.7%) (n=28) compared with surgery 11/24 (45.8%), (n=24), n.s. Data from two of the cohort studies, on symptom remission, were pooled in a meta-analysis, RR: 0.74 (95% CI: 0.27 to 2.05), n.s. (Figure 2). The third cohort study found no significant differences in symptom scores, mean (SD), between MWA: baseline 4.5 (0.9), at 12 months, 0.7 (0.7), and surgery: baseline 4.5 (0.9), at 12 months: 0.8 (0.7), n.s.

Figure 2. Symptoms change (remission) in cohort studies



Conclusion: It is uncertain whether TA results in any difference in symptom change compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Low certainty of evidence (GRADE ⊕OOO).

Complications (Appendix 4:3)

Major complications were reported in four RCTs (n=510), in 13 cohort studies (n=2,244), and in five case-series (n=13,022). Data on individuals with at least one major complication were pooled in meta-analyses for all four RCTs, with Peto OR: 0.63 (95% CI: 0.25 to 1.63), n.s. (Figure 3a), and for 11 of the cohort studies (surgery group data not available in Yan et al., 2023), with Peto OR: 0.39 (95% CI: 0.23 to 0.65), p=0.0004), (Figure 3b).

Figure 3a. Major complications reported in RCTs

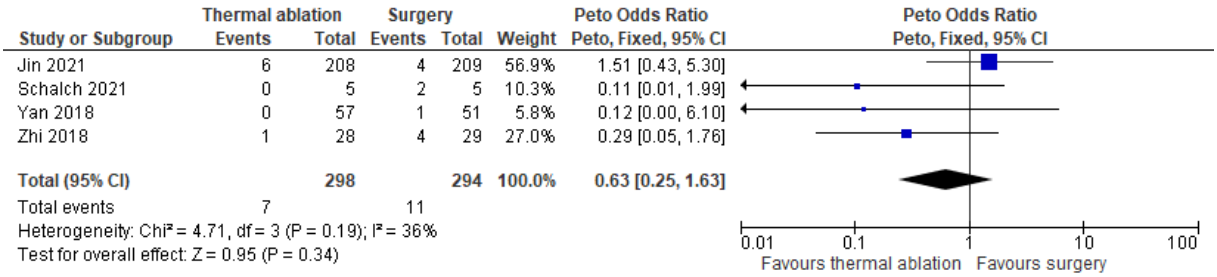
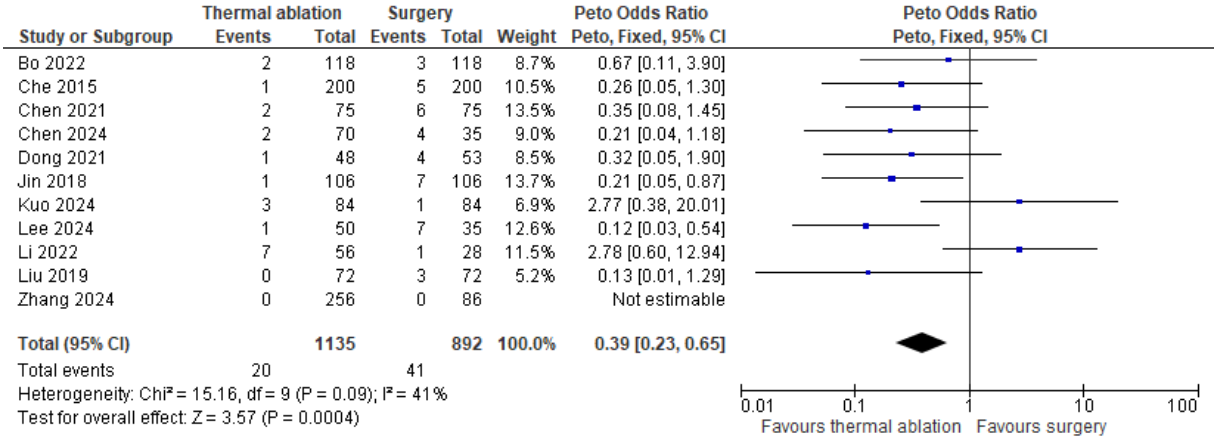


Figure 3b. Major complications reported in cohort studies



Conclusion: It is uncertain whether there is any difference in major complication rate with TA compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Very low certainty of evidence (GRADE ⊕OOO).

Relapse (Appendix 4:4)

Relapse was reported in three cohort studies (n=645). One of the cohort studies, with relapse defined as re-growth of treated nodule during follow-up period, occurred in 0.05% in the RFA group, compared with 2.5% the surgery group, n.s. (the number on individuals with relapse was not estimable, since each patient had either single- or multiple nodules at baseline). In the two remaining cohort studies, there were no relapse events.

Conclusion: It is uncertain whether there is any difference in relapse rate with TA compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Very low certainty of evidence (GRADE ⊕OOO).

Malignancy (Appendix 4:5)

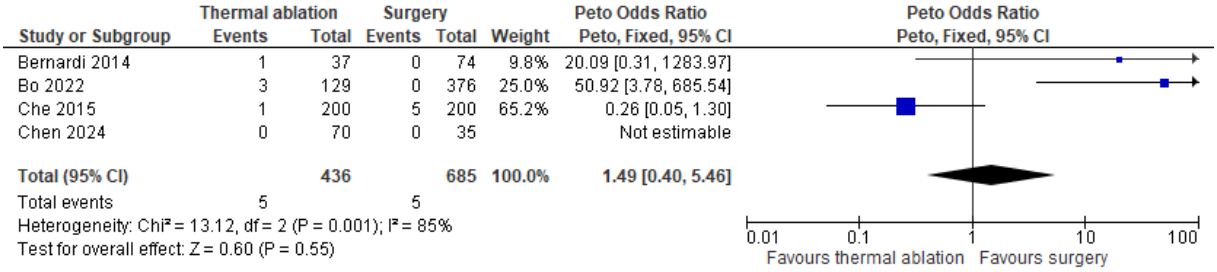
Detection of malignancy was reported in two cohort studies (n=279), with zero detected events in the TA groups, and a total of 15 malignancies detected in the specimens resected in the surgery groups., Peto OR: 0.15 (95% CI: 0.05 to 0.43), p=0.0004). As there were no specimens for microscopy in the TA groups, the frequency of unexpected malignancy is unknown.is unknown.

Conclusion: No conclusion can be drawn since there were no specimens for histopathological evaluations in the TA groups (no GRADE).

Re-intervention (Appendix 4:6)

Re-intervention was reported in four cohort studies (n=1,121), with Peto OR: 1.49 (95% CI: 0.40 to 5.46), n.s. (Figure 5).

Figure 5. Re-intervention reported in cohort studies



Conclusion: It is uncertain whether there is any difference in re-intervention rates with TA compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Very low certainty of evidence (GRADE ⊕OOO).

Mortality (Appendix 4:7)

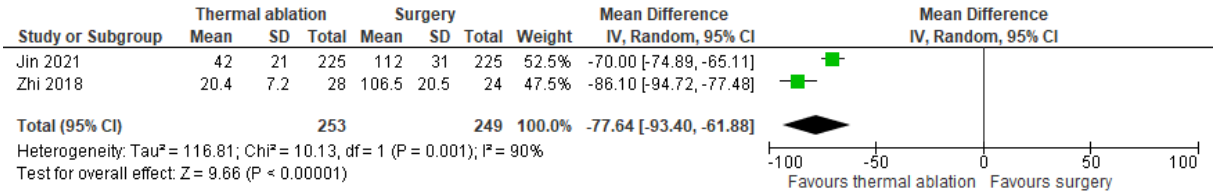
Mortality was studied in one RCT (n=52), with zero events.

Conclusion: It is uncertain whether there is any difference in mortality with TA compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Very low certainty of evidence (GRADE ⊕OOO).

Operation time (Appendix 4:8)

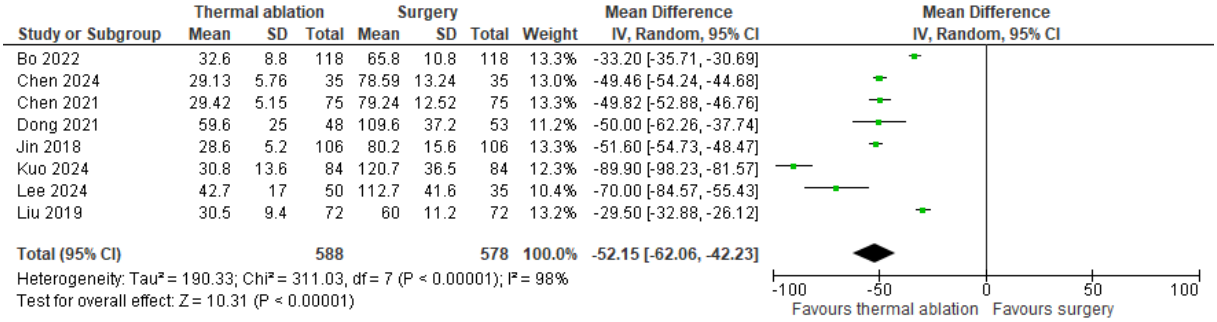
Operation time was reported in three RCTs (n=402), and in ten cohort studies (n=1,418). Data from two RCTs could be pooled in a meta-analysis with significantly reduced operation time for TA compared with surgery, MD: -77.64 (95%CI: -93.40 to –61.88) min., p<0.00001 (Figure 6a).

Figure 6a. Operation time reported in RCTs



Data from eight cohort studies could be pooled in a meta-analysis with significantly reduced operation time for TA compared with surgery, MD: -52.15 (95% CI: -62.06 to –42.23) min., p<0.00001 (Figure 6b).

Figure 6b. Operation time reported in cohort studies



Conclusion: Operation time is probably reduced with TA compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Moderate certainty of evidence (GRADE ⊕⊕⊕O).

Volume reduction rate (%) (Appendix 4:9)

Volume reduction rate for TA was reported in two RCTs (n=478), and in twelve cohort studies (n=2,005). For the two RCTs, pooled in a meta-analysis, the mean volume reduction for TA was: 79.79 (95% CI: 79.02 to 80.55) % (Figure 7a). For the seven cohort studies, pooled in a meta-analysis, the mean volume reduction for TA was 82.59 (95% CI: 77.06 to 90.10) % (Figure 7b).

Figure 7a. Volume reduction rate (%) for TA at 12 months reported in RCTs

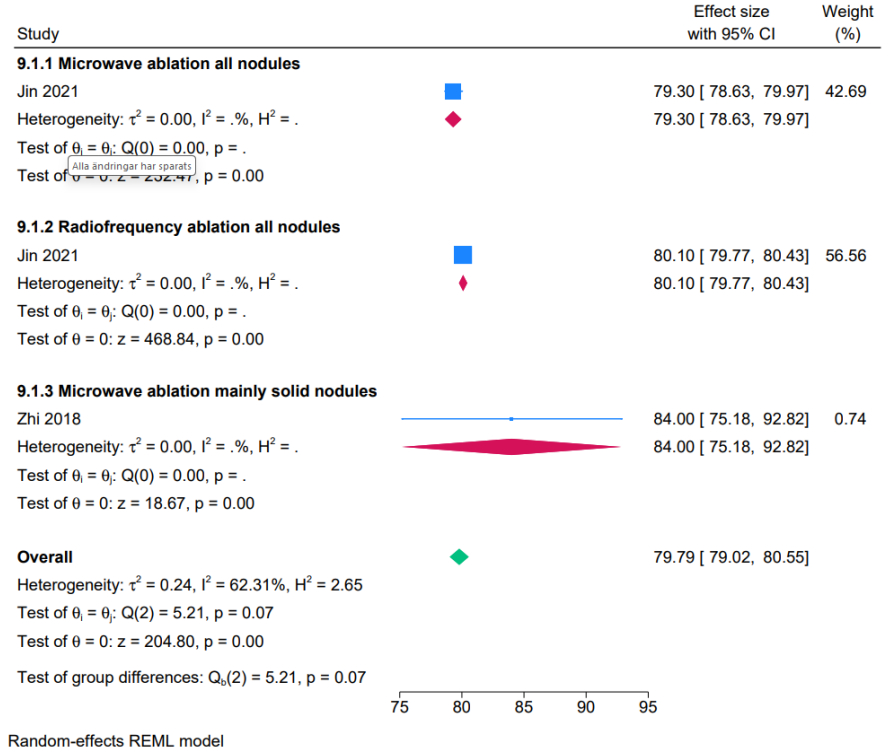


Figure 7b. Volume reduction (%) rate for TA at 12 months reported in cohort studies

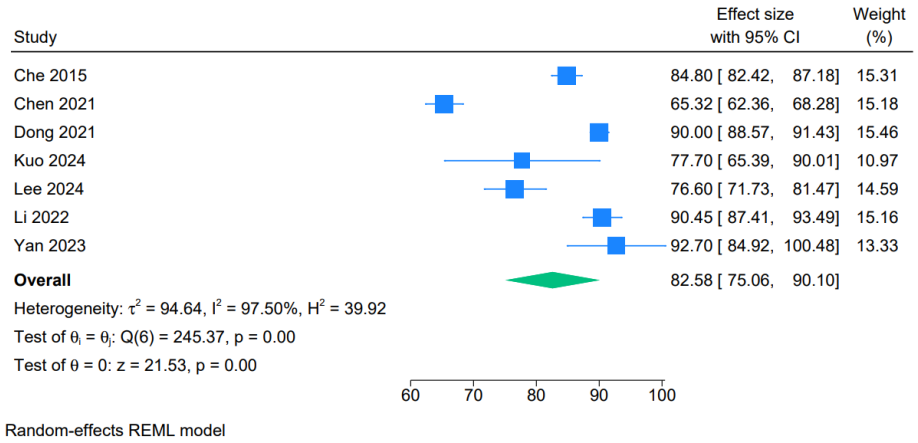
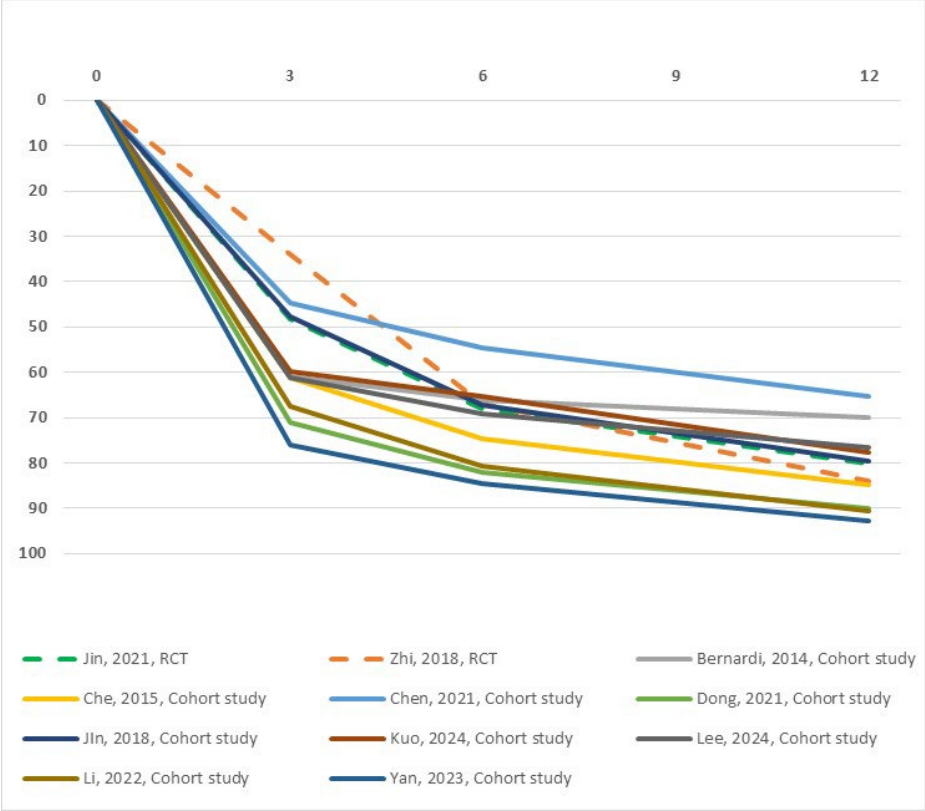


Figure 7c. Volume reduction (%) for TA after 0, 3, 6 and 12 months after TA

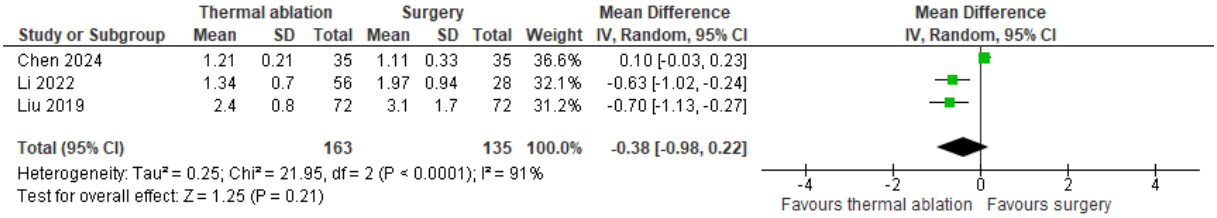


Conclusion: The mean volume reduction following TA of benign non-toxic or toxic thyroid nodules is approximately 80% after 12 months (no GRADE).

Biochemical response (Appendix 4:10)

Biochemical response in terms of Thyroid Stimulating Hormone (TSH)-levels was reported in four cohort studies (n=483). Three of the cohort studies could be pooled in a meta-analysis, with MD: -0.38 (95% CI: -0.98 to 0.22) µU/L, n.s., comparing TA with surgery (Figure 8).

Figure 8. Biochemical response P1 (at 6 months)

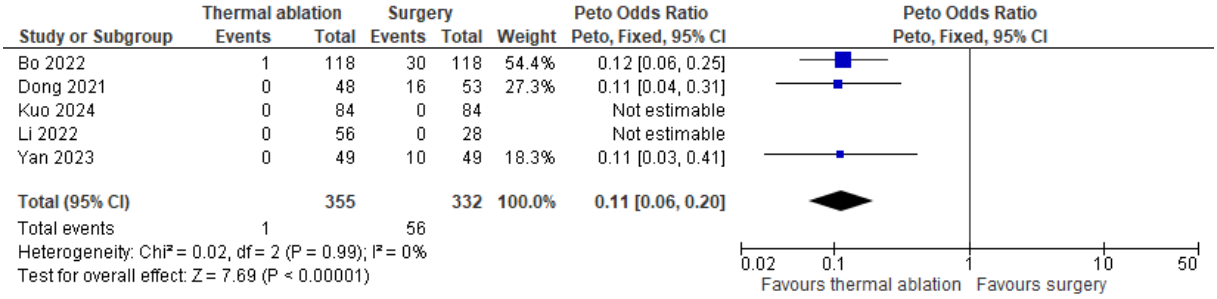


Conclusion: It is uncertain whether there is any difference in biochemical response with TA compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Very low certainty of evidence (GRADE ⊕OOO).

Need of hormone replacement therapy (Appendix 4:11)

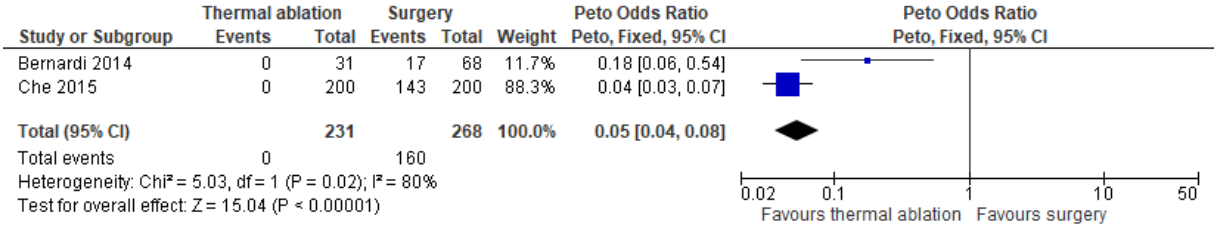
Need of hormone replacement therapy was reported in one RCT (n=52), and in seven cohort studies (n=1,241). The RCT reported event rates for need of hormone replacement therapy, in the TA group with 0/28 (0%), and in the surgery group with 1/24 (4.2%), n.s. For P1 (benign, non-toxic noduli), data from five cohort studies could be pooled in a meta-analysis with Peto OR: 0.11 (95% CI: 0.06 to 0.20), p<0.00001 (Figure 9a).

Figure 9a. Hormone replacement therapy P1



For P1+P2 (i.e. benign, non-toxic or toxic noduli), two cohort studies could be combined in a meta-analysis, with Peto OR: 0.05 (95% CI: 0.04 to 0.08), p<0.00001 (Figure 9b).

Figure 9b. Hormone replacement therapy P1+P2



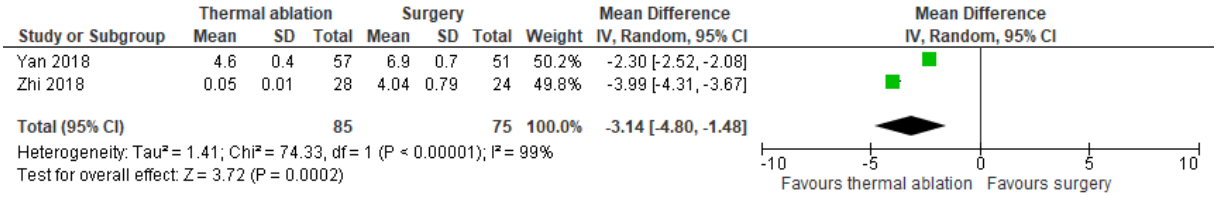
Conclusion: TA may reduce the need of hormone replacement therapy compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Low certainty of evidence (GRADE ⊕⊕OO).

Hospital stay (Appendix4:12)

Hospital stay was reported in two RCTs (n=160), and in eleven cohort studies (n=2,240).

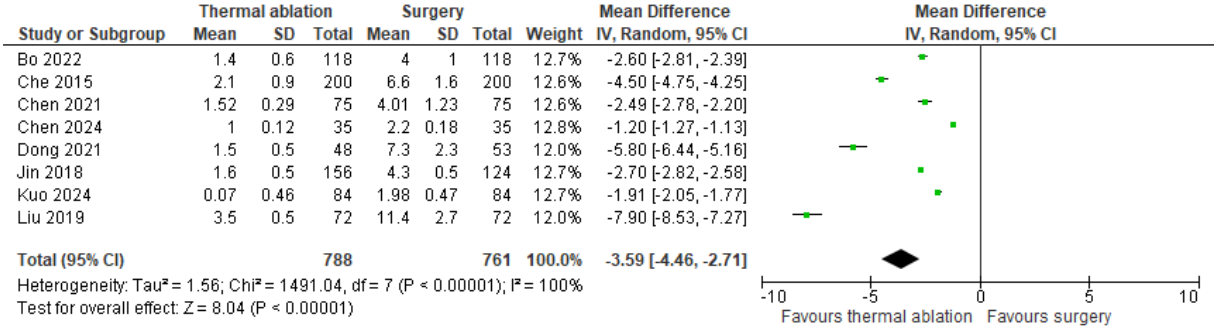
Hospital stay for surgical cases was markedly longer (4-7 days) compared with Swedish data (1-2 days). The RCTs were pooled in a meta-analysis, with MD: -3.14 (95% CI: -4.80 to -1.48), p=0.0002 (Figure 10a).

Figure 10a. Hospitalisation days reported in RCTs



The results for hospital stay could be pooled from eight of the cohort studies, with MD: -3.59 (95% CI: -4.46 to -2.71), p=0.00001 (Figure 10b).

Figure 10b. Hospitalisation days reported in cohort studies



Conclusion: The length of hospital stay may be reduced with TA compared with surgery in adults with benign non-toxic or toxic thyroid nodules. Low certainty of evidence (GRADE ⊕⊕OO).

Thermal ablation in Graves' Disease in adults (P3)

No controlled studies were identified for TA compared with surgery regarding this patient group.

Complications (Appendix 4:3)

Two case-series that reported complications were identified, one of which reported tachycardia, skin numbness and transient dysphonia) in 12/50 (24%) patients, and total complications rates, in the RFA- and MWA-group: 4/29 (13.8%) and 6/21 (28.6%), respectively. In the other case series, the major complications reported were hypothyroidism: 2/30, and thyrotoxicosis: 13/30 (i.e. 9 partial responses, 4 no response).

10 Ethical aspects

The introduction of TA as an alternative treatment option for patient in Region Västra Götaland with benign thyroid disorders with and without increased thyroid hormone levels should from an equality perspective consider that TA is since several years available as a standard treatment in other Scandinavian and European countries. In the evaluation of this new treatment option, it should also be considered that symptoms and severity of the conditions can vary significantly between individuals.

From a risk-benefit perspective, the present report provide evidence that the introduction of TA as a treatment option for patients with benign non-toxic and toxic thyroid nodules or Graves' disease would offer a less invasive outpatient alternative to surgical intervention, characterised by a shorter recovery period and a potentially diminished requirement for lifelong hormone replacement therapy. However, from the report it is evident that the effectiveness of TA regarding quality of life, alleviation of symptoms, and reduction in complications compared with surgery is uncertain.

Even though TA techniques can offer advantages they do not permit histopathological evaluation of the treated tissue. This represents a significant limitation compared to surgical excision, which provides a definitive histological diagnosis. Consequently, in cases where malignancy cannot be confidently excluded (Bethesda III and IV), surgical resection remains the preferred approach, as it ensures comprehensive histopathological examination and accurate diagnosis, which are not achievable through TA alone. In cases where TA is considered, two consecutive normal cytology reports (Bethesda II) should be required, knowing that, even in Bethesda II, unexpected malignancy has been reported in 1.5% of cases treated with surgery.

From a cost-effective perspective, the current report suggests that TA may represent a more economically favourable option, particularly in the context of healthcare cost containment within VGR.

The review shows that there are only few and small RCTs available from non-European populations and that the efficacy of TA compared with surgery is uncertain regarding critical outcomes such as major complications, malignancy, re-intervention or mortality. However, the report has not identified any evident obstacles that would limit clinical research and the further evaluation of critical and important outcome measures of TA in benign non-toxic and toxic thyroid nodules or Graves' disease.

11 Organisational aspects

Time frame for the putative introduction of the new health technology

After purchase of equipment and on-site training, treatment with TA could be initiated at most medical units that today manage patients with benign non-toxic or toxic thyroid nodules. A development over time where the technique is introduced over a 2-year period at one or two centres in the VGR and would be preferred in order to develop clinical expertise, facilitating quality registration and clinical research.

Present use of the technology in other hospitals in Region Västra Götaland

At present, TA of the thyroid is not performed in VGR.

Consequences of the new health technology for personnel

Pre-operative work-up and treatment of patients with benign non-toxic goitre (P1) is performed by endocrine surgeons at Carlanderska Hospital, Northern Älvsborg County Hospital, and Sahlgrenska University Hospital. Patients with hyperthyroidism (P2 and P3) are treated mainly by endocrinologists at Carlanderska Hospital, Sahlgrenska University Hospital and regional hospitals (Sjukhusen i Väster, Northern Älvsborg County Hospital, Södra Älvsborg County Hospital and Skaraborgs Sjukhus Skövde). Medical staff that will perform the treatments will be trained over a 3–6-month period by experienced consultant physicians from European medical centres. Introduction of the new technology will be supported by seminars and lectures given to all personnel engaged in the treatment of these patients, at these hospitals.

Consequences for other clinics or supporting functions at the hospital or in Region Västra Götaland

Patients eligible for TA are today treated with surgery (either hemi- or total thyroidectomy), RAI, or antithyroid drugs. Most patients (P1) undergo ultrasound and one selective cytology. A second benign cytology will be required before a patient may be considered for TA. For patients with toxic nodular thyroid disease (P2), ultrasound and selective cytology is not required, i.e. no additional examinations are necessary as compared with the current standard of care. Patients with Graves' disease (P3) are recommended to undergo ultrasound and selective cytologies when required. The overall flow of patients is not expected to change. However, some dedicated, large volume medical centres for TA of benign toxic and non-toxic nodules are expected to develop over time.

12 Economic aspects

The economic component of this report evaluates the societal costs associated with the treatment of patients in the VGR using surgical intervention and ablation (using cost estimates from other regions in Sweden and Denmark). The objective is to capture how the overall costs vary when a proportion of patients undergo ablation instead of surgery. From a societal perspective, both direct and indirect costs have been considered. Direct costs include healthcare expenses related to the treatment itself, while indirect costs encompass productivity losses due to sickness absence during treatment and follow-up periods. These estimated costs have also been compared with diagnosis-related group (DRG)-based costs per patient for inpatient care (complicated and uncomplicated) and outpatient care.

The cost analysis followed a four-step process, as outlined by Drummond et al. (2015): (1) identification of inputs, (2) quantification of inputs in physical units, (3) conversion into monetary values, and (4) adjustment for time differentials. To apply this framework to the estimation of surgical and ablation costs, the healthcare inputs, their quantities, unit costs, and useful life spans were identified by experts within the project team.

Present costs of currently used technologies

For surgical patients, the most substantial cost component was premises and staff (42%), followed by sickness absence (23%), use of technology (15%), and pharmaceuticals (15%). In 2024, the total estimated cost for surgery in 650 patients (VGR) was 40.4 MSEK, while the corresponding cost for 250 estimated ablation patients was 5.1 MSEK.

Expected costs of the new health technology (se I in PICO)

The primary cost driver for ablation patients was technology use (52%), followed by premises and staff (25%). Due to the significantly shorter duration of sickness absence for ablation patients, indirect costs constituted only 10% of the total, compared with 22% for surgical patients.

The cost for the generator was considered a capital asset, with a lifespan exceeding one year. In this case, annuitisation was used to estimate the annual equivalent cost, applying a 3% discount rate over a five-year period, as recommended by Drummond et al. (2015). All other inputs were considered recurrent in nature.

Total change in costs

Table 1 below presents both the per-patient and total costs in VGR, disaggregated by cost categories. The estimated total cost per patient was 62 kSEK for surgery and 20 kSEK for ablation. Direct costs accounted for 78% and 90% of the total per-patient costs for surgical and ablation procedures, respectively.

Table 1. Estimated total costs per patient and total costs for operation and ablation in 2024

Cost component	Kostnad per patient (SEK)			
	Operation	Share (%)	Ablation	Share (%)
Direct cost				
Premises including staff				
Surgeon /Operation theatre	10 000	42%	2 000	25%
Nurse/Post surgical care	4 000		2 000	
Medical Ward/Adm	12 000		1 000	
Technology use costs	-			
N. Recurrence monitoring	36		-	
Generator	-	15%	33	52%
Needles	-		10 000	
Other costs	9 000		400	
Medicine	-		-	
Anesthetics	2 000	15%	2 000	10%
Other medicne	7 428		-	
Tests	-		-	
Standard sampling	500	5%	500	2%
Laryngoscopy	2 500		-	
Costs for complication	-		-	
Recurrence savings	100		100	
Re-operation	500		-	
Lyryngoscopy control	-	1%	125	2%
Infection	-		50	
Bleeding	-		50	
L-Thyroxine treatment	250			
Sub-total: Direct costs	***48 314***	***78%***	***18 258***	***90%***
Indirect costs				
Sick leave	13 790	22%	1 970	10%
Sub-total: Indirect costs	***13 790***	***22%***	***1 970***	***10%***
Total costs per patient	***62 104***	***100%***	***20 228***	***100%***
Number of patients	650		250	
Total costs of VGR	**40 367 676**		**5 056 945**	

The costs of thyroid surgery per patient was extracted from the DRG list of VGR. For a complicated and an uncomplicated case, the cost was 75 kSEK and 64.5 kSEK respectively. An out-patient care for same type of patient accounted for 38.3 kSEK (Table 2).

Table 2. Cost* per patient in VGR, based on DRG-price

DRG-code	DRG-name	Cost per patient, SEK
L25C	Thyroid surgery, complicated	75,016
L25E	Thyroid surgery, uncomplicated	64,555
L25O	Thyroid surgery, outpatient care	38,307

*Calculated from DRG weight and price from VGR.

The comparative analysis of surgery, ablation, and DRG-based treatment costs indicates that ablation is significantly less costly per patient than the alternative approaches. From both societal and healthcare system perspectives, the cost per ablation patient amounts to 32.6% and 37.8%, respectively, of the cost per surgical patient. Furthermore, the estimated cost per ablation patient is also lower than the DRG-based costs for

complicated cases (24.3%), uncomplicated cases (28.3%), and outpatient care (47.7%) within VGR.

Incorporating health outcomes into the analysis would allow for a more comprehensive assessment of the cost-effectiveness and value-for-money of each treatment modality. Nevertheless, the current cost estimates suggest that TA may represent a more economically favourable option, particularly in the context of healthcare cost containment within VGR.

Possibility to adopt and use the new technology within the present budget

As the introduction and use of TA is expected to require few investments (Table 1) there is no risk for a displacement effect and the technology would reasonably be established within budget.

Available economic evaluations or cost advantages/disadvantages

The review by Qafesha et al. (Qafesha et al., 2024) also evaluated economical aspects and showed that TA was associated with significant shorter hospital stays and reduced procedure time.

13 Discussion

Summary of main results

This systematic review shows that, for all critical outcomes, the available evidence does not allow any conclusions about efficacy and safety for TA compared with surgery, i.e. for HRQoL, symptoms change, major complications, relapse rate, re-intervention, and mortality, as well as for TSH biochemical response (important for decision making). However, TA compared with surgery is probably associated with reduced operation time and may lead to reduced need for hormone replacement therapy and shorter length of hospital stay. The mean volume reduction rate following TA of benign non-toxic or toxic thyroid nodules was approximately 80% after 12 months. Regarding detection of unexpected malignancy, no conclusion could be drawn since there were no specimens for histopathological evaluations in the TA groups.
No controlled studies were identified for TA compared with surgery regarding patients with Graves' disease.

Overall completeness and applicability of evidence

There is a lack of evidence including long-term follow up studies (>10 years) evaluating complication rate, regrowth of nodules, frequency of malignancies, new nodules, hormonal replacement therapy and quality of life, measured with validated scales

specifically developed for thyroid disorders. Evaluation of malignancies present a specific methodological issue. The frequency of small thyroid cancer has increased over the last decades and there is therefore a need for improved methods to study and monitor presence of malignancies after TA.

Agreements and disagreements with other studies and reviews

Efficacy

In a systematic review of 16 studies (2 RCTs and 14 case-control studies) Ding et al. (2023) evaluated the efficacy of RFA or MWA ablation compared to conventional thyroidectomy. Ultrasound-guided TA was reported to be an excellent alternative for management of benign thyroid nodules and to have a beneficial efficacy and a significantly better safety profile when compared with hemi- or total thyroidectomy. Benefits regarding hospital stay and operation time were also seen. Furthermore, as in our present systematic review, the incidence of hypothyroidism and the subsequent need for life-long treatment with levothyroxine were found to be reduced. In addition to lower degree of hypothyroidism Qafesha et al. (2024) found in a review evaluating twenty-six studies (7 randomised controlled trials and 19 cohort studies) that RFA or MWA ablation provided improved cosmetic results.

Volume reduction rate

The primary efficacy of TA was evaluated in previous review by Guan et al. (2024). It was stated that most nodules can be cured with one treatment and that the complete ablation rate observed during follow-up was 84.5%. The review included 3 articles and showed an incidence of re-growth of nodules after TA (MWA) of 15.8%.

Safety

In the review by Ding et al. (2023) it was also found that the degree of postoperative pain could be decreased with TA. The safety of RFA and MWA was also evaluated in a review by Qafesha et al. (2024) where it was found that RFA and MWA ablation was associated with lower postoperative pain levels, and lower VAS score. It was also shown that conventional thyroid surgery for benign nodules had a higher incidence of hoarseness, parathyroid injury, and blood loss.

Implications for research

A well conducted national or Nordic RCT studying TA compared with surgery evaluating efficacy and safety would be of importance, and of scientific interest.

14 Future perspectives

Scientific knowledge gaps

The present report shows that there are only few and small RCTs available that evaluate TA compared with conventional surgery. There is thus a lack of high-quality well-designed RCTs evaluating patient preferences, quality of life, symptom changes, complication rate and costs, and this systematic review shows that the efficacy of TA compared with surgery is uncertain regarding critical outcomes such as major complications, malignancy, re-intervention or mortality. Furthermore, most studies identified in this systematic review are of non-European origin.

Ongoing research

A search in clinicaltrials.gov showed that there are two listed ongoing studies evaluating TA compared with surgery for benign thyroid nodules (P1). Three ongoing studies evaluate TA as treatment in subjects with relapsed Graves' disease (P3).

P1 Study 1
Title: Surgical Versus Non-Surgical Management of Thyroid Nodule.
ClinicalTrials.gov ID NCT04580199.
Sponsor Mahmoud Fahd.
Study completed 2022

P1 Study 2
Title: Thermal Ablation Vs Thyroidectomy for Large Benign Thyroid Nodules
ClinicalTrials.gov ID NCT06607133
Sponsor Ming-an Yu
Study completed 2027-12

P3 Study 1
Title: A Prospective Evaluation of Microwave Ablation (MWA) in the Treatment of Relapsed Graves' Disease
ClinicalTrials.gov ID NCT06506149
Sponsor The University of Hong Kong
Study completion 2026

P3 Study 2
Title: A Prospective Evaluation of Radiofrequency Ablation in the Treatment of Relapsed Graves' Disease.
ClinicalTrials.gov ID NCT06418919
Sponsor The University of Hong Kong
Study completed 2025

P3 Study 3
Title: Clinical Study of Ultrasound-guided Radiofrequency Ablation in the Treatment of Refractory Hyperthyroidism
ClinicalTrials.gov ID NCT06305871
Sponsor Zhang Bo
Study completed 2025

15 Participants in the project

The question was nominated by

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Declaration of interests

The authors report that they have no conflicts of interest related to the content of this HTA.

Project time

The HTA was accomplished during the period of 2024-12-09 to 2025-06-30.
Literature searches were conducted 2025-01-10.

Components of this Health Technology Assessment

- ✓ Description of methods
- ✓ PICO
- ✓ Full literature search
- ✓ Flowchart
- ✓ Selection based on relevance
- ✓ Quality assessment
- ✓ Data tabulation
- ✓ Evidence synthesis
- ✓ Meta-analysis
- ✓ Certainty of evidence by GRADE
- ✓ Summary
- ✓ Economical aspects
- ✓ Organisational aspects
- ✓ Ethical aspects
- ✓ Ongoing studies
- ✓ Excluded articles
- ✓ Participation of experts
- ✓ External review
- ✓ Knowledge gaps identified
- ✓ Conflict of interest reported

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:

Is radiofrequency or microwave ablation an efficient and patient safe alternative, compared with thyroid surgery, for treatment of adult patients with benign non-toxic, toxic nodules, and toxic diffuse autoimmune hyperthyroidism (Graves' disease).

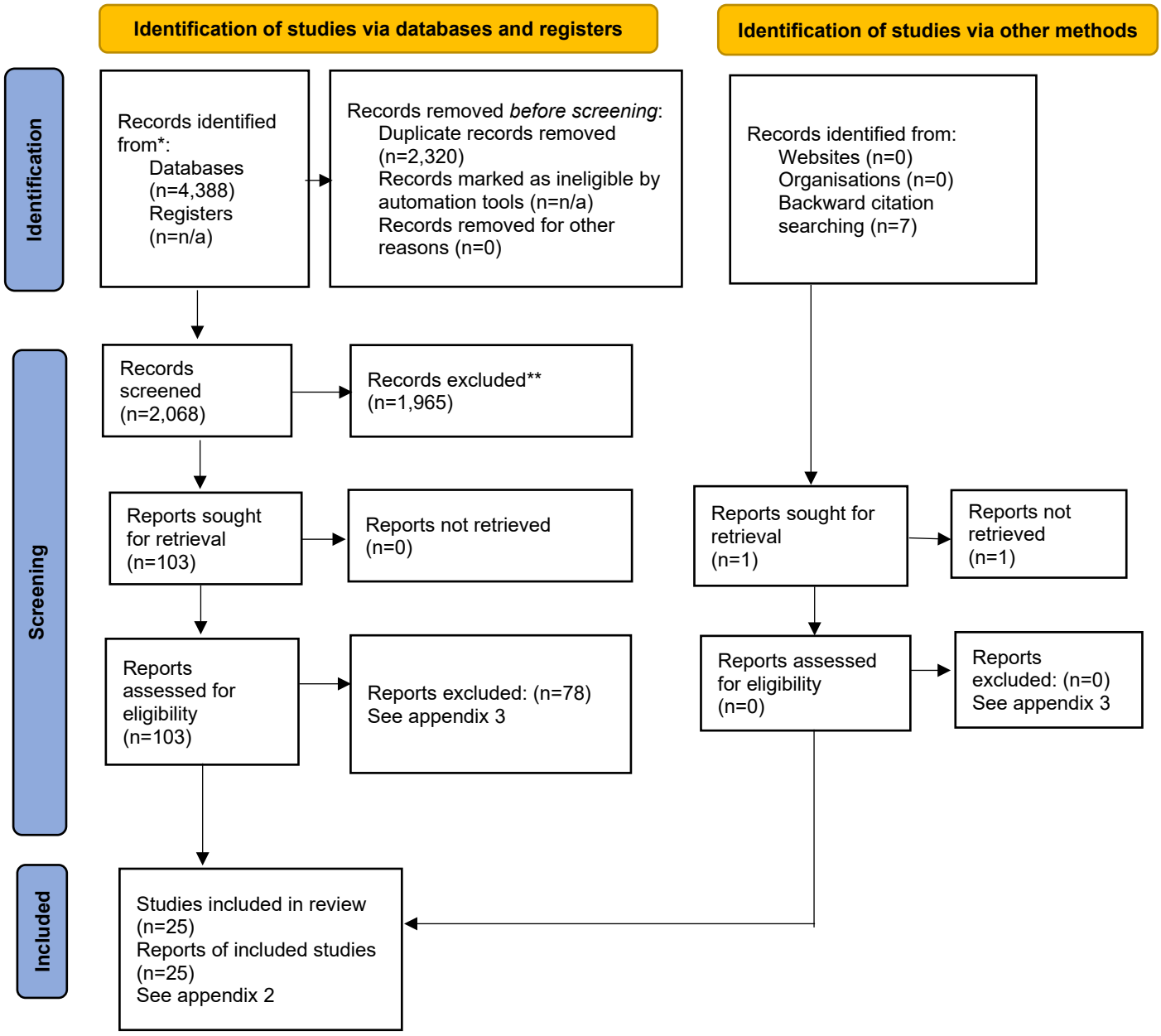
PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO	
P	P1: Adult patients with benign non-toxic nodules (as defined by authors) P2: Adult patients with toxic nodules P1+P2 if not reported separately (5% inclusion of P1 or P2 accepted in each group above) P3: Adult patients with toxic diffuse autoimmune hyperthyroidism (Graves' disease), suitable for surgery
I	Thermal ablation using radiofrequency or microwaves
C	Surgery (open or endoscopic) – Excluding routinely conducted total thyroidectomy, or local excision
O	*Critical for decision making* HRQoL Health-related quality of life (measured with validated scales) Symptoms change (measured with validated scales) Complications (post-intervention, and late) Relapse Malignancy Re-intervention Mortality *Important for decision making* Operation time (time of surgery) Volume reduction Biochemical response Need of hormonal treatment Hospital stay

Study design	
RCT	
Non-randomised controlled studies, >20 patients per group	
Case series for complications, >1,000 patients Case series P3 – no limitation regarding number of patients	
SR (commented upon)	
Publication year	Language
2005-	English
SR 2023-	

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page et al., 2021

Search strategies

Database: Ovid MEDLINE(R) ALL (OvidSP)
Date: 10 Jan 2025
No. of results: 1,319

#	Searches	Results
1	Thyroid Nodule/	8480
2	Graves Disease/	16562
3	(((thyroid or benign or toxic or hyperfunction* or hyper-function* or overproduc* or over-produc*) and nodule*) or AFTN* or thyroid adenoma* or thyroid tumour* or thyroid tumor*).ab,kf,ti.	33432
4	(((grave* or basedow*) adj3 (disease* or syndrome)) or ((autoimmune or auto-immune or grave*) adj3 (hyperthyroid* or hyper-thyroid*))).ab,kf,ti.	17352
5	(((toxic or nontoxic) adj2 goit*) or multinodular goit* or multi-nodular goit*).ab,kf,ti.	5225
6	1 or 2 or 3 or 4 or 5	58884
7	Ablation Techniques/	3761
8	exp Radiofrequency Ablation/	43912
9	(thermoablat* or ablat* or MWA or RFA).ab,kf,ti.	156728
10	7 or 8 or 9	164512
11	6 and 10	1709
12	child/ not (child/ and adult/)	1304713
13	11 not 12	1662
14	animals/ not (animals/ and humans/)	5262015
15	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or cow or cows or hamster or hamsters or koalas or rabbit or rabbits or swine or murine or porcine or horses or horse or goats or goat or cadaver or cadaveric).ti.	2248291
16	14 or 15	5736409
17	13 not 16	1640
18	limit 17 to yr="2009 -Current"	1387
19	**limit 18 to english**	**1319**

Database: Embase 1974 to 2025 January 09 (OvidSP)
Date: 10 Jan 2025
No. of results: 1,314

#	Searches	Results
1	*thyroid nodule/	10918
2	*Graves disease/	14062
3	(((thyroid or benign or toxic or hyperfunction* or hyper-function* or overproduc* or over-produc*) and nodule*) or AFTN* or thyroid adenoma* or thyroid tumour* or thyroid tumor*).ab,kf,ti.	50458
4	(((grave* or basedow*) adj3 (disease* or syndrome)) or ((autoimmune or auto-immune or grave*) adj3 (hyperthyroid* or hyper-thyroid*))).ab,kf,ti.	23096
5	(((toxic or nontoxic) adj2 goit*) or multinodular goit* or multi-nodular goit*).ab,kf,ti.	7039
6	1 or 2 or 3 or 4 or 5	78415
7	*ablation therapy/	8657
8	*radiofrequency ablation/	18536
9	*thermal ablation/	589

10	(thermoablat* or ablat* or MWA or RFA).ab,kf,ti.	239091
11	7 or 8 or 9 or 10	240484
12	6 and 11	2943
13	child/ not (child/ and adult/)	1531591
14	12 not 13	2846
15	animal/ not (animal/ and human/)	1241361
16	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or cow or cows or hamster or hamsters or koalas or rabbit or rabbits or swine or murine or porcine or horses or horse or goats or goat or cadaver or cadaveric).ti.	2436660
17	15 or 16	3370219
18	14 not 17	2832
19	limit 18 to (embase or medline)	1725
20	limit 19 to yr="2005 -Current"	1453
21	**limit 20 to english language**	**1314**

Database: Web of Science Core Collection

Entitlements: - WOS.SCI: 1970 to 2025, - WOS.AHCI: 1975 to 2025, - WOS.BHCI: 2005 to 2025, - WOS.BSCI: 2005 to 2025, - WOS.ESCI: 2020 to 2025, - WOS.ISTP: 1990 to 2025, - WOS.SSCI: 1970 to 2025, - WOS.ISSHP: 1990 to 2025

Date: 10 Jan 2025

No. of results: 1,755

#	Search Query	Results
1	(((thyroid or benign or toxic or hyperfunction* or hyper-function* or overproduc* or over-produc*) and nodule*) or AFTN* or "thyroid adenoma*" or "thyroid tumour*" or "thyroid tumor*") (Topic)	34943
2	(((grave* or basedow*) NEAR/2 (disease* or syndrome)) or ((autoimmune or auto-immune or grave*) NEAR/2 (hyperthyroid* or hyper-thyroid*))) (Topic)	18023
3	(((toxic or nontoxic or non-toxic) NEAR/1 goit*) or "multinodular goit*" or "multi-nodular goit*") (Topic)	4209
4	#3 OR #2 OR #1	53975
5	thermoablat* or thermo-ablat* or ablat* or MWA or RFA (Topic)	275743
6	#5 AND #4	2050
7	animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or cow or cows or hamster or hamsters or koalas or rabbit or rabbits or swine or murine or porcine or horses or horse or goats or goat or cadaver or cadaveric (Title)	2822669
8	#6 NOT #7	2028
9	#6 NOT #7 Timespan: 2005-01-01 to 2025-01-10	1807
10	**#6 NOT #7 and English (Languages) Timespan: 2005-01-01 to 2025-01-10**	**1755**

The websites listed below were visited 10 Jan 2025.

Source	Search terms / Browsing	No. of results	No. of relevant results

SBU www.sbu.se "Visa även träffar äldre än 5 år"	Ablation Radiofrekvensablation Mikrovågsablation	6 1 0	0 0 0
Folkehelseinstituttet (Norge) https://www.fhi.no/	Ablasjon Radiofrekvensablasjon Mikrobølgeablasjon	8 1 0	0 0 0
Behandlingsrådet (Danmark) https://behandlingsraadet.dk/	Browsat		0
Nationale Kliniske Anbefalinger og Retningslinjer (Danmark) https://www.sst.dk/da/Fagperson/Retningslinjer-og-procedurer/NKA-og-NKR/NKR-og-NKA-efter-omraade	Browsat		0
CAMTÖ https://www.regionorebrolan.se/sv/forskning/kontakt-och-organisation/hta-enheten-camto/	Browsat från 2023-		0
HTA Region Stockholm https://www.chis.regionstockholm.se/hta/rapporter/	Browsat från 2023-		0
Regional samverkansgrupp HTA (tidigare Metodrådet) i Sydöstra sjukvårdsregionen https://sydostrasjukvardsregionen.se/samverkansgrupper/hta/genomforda-bedomningar/	Browsat från 2023-		0
HTA Syd https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365	Browsat från 2023-		0
Medicinska rådet, Region Dalarna https://www.regiondalarna.se/plus/vard/utveckling-och-utbildning/kunskapsstyrning/vetenskapliga-radet/#:~:text=Vetenskapliga%20r%C3%A5det%20inr%C3%A4ttades%202024.,beslut%20i%20%C3%B6vergripande%20medicinska%20fr%C3%A5gor.	Browsat		0

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Reference lists
A comprehensive review of reference lists brought 7 new records.

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Project: Thermal ablation, thyroid

Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Length of Follow-Up	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Population	Men (n)	Outcome variables
Jin, 2021, China	RCT	15 months	MWA/RFA vs. surgery	MWA/RFA: 225 Surgery: 225,	MWA/RFA: 43 Surgery: 43	P1	Not reported	HRQoL (validated scales) Complications (post intervention and late) Operation time Volume reduction Length of hospital stay
Schalch, 2021, Brazil	RCT	1, 2, 3 months	RFA vs. surgery	RFA: 5 Surgery: 5	RFA: 45.3 Surgery:47.5	P1+P2	RFA: 0/5 Surgery:0/5	Complications
Yan, 2018, China	RCT	8, 24, 48 h	MWA vs. surgery	MWA: 57 Surgery: 51	MWA: 46 Surgery: 46	P1	MWA: 11/46 Surgery: 8/43	Complications (post intervention and late) Length of hospital stay
Zhi, 2018, China	RCT	12 months	MWA vs. surgery	MWA: 28 Surgery: 24	MWA: 54 Surgery: 52	P1	MWA 20/8 Surgery: 14/10	HRQoL (validated scales) Symptoms change Complications (post intervention and late) Mortality Operation time Volume reduction Biochemical response Hormone replacement therapy Length of hospital stay
Bernardi, 2014, Italy	Cohort study	12 months	RFA vs. surgery	RFA: 37 Surgery: 74	RFA: 58.3 Surgery: 54.9	P1+P2	RFA: 12/25 Surgery: 17/57	Symptoms change Complications (post intervention and late) Operation time Reintervention Volume reduction Biochemical response Hormone replacement therapy
Bo, 2022, China	Cohort study	12 months Median 19 months for nodule volume	MWA/RFA vs. surgery	MWA/RFA: 118 Open surgery: 118 Endoscopic surgery: 43	MWA/RFA: 50.9 Open surgery: 52.5 Endoscopic surgery: 35.3	P1	MWA/RFA: 18/100 Open surgery: 5/113 Endoscopic surgery: 4/39	Symptoms change Complications (post intervention and late) Operation time Volume reduction Hormone replacement therapy Length of hospital stay
Che, 2015, China	Cohort study	12 months	RFA vs. surgery	RFA: 200 Surgery: 200	RFA: 43.8 Surgery: 52.4	P1+P2	RFA: 35/165 Surgery: 46/154	Complications (post intervention and late) Relapse Volume reduction Hormone replacement therapy Length of hospital stay
Chen, 2021, China	Cohort study	12 months	MWA vs. surgery	MWA: 75 Surgery: 200	MWA: 42.3 Surgery: 42.4	P1	MWA: 28/22 Surgery: 29/21	Complications (post intervention and late) Operation time Volume reduction Biochemical response Length of hospital stay
Chen, 2024,	Cohort	6 months	MWA or RFA vs.	MWA: 35. RFA:	MWA: 42.6	P1	MWA: 12/23	HRQoL (validated scales)

Project: Thermal ablation, thyroid

Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Length of Follow-Up	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Population	Men (n)	Outcome variables
China	study		Surgery	35. Surgery: 35	RFA: 43.1 Surgery: 44.8		RFA: 12/22 Surgery: 10/25	Complications (post intervention and late) Operation time Volume reduction Biochemical response Length of hospital stay
Dong, 2021, China	Cohort study	12 months	MWA vs. Surgery	MWA: 48. Surgery: 53	MWA: 45.2 Surgery: 48.9	P1	MWA: 15/33 Surgery: 14/39	Symptoms change Complications (post intervention and late) Operation time Relapse Operation time Volume reduction Biochemical response Hormone replacement therapy Length of hospital stay
Jin, 2018, China	Cohort study	12 months	MWA vs. Surgery	MWA:156 Surgery:124	MWA: 39.6 Surgery: 45.4	P1	MWA: 58/98 Surgery: 40/84	Complications (post intervention and late) Operation time Length of hospital stay
Kuo, 2024, Taiwan	Cohort study	>12 months	RFA vs. Surgery (TOETVA)	RFA: 84 Surgery (TOETVA): 84	RFA: 47.2 Surgery (TOETVA): 45.6	P1	RFA: 8/76 Surgery (TOETVA): 7/77	Complications (post intervention and late) Malignancy Operation time Volume reduction Hormone replacement therapy Length of hospital stay
Lee, 2024, Hong Kong	Cohort study	12 months	RFA vs. Surgery	RFA: 50 Surgery: 35	RFA: 52.4 Surgery: 53.7	P1	RFA: 9/41 Surgery: 8/27	Complications (post intervention and late) Operation time Volume reduction
Li, 2022, China	Cohort study	12 months	MWA vs. Surgery	MWA: 56 Surgery: 28	MWA: 44 Surgery: 38	P1	MWA: 8/48 Surgery: 13/25	HRQoL (validated scales) Complications (post intervention and late) Volume reduction Biochemical response Hormone replacement therapy
Liu, 2019, China	Cohort study	6 months	MWA vs. Surgery	MWA: 72 Surgery: 72	MWA: 44.4 Surgery: 43.2	P1	MWA: 26/46 Surgery: 24/48	Complications (post intervention and late) Relapse Operation time Volume reduction Biochemical response Length of hospital stay
Yan, 2023, China	Cohort study	>24 months	MWA vs. Surgery	MWA: 49 Surgery: 49	MWA: 65.0 Surgery: 64.0	P1	MWA: 9/40 Surgery: 9/40	Complications (post intervention and late) Operation time Volume reduction Biochemical response Length of hospital stay

Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Length of Follow-Up	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Population	Men (n)	Outcome variables
								Hormone replacement therapy
Yue, 2016, China	Cohort study	6 months	RFA vs. Surgery	RFA: 137 Surgery: 267	RFA: 48.3 Surgery: 52.4	P1	RFA: 38/99 Surgery: 129/138	HRQoL (validated scales) Length of hospital stay
Zhang, 2024, China	Cohort study	6 months	MWA vs. Surgery	MWA: 368 Surgery: 92	MWA: 43.4 Surgery: 45.7	P1	MWA: 324/44 Surgery: 79/13	HRQoL (validated scales)
Baek, 2012 South Korea	Case series	No systematic follow-up	RFA	RFA: 1,459	41.2	P1	RFA: 190/1,459	Complications
Cai, 2024, China	Case series	12 months	RFA or MWA	RFA: 29 MWA: 21	RFA: 41 MWA: 43	P3	RFA: 5/29 MWA: 4/21	Complications
Cheng, 2017, China	Case series	Mean (months) RFA: 13.5 MWA: 13.9	RFA or MWA	RFA: 649 MWA: 603	RFA: 47.9 MWA: 47.1	P1, P2, P3	RFA: 140/649 MWA: 135/603	Complications
Fung, 2024, Hong Kong	Case series	12 months	RFA	RFA: 15	RFA: 37	P3	RFA: 1/15	Complications
Lee, 2019, South Korea	Case series	Mean (months) RFA: 9.9	RFA	RFA: 1,000	RFA: 49.2	P1*	RFA: 229/1,000	Complications
Liang, 2024, China	Case series	6 months	RFA or MWA	RFA: 5,173 MWA: 4,494	RFA: 44.2# MWA: 44.4#	P1*	RFA: 1,189/5,173# MWA: 1,030/4,494#	Complications
Liu, 2025, China	Case series	6 months	TA	TA: 3,971	TA: 48.3	P1*	898/3,071	Complications

* Benign nodules, not specified if also P2 and P3 were included, # In the total sample consisting of 9,667 patients, HRQoL: Health related quality of life, MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation, TOETVA: Transoral endoscopic thyroidectomy vestibular approach

Project: Thermal ablation, thyroid
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Al-Adhami, 2012	Wrong intervention: open surgery
Al-Adhami, 2013	Wrong intervention: open surgery
Austerlitz, 2024	Case series with too few patients
Ayoub, 2023	Economy only
Bernardi, 2018	Wrong O
Bernardi, 2020	Case series with no complications
Bernardi, 2023	Wrong comparison, case series with too few patients
Cai, 2021	Case series with too few patients
Carlisle, 2025	Economy only
Chorti, 2023	Systematic review – network meta-analysis
Chuanke, 2024	Case series with too few patients
Dauksiene, 2013	Wrong intervention, anti-thyroid drug treatment
Deandrea, 2019	Case series with too few patients
Deandrea, 2019	Case series with too few patients
Dhanasekaran, 2024	Case series with too few patients
Ding, 2023	Systematic review - commented
Dobnig, 2018	Case series with too few patients
Dou, 2021	Case series with too few patients
Elhefny, 2021	Wrong C - thyroidectomy only
Erturk, 2021	Case series with too few patients
Fu, 2023	Case series with too few patients
Fu, 2024	Wrong C – lumpectomy only
Fung, 2023	Same patients reported in Fung, 2024
Gao, 2021	Case series with too few patients
Giovanella, 2024	Systematic review, wrong comparison
Guan, 2023	Systematic review - commented
Happel, 2015	Wrong intervention: microwave ablation + radioiodine therapy. Too few patients
Javid, 2024	Systematic review, all included studies with too few patients
Jeong, 2008	Case series with too few patients
Jeong, 2024	Review with no meta-analysis or conclusions drawn. Mixed interventions.
Jin, 2021	Case series with too few patients
Jo, 2024	Case series with too few patients
Jung, 2018	Case series with too few patients
Kandil, 2022	Case series with too few patients
Kim, 2017	Case series with too few patients
Korkusuz, 2016	Case series with too few patients
Kuo, 2023	Economy only
Lee, 2020	Case series with too few patients
Lee, 2023	Case series with too few patients
Li, 2021	Case series with no complications
Li, 2021	Wrong P, not benign noduli
Li, 2023	Case series with too few patients
Lim, 2024	Systematic review with no comparison to surgery
Lin, 2022	Case series with too few patients
Liu, 2017	Case series with too few patients
Lu, 2024	Case series with too few patients
Luo, 2024	Missing outcome data
Mauri, 2022	Case series with too few patients
Miller, 2023	Wrong population – mixed patient categories
Motaghed, 2023	Case series with no complications
Noghabaei, 2024	Systematic review on endocrine disorders in general
Papi, 2023	Wrong/unclear C
Park, 2024	Case series with too few patients
Podrat, 2024	Wrong publication type, narrative review
Qafesha, 2024	Systematic review - commented

Project: Thermal ablation, thyroid
Appendix 3 - Excluded articles

Author, year	Reason for exclusion
Qian, 2024	Systematic review with no comparison to surgery
Qin, 2020	Wrong C – lumpectomy only
Russell, 2024	Case series with too few patients
Song, 2023	Case report
Sun, 2024	Systematic review with no comparison to surgery
Tang, 2018	Case series with too few patients
Wei, 2018	Case series with too few patients
Wu, 2017	Wrong comparison, MWA-arm too few patients to be included as case series
Wu, 2023	Case series with too few patients
Xia, 2021	Case series with too few patients
Xu, 2024	Systematic review, mixed population
Xu, 2024	Case series with too few patients
Yan, 2021	Case series with too few patients
Yang, 2022	Wrong P – mixed with malign noduli
Yao, 2025	Systematic review, too few patients in all included studies
Yarso, 2022	No results from therapy, description of endocrine surgery during Covid-pandemic
Yuan, 2024	Systematic review with no comparison to surgery
Yue, 2013	Case series with too few patients
Yue, 2017	Case series with too few patients
Zhang, 2023	Case series with no complications
Zhao, 2022	Case series with too few patients
Zhu, 2020	Case series with too few patients
Zufry, 2024	Systematic review with no comparison to surgery

Project: Thermal ablation, thyroid
Appendix 4:1
Outcome variable: HRQoL

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Jin, 2021, China	RCT	P1	I=MWA & RFA: 225 C=Surgery: 225	I=MWA & RFA: 27 C=Surgery: 24	At 15 months Score 410 MWA & RFA: 113/165 (68%)	At 15 months Adjusted effect size [#] AOR=0.34 (95%CI: 0.21 to 0.45), p<0.0001 Score 410 Surgery: 54/170 (32%)	[#] QoL was coded as an ordinal variance with four categories, since this outcome was extremely skewed in follow-up, and adjusted relevant baseline scores. Thyroid specific Quality -of-Life Questionnaire Scale Score 410: Portion reporting totally satisfied in each group.	+	?+	+
Zhi, 2018, China	RCT	P1	I= MWA: 28 C=Surgery: 24	I: 2 C: 6	Data extracted from Fig 2 Physical General Health 75 Mental Health 75	Data extracted from Fig 2 Physical General Health 70 Mental Health 70, p<0.05	MWA: SF-36 data. Better Physical general health and mental health score at 6 in the I group compared to C group. Improved physical general health and mental health score at 12 months (p<0.05) in the I group compared to C group.	?	?-	-
Chen, 2024, China	Cohort study	P1	I=RFA: 35 MWA: 35 C=Surgery: 35	I: 0 C: 0	Mean (SD) MWA: 89.25 (5.76) RFA: 88.98 (5.32)	Mean (SD) 85.67 (6.54), p=0.021	QoL EORTC QLQ C30	?	?+	?
Li, 2022, China	Cohort study	P1	I=MWA: 56 C=Surgery: 28	I: 0 C: 0	Mean (SD) Data extracted from fig 2 85 (15), ns	Mean (SD) Data extracted from fig 2 90 (15), ns	QoL EORTC QLQ C30 6 months global health. (no significant difference between groups)	?	?-	?
Yue, 2016, China	Cohort study	P1	I=RFA: 137 C=Surgery: 267	I: 0 C: 0	Mean HRQoL: 68.5 Vitality: 71.3 Mental health: 80.9	Mean HRQoL: 66.7 Vitality: 67.5 Mental health: 75.3	SF-36 data, 6 months data, HRQoL p=0.029; Vitality p<0.001; Mental health p=0.02, SD not available	+	?+	?
Zhang, 2024, China	Cohort study	P1	I=RFA: 368 C= Surgery: 92	I: 70 C: 18	Mean (SD): HAMA: 5.06 (0.61) HADS (A): 2.44 (0.28) HADS (D): 2.51 (0.31) HEI: 3.66 (0.48) PSQI: 5.45 (0.31)	Mean (SD): HAMA: 6.04 (0.80) ns HADS (A): 2.15 (0.50) ns HADS (D): 2.24 (0.52) ns HEI: 2.88 (0.70) ns PSQI: 6.77 (0.50) p=0.026		+	?+	?

Project: Thermal ablation, thyroid
Appendix 4:1
Outcome variable: HRQoL

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				

HADS: The Hospital and Anxiety Scale, HAMA: The Hamilton Anxiety Scale, HEI: The Huaxi Emotional Distress Index, MWA: microwave ablation, PSQI: The Pittsburgh Sleep Quality Index QoL EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire, RCT: randomised controlled trial, RFA: Radiofrequency ablation, SF-36: Short Form 36, Thyroid-specific Quality-of-Life (QoL) Questionnaire Scale: 41 items from score 0 (maximum total score: 410).

Project: Thermal ablation, thyroid
Appendix 4:2
Outcome variable: Symptoms change

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Zhi, 2018, China	RCT	P1	I=MWA: 30 C=Surgery: 30	I: 2 C: 6	10/28 (35.7%)	11/24 (45.8%), n.s*	Remission of nodule-related symptoms * Calculated from data with Fisher's exact test	?	?-	-
Bernardi, 2014, Italy	Cohort study	P1+P2	I=RFA: 37 C=Surgery: 74	I: 0 C: 0	11/37 (29.7%)	43/74 (58.1%), n.s.	Remission of nodule-related symptoms	?	?	?
Bo, 2022, China	Cohort study	P1	I1=MWA/RFA: 118 C1=Open surgery: 118 I2: MWA/RFA: 43 C2=Endoscopic surgery: 43	I1: 0 C1: 0 I2: 0 C2: 0	I1: Symptom relief, n.s. Full: 114/118 (96.6%) Partial: 2/118 (1.7%) No: 2/118 (1.7%) I2: Symptom relief Full: 40/43 (93.0%) Partial: 2/43 (4.7%) No: 1/43 (2.3%)	C1: Symptom relief, n.s. Full: 108/118 (91.5%) Partial: 5/118 (4.2%) No: 5/118 (4.2%) C2: Symptom relief, n.s. Full: 41/43 (95.3%) Partial: 2/43 (4.7%) No: 0/43 (0%)	Symptom scores collected by telephone interview Propensity score matched	?+	+	?+
Dong, 2021, China	Cohort study	P1	I=MWA: 48 C=Surgery: 53	I: 0 C: 0	Symptom scores, mean (SD) Baseline: 4.5 (0.9) At 12 months: 0.7 (0.7)	Symptom scores, mean (SD) Baseline: 4.5 (0.9) At 12 months: 0.8 (0.7), n.s.		?	?	?

MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Jin, 2021, China	RCT	P1	I=208 CI=209	I=17 CI=16	Total nr patients with ≥ 1 serious event: 6/208 (6%) (adjusted OR: 1.30, 95 CI: 0.57-3.08), n.s. MAJOR: RLN injury: 0/208 wound infection: 1/208 drainage tube >72 hrs: 0/208 readmission for dyspnoea: 1/208 trachea injury: 0/208 prolonged admission for observation: 2/208 MINOR: pain: 2/208 cough: 4/208 Haematoma: 1/208 blood loss > 50ml: 1/208 fever requiring antibiotics: 1/208	Total nr patients with ≥ 1 serious event: 4/209 (4%) (adjusted OR: 1.30, 95 CI: 0.57-3.08), n.s. MAJOR: RLN injury: 1/209 wound infection: 1/209 drainage tube >72 hrs: 1/209 readmission for dyspnoea: 1/209 trachea injury: 1/209 prolonged admission for observation: 2/209 MINOR: pain: 2/209 cough: 5/209 Haematoma: 1/209 blood loss > 50ml: 1/209 fever requiring antibiotics: 1/209	Open-label parallel-group RCT Inclusion: BTN ≥2 cm with compression/cosmetic symptoms Exclusion: age > 50 years RFA/MWA vs thyroidectomy (including partial lobectomy, lobectomy, subtotal and total thyroidectomy, endoscopic thyroidectomy) In the intervention group: any pain symptoms at 2 weeks: 32/186 (17%) and any pain symptoms at 6 weeks: 13/162 (8%), compared to the control group 65/187 (35%) and 17/166 (10%) respectively.	+	?+	-
Schalch, 2021, Brazil	RCT	P1	I=5 CI=5	0	Total nr patients with ≥ 1 serious event: 0/5 MAJOR: 0/5 MINOR: Oedema: 1/5 Transient paraesthesia, right arm: 1/5 Haematoma: 1/5	Total nr patients with ≥ 1 serious event: 2/5 MAJOR: Transient RLN injury: 1/5 Transient weak voice: 1/5 MINOR: 0/5	Inclusion criteria: BTN > 3cm with compressive/cosmetic symptoms. RFA vs thyroidectomy (not specified)	?-	?	-
Yan, 2018, China	RCT	P1+P2	I=57 CI=51	0	Total nr patients with ≥ 1 serious event: 0/57	Total nr patients with ≥ 1 serious event: 1/51	MWA vs partial/subtotal thyroidectomy	?-	?-	-

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
					MAJOR: 0/57 MINOR: 0/57	MAJOR: Hypocalcaemia and tetany: 1/51 MINOR: 0/51	P2 patients not specified in results			
Zhi, 2018, China	RCT	P1	I=28 CI=24	I=2 CI=6	Total nr patients with ≥ 1 serious event: 1/28 MAJOR: Transient hoarseness: 1/28 MINOR: Pain: 2/28	Total nr patients with ≥ 1 serious event: 4/24 MAJOR: Hoarseness: 2/24 (unknown transient/permanent) MINOR: Pain: 22/24 Numbness: 2/24	MWA vs hemithyroidectomy.	?-	?-	-
Bernardi, 2014, Italy	Cohort study	P1+P2	I=37 CI=74	0	Total nr patients with ≥ 1 serious event: 2/37 MAJOR: transient voice change: 1/37 thyrotoxicosis: 1/37 (transient) MINOR: pain: 2/37	Total nr patients with ≥ 1 serious event: 10/74 MAJOR: transient RLN injury: 6/74 transient hypocalcaemia: 4/74 wound complication: 2/74 MINOR: pain: 74/74	Inclusion criteria: BTN > 2 cm with compression/cosmetic/ thyrotoxic symptoms RFA vs hemithyroidectomy P2: n=32, 29% of total population, including 12 RFA and 20 hemithyroidectomy. Complications not separately specified for P2.	?	?	-
Bo, 2022, China	Cohort study	P1	I1=MWA/RFA: 118 C1=Open surgery: 118 I2=MWA/RFA: 43 C2=Endoscopic surgery: 43	I1: 0 C1: 0 I2: 0 C2: 0	I1: Total nr patients with ≥ 1 serious event: 2/118 MAJOR: Voice change: 2/118 MINOR: Cough while drinking: 1/118 Haematoma: 1/118	I1: Total nr patients with ≥ 1 serious event: 3/118 MAJOR: Voice change: 3/118 MINOR: Cough while drinking: 2/118 Hand numbness: 2/118 Haematoma: 1/118	Retrospective study of prospective data Inclusion criteria: BTN >1,5cm with compression/cosmetic symptoms Propensity score matching was applied, leading to 118	?+	+	-

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
					I2: Total nr patients with ≥ 1 serious event: 1/43 MAJOR: Voice change: 1/43 MINOR: 0/43	I2: Total nr patients with ≥ 1 serious event: 0/43 MAJOR: 0/43 MINOR: 0/43	RFA/MWA cases vs 118 thyroidectomy (not specified) cases and 43 RFA/MWA cases vs 43 Endoscopic Thyroidectomy cases.			
Che, 2015, China	Cohort study	P1+P2	n=400 I=200 CI=200	0	Total nr patients with ≥ 1 serious event: 1/200 MAJOR: Permanent hoarseness: 0/200 Transient hoarseness: 1/200 Nodule rupture: 1/200 MINOR: 0/200	Total nr patients with ≥ 1 serious event: 5/200 MAJOR: Permanent hoarseness:2/200 Transient hoarseness: 3/200 MINOR: Haematoma: 1/200	Inclusion: BTN with compression/cosmetic/thyrotoxic symptoms P2 population is not determined in the results. RFA vs hemi/total thyroidectomy	?	?-	-
Chen, 2024, China	Cohort study	P1	n=160 I: 70 CI: 35	0	Total nr patients with ≥ 1 serious event: 2/70 MAJOR: Hoarseness: 2/70 (unknown transient/permanent) MINOR: Haematoma: 2/70 Wound pain: 3/70 Adhesion of incision edges: 0/70	Total nr patients with ≥ 1 serious event: 4/35 MAJOR: Hoarseness: 4/35 (unknown transient/permanent) MINOR: Haematoma: 8/35 Wound pain: 9/35 Adhesion of incision edges: 6/35	Inclusion: BTN 0,5-4,2 cm MWA vs RFA vs thyroidectomy (not further specified) Propensity score matching applied, leaving n=35 in each group.	?	?+	-
Chen, 2021, China	Cohort study	P1	n=150 I=75 CI=75	0	Total nr patients with ≥ 1 serious event: 2/75 MAJOR: Hoarseness 1/75 Wound infection 1/75 MINOR: Nausea: 1/75 Neck Haematoma 0/75	Total nr patients with ≥ 1 serious event: 6/75 MAJOR: Hoarseness 4/75 Wound infection 2/75 MINOR: Nausea: 3/75 Neck Haematoma 1/75	Inclusion: BTN MWA vs subtotal thyroidectomy.	-	?-	-

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Dong, 2021, China	Cohort study	P1	n=101 I= 48 CI=53	0	Total nr patients with ≥ 1 serious event: 1/48 MAJOR: transient hoarseness / voice change: 1 /48 MINOR: Haematoma / haemorrhage: 1/48 pain: 4/48	Total nr patients with ≥ 1 serious event: 4/53 MAJOR: transient hoarseness / voice change: 2/53 wound infection: 2/53 MINOR: Haematoma / haemorrhage: 3/53 transient hypocalcaemia: 7/53 pain: 45/53	Inclusion: BTN > 4 cm MWA vs hemithyroidectomy	?	?	-
Jin, 2018, China	Cohort study	P1	n=280 I=156 CI=124	0	Total nr patients with ≥ 1 serious event: 1/106 MAJOR: transient RLN injury: 1 /106 MINOR: skin burn: 1/106	Total nr patients with ≥ 1 serious event: 7/106 MAJOR: transient RLN injury: 7 /106 MINOR: -	Inclusion: BTN ≥2 cm with compression/cosmetic symptoms MWA vs thyroidectomy (including partial) Propensity score matching applied, leaving 106 patients in each group.	?	+	-
Kuo, 2024, Taiwan	Cohort study	P1	n=221 I= 121 CI=100	0	Total nr patients with ≥ 1 serious event: 3/84 MAJOR: hoarseness: 0/84 infection: 0/84 tumour rupture: 3/84 MINOR: Haematoma or seroma: 1/84	Total nr patients with ≥ 1 serious event: 1/84 MAJOR: hoarseness: 0/84 infection: 1/84 MINOR: 0/84	Inclusion: unilateral BTN with cosmetic/compression symptoms RFA vs transoral endoscopic hemithyroidectomy Propensity score matching was applied, leaving n=84 in each group.	?-	?+	-
Lee, 2024, Hong Kong	Cohort study	P1	n=85 I= 50 CI=35	0	Total nr patients with ≥ 1 serious event: 1/50 MAJOR: Transient RLN injury: 1/50	Total nr patients with ≥ 1 serious event: 7/35 MAJOR: Pitch changes: 2/35 Transient RLN injury: 2/35	Inclusion: symptomatic BTN > 2cm RFA (single session) vs hemithyroidectomy All complications classified as minor by the authors.	?	?-	-

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
					MINOR: Transient neck swelling and bruising 3/50	Wound complications: 3/35 MINOR: Scar complications: 2/35				
Li, 2022, China	Cohort study	P1	n=84 I=56 CI=28	0	Total nr patients with ≥ 1 serious event: 7/56 MAJOR: Nodule rupture: 3/56 Transient RLN injury: 3/56 Transient Horner syndrome: 1/56 MINOR: 0/56	Total nr patients with ≥ 1 serious event: 1/28 MAJOR: Transient RLN injury: 1/28 MINOR: 0/28	Inclusion: BTN causing compressive / cosmetic / psychological problems, cystic BTN V<30ml, solid BTN V<20ml MWA vs hemithyroidectomy/ bilateral subtotal thyroidectomy	?	?-	-
Liu, 2019, China	Cohort study	P1	n=144 I=72 CI=72	0?	Total nr patients with ≥ 1 serious event: 0/72 MAJOR: 0/72 MINOR: pain: 4/72	Total nr patients with ≥ 1 serious event: 3/72 MAJOR: RLN injury: 2/72 (permanent / transient not determined) wound infection: 1/72 MINOR: Haematoma / haemorrhage: 2/72 pain: 24/72 neck congestion: 3/72 fever: 4/72	MWA vs hemi/total thyroidectomy	?+	?+	-
Yan, 2023, China	Cohort study	P1	n=230 I=49 CI=49	CI=132 (after PSM)	Total nr patients with ≥ 1 serious event: 0/49 MAJOR: 0/49	Total nr patients with ≥ 1 serious event: 11/49 MAJOR: Overall complications were present in 13/49 (26,5%) of the patients including minor and major complications. Complications were not	Inclusion: age ≥ 60y, BTN > 2 cm RFA vs hemithyroidectomy Propensity score matching was performed, leaving 49 cases in each group.	+	?+	-

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
					MINOR: 0/49	specified for this group after PSM.				
Zhang, 2024, China	Cohort study	P1	n=548 I=438 CI= 110	Questionnaire dropout for measuring psychological impacts: I=70 CI=18	Total nr patients with ≥ 1 serious event: 0/256 MAJOR: RLN injury: 0/256 MINOR: pain score: 1,61 ± 1,45 (p=0,708)	Total nr patients with ≥ 1 serious event: 0/86 MAJOR: RLN injury: 0/86 MINOR: pain score: 1,57 ± 1,57(p=0,708)	Inclusion: BTN > 2 cm MWA vs hemithyroidectomy Propensity score matching was performed, leaving 256 cases in MWA group vs 86 in thyroidectomy group.	+	?+	-
Baek, 2012 South Korea	Case series	P1	n=1,459	0	MAJOR: voice change: 15/1,459 nodule rupture: 2/1,459 brachial plexus injury: 1,/1459 MINOR: Haematoma/haemorrhage: 15/1459 skin burn: 4/1,459 fever: 4/1,459 vomiting: 9/1,459 pain: 38/1,459 cough: 3/1,459 vasovagal reaction: 5/1,459		Multicentre, minimal experience ≥ 10 RFA All patients had compression/cosmetic symptoms and BTN>2cm, normal TSH. Major complication rate was lower in patients treated by experienced operators (0,7% vs 2,9%, p=0,051).			
Cheng, 2017, China	Case series	P1	n=1,252		MAJOR: 71 (31 RFA + 40 MWA) Voice change: 64 (29 RFA + 35 MWA) Nodule rupture (with/without infection): 6 (2 RFA + 4 MWA) Sympathetic nerve injury: 1 (0 RFA + 1 MWA) MINOR:		RFA n=649; MWA n=603			

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
					88 (13 RFA + 15 MWA) Haemorrhage/Haematoma: 25 fall (13 RFA + 12 MWA) Vomiting: 1 (0 RFA + 1 MWA) Skin burn: 1 (0 RFA + 1 MWA) Pain requiring oral analgesics: 37 (20 RFA + 17 MWA) Coughing: 1 (0 RFA + 1 MWA) Mild fever: 22 (12 RFA + 10 MWA)					
Lee, 2019, South Korea	Case series	P1	n=1,000	0	MAJOR: transient voice change: 4/1000 wound infection: 3/1000 MINOR: localised oedema: 15/1000		Retrospective analysis of a prospective database Inclusion: BTN with subjective symptoms Intervention: RFA			
Liang, 2024, China	Case series	P1	RFA: 2,827 MWA: 2,513		MAJOR: 5,340 (MWA 49 + RFA 76) Hoarseness: 22 (MWA 8 + RFA 14) SAN – 4 (MWA 4 + RFA 0) MINOR: (MWA 91 + 76) Haemorrhage: 102 (MWA 37 + RFA 65) Local pain: 95 (MWA 52 + RFA 43) Radiating pain: 19 (MWA 10 + RFA 9) Dizziness: 14 (MWA 8 + RFA 6) Dysphagia: 12 (MWA 6 + RFA 6) Cough: 6 (MWA 2 + RFA 4) Vomiting: 10 (MWA 5 + RFA 5)					

Project: Thermal ablation, thyroid
Appendix 4:3
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
					Skin burn: 0 (MWA 0 + RFA 0) Numbness: 3 (MWA 3 + RFA 0) Vasovagal reaction: 8 (MWA 5 + RFA 3)					
Liu, 2025, China	Case series	P1	TA: 4,325	325	Thyroid nodule rupture: 8/3,971		Unclear if also P2, P3			
P3 - adult patients with Graves disease										
Cai, 2024, China	Case series	P3	n=40 RFA: 29, MWA: 21	0	MAJOR: - MINOR: Transient dysphonia: 5 (RFA 1 + MWA 4) Tachycardia: 5 (RFA 4 + MWA 1) Skin numbness: 2 (RFA 0 + MWA 2)					
Fung, 2024, Hong Kong	Case series	P3	n=30	0	MAJOR: hypothyroidism: 2/30 thyrotoxicosis: 13/30 (i.e. 9 partial responses, 4 no response) MINOR: -		Inclusion: relapsed Graves' disease without compressive goitre intervention: RFA			

BTN: benign thyroid nodule, MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation

Project: Thermal ablation, thyroid
Appendix 4:4
Outcome variable: Relapse

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Che, 2015, China	Cohort study	P1+P2	I=RFA: 200 C=surgery: 200	I: 0 C: 0	0.05%	2.5%, n.s.	Defined as the appearance of a new goiter after treatment	?	?-	-
Dong, 2021, China	Cohort study	P1	I=MWA: 48 C=Surgery: 53	I: 0 C: 0	0	0	Number of P1 subjects with nodules more than 4 cm at baseline and regrowth of nodules after intervention.	?	?	?
Liu, 2019, China	Cohort study	P1	MWA:72 Kir:72	I: 0 C: 0	0/72	0/72		?+	?+	-

MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation

Project: Thermal ablation, thyroid
Appendix 4:5
Outcome variable: Malignancy

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Bernardi, 2014, Italy	Cohort study	P1+P2	I=RFA 37 C=74 Hemithyr	0	0/37	6/74 ns	5 micro-PTC 1 PTC	?	?	?
Kuo, 2024, Taiwan	Cohort study	P1	I=RFA: 84 I=TOEThVA: 84	0	0/84	9/84	7 micro-PTC 1 FVPTC 1 FTC	?-	?+	?

FTC: follicular thyroid carcinoma, FVPTS: follicular variant of papillary thyroid carcinoma, micro-PTC: Papillary thyroid microcarcinoma, PTC: papillary thyroid carcinoma, MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation, TOEThVA: Transoral endoscopic hemi-thyroidectomy vestibular approach

Project: Thermal ablation, thyroid
Appendix 4:6
Outcome variable: Re-intervention

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Bernardi, 2014, Italy	Cohort study	P1+P2	I: 37 C: 74	I: 0 C: 0	1/37 (2.7%)	0/74 (0%), n.s.	Data after 6 months follow up	?	?	-
Bo, 2022, China	Cohort study	P1	I1=MWA/RFA: 118 C1=Open surgery: 118 I2=MWA/RFA: 43 C2=Endoscopic surgery: 43	I1: 0 C1: 0 I2: 0 C2: 0	3/129 (2.3%)	0/376 (0%), n.s.		?+	+	-
Che, 2015, China	Cohort study	P1+P2	I=RFA: 200 C=surgery: 200	I: 0 C: 0	1/200 (0.05%)	5/200 (2.5%), n.s.		?	?-	-
Chen, 2024, China	Cohort study	P1	I=RFA: 35, MWA: 35 C=Surgery: 35	I: 0 C: 0	0/70 (0%)	0/35 (0%), n.s.		?	?+	-

MWA: microwave ablation, RFA: Radiofrequency ablation

Project: Thermal ablation, thyroid
Appendix 4:7
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Zhi, 2018, China	RCT	P1	I=MWA: 30 C=Surgery: 30	I: 2 C: 6	0/28 (0%)	0/24 (0%), n.s	I=MWA: 30 C=Surgery: 30	?/-	?/-	-

MWA: microwave ablation, RCT: randomised controlled trial

Project: Thermal ablation, thyroid
Appendix 4:8
Outcome variable: Operation time

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Jin, 2021, China	RCT	P1	I=MWA & RFA: 225 C=Surgery: 225	I: 17 C: 16	MWA & RFA: 42 (21)	112 (31)	Mean (SD) No p-value	+	?+	+
Schalch, 2021, Brazil	RCT	P1	I=RFA: 5 C=Surgery: 5	I: 0 C: 0	RFA: mean (range) 71.4 (40-118)	Surgery: mean (range) 90 (60-120) p=0.29	Probably only P1	?-	?	?-
Zhi, 2018, China	RCT	P1	I=MWA: 28 C=Surgery: 24	I: 2 C: 6	Mean (SD): 20.4 (7.2)	Mean (SD): 106.5 (20.5), p<0.001		?-	?-	-
Bernardi, 2014, Italy	Cohort study	P1+P2	I=37 C=74	I: 0 C: 0	45	80	No p-value	?	?	?
Bo, 2022, China	Cohort study	P1	I1=MWA/RFA: 118 C1=Open surgery: 118 I2=MWA/RFA: 43 C2=Endoscopic surgery: 43	I1: 0 C1: 0 I2: 0 C2: 0	I1: Mean (SD) 32.6 (8.8) I2: Mean (SD) 29.6 (8.0)	C1: Mean (SD) 65.8 (10.3), p<0.001 C2: Mean (SD) 71.9 (10.0), p<0.001	Probably only P1	?+	+	?+
Chen, 2024, China	Cohort study	P1	I=MWA: 75 C=Surgery: 75	I: 0 C: 0	I: Mean (SD) 29.42 (5.15)	C: Mean (SD) 79.24 (12.52), p<0.05		?	?+	?
Chen, 2021, China	Cohort study	P1	I1=MWA: 35 I2=RFA: 35 C=Surgery: 35	I1: 0 I2: 0 C: 0	I1: Mean (SD) 28.26 (6.19) I2: Mean (SD) 29.13 (5.76)	C: Mean (SD) 78.59 (13.24), p<0.001		-	?-	?
Dong, 2021, China	Cohort study	P1	I= MWA:48 C=Surgery: 53	I: 0 C: 0	Mean (SD) 59.6 (25)	Mean (SD) 109.6 (37.2), p<0.0001	P1 > 4 cm	?	?	?
Jin, 2018, China	Cohort study	P1	I=MWA: 106 C=Surgery: 106	I: 0 C: 0	Mean (SD) 28.6 (5.2)	Mean (SD) 80.2 (15.6), p<0.0001		?	+	+
Kuo, 2024, Taiwan	Cohort study	P1	I=RFA: 84 I=TOEThVA: 84	I: 0 C: 0	Mean (SD) 30.8 (13.6)	Mean (SD) 120.7 (36.5), p<0.0001		?-	?+	?

Project: Thermal ablation, thyroid
Appendix 4:8
Outcome variable: Operation time

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Lee, 2024, Hong Kong	Cohort study	P1	RFA: 50 Surgery: 35	I: 0 C: 0	Mean (SD) 42.7 (17.0)	Mean (SD) 112.7 (41.6), p<0.001		?	?-	?-
Liu, 2019, China	Cohort study	P1	MWA:72 Kir:72	I: 0 C: 0	Mean (SD) 30.5 (9.4)	Mean (SD) 60.0 (11.2), p<0.0001		?+	?+	?-
Yan, 2023, China	Cohort study	P1	RFA: 49 Kir: 49	I: 0 C: 0	Median (IQR) 4.8 (4.1)	Median (IQR) 95.0 (62.0) p<0.001		+	?+	?

MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation

Project: Thermal ablation, thyroid
Appendix 4:9
Outcome variable: Volume reduction

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Jin, 2021, China	RCT	P1	I1=MWA: 89 I2=RFA: 112 C= Surgery: 225	I1+I2: 24 C: 16	I1: Volume reduction rate % (SD) 47.9 (10.2) at 3 months 67.8 (7.9) at 6 months 79.3 (3.2) at 12 months I2: Volume reduction rate % (SD) (n=112) 48.2 (11.3) at 3 months 68.1 (8.1) at 6 months 80.1 (1.8) at 12 months			+	?+	+
Zhi, 2018, China	RCT	P1	I=MWA: 28 C=Surgery: 24	I:2 C:6	Baseline: 17.11 (14.41) ml (3 months): 3.01 ml (2.74) ml (75.9%), p<0.01; (6 months): 1.70 (2.08) ml (88.4%), p<0.01; (12 months): 0.69 (0.89) ml, (95.2%), p<0.01 Volume reduction rate % (SD) Mainly solid nodules (n=5): 34 (22) (3 months) 67 (20) (6 months) 84 (9) (12 months) Mainly cystic nodules (n=23): 84 (12) (3 months) 89 (12) (6 months) 97 (3) (12 months)		Mean	?-	?-	-
Bernardi, 2014, Italy	Cohort study	P1+P2	I=37 C=74	I: 0 C: 0	Volume reduction rate % 61 (3 months) 66 (6 months) 70 (12 months)	100	SD not reported	?	?	?
Bo, 2022, China	Cohort study	P1	I=129 C=376	I1: 0 C1: 0 I2: 0 C2: 0	Volume reduction rate % (SD) 80.7 (21.1) (12-36 months)	100	Probably only P1 Median 19 (range: 12-36) months follow-up.	?+	+	?+

Project: Thermal ablation, thyroid
Appendix 4:9
Outcome variable: Volume reduction

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Che, 2015, China	Cohort study	P1+P2	I: 200 C: 200	I: 0 C: 0	Volume reduction rate % (SD) 61.3 (37.6) (3 months), n.s. 74.6 (23.3) (6 months), n.s. 84.8 (17.1) (12 months), p=0.002			?	?-	?
Chen, 2024, China	Cohort study	P1	MWA: 75 Kir: 75	I: 0 C: 0	Volume reduction rate % (SD) 44.59 (14.74) (3 months) 54.61 (15.23) (6 months) 65.32 (12.97) (12 months)			?	?+	?
Chen, 2021, China	Cohort study	P1	RF: 35 MWA: 35 Surgery: 35	I: 0 C: 0	Volume reduction rate % MWA: 74 (30-92) (6 months) RFA: 81 (62-96) (6 months)		Median and range	-	?-	?
Dong, 2021, China	Cohort study	P1	I= MWA:48 C=Surgery: 53	I: 0 C: 0	Volume reduction rate % (SD) 71 (11) (3 months) 82 (9) (6 months) 90 (5) (12 months)		P1 > 4 cm	?	?	?
Jin, 2018, China	Cohort study	P1	MWA: 156 Kir: 124	I=MWA & RFA: 27 C=Surgery: 24	Volume reduction rate % 47.6 (3 months) 67.2 (6 months) 79.6 (12 months)			?	+	+
Kuo, 2024, Taiwan	Cohort study	P1	I=RFA: 84 C=TOEThVA: 84	I: 0 C: 0	Volume reduction rate % (SD) 59.8 (7.17) (3 months) 65.3 (27.9) (6 months) 77.7 (57.2) (12 months)			?-	?+	?
Lee, 2024, Hong Kong	Cohort study	P1	RFA: 50 Surgery: 35	I: 5, at 3 and 6 months, and 20, at 12 months C: 0	Volume reduction rate % (SD) 61.3 (18.5) (3 months), n=45 69.1 (19.7) (6 months), n=45 76.6 (17.4) (12 months), n=30			?	?-	?-
Li, 2022, China	Cohort study	P1	MWA: 56 Surgery: 28	I: 0 C: 0	Volume reduction rate % (SD) 67.5 (23.1) (3 months) 80.7 (18.6) (6 months) 90.45 (11.51) (12 months)			?	?-	?
Liu, 2019, China	Cohort study	P1	MWA:72 Kir:72	I: 0 C: 0	Nodule volume, mean (SD) 3.6 (0.7) cm^3, before surgery 1.2 (0.2) cm^3, at 3 months 0.6 (0.3) cm^3, at 6 months			?+	?+	?-

Project: Thermal ablation, thyroid
Appendix 4:9
Outcome variable: Volume reduction

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Yan, 2023, China	Cohort study	P1	RFA: 49 Kir: 181 - (49 PSM)	I: 0 C: 0	Nodule volume, mean (SD) 75.9 (18.8) (3 months) 84.6 (26.2) (6 months) 92.7 (27.5) (12 months)		Data from supplement, Table 4	+	?+	?

MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation, TOEThVA: Transoral endoscopic hemi-thyroidectomy vestibular approach

Project: Thermal ablation, thyroid
Appendix 4:11
Outcome variable: Need of hormonal treatment

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Zhi, 2018, China	RCT	P1	I=MWA: 28 C=Surgery: 24	I: 2 C: 6	0/28 (0%)	1/24 (4.2%), n.s.*	* p-value calculated from data with Fisher's exact test.	?-	?-	-
Bernardi, 2014, Italy	Cohort study	P1+P2	I=RFA: 37 C=Surgery: 74	I: 0 C: 0	0/31 (0%)	17/68 (25%), p<0.05	P2 I: 4/12 no ATD P2 C: 20/20 no ATD	?	?	?
Bo, 2022, China	Cohort study	P1	I1=MWA/RFA: 118 C1=Open surgery: 118 I2=MWA/RFA: 43 C2=Endoscopic surgery: 43	I1: 0 C1: 0 I2: 0 C2: 0	I1: 1/118 (0.8%) I2: 0/43 (0%)	C1: 30/118 (25.4%), p<0.001 C2: 8/43 (18.6%), p<0.01	Post-operative levothyroxine use	?+	+	?+
Che, 2015, China	Cohort study	P1+P2	I=RFA:200 C=Surgery: 200	I: 0 C: 0	0/200 (0%)	143/200 (71.5%), p=0.002	Post-operative levothyroxine use	?	?-	?
Dong, 2021, China	Cohort study	P1	I=MWA:48 C=Hemithyroidectomy: 53	I: 0 C: 0	0/48 (0%)	16/53 (30.2%), p<0.0001	Hypothyroidism P1 > 4 cm	?	?	?
Kuo, 2024, Taiwan	Cohort study	P1	I=RFA: 84 C=TOETVA: 84	I: 0 C: 0	0/84 (0%)	0/84 (0%)	p-value not reported	?-	?+	?
Li, 2022, China	Cohort study	P1	I=MWA: 56 C=Thyroidectomy: 28	I: 0 C: 0	0/56 (0%)	0/28 0%)	p-value not reported	?	?-	?
Yan, 2023, China	Cohort study	P1	I=RFA: 49 C=Kir: 49	I: 0 C: 0	0/49 (0%)	10/49 (20.4%), p<0.001	Hypothyroidism	+	?+	?

ATD: antithyroid drug treatment, MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation, TOETVA: Transoral endoscopic thyroidectomy vestibular approach.

Project: Thermal ablation, thyroid
Appendix 4:10
Outcome variable: Biochemical response

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Chen, 2024, China	Cohort study	P1	MWA: 75 Surgery: 75	I: 0 C: 0	Mean (SD) 5.02 (0.84) µU/L	Mean (SD) 8.39 (1.35) µU/L, p<0.001	Time period not described	?	?/+	?
Chen, 2021, China	Cohort study	P1	RFA: 35 MWA: 35 Surgery: 35	I: 0 C: 0	Mean (SD) MWA: 1.21 (0.25) µU/L RFA: 1.21 (0.21) µU/L	Mean (SD) 1.11 (0.33) µU/L, p=0.002	6 months	-	?/-	?
Li, 2022, China	Cohort study	P1	MWA: 56 Surgery: 28	I: 0 C: 0	Mean (SD) 1.71 (1.12) µU/L, (3 months) 1.34 (0.70) µU/L, (6 months)	Mean (SD) 2.37 (1.24) µU/L, (3 months), p=0.013 1.97 (0.94) µU/L, (6 months), p=0.002		?	?/-	?
Liu, 2019, China	Cohort study	P1	MWA:72 Surgery:72	I: 0 C: 0	Mean (SD) 2.3 (0.7) µU/L, (3 months) 2.4 (0.8) µU/L, (6 months)	Mean (SD) 3.1 (1.9) µU/L, (3 months), p<0.05 3.1 (1.7) µU/L, (6 months), p<0.05		?/+	?/+	?-

MWA: microwave ablation, RCT: randomised controlled trial, RFA: Radiofrequency ablation

Project: Thermal ablation, thyroid
Appendix 4:12
Outcome variable: Hospitalisation days

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Jin, 2021, China	RCT	P1	I=MWA & RFA: 225 C=Surgery: 225	I: 17 C: 18	33/208 (16%)	202/209 (97%), p<0.0001	Number of subjects with a post operative hospital stay >24h, Calculated from data with Fisher's exact test	+	?+	+
Schalch, 2021, Brazil	RCT	P1	I=RFA: 5 C=Surgery: 5	I: 0 C: 0	Mean (SD): 8.6h (0.36 days)	Mean (SD): 26.2h (1.1 days), p=0.01		?-	?	?-
Yan, 2018, China	RCT	P1+P2	I=MWA: 57 C=Surgery: 51	I: 0 C: 0	Mean (SD): 4.6 (0.4) days	Mean (SD): 6.9 (0.7) days, p=0.0001		?-	?-	?-
Zhi, 2018, China	RCT	P1	MWA: 28 Kir: 24	I: 2 C: 6	Mean (SD): 0.05 (0.00) days	Mean (SD): 4.04 (0,79) days, p<0.001		?-	?-	-
Bernardi, 2014, Italy	Cohort study	P1+P2	I=RFA: 37 C=Hemithyroidectomy: 74	I: 0 C: 0	Mean: I: <1	Mean: C: 2.33	p value not reported	?	?	?
Bo, 2022, China	Cohort study	P1	I1=MWA/RFA: 118 C1=Open surgery: 118 I2=MWA/RFA: 43 C2=Endoscopic surgery: 43	I1: 0 C1: 0 I2: 0 C2: 0	I1: Mean (SD) 1.4 (0.6) I2: Mean (SD) 0.8 (0.6)	C1: Mean (SD) 4.0 (1.0), p<0.001 C2: Mean (SD) 3.6 (1.1), p<0.001		?+	+	?+
Che, 2015, China	Cohort study	P1+P2	I=RFA: 200 C=surgery: 200	I: 0 C: 0	Mean (SD) 2.1 (0.9) days	Mean (SD) 6.6 (1.6), p=0.001		?	?-	?
Chen, 2024, China	Cohort study	P1	MWA: 75 Surgery: 75	I: 0 C: 0	Mean (SD) 1.52 (0.29)	Mean (SD) 4.01 (1.23), p<0.05		?	?+	?
Chen, 2021, China	Cohort study	P1	I1=MWA: 35 I2=RFA: 35 C=Surgery: 35	I1: 0 I2: 0 C: 0	Mean (SD) MWA: 1.0 (0.13) days. p<0.001 RFA: 1.0 (0.12) days, p<0.001	Mean (SD) C: 2.2 (0.18) days		-	?-	?
Dong, 2021, China	Cohort study	P1	I=MWA: 48 C=Surgery: 53	I: 0 C: 0	Mean (SD) 1.5 (0.5) days	Mean (SD) 7.3 (2.3) days, p<0.0001	P1 > 4 cm	?	?	?
Jin, 2018, China	Cohort study	P1	I=MWA: 156 C= Surgery: 124	I: 0 C: 0	Mean (SD) 1.6 (0.5) days	Mean (SD) 4.3 (0.5) days, p<0.0001		?	+	+

Project: Thermal ablation, thyroid
Appendix 4:12
Outcome variable: Hospitalisation days

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Type of patients	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
					Intervention	Control				
Kuo, 2024, Taiwan	Cohort study	P1	I=TA: 84 C=TOETVA: 84	I: 0 C: 0	Mean (SD) 0.07 (0.46) days	Mean (SD) C: 1.98 (0.47) days, p<0.0001		?-	?+	?
Liu, 2019, China	Cohort study	P1	MWA:72 Surgery:72	I: 0 C: 0	Mean (SD) 3.5 (0.5) days	Mean (SD) C: 11.4 (2.7) days, p<0.0001		?+	?+	?-
Yan, 2023, China	Cohort study	P1	I=RFA: 49 C= Surgery: 49	I: 0 C: 0	Median 0	Median 8.0 (IQR 4.0)	p value not reported	+	?+	?
Yue, 2016, China	Cohort study	P1	I=RFA: 137 C=Surgery: 267	I: 0 C: 0	Mean 2.6	Mean 5.3, p<0.001	SD not reported	+	?+	?

MWA: microwave ablation, RCT: randomised controlled trial, RFA: radiofrequency ablation, TA: thermal ablation, TOETVA: Transoral endoscopic thyroidectomy vestibular approach.