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Austrian Institute for
Health Technology Assessment
GmbH

Thermoablation for benign thyroid nodules

Systematic Review

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Conflict of interest

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

AEs ..... Adverse events
CE..... Conformité européenne/European conformity
ENT..... Otorhinolaryngology
EQ-5D ..... EuroQol 5-dimension questionnaire
EU ..... European Union
EUnetHTA ..... European Network for Health Technology Assessment
EU-TIRADS..... The European Thyroid Association Thyroid Imaging Reporting and Date System
FNA..... Fine needle aspiration
GRADE..... Grading of Recommendations, Assessment, Development and Evaluations
HIFU..... High intensity focused ultrasound
HRQoL ..... Health-related quality of life
ILP ..... interstitial laser photocoagulation
INAHTA..... The International Network of Agencies for Health Technology Assessment
IQR..... Interquartile range
MWA..... Microwave ablation
N..... Number
NA ..... Not applicable
Na(^{131}I) ..... Sodium iodine I-131
NR..... Not reported
NRSI ..... Nonrandomised studies of interventions
ÖGK..... Österreichische Gesundheitskasse/Austrian Public Health Insurance
OR ..... Odds ratio
PICO ..... Popultion, Intervention, Comparator, Outcome
PRISMA..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL ..... Quality of life
RAI..... Radioidine
RCT..... Randomised controlled trial
RFA..... radiofrequency ablation
RoB..... Risk of bias
RoB2..... Cochrane Risk of Bias 2
ROBINS-I..... Risk Of Bias In Non-randomised Studies – of Interventions
SAEs..... Serious adverse events
SF-36..... The 36-Item Short Form Health Survey
TSH..... Thyroid stimulating hormone
T3 ..... Triiodothyronine
T4 ..... Thyroxine
UGPL..... Ultrasound-guided percutaneous laser
US..... Ultrasound
US/USA ..... United States (of America)
VRR..... Volume rate reduction
WHO-ICTRP ..... World Health Organisation International Clinical Trials Registry Platform

Executive Summary

Introduction

Health Problem

Thyroid nodules are typically benign growths on the parenchymal surface of the thyroid gland, and are estimated to affect approximately 5% of the global population. Increased risk of nodule development has been associated with ionising radiation exposure, low iodine intake, metabolic syndrome, female sex and increased age. Although most thyroid nodules are asymptomatic and do not require treatment, occasionally nodules can cause compression of surrounding structures in the neck, cosmetic concerns, and changes in thyroid function. In such cases, treatments are considered to alleviate symptoms.

thyroid nodules: benign growths

5% global population

Description of Technology

Thermoablation is a technique that utilises extreme high and low temperatures to initiate destruction of tumour tissue in situ. There are several forms of thermoablation devices, including microwave ablation (MWA), radiofrequency ablation (RFA), high intensity focused ultrasound (HIFU) and ultrasound guided percutaneous laser (UGPL). These systems aim to promote coagulative necrosis of nodules, allowing the nodule remnants to be reabsorbed by the body, decreasing nodule size. These technologies may be used as an alternative to traditional thyroidectomy surgery or radioiodine (RAI) for the treatment of benign nodules.

thermoablation (TA): temperature to initiate destruction

forms: MWA, RFA; HIFU, UGPL; comparators: surgery, RAI

Methods

A systematic search was conducted to evaluate the effectiveness and safety of thermoablation compared with thyroidectomy or radioiodine (RAI) for benign thyroid nodules. Medline, Embase, the Cochrane Library and the International Network of Agencies for Health Technology Assessment (INAHTA) were searched from inception up to 14 December 2023. The search was limited to articles published in English or German, and in Medline and Embase to only randomised controlled trials (RCTs) or non-randomised studies of interventions (NRSI) conducted in humans. Publication type filters were also implemented. Two authors independently conducted study selection, data extraction and quality appraisal. Any disagreements were resolved by a third author. The quality of the included studies was assessed using the RoB2 (Cochrane Risk of Bias 2) tool and ROBINS-I (Risk of Bias In Non-randomised Studies Of Interventions) tool, and the certainty of the evidence was rated according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

project objective: efficacy & safety of TA in patients with benign thyroid nodules

systematic search in 4 databases

study selection, extraction & quality assessment

Results

Available evidence

A total of four RCTs and five retrospective propensity score matched NRSIs assessing the effectiveness of thermoablation for benign thyroid nodules met the predefined inclusion criteria. Of the four RCTs all reported safety outcomes, compared to only four of five NRSIs.

available evidence: 4 RCTs & 5 NRSIs

Clinical effectiveness and safety

Thermoablation vs. radioiodine (RCT evidence)

One RCT compared interstitial laser photocoagulation (ILP) to RAI in adult patients with benign thyroid nodules. Overall, the strength of RCT evidence for the effectiveness and safety of thermoablation in comparison to RAI is very low.

RCT evidence:
1 RCT (ILP vs RAI)
low overall strength of evidence

A time-dependent trend in decreasing nodule volume (VRR) was reported between thermoablation and RAI, however no significant between group differences were reported at six months. At six months, significant differences between thermoablation and RAI were reported for serum TSH, with TSH levels normalising in seven of 14 participants in the thermoablation group and 15 of 15 participants in the RAI group (all participants had subclinical hyperthyroidism or hyperthyroidism at baseline). Reports of postprocedural hyperthyroidism were reported in two of 15 patients in the RAI group and none in the thermoablation group. No differences in FT4 (free thyroxine) index, FT3 index or anti-TPOAb (thyroid peroxidase antibodies) were observed. Overall, any AEs were reported in six of 14 (42.9%) participants in the thermoablation treatment group and two of 15 (13.3%) participants in the RAI group at six months.

nodule volume:
TA vs RAI, ns difference
TSH:
ss difference favouring RAI

postprocedural hyperthyroidism:
IG: 0 vs CG: 2/15

Symptom reduction, cosmetic appearance improvements, quality of life, nodule recurrence rate and SAEs were not reported.

outcomes NR

Thermoablation vs. thyroidectomy (RCT evidence)

Four RCTs compared MWA to conventional thyroidectomy in adult patients with benign thyroid nodules. Overall, the strength of RCT evidence for the effectiveness and safety of thermoablation in comparison to thyroidectomy is very low.

4 RCTs:
MWA vs thyroidectomy
very low overall evidence

A time-dependent trend in decreasing nodule volume (VRR) was reported in patients receiving thermoablation on a study-level up to 12 months. This volume reduction did not affect thyroid function, which ultimately remained unchanged. VRR in the thyroidectomy group was not reported, as the nodules were completely resected. One RCT found that in participants who reported nodule-related symptoms at baseline in both the thermoablation and thyroidectomy group, all symptoms were resolved by 12 months. Further, another RCT investigated specific nodule-related symptoms – peculiar sense in throat, dysphasia and compression on trachea – at 15 months, observed statistically significant between group differences in favour of thyroidectomy. At 12 months, excellent cosmetic results were reported by all participants in the thermoablation group, whilst only 83.3% of participants in the thyroidectomy group reported excellent cosmetic results.

VRR: no effect on thyroid function with TA

1 RCT: all symptoms resolved with TA

peculiar sense in throat:
ss difference favouring thyroidectomy

At 15 months, one RCT reported a significant difference in thyroid-specific QoL scale TS between the two groups. The thyroid-specific QoL scale domains of total psychological wellbeing, and total social wellbeing were found to be statistically significantly in favour of thermoablation, whereas total physical wellbeing was found to be statistically significantly in favour of thyroidectomy. Furthermore, when evaluating the 36-Item Short Form Health Survey (SF-36), a second RCT found that patients who underwent thermoablation had better general health and mental health scores compared to those who underwent thyroidectomy at 12 months ($p<0.05$, for both).

thyroid-specific QoL scale:
ss difference favouring TA

better general health with TA

At 15 months, any SAEs were reported in six (3%; 6/208) participants in the thermoablation treatment group and eight (4%; 8/209) participants in the conventional thyroidectomy group. Between two days and 15 months, any AEs were reported in 13 (4.44%; 13/293) participants in the thermoablation treatment group and 42 (14.79%; 42/284) participants in the conventional thyroidectomy group.

SAEs:
IG:6/208 vs CG: 8/209

AEs:
IG: 13/293 vs CG: 42/284

Nodule recurrence was not reported.

Thermoablation vs. thyroidectomy (NRSI evidence)

In adult patients with benign thyroid nodule, two NRSIs compared RFA to thyroidectomy, one NRSI compared MWA to thyroidectomy, one NRSI compared both MWA and RFA (combined) to thyroidectomy, and one NRSI compared HIFU to open lobectomy. Overall, the strength of NRSI evidence for the effectiveness and safety of thermoablation in comparison to thyroidectomy is very low.

5 NRSI (HIFU; RFA, MWA, or combined vs thyroidectomy)

A time-dependent trend in decreasing nodule volume (VRR) was reported in patients receiving thermoablation across studies up to 24 months. VRR in the thyroidectomy group was not reported, as the nodules were completely resected. Only one nodule with regrowth was detected across the NRSI. Between six and 26 months, postprocedural hypothyroidism was reported in one (0.3%; 1/393) participants in the thermoablation treatment group and 52 (13.2%; 52/393) participants in the thyroidectomy group. No significant differences in cosmetic appearance improvement or symptom reduction were reported between groups, however both the thermoablation and thyroidectomy group reported significant differences in cosmetic score and symptom score from baseline to 12 months.

VRR decrease with TA

hypothyroidism:
IG: 1/393 vs CG: 52/393

ns differences cosmetic appearance or symptom reduction between groups

When evaluating SF-36, general health, vitality, and mental health were all statistically significant if favour of thermoablation when compared to thyroidectomy at six months. At six to 36 months, any AEs were reported in 11 (2.8%; 11/393) participants in the thermoablation treatment group and 22 (5.6%; 22/393) participants in the conventional thyroidectomy group.

SF-36, general health:
ss difference favouring TA

SAEs were not reported.

Upcoming evidence

Three ongoing RCTs on the use of thermoablation for benign thyroid nodules were identified. One RCT will investigate the use of RFA compared to RAI to assess the rates of hyperthyroidism. One RCT will investigate the use of MWA compared to open surgery to assess VRR and treatment effectiveness rates. One RCT will investigate the use of HIFU compared to no treatment to assess treatment effectiveness rate, symptoms score improvement, and AEs.

3 ongoing RCTs

Discussion

The methodology of this review has numerous notable advantages, primarily stemming from its systematic approach and thorough search strategies. The comprehensive search strategy and the independent review of studies by two reviewers provides confidence that the included studies accurately reflect the available evidence base.

advantages: systematic approach and search strategy

evidence gaps

The most significant gap in the evidence relates to the lack of high-quality comparative evidence comparing thermoablation to thyroidectomy or RAI in adult patients with benign thyroid nodules.

questionable applicability

Applicability issues have also been identified in the current evidence-base. For example, the geographic location of the included studies is likely to pose a concern to the generalisability of results to the Austrian setting. Of the included studies, nine of ten have been conducted in China, which is a developing upper middle-class country, whereas Austria is a developed high-class country.

Conclusion

TA vs RAI: low-certainty evidence ss improvement in thyroid function (RAI)

One RCT with a small sample size evaluated the safety and effectiveness of thermoablation compared to RAI. Based on this very low certainty evidence, in patients with hyperfunctional nodules, both interventions significantly reduced nodule volume at six months, with no significant differences reported between interventions; however, thyroid function was significantly improved in the RAI group but not in the thermoablation group. No significant differences in the safety profile of these interventions were observed.

TA vs thyroidectomy: low-certainty evidence, ss fewer AE (TA)

Very low quality RCT and NRSI evidence was available to evaluate the safety and effectiveness of thermoablation compared to thyroidectomy. Heterogenous results were reported for effectiveness, and significantly fewer adverse events favouring thermoablation.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Schilddrüsenknoten: gutartige Veränderungen

mögliche Symptome bei Knotenwachstum

Schilddrüsenknoten sind gutartige Veränderungen an der Schilddrüse, die etwa 5 % der Bevölkerung betreffen. Die meisten solcher Knoten sind asymptomatisch und erfordern daher keine Behandlung. Schilddrüsenknoten können aber wachsen und aufgrund ihrer zunehmenden Größe Symptome verursachen. Zu möglichen Symptomen zählen die Kompression umliegender anatomischer Strukturen im Halsbereich, Schwierigkeiten beim Atmen und Schlucken oder kosmetische Bedenken. In solchen Fällen werden Behandlungen erwogen, um die Lebensqualität der Betroffenen zu verbessern.

Klassifikation: Zusammensetzung oder physiologische Funktion

Die Diagnose benigner Schilddrüsenknoten erfolgt durch Ultraschall, wobei die Klassifikation anhand ihrer Zusammensetzung (z. B. solide oder zystisch) oder ihrer physiologischen Funktion erfolgt. Sogenannte „heiße Knoten" sind Schilddrüsenknoten, welche eine Schilddrüsenüberfunktion verursachen können, während „kalte Knoten" keine Auswirkungen auf die Schilddrüsenfunktion haben. Das Risiko für die Entwicklung von Knoten steigt mit ionisierender Strahlenexposition, geringer Jodzufuhr, metabolischem Syndrom, weiblichem Geschlecht und höherem Alter.

Beobachtung mittels Ultraschall

etablierte Techniken: Radiojodtherapie, OP

Aktuelle Ansätze umfassen regelmäßige körperliche Untersuchungen, die Überprüfung des Hormonstatus und die Beobachtung von Form und Größe der Knoten mittels Ultraschall. Wenn eine Intervention erforderlich ist, können etablierte Techniken wie die Radiojodtherapie oder eine Operation in Betracht gezogen werden, wobei in der Regel ein Schilddrüsenlappen entfernt wird. Es ist jedoch zu beachten, dass nicht jede/r Patient*in für eine Operation geeignet ist. Das primäre therapeutische Ziel der Behandlung ist die Verbesserung der Symptome. Daneben auch der Erhalt oder die Wiederherstellung einer normalen Schilddrüsenfunktion, sowie eine kosmetische Verbesserung.

Beschreibung der Technologie

Thermoablation (TA) als minimal-invasives Verfahren → hohe und niedrige Temperaturen

Formen: MWA; RFA; HIFU, UGLP

Ziel: Koagulationsnekrose

Die Thermoablation stellt ein minimal invasives Verfahren dar, welches sowohl sehr hohe als auch niedrige Temperaturen nutzt, um eine gezielte Auflösung von Tumorgewebe zu bewirken. Es existieren verschiedene Varianten dieser Technik, darunter die Mikrowellenablation (MWA), Radiofrequenzablation (RFA), hochintensive fokussierte Ultraschallablation (HIFU) und ultraschallgeführte perkutane Lasertherapie (UGLP). Diese Systeme haben das gemeinsame Ziel, die Koagulationsnekrose zu fördern, was dazu führt, dass der Körper Tumorreste resorbiert und die Größe der Knoten abnimmt. MWA erzeugt die erforderliche Temperatur an der Antennenspitze mithilfe eines elektromagnetischen Feldes, während bei RFA ein geschlossener Stromkreislauf gebildet wird, durch den Strom fließt. HIFU verwendet fokussierten Ultraschall, um hohe Temperaturen zu erreichen. Die Laserablation erwärmt das Gewebe durch elektromagnetische Strahlung. Die Thermoablation kann als Alternative zu konventionellen Schilddrüsenoperationen (Thyreoidektomien) oder Therapien mit radioaktivem Jod (RJT) eingesetzt werden.

Methoden

Dieser Bericht bewertet die Sicherheit und Wirksamkeit der Thermoablation im Vergleich zur Radiojodtherapie oder Thyreoidektomie bei erwachsenen Patient*innen mit benignen Schilddrüsenknoten.

Ziel: Sicherheit und Wirksamkeit der TA bei Erwachsenen

Die systematische Literatursuche wurde am 14. Dezember 2023 in vier medizinischen Datenbanken durchgeführt. Die folgenden Datenbanken wurden durchsucht: Medline, Embase, The Cochrane Library und die INAHTA Database. Es wurden randomisierte kontrollierte Studien, sowie retrospektive nicht randomisierte kontrollierte Studien (NRSI mit Propensity-Score Matching) eingeschlossen.

systematische Literatursuche in 4 Datenbanken

RCTs und NRSIs

Die Studienauswahl, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei Autor*innen unabhängig voneinander durchgeführt. Die Bewertung der Vertrauenswürdigkeit der eingeschlossenen randomisiert kontrollierten Studien (RCTs) erfolgte mit dem Cochrane Risk of Bias Tool v.2 (RoB2), die Bewertung der nicht randomisierten Studien mit dem Risk Of Bias In Non-randomised Studies of Interventions-Tool (ROBINS-I). Die Vertrauenswürdigkeit in die Evidenz wurde nach dem GRADE-Bewertungsschema (Grading of Recommendations, Assessment, Development and Evaluations) eingestuft.

Studienauswahl, Extraktion und Bewertung der Vertrauenswürdigkeit von 2 Wissenschafter*innen

Klinische Wirksamkeit

Die folgenden Endpunkte wurden für die Bewertung der Wirksamkeit als entscheidend definiert:

klinische Wirksamkeit: entscheidende Endpunkte

- Knoten-Volumenreduktionsrate
- Symptomreduktion
- Verbesserungen des Erscheinungsbilds
- Schilddrüsenfunktion
- Lebensqualität
- Knoten-Rezidivrate

Sicherheit

Die folgenden Endpunkte wurden für die Bewertung der Sicherheit als entscheidend definiert:

Sicherheit: entscheidende Endpunkte

- Schwerwiegende Komplikationen
- Komplikationen

Ergebnisse

Verfügbare Evidenz

Insgesamt wurden vier RCTs und fünf Beobachtungsstudien identifiziert, die die vordefinierten Einschlusskriterien erfüllten. Insgesamt wurden in den RCTs 648 Patient*innen im Alter von 43 bis 58 Jahren inkludiert, in den Beobachtungsstudien (NRSIs) waren es 1.604 Patient*innen zwischen 35 und 65 Jahren (in der Propensity-Score Matched Kohorte). Die Nachbeobachtungszeiten betrugen in den RCTs 48 Stunden bis 15 Monate, in den Beobachtungsstudien 6 bis 36 Monate.

4 RCTs, 5 NRSIs

RCTs: FU 48h – 15 Monate
NRSIs: FU 6 – 36 Monate

- RCTs:
  - Interstitielle Laserkoagulation versus Radiojodtherapie (1 RCT)
  - Mikrowellenablation versus Thyreoidektomie (2 RCTs)
  - Mikrowellenablation oder Radiofrequenzablation versus Thyreoidektomie (1 RCT)
- NRSIs:
  - Radiofrequenzablation versus Thyreoidektomie (2 NRSIs)
  - Mikrowellenablation versus Thyreoidektomie (1 NRSIs)
  - Mikrowellen- und Radiofrequenzablation versus Thyreoidektomie (1 NRSI)
  - Hochfokussierte Ultraschallablation versus Thyreoidektomie (1 NRSI)

RCTs:

Laserkoagulation vs. RJT MWA/RFA vs. Thyreoidektomie

NRSIs:

RFA/MWA/MWA + RFA/HIFU vs. Thyreoidektomie

Vertrauenswürdigkeit der Evidenz

Von den eingeschlossenen RCTs wurden alle mit einem hohen RoB bewertet. Kritikpunkte waren fehlende Daten und eine mögliche Verzerrung der Ergebnisse aufgrund unterschiedlicher Messungen der Endpunkte. Insgesamt ist die Vertrauenswürdigkeit der Evidenz nach GRADE für den Vergleich Thermoablation versus Radiojodtherapie, sowie Thermoablation versus Thyreoidektomie mit sehr niedrig einzustufen.

alle RCTs: hohes RoB

Von den eingeschlossenen Beobachtungsstudien wurden eine mit moderatem und vier mit hohem RoB aufgrund fehlender Daten, möglichem Einfluss von Störgrößen (beispielsweise die Knotengröße zu Beginn der Studie), sowie möglichem Informationsbias bewertet. Insgesamt ist die Vertrauenswürdigkeit der Evidenz nach GRADE ebenfalls mit sehr niedrig einzustufen.

1 NRSI moderates RoB
4 NRSIs hohes RoB

Klinische Wirksamkeit und Sicherheit

Thermoablation versus Radiojodtherapie (Evidenz von RCT)

Ein RCT verglich interstitielle Laserkoagulation (ILK) mit Radiojodtherapie. Das Knotenvolumen wurde in beiden Gruppen innerhalb von sechs Monaten reduziert, zwischen den Gruppen wurde kein statistisch signifikanter Unterschied festgestellt. Der Serumspiegel des Schilddrüsen-stimulierenden Hormons (TSH) normalisierte sich nach der RJT (nach sechs Monaten) bei statistisch signifikant mehr Patient*innen im Vergleich zur Laserkoagulation (ILK: 7/14 versus RJT: 15/15). Nach der Therapie wurde bei zwei von 15 Patient*innen in der RJT-Gruppe eine Schilddrüsenunterfunktion (Hypothyreose) festgestellt, in der ILK-Gruppe keine (nicht statistisch signifikant). Andere funktionelle Unterschiede wurden nicht identifiziert.

TA vs. RJT
ns Unterschied Volumenreduktion

ss Unterschied TSH-Spiegel zugunsten RJT

Hypothyreose: IG 0/15 vs. CG 2/15

Andere Endpunkte (Symptomreduktion, Verbesserung des Erscheinungsbildes, Lebensqualität, Knoten-Rezidivrate und schwerwiegende Komplikationen) wurden nicht berichtet.

Ein RCT berichtete bei sechs (42,9 %) Patient*innen in der ILK-Gruppe und bei zwei (13,3 %) Patient*innen in der RJT-Gruppe Komplikationen nach sechs Monaten.

Komplikationen: IG 42,9 % vs. CG 13,3 %

Thermoablation versus Thyreoidektomie (Evidenz von RCTs)

3 RCTs MWA vs. Thyreoidektomie:

ss Verbesserung knotenbezogener Symptome zugunsten Thyreoidektomie

Drei RCTs verglichen die MWA mit der Thyreoidektomie. Das Knotenvolumen wurde in der MWA-Gruppe innerhalb von 12 Monaten reduziert (nicht berichtet in der Kontrollgruppe, da Knoten vollständig entfernt wurden), ohne die Schilddrüsenfunktion zu beeinflussen. Ein RCT berichtete, dass nach MWA und Operation alle knotenbezogenen Symptome nach 12 Monaten behoben waren. Ein weiterer RCT zeigte eine statistisch signifikante Verbesserung der knotenbezogenen Symptome zugunsten der Thyreoidektomie. Exzellente kosmetische Ergebnisse wurden bei allen MWA-Patient*innen nach 12 Monaten berichtet, während in der Kontrollgruppe 83,3 % der Patient*innen exzellente kosmetische Ergebnisse erzielten.

ss Unterschied: QoL psychisches und soziales Wohlbefinden → IG

physisches Wohlbefinden → CG

Nach 15 Monaten wurde in einer Studie ein statistisch signifikanter Unterschied in der Skala, welche die schilddrüsenspezifische Lebensqualität misst, zwischen den beiden Gruppen festgestellt: die Domänen „psychisches Wohlbefinden“ und „soziales Wohlbefinden“ waren statistisch signifikant zugunsten der Thermoablation, während das physische Wohlbefinden statistisch signifikant zugunsten der Kontrollgruppe war. Darüber hinaus zeigten Patient*innen, die sich einer Thermoablation unterzogen hatten, bei der Auswertung des SF-36 bessere Ergebnisse in den Domänen „allgemeine Gesundheit“ und „psychische Gesundheit“ im Vergleich zu denen, die eine Operation hatten ($p<0,05$ in beiden Gruppen).

1 RCT: schwerwiegende Komplikationen: IG 3 % vs CG 4 % Komplikationen: IG 4,4 % vs CG 14,8 %

In einem RCT wurden schwerwiegende Komplikationen bei sechs (3 %; n= 208) Personen in der Thermoablationsgruppe und bei acht (4 %; 8/209) in der Kontrollgruppe nach 15 Monaten berichtet. In einem anderen RCT wurden Komplikationen bei 13 (4,44 %;13/293) Patient*innen in der Thermoablationsgruppe und bei 42 (14,79 %; 42/284) Patient*innen, die eine Operation hatten, zwischen zwei Tagen und 15 Monaten berichtet.

Zum Endpunkt Knoten-Rezidivrate wurde nicht berichtet.

Thermoablation versus Thyreoidektomie (Evidenz von Beobachtungsstudien)

Hypothyreose: IG 0,3 % vs. CG 13,2 %

ss Verbesserung innerhalb beider Gruppen: Symptomreduktion und Erscheinungsbild

Auch bei den Patient*innen der Beobachtungsstudien wurde mit Thermoablation eine Abnahme des Knotenvolumens nach 24 Monaten beobachtet (nicht berichtet in der Kontrollgruppe, da Knoten vollständig entfernt wurden). In einer Studie wurde ein Rezidiv (0,8 %, 1/129) während des gesamten Untersuchungszeitraums berichtet. Zwischen sechs und 26 Monaten wurde bei einer Person (0,3 %; 1/393) in der Interventionsgruppe und bei 52 Personen (13,2 %; 52/393) in der Kontrollgruppe eine postprozedurale Hypothyreose berichtet. Signifikante Unterschiede wurden hinsichtlich der Endpunkte „Symptomreduktion“ und „kosmetisches Erscheinungsbild“ in beiden Gruppen vom Ausgangspunkt bis zu 12 Monaten beobachtet.

QoL: ss Verbesserung SF-36 zugunsten TA

Bei der Auswertung des SF-36 zeigten sich nach sechs Monaten die allgemeine Gesundheit, Vitalität und psychische Gesundheit statistisch signifikant besser zugunsten der Thermoablation im Vergleich zur Operation.

1 NRSI: Komplikationen: IG 2,8 % vs CG 5,6 %

Eine Beobachtungsstudie berichtete unerwünschte Ereignisse bei 11 Personen (2,8 %; 11/393) in der Thermoablationsgruppe und bei 22 Personen (5,6 %; 22/393) in der Kontrollgruppe nach sechs bis 36 Monaten. Es wurden keine schwerwiegenden Komplikationen berichtet.

Laufende Studien

3 laufende RCTs

Es konnten drei laufende RCTs zur Thermoablation von benignen Schilddrüsenknoten identifiziert werden. Ein RCT untersucht das Auftreten einer Hyperthyreose bei RFA und RJT. Ein weiteres RCT überprüft die Reduktion des Knotenvolumens und die Wirksamkeit von MWA im Vergleich zur offenen Operation. Ein RCT setzt sich mit der Wirksamkeit, der Symptomverbesserung und den Komplikationen der HIFU im Vergleich zu keiner Behandlung auseinander.

Diskussion

Mangel an vertrauenswürdiger Evidenz

keine Metaanalyse

TA vs. RJT: einige Endpunkte nicht berichtet

häufigster Vergleich: RFA vs. Thyreoidektomie

fragliche Übertragbarkeit auf Österreich (9/10 Studien aus China)

Der Vergleich zwischen Thermoablation und Radiojodtherapie sowie Thyreoidektomie bei erwachsenen Patient*innen weist einen Mangel an hochwertiger, vertrauenswürdiger Evidenz auf. Dies begrenzt die Möglichkeit, valide Schlussfolgerungen zur Wirksamkeit und Sicherheit von Thermoablation im Vergleich zu Thyreoidektomie oder Radiojodtherapie zu ziehen. Aufgrund dieser Limitationen (direkte Vergleichbarkeit von Thermoablation mit unterschiedlichen Methoden, die Heterogenität und der Mangel an berichteten Ergebnissen) konnte keine Metaanalyse durchgeführt werden. Es fehlt Evidenz, die auf RCTs basiert, um Symptomreduktion, kosmetische Verbesserung, Lebensqualität oder Rezidive bei Erwachsenen mit gutartigen Schilddrüsenknoten nach Thermoablation zu bewerten. Darüber hinaus wurde keine Beobachtungsstudie identifiziert, um die Thermoablation im Vergleich zur Radiojodtherapie zu untersuchen. Der häufigste Vergleich in der identifizierten Literatur war RFA versus Thyreoidektomie. Dies wirft die Frage auf, ob die Evidenz auf alle thermoablativen Interventionen (z. B. RFA, MWA, HIFU, ILP) übertragbar ist. Zusätzlich muss die Übertragbarkeit der vorliegenden Studien auf die österreichische Bevölkerung (neun der zehn Studien stammen aus China) hinterfragt werden. Zudem sind Einschränkungen hinsichtlich der Art der untersuchten Schilddrüsenknoten und der Berichterstattung über Komplikationen zu konstatieren.

Schlussfolgerung

limitierte Evidenz für TA vs. RJT: mögliche Volumenreduktion und Verbesserung der Schilddrüsenfunktion mit RJT

Die vorliegende Evidenz deutet darauf hin, dass sowohl die Thermoablation als auch die Radiojodtherapie bei benignen Schilddrüsenknoten das Volumen der Knoten reduzieren können. Die Radiojodtherapie zeigte aber eine mögliche Überlegenheit in der Verbesserung der Schilddrüsenfunktion. Die Evidenz ist in Bezug auf Sicherheit nicht eindeutig, zeigt jedoch keine Unterlegenheit der Thermoablation. Die Verlässlichkeit der Evidenz ist für diesen Vergleich jedoch gering.

limitierte Evidenz: TA vs. Thyreoidektomie mögliche Reduktion der Komplikationen nach TA

Es lag Evidenz mit sehr geringer Vertrauenswürdigkeit vor, um die Sicherheit und Wirksamkeit der Thermoablation im Vergleich zur Thyreoidektomie zu bewerten, sowohl in RCTs als auch in Beobachtungsstudien. Heterogene Ergebnisse wurden für die Wirksamkeit berichtet, wobei die Evidenz auf weniger unerwünschte Ereignisse nach thermoablativen Interventionen hindeutet. Eine Re-evaluierung wird empfohlen.

kein eindeutiger Zusatznutzen

Die vorliegende Evidenz zeigt keinen eindeutigen Zusatznutzen zugunsten der Thermoablation im Vergleich zur Radiojodtherapie oder Thyreoidektomie.

1 Background

1.1 Overview of the disease, health condition and target population

Overview of the disease or health condition[1]

gutartige Schilddrüsenknoten: Veränderungen an Schilddrüse

Benign nodules of varied compositions can form on the parenchymal surface of the thyroid gland, located in the neck and closely associated with the trachea [1]. The thyroid gland produces the hormones thyroxine (T4) and triiodothyronine (T3), which control metabolism within the body. These hormones bind to genes associated with the control of metabolic rate and thermoregulation [1].

Knoten: Diagnostik mittels Ultraschall meistens gutartig und asymptomatisch

Thyroid nodules can be detected through ultrasound (US) imaging and are distinct from surrounding functional thyroid tissue on the surface of the gland [2]. Most thyroid nodules are benign and asymptomatic, with only a small number of detected nodules being malignant upon pathological investigation (≈5%) [3].

Klassifizierung nach Zusammensetzung der Knoten (z. B. zystisch oder solide)

Benign thyroid nodules can be classified based on tumour composition. Nodules can be classified as solid, spongiform, mixed or cystic upon imaging evaluation, with each subclass having different risks of growth and malignancy, and response to treatments [2, 4].

Klassifizierung nach Funktion: Überfunktion („heiße Knoten") oder Unterfunktion („kalte Knoten") möglich

Nodules can also be classified based on physiological function. Hyperfunctioning nodules, also known as "hot nodules" take up more radioiodine (RAI) than surrounding thyroid tissue upon imaging due to increased sodium iodine symporter proteins on the surface of tumour cells [5, 6]. Non-functioning, hypofunctioning or "cold" nodules take up less RAI than adjacent healthy tissue, and are often solid or mixed in composition [4]. A greater risk of malignancy is associated with hypofunctional nodules, whereas malignancy of hyperfunctional nodules is rare [2].

Prävalenz: 5 % der Weltbevölkerung

ca. 5 % der Betroffenen haben Symptome

Thyroid nodules are estimated to effect approximately 5% of the global population, with an increased incidence of nodules associated with the increased use and implementation of imaging procedures such as US [7]. Most cases of benign thyroid nodules do not require treatment and are monitored conservatively. However, approximately 5% of patients diagnosed with thyroid nodules will experience compressive symptoms associated with nodule growth and expansion, or nodules that promote the onset of functional disease, requiring intervention to alleviate symptoms [3].

Fokus auf benigne Knoten

Benign thyroid nodules, regardless of subclassification, are the focus of this report.[2]

[1] **A0002** – What is the disease or health condition in the scope of this assessment?

[2] **A0007** – What is the target population in this assessment?

Benign thyroid nodule risk factors and disease course

There are several risk factors associated with the development of thyroid nodules[3]. One of the most well-established factors promoting the development of both benign and malignant nodules is ionising radiation, especially when focused on the head and neck and when exposure occurs during childhood [8]. Radiation exposure can cause cellular damage, genetic destabilisation and mutagenicity, which promotes uncontrolled cell growth resulting in the formation of tumours [9]. Iodine deficiency can also be a predictive factor in the development of thyroid nodules. An investigation in Denmark observed that following the mandatory fortification of iodine in table salt and bread, the prevalence of thyroid nodules reduced significantly amongst the population [10]. Lack of dietary iodine may contribute to thyroid hyperplasia or may contribute to thyrocyte (thyroid follicular cell) DNA mutagenesis and cell growth [11]. The presence of metabolic syndrome may also increase the risk of nodule formation, with factors such as obesity, hypertension, abnormal glucose metabolism, and high cholesterol levels increasing the risk of nodule development [12]. Thyroid nodules are also more frequently diagnosed in women [13] and among older people [14].

Risikofaktoren: Exposition durch ionisierende Strahlen im Kindesalter, Jodmangel,

metabolisches Syndrom,

weibliches Geschlecht

und Alter

Typically, benign thyroid nodules are asymptomatic and do not require treatment, often remaining the same size or gradually shrinking over time [2].[4] Consistent monitoring via US ensures that changes in nodule structure, shape, composition and functionality can be monitored closely [2]. Occasionally, benign nodules can grow, resulting in comorbidities related to compression of the thyroid gland and surrounding structures in the neck, or cosmetic concerns associated with the visible presence of the nodule [13]. In such cases, interventions such as surgery, RAI or minimally invasive treatments such as ethanol ablation or thermoablation may be recommended [15].

Beobachtung mittels Ultraschall

bei Wachstum: mögliches Auftreten von Symptomen

Behandlung notwendig

Effects of the disease or health condition on the individual and society

Although typically asymptomatic, patients with benign thyroid nodules may develop a range of compressive and endocrine symptoms associated with nodule growth and transformation[5]. Difficulty swallowing, voice changes, altered physical appearance and pain and discomfort can be of concern for patients and physicians following the growth of benign thyroid nodules [16]. Often these symptoms are not immediately life-threatening but can be distressing for patients, especially in cases where thyroid nodules compress the trachea, causing dyspnea (shortness of breath) [16]. Benign thyroid nodules can also cause hormonal changes, resulting in a broader effect on metabolism. Nodule growth can promote the onset of metabolic dysfunction, with different types of thyroid nodules increasing and decreasing T3 and T4 synthesis, resulting in hyper- or hypothyroidism [17]. Such conditions can cause weight fluctuations, fatigue, changes in bowel function and changes in heart rate [18].

mögliche Symptome: Schluckbeschwerden, Veränderungen der Stimme und des Aussehens, Schmerzen, Unbehagen

Einfluss auf die Schilddrüsenfunktion: Gewichtsschwankungen, Müdigkeit, Verdauungsstörungen

There are psychosocial symptoms of benign thyroid nodules in addition to physical symptoms and comorbidities. Patients may also experience anxiety due to the presence of the nodule, and uncertainty regarding its potential transformation over time.

Behandlung kann eine psychosoziale Herausforderung darstellen

[3] **A0003** – What are the known risk factors for thyroid nodules?

[4] **A0004** – What is the natural course of thyroid nodules?

[5] **A0005** – What is the burden of disease for patients with thyroid nodules?

There is estimated to a be a high global incidence of thyroid nodules, particularly in countries with a reduced iodine intake [19].[6] High rates of diagnosis have resulted a significant economic cost associated with disease treatment and patient care. In a cost effectiveness analysis conducted by Cheung et al., they estimated that the total cost associated with the screening and management of all thyroid nodule types in the USA would exceed $25.1 billion [20]. Ongoing US screening, pathological and cytology testing, surgical and treatment costs and ongoing patient support contribute heavily to this value, with many patients requiring ongoing care and management following an initial diagnosis [20].

hohe Inzidenz in Ländern mit reduzierter Jodaufnahme

höhere Inzidenz aufgrund besserer Diagnostik

Prevalence of benign thyroid nodules in the population[7]

There is limited research and data on the prevalence of benign thyroid nodules in Austria. One study that mapped the global prevenance of thyroid nodules in the general population reported a prevalence of 8.47% in Austria [7]. However, these results must be interpreted with caution as this prevalence included both benign and malignant nodules, with results reported from a single study of 118 patients [7].

Prävalenz in Österreich unklar; 1 Studie berichtet eine Prävalenz von ca. 8,47 %

As noted previously, female gender, previous head and neck radiation exposure and obesity have been reported to increase the risk of thyroid nodules [7]. Based on results from the global mapping study of both benign and malignant thyroid nodules, females had a 1.5-fold higher risk of developing the disease (females: 36.5% vs male: 23.5%), with prevalence in both genders increasing with age (<30 years: 10.59%, 30-39: 17.28%, 40-49: 24.89%, 50-59: 33.37%, 60-69: 41.97%, >70 years: 44.66%) [7]. Additionally, an increased prevalence was observed in those who are overweight (36.96%) or obese (40.96%) compared to those who are of a normal weight (30.38%) [7]. Solid thyroid nodules (68.39%) were also found to be more prevalent than mixed (42.76%) and cystic nodules (6.27%).

Frauen haben ein 1,5-fach höheres Risiko, eine Krankheit zu entwickeln

erhöhtes Risiko im Alter und bei Übergewicht

1.2 Current clinical practice

Current clinical management of the disease or health condition[8]

According to the 2023 European Thyroid Association's clinical practice guidelines for thyroid nodule management, upon suspicion of thyroid nodules, physicians are expected to evaluate risk factors based on family history and a physical examination of the neck [2]. Pathological testing will be ordered to assess biochemical changes associated with the onset of the condition. Normally, thyroid stimulating hormone (TSH), free T4 and free T3 functional tests are conducted to assess hormonal changes associated with thyroid lesion formation. Other testing for TSH receptor antibody and thyroid peroxidase will be conducted if deemed relevant based on preliminary TSH results [21].

Guideline 2023 der Europäischen Schilddrüsengesellschaft (ETA)

[6] **A0006** – What are the consequences of thyroid nodules for the society?

[7] **A0023** – How many people belong to the target population?

[8] **A0024** – How are thyroid nodules currently diagnosed according to published guidelines and in practice?

Studies have suggested that hyperfunctional thyroid nodules present a low malignancy risk and indicate a different course of treatment [2, 22].

Bildgebende Verfahren (Ultraschall) zur Diagnostik

TIRADS: standardisiertes Verfahren zur Beurteilung von sonografisch detektierten Schilddrüsenknoten

To support pathological testing, an US is suggested for all patients suspected of having nodular thyroid disease to assess malignancy risk and the degree of nodule formation. Supplementary forms of US imaging for nodule evaluation and diagnosis include doppler imaging, elasto-sonography and contrast-enhanced US which can also be used to determine the presence of hyperfunctional nodules [2]. Based on such diagnostic protocols, the necessity for fine needle aspiration (FNA) is determined. In Europe, this can depend on the relevant European Thyroid Imaging and Reporting Data System (EU-TIRADS) category that the nodules have been allocated to. This system is used to categorise thyroid nodules based on US imaging. It considers factors including shape, size, margins, microcalcifications and hypoechogenicity [23]. Nodules ranking into a higher EU-TIRADS category, indicative of an increased risk of malignancy development may be tested further using FNA [2]. If nodules have a low EU-TIRADS category or where FNA findings do not indicate a high-risk growth, follow up testing via US is recommended over the course of months to years post-diagnosis [24].

konservative Behandlung

Ultraschallscreening, pathologische Untersuchungen

Bei Symptomen: Radiojodtherapie (RJT), OP, oder Thermoablation (TA)

Among patients with defined benign thyroid nodules, treatment and monitoring approaches are typically conservative.[9] In the absence of symptoms and a low risk of nodule malignancy, patients typically undergo watchful waiting with regular US and pathological testing [3]. Benign nodules that cause compressive or cosmetic symptoms affecting quality of life may require treatment [16]. This may involve the use of RAI therapy, surgery, or minimally-invasive interventions. Minimally invasive therapies including thermoablation have been employed in the treatment of thyroid nodules in cases where patients are not eligible candidates for surgery or RAI due to existing comorbidities or risks of complications [15]. Minimally invasive therapies have several benefits including limited associated complications, no use of general anaesthesia and short procedure lengths [2].

RJT – wenn OP nicht möglich

Prästimulation mit rhTSH bei Patient*innen mit geringer Jodaufnahme

RAI therapy is typically recommended in cases where patients are not eligible for surgical intervention due to complication risk, or have a hyperfunctioning thyroid nodule that has induced a state of hyperthyroidism [2, 25]. This involves intake of RAI (I-131), which kills nodule cells. This therapy may not be effective in all patients, especially those with low iodine uptake. In this case, pre-stimulation with recombinant human (rh)TSH may be recommended to ensure as much uptake as possible. In some cases, RAI may induce hypothyroidism in the long-term period following treatment, therefore long-term patient follow up may be necessary [2, 25].

OP bei symptomatischen Knoten, >4cm

Kontraindikationen bei OP

Nebenwirkungen bei OP möglich

Resective surgery may be recommended in patients with symptomatic benign thyroid nodules, or in cases where nodules have an indeterminate cytology to provide definitive diagnosis for patients with suspicious nodules [2]. Typically, surgery is recommended in cases where patients have solid nodules that are over four cm in size [26]. Not all patients are candidates for thyroidectomy surgery. Contraindications include those with Hasimoto's or Graves' disease, pregnancy or those who are on anticoagulant or antiplatelet therapies [27]. Further, some patients may refuse surgery due to associated risks including bleeding, infection and vocal cord paralysis [28, 29].

[9] **A0025** – How are thyroid nodules currently managed according to published guidelines and in practice?

1.3 Features of the intervention

Features of the technology and comparators

Thermoablation is a minimally-invasive technique utilised for the removal of both cancerous and benign tumours. The intervention uses high and low temperatures generated by different technologies to induce coagulative necrosis of nodule tissue, causing destruction of thyroid growths [30].[10]

TA: Entfernung von gutartigen und bösartigen Tumoren

There are several forms of thermoablation, including microwave ablation (MWA), radiofrequency ablation (RFA), high intensity focused ultrasound (HIFU) and US-guided percutaneous laser (UGPL). MWA uses a generator to produce a high-frequency electromagnetic field at the tip of an antenna, inserted into a nodule to generate high internodular temperatures (>150°C) to cause extensive cell death and necrosis of nodules [30]. RFA involves the insertion of an electrode into the lesion site and the use of a grounding pad on a patients skin to produce a closed RFA circuit, creating an energy flux and high temperature around the site of the inserted electrode, promoting the onset of coagulative necrosis [31]. Converging acoustic pressure waves generated with a HIFU transducer causes microscopic tissue shearing and high frictional heat within tumours, promoting thermoablation in HIFU [32]. Laser ablation typically involves the insertion of a laser under US-guidance, which uses electromagnetic radiation to penetrate tissue and induce local heating, protein denaturation and cell death [30]. Thermoablation is typically guided by US imaging to ensure the intervention is being applied on the correct region to maximise safety and efficacy.

Formen: MWA, RFA, HIFU, UGPL; MWA: elektromagnetisches Feld; RFA: Elektrodeninsertion; HIFU: gebündelte Ultraschallwellen

TA Ultraschall-geleitet

Thermoablation is a treatment modality for several disorders including cancers of hepatic, renal and bone origin [30, 33, 34].[11] Various forms of thermoablation have also been described as effective therapies in the treatment and management of neurological disorders, including epilepsy and vascular conditions including varicose veins [35, 36]. Thermoablation involves the use of high (above 80°C) and low temperature (below –20°C) to promote the onset of coagulative necrosis of tumour growths, allowing resulting dead tissue to be reabsorbed by the body over time [30].

mehrere Indikationen für Thermoablation (u. a. Leber- und Nierenkrebs); Behandlung von neurologischen Erkrankungen (u. a. Epilepsie)

Several forms of thermoablation technologies have received CE marking as defined in Table 1-1.[12] The MWA ECO 200G device has received CE marking certification [37], as well as the RFA device AK-F200 [37] and the HIFU device, Echopulse® [38]. Currently, the UGPL device considered in this report (Delta 15 Diode Laser) has not received CE marking.

CE-Kennzeichnung

[10] **B0001** – What are thermoablation, thyroidectomy, and radioiodine?

[11] **A0001** – For which health conditions, and for what purposes is thermoablation used?

[12] **A0020** – For which indications has thermoablation received marketing authorisation or CE marking?

Table 1-1: Features of the intervention

	Name	Proprietary name	Manufacturer/Country	Class/GMDN Code[13]	Certificaton
Intervention/ Technology	MWA	MTI-5DT[14]	Betters Medical/China	NR	NR
		Xphere-Tip®[15]	MayBlate™/Denmark	NR	NR
		ECO 200G[16]	ECO Medical/ China	Class II	CE-mark[17]
	RFA	Celon Power[18]	Olympus/Germany	Class I[19]	NR
		AK-F200[20]	Apro/Korea	NR	CE, ISO 13485
		Cool-Tip™[21]	Covidien/Ireland	NR	NR
		Rita 1500X RF generator[22]	AngioDynamics/USA	NR	NR
	HIFU	Echopulse®[23]	Theraclion/France	Class IIb	CE Nr. 0120
	Laser	Delta 15 Diode Laser[24]	AngioDynamics/USA	NR	NR

Abbreviations: MWA – microwave ablation, RFA – radiofrequency ablation, HIFU – high intensity frequency ultrasound, NR – not reported.

Note: The list does not include the associated parts for each system, such as applicators, of which there may be several. This is not an exhaustive list.

OP: Lobektomie – Lappenentfernung unter Vollnarkose

meistens Hemithyreoidektomie

Surgical resection of thyroid nodules has been common practice for many years, particularly in cases of nodule growth or transformation [2]. Open lobectomy (hemithyroidectomy) is the most frequent form of resective thyroid surgery. It involves the removal of one complete lobe of the thyroid under general anaesthesia [54]. This entirely removes the nodules and underlying thyroid tissue, and allows this tissue to undergo cytology testing to further assess for malignancy risk, as it is more reliable than FNA alone [55]. Near total thyroidectomy is not typically performed in benign cases of thyroid nodules unless indicated, especially when patients have coincident thyroid diseases or bilateral nodules [3].

RJT nicht invasives Verfahren, bei Hyperthyreose

In many cases, RAI therapy may be preferred to thyroidectomy due to its non-invasive nature, removing risks associated with surgical intervention. It is typically used in cases where nodules have induced hyperthyroidism within a patient. RAI doesn't have a significant effect on nodule size, and is more frequently employed to treat endocrine disorders resulting from nodule development [15]. Hyperfunctioning nodules readily take up RAI (I-131), destroying follicular cells, reducing thyrotoxicosis, and slightly reducing thyroid volume [15, 56].

[13] Guidance on classification of medical devices (2021) rates high-frequency electrosurgical generators, and electrocautery equipment, including their electrodes as Class IIb [39].

[14] Device [40] used in Jin 2018 and 2021 [41, 42], probably not available in Austria.

[15] Device [43] used in Zhi 2018 [44].

[16] Device [45] used in Bo 2022 [37].

[17] CE number not reported.

[18] Device [46] used in Yan 2016 & 2023 [47, 48].

[19] Protection class I.

[20] Device (RF 150/300) [49] used in Bo 2022 [37].

[21] Device [50] identified via hand search.

[22] Device [51] identified via hand search.

[23] Device [52] used in Dossing 2007 [38].

[24] Device [53] probably not available in Austria.

Komplikationen nach Operationen: u. a. Hypokalzämie, Hämatome, Infektionen, Nervenlähmung, Hormonersatztherapie

Surgical treatment of benign thyroid nodules via total or hemithyroidectomy is associated with several complications including hypocalcaemia, haematoma, infection and laryngeal nerve paralysis [57].[25] Such complications may require long-term follow up and treatment and can cause significant patient distress. Further, approximately 50% of patients will be required to undergo hormone replacement therapy due to the lack of functional thyroid tissue following a near complete lobectomy [58]. Finally, not all patients with benign thyroid nodules are candidates for surgery, with factors including age, medication history and anaesthesia tolerance affecting a patient's suitability for thyroidectomy [27].

Nebenwirkungen RJT: Schwellungen, Thyreoiditis, Hypothyreose, erhöhtes Krebsrisiko

RAI has many associated side effects due to the toxicity of the treatment. Side effects associated with the treatment include thyroid swelling and thyroiditis, sialadenitis and hypothyroidism [59]. Additionally, the use of RAI may increase the risk of cancer development through irradiation of the remaining non-diseased thyroid tissue, bone marrow and bladder, as these cells also feature many iodine transporters and readily uptake iodine [59]. Similarly to surgical intervention, not all patients are candidates for RAI therapy. Pregnancy and breastfeeding are absolute contraindications for the use of RAI, and it is not administered in patients under five years of age [25]. Patients who smoke or have very large goiters may also not be eligible for this treatment [25].

TA: minimal invasiv, keine Narkose notwendig; wenige Nebenwirkungen

bei dysfunktionalen soliden, benignen Schilddrüsenknoten

Thermoablation is claimed to be an effective method of reducing thyroid nodule volume [60]. It is a minimally-invasive technique that does not require the use of general anaesthesia, and is believed to have few associated complications [2]. Side effects of thermoablation techniques are reported to be uncommon and minor with the most frequently reported complications including minor pain and self-resolving haematoma [61]. Thermoablation is recommended as a first-line therapy for non-functioning, solid, benign thyroid nodules by the European Thyroid Association, especially in cases where patients are not suitable candidates for thyroidectomy or RAI therapy [2]. The implementation and support for the use of thermoablative procedures is currently limited by the lack of long-term follow up data from the patient population [2].

OP und RJT sind gut etablierte Behandlungsmethoden

Surgical intervention for the treatment of benign thyroid nodules has been utilised since the development of early medicine [62].[26] RAI has been utilised in the treatment of thyroid nodules since the 1940's [63]. Both surgery and RAI are well established interventions for the treatment of cancerous and benign thyroid nodules.

TA Durchführung seit mehreren Jahren

bislang nur wenige TAs in Österreich im letzten Jahr

Thermoablative therapies have been utilised as a form of nodule and tumour treatment in different capacities over many decades [64]. More recently, such therapies have been applied in the treatment of thyroid nodules, with RFA first described as a treatment for thyroid nodules in 2002, whilst other thermoablative procedures including MWA, HIFU and UGPL were introduced as treatment options in the 2010's [65-68]. Information provided by the submitting hospital reported that a total of five thermoablative procedures were administered last year for the treatment of benign thyroid nodules; however, the exact procedural numbers in Austria may vary.[27] It is es-

[25] **B0002** – What is the claimed benefit of thermoablation in relation to thyroidectomy and radioiodine?

[26] **B0003** – What is the phase of development and implementation of thermoablation, thyroidectomy, and radioiodine?

[27] **A0011** – How much are thermoablation, thyroidectomy and radioiodine utilised?

timated that within the next year this number will grow to 50 with the implementation of the technologies within the Austrian health care system (information provided by submitting hospitals).

Administration, investments, personnel and tools required to use the technology and the comparator(s)

Thyreoidektomie: Endokrinolog*innen, stationäre Aufnahme

Thyroidectomy surgery is typically performed by surgeons specialising in endocrinology and is often completed in an inpatient setting at a hospital [21].[28] Ongoing follow-up and monitoring may be completed by general practitioners, endocrinologists or otorhinolaryngology (ENT) specialists.

RJT: Nuklearmediziner*innen, ambulanter Eingriff

RAI therapy is performed under the provision and guidance of a nuclear medicine specialist, who will determine optimal treatment dosimetry and monitor patients' physiological response to treatment [25, 59]. RAI treatments are administered in an outpatient nuclear medicine unit if the administered patient dose does not exceed the allowed threshold based on radiation protection law and unless patients are affected by comorbidities that may complicate the treatment regime; such patients or those who require higher doses may be referred to an inpatient facility [25].

TA: u. a. Radiolog*innen und Nuklearmediziner*innen, ambulanter Eingriff

Thermoablation procedures are typically performed by a radiologist or nuclear medicine specialist (information provided by submitting hospitals). They may also be performed by other surgeons including ear nose and throat specialists or endocrinologists. Typically, thermoablation is performed in outpatient settings, with patients able to recover at home following the procedure [24]. Patients are directed back to specialists and general practitioners following the procedure for follow up and additional monitoring if necessary.

vor Entscheidung der Therapie werden Bildaufnahmen und Testungen gemacht

There are several special premises to consider in the use of thermoablation, thyroidectomy, and RAI in the treatment of benign thyroid nodules.[29] Prior to treatment for benign thyroid nodules, patients will undergo thyroid imaging and pathological testing to assess suitability for each treatment modality [2].

TA als Ultraschall-geführter Eingriff

In patients receiving thermoablation, accompanying US-guidance will also be required in completion of ablative technique to effectively guide physicians performing the procedure [24].

je nach Ablationstechnik, werden unterschiedliche Geräte benötigt

The equipment required to perform thermoablation will depend on the technology being utilised. In the case of MWA, a microwave generator, a coaxial cable and internally cooling antenna will be required [24].[30] RFA requires the use of a radiofrequency generator and an electrode needle; collecting pads may be required depending on the specific device [69]. HIFU utilises a US unit with an energy generator, an articulated arm and associated treatment head, and a computer interface [70]. UGPL utilises a laser fibre inserted under the guidance of a multifrequency US probe and a continuous wave laser to induce tissue ablation [71]. All above technologies also require the use of surgical consumables, local anaesthesia and occasionally mild sedatives such as midazolam to provide pain relief and relaxation [24].

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[28] **B0004** – Who administers thermoablation, thyroidectomy, and radioiodine, and in what context and level of care are they provided?

[29] **B0008** – What kind of special premises are needed to use thermoablation, thyroidectomy, and radioiodine?

[30] **B0009** – What supplies are needed to use thermoablation, thyroidectomy, and radioiodine?

Thyroidectomy procedures are intensive and require complete patient sedation and general anaesthetic, in addition to surgical tools and consumables. Tools such as scalpels, sutures or haemostatic clips, nerve monitors or stimulators for laryngeal nerve assessment, tissue trays and other surgical consumables may be required [72].

Thyreoidektomien benötigen u. a. eine Vollnarkose

RAI treatment requires the administration of an oral iodine capsule or intravenous administration of Na[^{131}I]. Consumables associated with the removal and control of contaminated material are also required following administration of the treatment [25].

RJT wird entweder oral oder intravenös verabreicht

Regulatory & reimbursement status

Patients who undergo RFA treatment for thyroid nodules are reimbursed 50% of treatment costs (€1377) by the Österreichische Gesundheitskasse – ÖGK (Austrian health insurance fund) [73]. Other forms of thermoablative treatments including MWA, HIFU and UGPL are not included in the Austrian health benefit catalogue and hence they are not fully reimbursable services in the Austrian Health care system. Furthermore, surgery (including total and partial thyroidectomy) and radioiodine (ranging from low dose without TSH, to high dose with additional TSH) are reimbursable treatments listed in the Austrian health benefit catalogue [74].[31]

keine volle Kostenrückerstattung, ca. 50 % der Kosten von der ÖGK übernommen

[31] **A0021** – What is the reimbursement status of thermoablation?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

In adult patients with benign thyroid nodules, is thermoablation in comparison to surgical thyroidectomy or RAI more effective and safe concerning nodule volume reduction rate (VRR), symptom reduction, cosmetic appearance improvement, thyroid function, health-related quality of life (HRQoL), nodule recurrence rate, adverse events (AEs) and serious adverse events (SAEs)?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	**Adult patients with benign thyroid nodules** *MeSH terms:* thyroid nodule *Emtree terms*: benign thyroid nodule *ICD-11 Codes:* 5A00.11 Iodine-deficiency-related multinodular goitre, 5A01.1 Nontoxic single thyroid nodule, 5A01.2 Nontoxic multinodular goitre, 5A02.1 Thyrotoxicosis with toxic single thyroid nodule, 5A02.2 Thyrotoxicosis with toxic multinodular goitre. **Rationale:** Thermoablation is recommended for benign thyroid nodules by international clinical practice guidelines [2, 15]. Subclasses (i.e. cystic, solid, etc.) have not been specified in order to keep the eligible studies broad.
Intervention	**Thermoablation using any of the following devices:** ■ Radiofrequency ablation (RFA) ■ Ultrasound-guided percutaneous laser (UGPL) ■ Microwave ablation (MWA) ■ High-intensity focused ultrasound (HIFU) *MeSH terms:* radiofrequency ablation, laser therapy, ablation techniques, microwaves, high intensity focused ultrasound ablation. *Emtree terms:* thermal ablation, radiofrequency ablation, laser therapy, microwave thermotherapy, microwave ablation device, ultrasound guided percutaneous microwave ablation high intensitt focused ultrasound. **Rationale:** Informed by information of the submitting hopsital, and international clinical practice guidelines [2, 15].
Control	■ **Surgical thyroidectomy** ■ **Radioiodine (RAI)** **Rationale:** Surgical thyroidectomy and RAI are recommended alternative to thermoablation by international clinical practice guidelines [2, 15].
Outcomes	**Efficacy** ■ Nodule volume reduction rate (VRR) ■ Symptom reduction (overall, compressive) ■ Cosmetic appearance improvement ■ Thyroid function (reduction of hyperthyroidism) ■ Health-related quality of life (SF-36) ■ Nodule recurrence rate

Outcomes *(continuation)*	**Safety** ■ Any adverse event (AEs; e.g. pain, dysphonia, skin irritation, haematoma, etc.) ■ Any serious adverse event (SAEs; e.g. death, life-threatening illness or injury, burns, nerve injury, etc.) **Rationale:** Informed by existing systematic reviews of thermoablation, identified through a scoping search of the literature [67, 75-77].
Study design	■ Randomised controlled trials (RCTs). ■ In the absence of sufficient data from randomised controlled trials, non-randomised studies of interventions (NRSI) that included propensity-score matching were included. **Excluded:** Non-peer reviewed studies, conference abstracts, comments, editorials, reviews, systematic reviews, meta-analyses, consensus statements, guidelines, case reports, articles not published in English or German, animal studies.

Abbreviations: AEs – adverse events, HIFU – high-intensity focused laser, MWA – microwave ablation, NRSI – nonrandomised studies of interventions, RAI – radioiodine, RCT – randomised controlled trial, RFA – radiofrequency ablation, SAEs – serious adverse events, SF-36 – short form-36, UGPL – ultrasound-guided percutaneous laser, VRR – volume rate reduction

3 Methods

3.1 Research questions

EUnetHTA Core Model®

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment. Please refer to Appendix (Table A-10 to Table A-13) for the detailed research questions.

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on 14 December 2023 in the following databases:

- Medline via Ovid
- Embase.com
- The Cochrane Library
- International HTA Database (INAHTA)

systematische Suche: 623 Treffer (nach Deduplizierung)

The systematic search was limited to articles published in English or German and in Medline and Embase to only randomised controlled trials (RCTs) or non-randomised studies of interventions (NRSIs) conducted in humans. Publication type filters were also implemented to exclude conference abstracts, comments, editorials, reviews, meta-analyses, consensus statements, guidelines and case reports. After deduplication, overall 623 citations were included. The specific search strategy employed can be found in the Appendix.

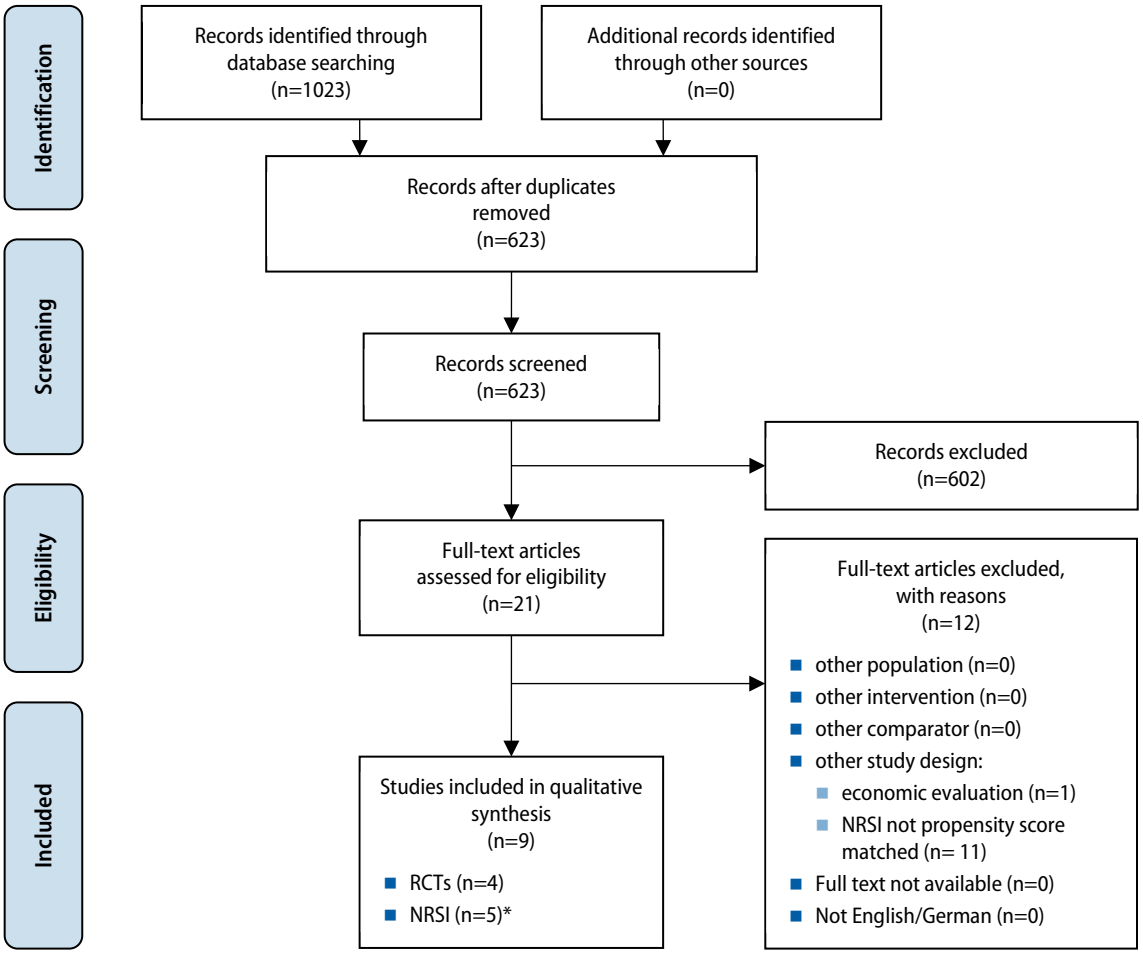
Suche nach laufenden Studien ergab 31 Treffer

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 5 January 2024 resulting in 31 potential relevant hits (ongoing trials not included in evidence base, see Table A-9).

3.2.2 Flow chart of study selection

Overall 623 hits were identified. No additional citations were found through handsearching. The references were screened by two independent researchers (KN, MR), and a third researcher (TV) was involved to resolve disagreements. The selection process is displayed in Figure 3-1.

keine zusätzlichen Studien durch Handsuche, insges. 623 Publikationen identifiziert; Literaturauswahl: 9 Studien eingeschlossen



Abbreviations: NRSI: nonrandomised studies of interventions, RCT: randomised controlled trial.
*Notes: *Retrospective propensity score matched NRSI*

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Bewertung von Studienvertrauenswürdigkeit und Verzerrungsrisiko

Certainty was assessed using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs [78], and the Risk Of Bias In Non-randomised Studies Of Interventions (ROBINS-I) tool for NRSIs [79](see Table A-3 and Table A-4). The certainty of the data was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [80].

systematische Datenextraktion und Kontrolle nach dem 4-Augen Prinzip

One reviewer (KN or MR) systematically extracted relevant data from the included studies into data extraction tables that were designed and tested *a priori*. A second reviewer (KN or MR) cross-checked the data extraction tables for accuracy. Risk of bias (RoB) appraisal was conducted in duplicate by two reviewers (KN and MR); differences were settled via consensus. For data extraction and RoB, a third reviewer was called upon to settle any disagreements. One reviewer (KN) analysed the certainty of the data using GRADE, and a second reviewers (TV) validated the analysis.

3.2.4 Synthesis

Evidenzsynthese mittels GRADE

The questions were answered in plain text format with reference to GRADE [80] evidence tables, which are reported in the Appendix (Table A-5). Results were summarised in Table A-1 and Table A-2 of the Appendix. For the purposes of this evaluation, all thermoablation techniques have been considered to be equivalent from a policy perspective, and have been grouped as an overall class of device for comparison against surgical resection or RAI.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

entscheidende Endpunkte für Wirksamkeit

The following outcomes were defined as *crucial* to derive a recommendation:

- **Nodule volume reduction rate (VRR)** is the primary measure to monitor treatment success for benign thyroid nodules. To measure nodule VRR, firstly, nodule volume (V) is calculated using the equation:

$$V \times \pi W \times D \times \frac{L}{6};$$

  where V is volume, W is width, D is depth and L is length (all in centimetres) of the thyroid nodule. The VRR is then calculated as: VRR (%) = (initial volume – final volume)/initial volume x 100.

Symptomreduktion

- **Symptom reduction** in this context relates to physical, non-cosmetic symptoms of benign thyroid nodules, including pressure in the neck, pain, cough, discomfort, foreign body sensation and dysphasia [81]. Symptom score can be self-measured by patients using a 10 cm visual analogue scale (grade 0–10) [81]. The symptom score is measured pre- and post-operatively (follow-up duration may vary) to assess symptom reduction.

Verbesserung des Erscheinungsbilds

- **Cosmetic appearance improvement** is related to VRR, and is a measure of how visible thyroid nodules are. Cosmetic appearance improvement is measured via a cosmetic score. Cosmetic score is measured by a physician, typically on a scale from 1 to 4. (1: no palpable mass; 2: no cosmetic problem but palpable mass; 3: a cosmetic problem on swallowing only; and 4: a readily detected cosmetic problem) [81].

Schilddrüsenfunktion

- **Thyroid function** in the context of benign thyroid nodules relates to measuring biomarkers and symptoms of hyperthyroidism. Thyroid function is measured using TSH, free T3, and free T4 [21].

HRQoL und QoL

- **Health-related quality of life (HRQoL)** and **disease-specific quality of life (QoL)** are patient-reported outcomes of overall health status measured via the assessment physical, mental, emotional and social functioning. They are measured with established instruments (e.g. Short Form 36-item health survey [SF-36] [82], EuroQol 5-dimension questionnaire [EQ-5D] [83] or Thyroid-Specific QoL Questionnaire Scale [84]). Other patient-reported outcome measures exist to assess the disease-specific impact of thyroid disease on QoL.

Knoten-Rezidivrate

- **Nodule recurrence rate** is a marker of long-term treatment success. Techniques such as US-guided biopsy, fine-needle aspirate for detecting the presence of triglyceride, and fluorodeoxyglucose-positron emission tomography-computed tomography are used to detect nodule recurrences [85]. Three different definitions of recurrence have been suggested: (1) nodules containing ≥1 mL of cystic fluid, (2) a volume reduction ratio of <50%, and (3) a vascular solid component in treated nodules [86].

4.1.2 Outcomes safety

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidende Endpunkte für Sicherheit: schwerwiegende Komplikationen

- **Serious adverse events (SAEs)** are defined as '*an adverse event (AE) that results in death, is life-threatening, leads to hospitalisation (or prolonged existing hospitalisation), results in persistent or significant disability, a birth defect, or any other important medical event that may jeopardise the patient or require medical intervention to prevent any of the outcomes listed above [87].*' AEs deemed as serious by the study investigators of each trial have been considered relevant.

Komplikationen

- **Adverse events (AEs)**, irrespective of severity, are defined as any unanticipated medical incident in a patient that has received a treatment, which does not have to be causally related to the treatment administered [87]. AEs identified and deemed relevant by the study investigators of each trial have been considered relevant.

4.2 Included studies

4.2.1 Included studies effectiveness and safety

Study characteristics

A total of four RCTs and five retrospective propensity score matched NRSI assessing the effectiveness of thermoablation for benign thyroid nodules met the predefined inclusion criteria. Of the four RCTs all reported on the safety of thermoablation, whereas only four of five NRSIs reported safety outcomes.

4 RCTs und 5 retrospektive NRSIs (Propensity Score Matching) inkludiert

One RCT compared interstitial laser photocoagulation (ILP) to RAI, with the other three RCTs comparing MWA to conventional thyroidectomy. A total of 648 (range: 30-450) participants were included across the four RCTs. Three RCTs were conducted in China, and one was conducted in Denmark. Follow-up durations of the RCTs ranged from 48 hours to 15 months. Nodule recurrence was not assessed in any of the included RCTs.

1 RCT: UGPL vs RJT
2 RCTs MWA vs Thyreoidektomie
1RCT MWA oder RFA vs Thyreoidektomie

All of the included NRSIs compared thermoablation to thyroidectomy. Two NRSIs compared RFA to thyroidectomy, one NRSI compared MWA to thyroidectomy, one NRSI compared both MWA and RFA (combined) to thyroidectomy and one NRSI compared HIFU to open lobectomy. A total of 1,604 (range: 185-505) participants were included across the five NRSI before propensity score matching, and 1,002 (range: 98-216) participants after propensity score matching. Follow-up durations of the NRSI ranged from six months to 36 months. All five NRSI were conducted in China. SAEs were not assessed in any of the included NRSI.

2 NRSIs: RFA vs Thyroidektomie
1 NRSI: MWA vs Thyroidektomie
1 NRSI: HIFU vs Lobektomie
1 NRSI: RFA + MWA vs Thyreoidektomie

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-5.

Studiencharakteristika und Ergebnisse im Anhang

Population characteristics

Participants in the included RCTs were predominately female (n=131 females and n=58 males, n=9 loss to follow-up; one study of 450 participants did not report sex), with the average age of participants ranging from 43 and 58 years. The inclusion criteria of three RCTs stated that the benign nature of the nodule was required to be confirmed via FNA according to the American Bethesda System for Reporting Thyroid Cytopathology (Bethesda Class II) before treatment. Three of the RCTs also had restrictions on maximum size/diameter of the thyroid nodule and additional feature requirements (e.g. increasing rapidly in volume). Other study-specific clinical features were also of importance for inclusion into each of the RCTs (e.g. hyperthyroidism, thyroid nodule-related symptoms such as compressive symptoms or cosmetic concerns, or anxiety about malignant transformation).

RCTs: mehr Frauen als Männer; Alter zwischen 43 und 58 Jahren

Participants in the included NRSI were predominantly female (n=781 females and n=221 males), with mean age ranging between 35 and 65 years after propensity score matching. The inclusion criteria stated that patients were required to have compressive symptoms, cosmetic problems or discomfort in the neck. The benign nature of the nodule was required to be confirmed via FNA or core-needle biopsy examined according to the American Bethesda System for Reporting Thyroid Cytopathology (Bethesda Class II) before treatment. Four of the NRSIs also had restrictions on maximum size/diameter of the thyroid nodule and additional feature requirements (e.g. solid or predominately solid nodule, treatable ablation depth between the skin and nodule centre). Three of the NRSI also required participants to have serum levels of thyrotropin and thyroid hormone within normal levels.

NRSIs: mehr Frauen als Männer; Alter zwischen 35 und 79 Jahren

Patient*innen-charakteristika und Ergebnisse im Anhang

Population characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-5.

4.3 Results

4.3.1 Morbidity

Nodule volume reduction (VRR)[32]

One RCT reported VRR between thermoablation and RAI. At one, three and six months postoperatively, a trend in decreasing nodule volume was observed in both the thermoablation group (1 month: 32.04±5%, 3 months: 40.82±5%, 6 months: 44±5%) and RAI group (1 month: 15.19±12%, 3 months: 38.10±13%, 6 months: 47±8%). No significant between group differences were reported at 6 months (p=0.73). The overall GRADE certainty of evidence was assessed to be very low.

1 RCT (TA vs RJT) VRR: keine ss Unterschiede

Two RCTs reported VRR between thermoablation and thyroidectomy [42, 44]. With the complete removal of the thyroid gland, VRR in the thyroidectomy group was not reported. In those who received thermoablation, similar decreasing nodule volume trends were observed within studies. Jin 2021 [42] reported reductions of 15.4±7.2%, 48.2±11.3%, 68.1±8.1 and 80.1±1.8% at

2 RCTs (TA vs OP) VRR: keine ss Unterschiede

[32] **D0005** – How does thermoablation affect symptoms (severity, frequency) of the thyroid nodules?

one, three, six and 12 months for RFA, and 15.3±7.1%, 47.9±10.2%, 67.8±7.9 and 79.3±3.2% at one, three, six and 12 months for MWA. Zhi [44] reported reductions of 75.9%, 88.4%, and 95.2% at three, six and 12 months. The overall GRADE certainty of evidence was assessed to be very low.

VRR reported in 4 NRSIs demonstrated a trend in decreasing nodule volume over time (6 months: 64±26%, 12 months: 79.6±10.2%, 19 months: 80.7±21.1%, 24 months: 94.1±15.0%) in the thermoablation treatment group, noting that this trend is observed across studies and is therefore subject to possible confounding [37, 41, 48, 54]. With the complete removal of the thyroid gland, VRR in the thyroidectomy group was not reported. The overall GRADE certainty of evidence was assessed to be very low.

4 NRSIs:
VRR
keine ss Unterschiede,
Confounding möglich

Symptom reduction[32]

Symptom reduction was not reported in the one RCT comparing thermoablation and RAI in patients with benign thyroid nodules [38].

Symptomreduktion:
1 RCT (TA vs RJT)
nicht berichtet

Two RCTs comparing thermoablation to thyroidectomy reported symptom reduction [42, 44]. Zhi 2018 [44] reported baseline nodule-related symptoms in ten participants in the thermoablation group (35.7%; n=28) and eleven participants in the thyroidectomy group (45.8%; n=24). By 12 months, remission of nodule-related symptoms was reported by all participants. Whereas Jin 2021 [42] reported statistically significant between group differences in favour of thyroidectomy, with fewer patients experiencing a peculiar sense in throat (OR 0.31 [95% CI 0.20 to 0.49], p<0.0001), dysphasia (OR 0.32 [95% CI 0.23 to 0.45], p<0.0001), and compression on trachea (OR 0.14 [95% CI 0.07 to 0.21], p<0.0001) at 15 months. No statistically significant difference was reported in the proportion of patients experiencing hoarseness (OR 0.81 [95% CI 0.32 to 1.59], p=0.87) at 15 months. The overall GRADE certainty of evidence was assessed to be very low.

2 RCTs
(TA vs Thyreoidektomie):
ss Unterschied bei
"unangenehmes Gefühl
im Hals"
ns Unterschied Heiserkeit

GRADE:
sehr niedrige Qualität

Two NRSI reported symptom reduction score [37, 48], whilst one NRSI reported symptom improvement score [54]. Yan 2023 [48] reported that the symptom score significantly decreased from median 3 (IQR 2) to median 1 (IQR 1) in the thermoablation group (P=.001), and median 5 (IQR 4) to median 2 (IQR 2) in the thyroidectomy group (P<.001) from baseline to 12 months. Bo 2022 [37] reported between group differences in symptom score after thermoablation or thyroidectomy at median 19 months. No significant differences in symptom score were observed between thermoablation and conventional thyroidectomy (median 2 [IQR 2–2] vs median 2 [IQR 1.5–2]; p=0.826) or thermoablation and endoscopic thyroidectomy (median 1 [IQR 1–2] vs median 1 [IQR 0–2]; p=0.356). Lang 2019 [54] reported on symptom improvement score at 6 months after treatment in thermoablation and lobectomy patients. Overall, 20 (26%), 30 (39%) and 23 (30%) patients in the thermoablation group reported slight, moderate and significant symptom improvement, respectively. In the lobectomy group, 15 (20%), 33 (43%) and 19 (25%) patients reported slight, moderate and significant symptom improvement, respectively. No improvements in symptoms were reported by 4 (5%) patients in the thermoablation group and 10 (13%) patients in the lobectomy group. The overall GRADE certainty of evidence was assessed to be very low.

2 NRSIs:
Symptomreduktions- oder
1 NRSI: Symptom-
verbesserungsscore
1 NRSI: ss Unterschied
zugunsten der TA
1 NRSI: ns Unterschied

GRADE:
niedrige Qualität

Cosmetic appearance improvement[32]

Cosmetic appearance improvement was not reported in the one RCT comparing thermoablation and RAI in patients with benign thyroid nodules [38].

One RCT comparing thermoablation to thyroidectomy reported on cosmetic appearance improvements [44]. At baseline, all participants in the intervention and comparator group reported cosmetic concerns prior to treatment (n=28 and n=24, respectively). At 12 months, excellent cosmetic results were reported by all participants in the thermoablation group (100%; n=28), whilst 20 participants reported excellent cosmetic results in the thyroidectomy group (83.3%; n=24). The overall GRADE certainty of evidence was assessed to be very low.

Three NRSI reported on cosmetic appearance improvement between thermoablation and thyroidectomy [37, 41, 48]. Yan 2023 [48] reported that the cosmetic score significantly decreased from median 3 (IQR 1.5) to median 1 (IQR 1) in the thermoablation group (P=.001), and median 4 (IQR 2) to median 0 (IQR 0) in the thyroidectomy group (P=.001) from baseline to 12 months. Bo 2022 [37] reported between group differences in cosmetic score after thermoablation or thyroidectomy at median 19 months. No significant differences in cosmetic score were observed between thermoablation and conventional thyroidectomy (median 1 [IQR 1–1] vs median 1 [IQR 1–1]; p= 0.946) or thermoablation and endoscopic thyroidectomy (median 1 [IQR 1–2] vs median 1 [IQR 1–1]; p=0.196). Jin 2018 [41] narratively reported that better cosmetic effect was observed in the thermoablation group compared to the thyroidectomy group. The overall GRADE certainty of evidence was assessed to be very low.

Verbesserung des Erscheinungsbilds: RCT (TA vs RJT): nicht berichtet

1 RCT (TA vs Thyreoidektomie): exzellente Ergebnisse nach 12 Monaten in TA-Gruppe

3 NRSI berichten Verbesserungen des Erscheinungsbilds
1 NRSI: ss Unterschied zugunsten TA

2 NRSI: ns Unterschied

GRADE: sehr niedrige Qualität

Nodule recurrence rate[33]

Nodule recurrence rate was not reported in the RCTs comparing thermoablation to RAI [38] or thermoablation to thyroidectomy [42, 44, 47].

Two NRSI assessed nodule recurrence rate between thermoablation and thyroidectomy [37, 48]. At median follow-up of 19 (range: 12-36) months, Bo 2022 reported that one nodule (0.8%; n=129) with regrowth was identified, with additional ablation performed in three nodules (2.3%; n=129). At median follow-up of 27.3 months in the thermoablation group, Yan 2023 reported that no nodule regrowth was detected, with six ablated nodules (12.2%) disappearing during the follow-up period. The overall GRADE certainty of evidence was assessed to be very low.

Knoten-Rezidivrate nicht berichtet in RCTs

2 NRSIs: TA vs Thyeroidektomie, 0.8 % und 2.3 % bei TA

Thyroid function[34]

Thyroid function was reported by one RCT comparing thermoablation and RAI in patients with benign thyroid nodules and subclinical hyperthyroidism or hyperthyroidism [38]. Between group serum TSH was assessed at baseline and at 6 months. At baseline no significant differences were observed between the thermoablation and RAI group (median 0.03 mU/ml [Range: <0.001–0.20 mU/ml] vs median 0.02 mU/ml [Range: <0.001–0.27 mU/ml]; p=0.91). By 6 months, a significant difference was observed between the thermoabla-

Schilddrüsenfunktion: 1 RCT (TA vs RJT), ss Unterschied nach 6 Monaten zugunsten TA

[33] **D0006** – How does thermoablation affect progression (or recurrence) of thyroid nodules?

[34] **D0011** – What is the effect of thermoablation on patients' body functions?

tion and RAI group (median 0.32 mU/ml [Range: <0.001–0.82 mU/ml] vs median 1.21 mU/ml [Range: 0.43–2.58 mU/ml]; p=0.02). With normal serum TSH values falling between 0.3–4.0 mU/ml, all participants in the RCT had subnormal levels (i.e. subclinical hyperthyroidism or hyperthyroidism) at baseline, with 7 (50%; n=14) participants levels in the thermoablation group normalising, and 15 (100%; n=15) participants levels in the RAI group normalising by 6 months postoperatively. Postprocedural hypothyroidism was reported in two (13%; n=15) patients in the RAI group at six months, and not observed in the thermoablation group. No differences in FT4 index, FT3 index or anti-TPOAb were observed at baseline or six months. The overall GRADE certainty of evidence was assessed to be very low.

1 RCT (TA vs Thyreoidektomie), Schilddrüsenfunktion wurde nicht beeinträchtigt

Thyroid function was reported by one RCT comparing thermoablation and thyroidectomy in patients with benign thyroid nodules [44]. This RCT was assessed as having a high RoB. Zhi 2018 [44] reported that, *"the volume reduction achieved by MWA did not affect thyroid function, which remained unchanged throughout the 12-month follow-up period"*. Refer to Table A-1 for digitised approximations of serum TSH levels at one, and 12 months of follow-up. The overall GRADE certainty of evidence was assessed to be very low.

4 NRSIs: postprozedurale Hypothyreose, IG: 0,3 % vs CG: 13,2 %

Four NRSI reported postprocedural hypothyroidism when comparing thermoablation to thyroidectomy in patients with benign thyroid nodules [37, 41, 48, 54]. Overall, postprocedural hypothyroidism was reported in one participant (0.3%; n=393) in the thermoablation treatment group and 52 participants(13.2%; n=393) in the thyroidectomy group between six to 36 months. The overall GRADE certainty of evidence was assessed to be very low.

Health-related quality of life (HRQoL)[35,36]

QoL: nicht berichtet in 1 RCT (TA vs RJT)

HRQoL was not reported in the one RCT comparing thermoablation and RAI in patients with benign thyroid nodules [38].

1 RCT (TA vs Thyreoidektomie): ss Unterschied nach 15 Monaten zugunsten Thyreoidektomie

Thyroid-specific QoL was reported by one RCT comparing thermoablation to thyroidectomy in patients with benign thyroid nodules [42]. At baseline, the thyroid-specific QoL scale total score (TS) did not differ between thermoablation (Median 118.9 [IQR 64.4 to 195.6]; n=218) and thyroidectomy (Median 117.3 [IQR 60.2 to 179.2]; n=218). At 15 months, a significant difference in thyroid-specific QoL scale TS between the two groups favouring thyroidectomy was reported (OR 0.34 [95% CI 0.21 to 0.45], p<0.0001). Additionally, at 15 months the thyroid-specific QoL scale domains of total psychological wellbeing and total social wellbeing were found to be statistically significantly (p=0.0018 and p=0.0056, respectively) in favour of the thermoablation group, whereas, total physical wellbeing was found to be statistically significantly (p=0.0079) in favour of the thyroidectomy group. No statistically significant difference (p=0.24) was reported between the groups regarding the total spiritual wellbeing score. The overall GRADE certainty of evidence was assessed to be very low.

1 RCT (TA vs Thyreoidektomie): ns Unterschied, Verbesserung bei TA

Furthermore, SF-36 was reported by one RCT comparing thermoablation to thyroidectomy in patients with benign thyroid nodules [44]. At 12 months, this RCT concluded that compared to patients who underwent thyroidectomy, those who underwent thermoablation had better general health and mental health scores (p<0.05, for both). Refer to Table A-1 for digitised approxima-

[35] **D0012** – What is the effect of the technology on generic health-related quality of life?

[36] **D0013** – What is the effect of the technology on disease-specific quality of life?

tions for scores of each domain assessed by the SF-36 instrument. The overall GRADE certainty of evidence was assessed to be very low.[37]

SF-36 was also assessed by one NRSI comparing thermoablation to thyroidectomy [88]. At six months, general health was significantly improved from baseline in the thermoablation group alone (p=0.012), whilst role-emotion and mental health was significantly improved in both the thermoablation (p=0.007 and p=0.002, respectively) and thyroidectomy (p=0.049 and p=0.011, respectively) groups. Additionally, general health, vitality, and mental health were all statistically significant if favour of thermoablation when compared to thyroidectomy at six months (p=0.029, p<0.001, p=0.038, respectively). The overall GRADE certainty of evidence was assessed to be very low.

1 NRSI:
ss Unterschied nach 6 Monaten zugunsten TA

4.3.2 Patient safety

Serious adverse events (SAEs)[38]

SAEs were not reported in the RCT comparing thermoablation to RAI or thyroidectomy in patients with benign thyroid nodules [38].

One RCT reported SAEs in patients with benign thyroid tumors when comparing thermoablation to conventional thyroidectomy [42]. Overall, any SAEs were reported in six participants (3%; n=208) in the thermoablation treatment group and eight participants (4%; n=209) in the conventional thyroidectomy group at 15 months. SAEs included infection, pain, recurrent laryngeal nerve injury, prolonged admission for observation, readmission for investigation of shortness of breath and requiring a drainage tube for longer than 72 hours. None of the included NRSI reported SAEs. The overall GRADE certainty of evidence was assessed to be very low.

schwerwiegende Nebenwirkungen:
1 RCT (TA vs RJT):
nicht berichtet

1 RCT
(TA vs Thyreoidektomie):
IG: 3 % vs CG: 4 % Fälle

Adverse events (AEs)[38]

One RCT reported AEs in patients with benign thyroid tumours when comparing thermoablation to RAI [38]. Overall, any AEs were reported in six participants (42.9%; n=14) in the thermoablation treatment group and two participants (13.3%; n=15) in the RAI group at six months. The overall GRADE certainty of evidence was assessed to be very low.

Nebenwirkungen:
1 RCT (TA vs RJT):
IG: 42,9 % vs CG: 13,3 %

Three RCTs reported AEs in patients with benign thyroid tumours when comparing thermoablation to conventional thyroidectomy [42, 44, 47]. Overall, any AEs were reported in 13 (4.44%; n=293) participants in the thermoablation group and 42 (14.79%; n=284) participants in the conventional thyroidectomy group at two days to 15 months. The overall GRADE certainty of evidence was assessed to be very low.

3 RCTs (TA vs Thyreoidektomie):
IG: 4,4 % vs CG: 14,8 %

Four NRSI reported AEs in patients with benign thyroid tumours when comparing thermoablation to conventional thyroidectomy/thyroid lobectomy [37, 41, 48, 54]. Overall, any AEs were reported in 11 participants (2.8%; n=393) in the thermoablation treatment group and 22 participants (5.6%; n=393) in the conventional thyroidectomy/thyroid lobectomy group at 6 to 36 months. The overall GRADE certainty of evidence was assessed to be very low.

4 NRSIs:
IG: 2,8 % vs CG: 5,6 %

Refer to Table A-2 for further details on the types of AEs reported.

[37] **D0012** – What is the effect of the technology on generic health-related quality of life?

[38] **C0008** – How safe is thermoablation in comparison to radioiodine and thyroidectomy?

5 Quality of evidence

Verzerrungsrisiko: Cochrane Risk of Bias 2 tool und ROBINS-I-tool

The risk of bias for individual outcomes of the included RCTs was assessed with the Cochrane Risk of Bias 2 tool [78], with the risk of bias in NRSI assessed using the ROBINS-I tool [79]. Results of the appraisals are presented in Table A-3 and Table A-4 in the Appendix.

Vertrauenswürdigkeit der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [80] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [80].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = 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;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Beurteilung nach GRADE, siehe Anhang

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-5.

RCT (TA vs RJT): sehr niedrig

Overall the strength of RCT evidence for the effectiveness and safety of thermoablation in comparison to RAI is very low. No data was available to assess symptom reduction, cosmetic appearance improvement, QoL or nodule recurrence rate, SAEs.

RCT (TA vs OP): sehr niedrig

Overall the strength of RCT evidence for the effectiveness and safety of thermoablation in comparison to thyroidectomy is very low. No data was available to assess nodule recurrence rate.

NRSI (TA vs OP) sehr niedrig

Overall the strength of NRSI evidence for the effectiveness and safety of thermoablation in comparison to thyroidectomy is very low. No data was available to assess SAEs.

Table 5-1: Summary of findings table of thermoablation vs radioiodine (RCTs)

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Nodule volume reduction ratio (%) **Follow-up: 6 months**	I: 44±5%, C: 47±8%, p=0.73			29 (1 RCT)	⨁◯◯◯ Very low[a,b]	VRR reduced in both groups, but differences between groups was not significantly different at 6 months.
Symptom reduction – **Not reported**	-	-	-	-	-	Not reported
Cosmetic appearance improvement – **Not reported**	-	-	-	-	-	Not reported
Thyroid function – serum TSH (mU/ml) **Follow-up: 6 months**	**Baseline:** I: 0.03 (<0.001–0.20), C: 0.02 (<0.001–0.27), p=0.91 **6 months:** I: 0.32 (<0.001–0.82), C: 1.21 (0.43–2.58), p=0.02			29 (1 RCT)	⨁◯◯◯ Very low[a,b]	Thyroid function was signficantly improved in the the RAI arm compared to thermoablation arm at 6 months.
Quality of life – **Not reported**	-	-	-	-	-	Not reported
Nodule recurrence rate – **Not reported**	-	-	-	-	-	Not reported
Adverse events **Follow-up: 6 months**	133 per 1,000	293 more per 1,000 (from 31 fewer to 1,000 more)	RR 3.20 (0.77 to 13.36)	29 (1 RCT)	⨁◯◯◯ Very low[a,b]	More reported adverse events in the thermoablation arm, but this difference was not statistically significant.

Abbreviations: CI – confidence interval, C – comparator, I – intervention, RCT – randomised controlled trial, TSH – thyroid stimulating hormone, VRR – volume rate reduction.

Explanations:

[a] *Dossing 2007 assessed as having a high risk of bias.*

[b] *Very small sample size (between 1-99 participants).*

Table 5-2: Summary of findings table of thermoablation vs thyroidectomy (RCTs)

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Nodule volume reduction rate (%) **Follow-up: 12 months**	**Jin 2021 – 12 months – VRR (%)** I: RFA- 80.1±1.8%; MWA- 79.3±3.2%, C: NR **Zhi 2018 – 12 months – VRR (%)** I: 95.2%±NR (p<0.01), C: NR			451 (2 RCTs)	⨁◯◯◯ Very low[a,b]	Nodule volume reduction was not reported in the comparator arm as the entire nodule and part of the thyroid gland were excised. VRR decreased 15-95% from 3 to 12 months in the thermoablation arm.

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Symptoms **Follow-up: range 12 months to 15 months**	**Jin 2021 – 15 months** ■ Peculiar sense in throat: 35/175 (20%) vs 19/175 (11%); OR 0.31 (95% CI 0.20 to 0.49), p<0.0001 ■ Dysphasia: 9/124 (7%) vs 4/142 (3%); OR 0.32 (95% CI 0.23 to 0.45), p<0.0001 ■ Compression on trachea: 6/129 (5%) vs 1/135 (<1%); OR 0.14 (95% CI 0.07 to 0.21), p<0.0001 ■ Hoarseness: 0 (0%) vs 1 (<1%); OR 0.81 (95% CI 0.32 to 1.59), p=0.87 **Zhi 2018 – 12 months** Remission of nodule-related symptoms: 10/28 vs 11/24			402 (2 RCTs)	⨁◯◯◯ Very low[a,b]	Results between RCTs were heterogenous. One study reported significantly fewer symptoms in the thyroidectomy arm at 15 months; the other reported no difference in symptom improvement between groups at 12 months.
Cosmetic appearance improvement **Follow-up: 12 months**	833 per 1,000	917 per 1,000 (608 to 1,000)	RR 1.10 (95% CI 0.73 to 1.67)	52 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	All patients in both treatment arms had cosmetic concerns prior to treatment. There was no significant difference between groups in terms of cosmetic improvement at 12 months.
Thyroid function – s erum TSH (mIU/ml) **Follow-up: 12 months**	**Baseline:** I: 1.85±1.17, C: 1.76±0.83 **12 months:** I: 2.10 (NR), C: 2.81 (NR)			52 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	Unchanged from baseline, no differences between groups.
Quality of life (Thyroid-specific QoL/SF-36) **Follow-up: range 12 months to 15 months**	**Zhi 2018 – 12 months – SF-36** "Compared to patients who underwent surgery, those who underwent MWA had better general health and mental health scores" (p<0.05) **Jin 2021 – 15 months – Thyroid-specific QoL scale total score** **Baseline:** I: 118.9 (64.4 to 195.6), n=218; C: 117.3 (60.2 to 179.2), n=218 **15 months:** OR 0.34 (95% CI 0.21 to 0.45), p<0.0001.			408 (2 RCTs)	⨁◯◯◯ Very low[a,b]	Both studies reported a statistically significantimrpovement in quality of life favouring thermoablation.
Nodule recurrence rate – Not reported	-	-	-	-	-	Not reported
Adverse events (SAEs & AEs) **Follow-up: range 2 days to 15 months**	173 per 1,000	102 fewer per 1,000 (from 129 fewer to 53 fewer)	RR 0.41 (0.25 to 0.69)	577 (3 RCTs)	⨁◯◯◯ Very low[a,d]	Significantly less reported SAEs and AEs in the thermoablation arm.

Abbreviations: AEs – adverse events, CI – confidence interval, C – comparator, I – intervention, MWA – microwave ablation, NR – not reported, QoL – quality of life, RCT – randomised controlled trial, RFA – radiofrequency ablation; SAEs – serious adverse events; SF-36 – short-form 36, TSH – thyroid stimulating hormone, VRR – volume rate reduction.

Explanations:

[a] *Jin 2021, Yan 2018 and Zhi 2018 assessed as having a high risk of bias;*

[b] *Imprecision downgraded due to study setting (China);*

[c] *sample size = 1-99;*

[d] *Imprecision downgraded due to Yan 2018 only investigating AEs to 48 hours and study setting (China).*

Table 5-3: Summary of findings table of thermoablation vs thyroidectomy/lobectomy (NRSI)

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Nodule volume reduction **Assessed with: Longest follow-up** **Follow-up: range 6 months to 24 months**	**Lang 2019 – 6 months – VRR (%)** I: 64±26% vs C: NR **Jin 2018 – 12 months – VRR (%)** I: 79.6±10.2% vs C: NR **Bo 2022 – 19 months – VRR (%)** TA: 80.7±21.1% vs ConT/ER: NR **Yan 2023 – 24 months – VRR (%)** I: 94.1% (15.0) vs C: 100%			786 (4 non-randomised studies)	⨁◯◯◯ Very low[a,b,c,d]	Nodule volume reduction was not reported in the comparator arm as the entire nodule and part of the thyroid gland were excised. VRR decreased 64-94% from 6 to 24 months.
Symptom reduction **Assessed with: symptom score** **Follow-up: range 6 months to 36 months**	**Lang 2019 – 6 months (% of patients)** *0 (no improvement):* I: 4 (5), C: 10 (13) *1 (slight improvement):* I: 20 (26), C: 15 (20) *2 (moderate improvement):* I: 30 (39), C: 33 (43) *3 (significant improvement):* I: 23 (30), C: 19 (25) **Yan 2023 – 12 months** I: Median: 1 (IQR 1)*, C: Median: 2 (IQR 2)** * RFA change from baseline to 12 months (P=.001) ** ConT change from baseline to 12 months (P<.001) **Bo 2022 – Median 19 (Range: 12-36) months** I: Median 2 (IQR 2-2); ConT: Median 2 (IQR 1.5-2), p=0.826 I: Median: 1 (IQR 1-2); ET: Median: 1 (0-2), p=0.356			574 (3 non-randomised studies)	⨁◯◯◯ Very low[b,c,e]	No difference in symptom reduction between groups.
Cosmetic appearance improvement **Assessed with: cosmetic score** **Follow-up: range 12 months to 36 months**	**Yan 2023 – 12 months** I: Median: 1 (IQR: 1)*, C: Median: 0 (IQR: 0)** * RFA change from baseline to 12 months (P=.001) ** ConT change from baseline to 12 months (P=.001) **Jin 2018 – 12.8 months** "A better cosmetic effect in the US-guided MWA group compared to the conventional thyroidectomy group." **Bo 2022 – Median 19 (range: 12-36) months** I: Median: 1 (Range: 1–2), C: Median: 1 (Range: 1–1), p=0.196			622 (3 non-randomised studies)	⨁◯◯◯ Very low[b,c,f]	No difference in cosmetic score between groups.
Thyroid function (assessed via hypothyroidism) **Follow-up: range 6 months to 36 months**	132 per 1,000	3 fewer per 1,000 (from 0 to 18)	RR 0.0192 (0.0026 to 0.1383)	786 (4 non-randomised studies)	⨁◯◯◯ Very low[a,c]	0.3% and 13.3% reported hyperthyroidism in the thermoablation and thyroidectomy groups, respectively.

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Quality of life (SF-36) **Follow-up: 6 months**	**Yue 2016 – 6 months – SF-36:** *General health (p=0.029):* I: 68.5*, C: 66.7 * Significantly improved from baseline (p=0.012) *Vitality (p<0.001):* I: 71.3, C: 67.5 *Role-emotional:* I: 96.6*, C: 94.4** * Significantly improved from baseline (p=0.007) ** Significantly improved from baseline (p=0.049) *Mental health (p=0.038):* I: 80.9*, C: 79.3** * Significantly improved from baseline (p=0.002) ** Significantly improved from baseline (p=0.011)			216 (1 non-randomised study)	⨁◯◯◯ Very low[c,g]	SF-36 domains of general health, mental health and vitality were statistically significantly in favour of thermoablation at 6 months.
Nodule recurrence rate **Follow-up: range 12 months to 36 months**	**Bo 2022** – *"Only one nodule (0.8%, 1/129) with regrowth was identified at the final follow-up point. Additional ablation was performed in three nodules (2.3%, 3/129)."* **Yan 2023** – *"Nodule regrowth was not detected. Six ablated nodules (12.2%) disappeared during the follow-up."*			420 (2 non-randomised studies)	⨁◯◯◯ Very low[c,h]	No differences in nodule recurrence rate.
Adverse events (any) **Follow-up: range 6 months to 36 months**	56 per 1,000	38 fewer per 1,000 (from 47 fewer to 18 fewer)	RR 0.33 (0.16 to 0.67)	786 (4 non-randomised studies)	⨁◯◯◯ Very low[a,c]	Significantly less reported AEs in the thermoablation arm.

Abbreviations: CI – confidence interval, C – comparator, ConT – conventional thyroidectomy, ET – endoscopic thyroidectomy, I – intervention, IQR – interquartile range, NR – not reported, NRSI – nonrandomised studies of interventions, QoL – quality of life, RFA – radiofrequency ablation, SF-36 – short-form 36, TA – thermoablation, VRR – volume rate reduction.

Explanations:

[a] *Overall risk of bias is high (Bo 2022, Lang 2019, Yan 2023) and moderate (Jin 2018);*

[b] *Due to the time-varied nature of the outcome, it is not appropriate to evaluate inconsistency because studies reported outcomes at different time points.;*

[c] *Imprecision downgraded due to study setting (China);*

[d] *Large margins (±);*

[e] *Overall risk of bias is high (Bo 2022, Lang 2019, Yan 2023);*

[f] *Overall risk of bias is high (Bo 2022, Yan 2023), and moderate (Jin 2018);*

[g] *Overall risk of bias is high (Yu 2016);*

[h] *Overall risk of bias is high (Bo 2022, Yan 2023).*

6 Discussion

6.1 Summary of findings

The objective of this HTA was to evaluate the effectiveness and safety of thermoablation compared to thyroidectomy and RAI in adult patients with benign thyroid nodules. A total of four RCTs and five retrospective propensity score matched NRSIs met the predefined inclusion criteria.

Ziel: Evaluierung TA im Vergleich zu OP und RJT; 4 RCTs, 5 NRSIs

Thermoablation vs radioiodine (RCT evidence)

One RCT compared interstitial laser photocoagulation (ILP) to RAI in adult patients with benign thyroid nodules. Overall, the strength of RCT evidence for the effectiveness and safety of thermoablation in comparison to RAI was very low.

ILP vs RJT niedrige Vertrauenswürdigkeit

A time-dependent trend in decreasing nodule volume (VRR) was reported between thermoablation and RAI, however no significant between group differences were reported at six months. At six months, significant differences between thermoablation and RAI were reported for serum TSH, with TSH levels normalising in seven of 14 participants in the thermoablation group and 15 of 15 participants in the RAI group (all participants had subclinical hyperthyroidism or hyperthyroidism at baseline). Reports of postprocedural hyperthyroidism were reported in two of 15 patients in the RAI group and none in the thermoablation group. No differences in FT4 index, FT3 index or anti-TPOAb were observed. Overall, any AEs were reported in six (42.9%) participants in the thermoablation treatment group and two (13.3%) participants in the RAI group at six months.

Volumen-reduktionsrate: ns Unterschied ss Unterschied TSH (zugunsten TA)

Hypothyreose IG:2 vs CG: 0

Symptom reduction, cosmetic appearance improvements, quality of life, nodule recurrence rate and SAEs were not reported.

einige Endpunkte nicht berichtet

No relevant NRSI evidence comparing thermoablation to RAI was identified.

kein NRSI zu TA vs RJT

Thermoablation vs thyroidectomy (RCT evidence)

Four RCTs compared MWA to conventional thyroidectomy in adult patients with benign thyroid nodules. Overall the strength of RCT evidence for the effectiveness and safety of thermoablation in comparison to thyroidectomy is very low.

4 RCTs (MWA vs Thyreoidektomie): Qualität niedrig

A time-dependent trend in decreasing nodule volume (VRR) was reported in patients receiving thermoablation on a study-level up to 12 months. This volume reduction did not affect thyroid function, which ultimately remained unchanged. VRR in the thyroidectomy group was not reported, as the nodules were completely resected. One RCT found that in participants who reported nodule-related symptoms at baseline in both the thermoablation and thyroidectomy group, all symptoms were resolved by 12 months. Further, another RCT investigated specific nodule-related symptoms – peculiar sense in throat, dysphasia and compression on trachea – at 15 months, observed statistically significant between group differences in favour of thyroidectomy. At 12 months, excellent cosmetic results were reported by all participants in the thermoablation group, whilst only 83.3% of participants in the thyroidectomy group reported excellent cosmetic results.

VRR: Abnahme, keine Auswirkung auf Schilddrüsenfunktion

1 RCT: keine Symptome nach 12 Monaten

At 15 months, one RCT reported a significant difference in thyroid-specific QoL scale TS between the two groups. The thyroid-specific QoL scale domains of total psychological wellbeing, and total social wellbeing were found to be statistically significantly in favour of the thermoablation group, whereas, total physical wellbeing was found to be statistically significantly in favour of the thyroidectomy group. Furthermore, when evaluating SF-36, a second RCT found that patients who underwent thermoablation had better general health and mental health scores compared to those who underwent thyroidectomy at 12 months ($p<0.05$, for both).

QoL: ss Unterschied zugunsten TA (spezifischer Score)

ss Unterschied generelle Gesundheit zugunsten TA

At 15 months, any SAEs were reported in six (3%; n=208) participants in the thermoablation treatment group and eight (4%; n=209) participants in the conventional thyroidectomy group. Between two days and 15 months, any AEs were reported in 13 (4.44%; n=293) participants in the thermoablation treatment group and 42 (14.79%; n=284) participants in the conventional thyroidectomy group.

Schwerwiegende Komplikationen IG: 3 % vs CG: 4 %, Komplikationen IG: 4,4 % vs CG: 14,8 %

Nodule recurrence was not reported.

Thermoablation vs thyroidectomy (NRSI evidence)

In adult patients with benign thyroid nodules, two NRSIs compared RFA to thyroidectomy, one NRSI compared MWA to thyroidectomy, one NRSI compared both MWA and RFA (combined) to thyroidectomy, and one NRSI compared HIFU to open lobectomy. Overall, the strength of NRSI evidence for the effectiveness and safety of thermoablation in comparison to thyroidectomy is very low.

NRSI-Evidenz: HIFU, RFA, MWA und Kombination vs Thyreoidektomie

A time-dependent trend in decreasing nodule volume (VRR) was reported in patients receiving thermoablation across studies up to 24 months. VRR in the thyroidectomy group was not reported, as the nodules were completely resected. Only one nodule with regrowth was detected across the NRSI. Between six and 26 months, postprocedural hypothyroidism was reported in one (0.3%; n=393) participants in the thermoablation treatment group and 52 (13.2%; n=393) participants in the thyroidectomy group. No significant differences in cosmetic appearance improvement or symptom reduction were reported between groups, however both the thermoablation and thyroidectomy group reported significant differences in cosmetic score and symptom score from baseline to 12 months.

VRR: Reduktion in TA, nicht berichtet bei Thyreoidektomie (Totalresektion)

Hypothyreose IG: 0,3 % vs CG 13,2 %

ns Unterschied Aussehen und Symptome

When evaluating SF-36, general health, vitality, and mental health were all statistically significant in favour of thermoablation when compared to thyroidectomy at 6 months. At 6 to 36 months, any AEs were reported in 11 (2.8%; n=393) participants in the thermoablation treatment group and 22 (5.6%; n=393) participants in the conventional thyroidectomy group.

SF-36 ss Unterschied zugunsten TA

SAEs were not reported.

6.2 Evidence gaps and ongoing clinical trials

Evidence gaps

Lücken in Evidenzlage

The most significant gap in the evidence relates to the lack of high-quality comparative evidence comparing thermoablation to thyroidectomy or RAI in adult patients with benign thyroid nodules. The conduct of well-designed RCTs and NRSIs will be of great value to address the research question of interest.

limitierte Evidenz: direkter Vergleich TA und andere Komparatoren

keine NRSI für RJT

Limited evidence was available to directly compare thermoablation to other comparators, with heterogeneity and scarcity in the reported outcomes disallowing the conduct of meta-analyses in this HTA. Regarding the outcomes of interest, no RCT evidence was available to assess symptom reduction, cosmetic appearance improvement, QoL or nodule recurrence rate in adults with benign thyroid nodules when comparing thermoablation to RAI. Furthermore, no NRSIs were identified to investigate this comparison. Furthermore, no RCT evidence was available to assess symptom reduction, cosmetic appearance improvement, QoL or nodule recurrence rate in adults with benign thyroid nodules when comparing thermoablation to thyroidectomy.

Ongoing clinical trials

Suche nach laufenden Studien: 6 RCTs

Ergebnisse bis 2028

To address possible gaps in the evidence-base, clinical trial registries were searched to investigate current ongoing clinical trial. Three ongoing RCTs on the use of thermoablation for benign thyroid nodules were identified. One RCT will investigate the use of RFA compared to RAI to assess the rates of hyperthyroidism. One RCT will investigate the use of MWA compared to open surgery to assess VRR and treatment effectiveness rates. One RCT will investigate the use of HIFU compared to no treatment to assess treatment effectiveness rate, symptoms score improvement, and AEs. The sponsor organisations for these ongoing RCTs are located across Europe and Asia, including France, the Netherlands, and China. Two RCT reported a primary completion date, one being 1 November 2024 and the other being December 2028.

6.3 Limitations of the assessment

Limitations of the methodology

Vorteile: systematische Methodik, Suchstrategie

The methodology of this review has numerous notable advantages, primarily stemming from its systematic approach and thorough search strategies. The comprehensive search strategy and the independent review of studies by two reviewers provides confidence that the included studies accurately reflect the available evidence base.

Limitationen: nur RCTs und NRSIs (Propensity Score Matching)

However, it is essential to acknowledge that systematic reviews have shortcomings. The first limitation lies within the study selection methods used to identify potentially relevant literature. Only RCTs and propensity score matched NRSI were eligible for inclusion, thus additional literature to answer the research question may have been excluded. Most importantly, other comparative evidence from NRSI which were not propensity score matched

were excluded from this HTA. However, it became evident that even though the highest quality evidence was sought and selected, this was not equally reflected in the risk of bias and overall quality of evidence assessment conducted via GRADE – with all outcomes assessed to be of very low-quality evidence. Therefore, it is unlikely that the inclusion of lower levels of evidence would have sufficiently strengthened the overall quality of evidence.

Secondly, this HTA may suffer from an absence of extensive grey literature searches, such as specialty societies and the restriction of included articles to English and German language only, meaning studies published in other languages may have been missed.

keine Suche nach grauer Literatur

Limitations of the evidence

As previously mentioned, the biggest limitation regarding the evidence is that available data across the RCTs and NRSI was limited or scarce for a variety of outcomes. This limited the possibility to draw strong, evidence-based conclusion on the effectiveness and safety of thermoablation compared to thyroidectomy or RAI. Furthermore, although there are numerous thermoablative technologies, the most common comparison in the identified literature was RFA vs thyroidectomy. Raising the question as to whether the thermoablative interventions (i.e. RFA, MWA, HIFU, ILP) are substantially similar enough to draw a single conclusion.

Limitation Evidenz: wenige Endpunkte berichtet, valide Schlussfolgerung nicht möglich

Finally, a range of applicability issues have been identified in the current evidence-base. Firstly, the geographic location of the included studies is likely to pose a concern to the generalisability of results to the Austrian setting. Of the included studies, eight of nine have been conducted in China, which is a developing upper middle-class country, whereas Austria is a developed high-class country. Secondly, although cystic nodules have been reported to be the most prevalent type of benign thyroid nodule [7], two NRSIs were restricted to only solid or predominately solid thyroid nodules [41, 48]. With all other included studies not excluding based on nodule type, this may introduce a level of heterogeneity into the analysis. Finally, one RCT only reported early onset AEs at 48 hours [47]. This may not be a sufficient amount of time to capture all relevant events relating to either the intervention or comparator.

die meisten Studien aus China: Übertragbarkeit auf Österreich fraglich

Studien heterogen bzgl. klinischer Charakteristika der Knoten

6.4 Conclusion

Based on very low certainty evidence, in patients with hyperfunctional nodules, both thermoablation and RAI significantly reduced nodule volume at six months, with no significant differences reported between interventions; however, thyroid function was significantly improved in the RAI group but not in the thermoablation group. No significant differences in the safety profile of these interventions were observed.

geringe Vertrauenswürdigkeit der Evidenz: Schilddrüsenfunktion ss besser mit RJT

Very low quality RCT and NRSI evidence was available to evaluate the safety and effectiveness of thermoablation compared to thyroidectomy. Heterogenous results were reported for effectiveness, and significantly fewer adverse events favouring thermoablation.

geringe Vertrauenswürdigkeit der Evidenz: TA vs OP, ss weniger Komplikationen mit TA

7 Evidence based conclusion

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlung

Table 7-1 Evidence based conclusions

	Strong evidence for added benefit in routine use
	Evidence indicates added benefit in specific indications
	Less robust evidence indicating an added benefit in routine use or in specific indications
X	**No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest**
	Strong evidence indicates that intervention is ineffective and or harmful

Reasoning:

Begründung

The current evidence is not sufficient to prove that thermoablation is as effective but safer than the comparator(s). New study results will potentially influence the effect estimate.

Based on the limited ongoing clinical trials of thermoablation compared to RAI, no treatment and open thyroidectomy, re-evaluation is not recommended prior to 2028.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Thermoablation: Results from randomised controlled trials

Author, year	Dossing 2007 [38]	Jin 2021 [42]	Yan 2018 [47]	Zhi 2018 [44]
Country	Denmark	China	China	China
Sponsor	This study was supported economically by the Agnes and Knut Mørk Foundation, the Novo Nordisk Foundation, the A P Møller Relief Foundation and the A J Andersen and Wife Foundation.	Nil	Nil	Nil
Intervention/Product	Interstitial laser photocoagulation: A Logiq 500 US scanner (GE Medical Systems, Milwaukee, WI, USA) with a 12 MHz linear transducer (type 739L) mounted with a needle steering device for precise US-guided punctures was used. Under sterile conditions and guided by US, the laser fibre (0.4 mm in diameter) was positioned in the thyroid nodule through the lumen of an 18 gauge (1.2 mm) needle and preceded by local anaesthesia with lidocaine (10 mg/ml). The needle was withdrawn at least 20 mm leaving the end of the fibre in direct contact with the tissue. Patients were then treated with an output power of 2.5-3.5 W, depending on pretreatment nodule volume and the position of the nodule. The entire procedure was performed with an infrared diode (model 15; Diomed, Cambridge, England) laser power source and under continuous US-guidance.	MWA: Microwave system (MTI-5DT, Changcheng Medical Instruments Cooperation, Nanjing, China, YZB National 7534-2013) and MWA antenna (Z16.100) RFA: NR	MWA: Antenna inserted from the isthmus to the lateral part of a targeted nodule and microwave ablation (power: 25 W-35 W) was performed with moving shot technique. A heat-generated hyperechoic zone of ablation encompassing the entire nodule was created.	MWA: MWA therapy instrument used was a KY-2000 (Kangyou Medical, Nanjing, China) that consists of a microwave generator, a flexible low-loss coaxial cable, and a cooled shaft antenna. During the MWA, a power output of 30-50W and frequency of 2450 MHZ were used. Under US guidance, a moving shot technique was used to release microwave energy from the moving electrode until the hyperechoic zone was filled with the treated portion of the nodule.
Comparator	Radioiodine (RAI): Given as a single dose calculated as 3.7 MBq/g total thyroid mass (estimated by planimetric ultrasonography), corrected to a 100% thyroid uptake of RAI after 24 hours.	Conventional thyroidectomy: The thyroid goiter was dissected with an US knife (Johnson&Johnson Inc., New Brunswick, NJ, USA).	Conventional thyroidectomy: Subtotal thyroidectomy or thyroid nodule resection was performed with meticulous capsular dissection technique.	Conventional thyroidectomy (hemi-thyroidectomy): The thyroid isthmus was removed to expose the trachea. The suspensory ligaments of thyroid were amputated and the cricothyroid artery and arteriae thyreoidea inferior were isolated and ligated while preserving the rami posterior. The unilateral thyroid gland was completely resected and sent for pathologic examination. Nerves were identified and preserved.
Study design	Randomised controlled trial	Open label, randomised controlled trial	Randomised controlled trial	Randomised controlled trial
Number of pts	n=30 I:15; C:15	n=450 I: 225 (MWA: 89, RFA: 112); C: 225	n=108 I: 57; C: 51	n=60 I: 30; C: 30

Author, year	Dossing 2007 [38]	Jin 2021 [42]	Yan 2018 [47]	Zhi 2018 [44]
Inclusion criteria	Median thyroid nodule volume of 9.8 ml (range 3.0 to 43.0 ml) and a median total thyroid volume of 25.0 ml (11.0 to 50.0 ml), referred due to subclinical or mild hyperthyroidism or a thyroid nodule. All patients had a solitary hot thyroid nodule, evaluated clinically, scintigraphically and by US. The latter demonstrated increased vascularization by colour Doppler. None had prior radiation to the neck or symptoms/findings suggestive of thyroid malignancy (rapidly growing, firm/adherent nodules, compression symptoms/regional lymphadenopathy).	(a) BTNs were over 2 mm apart from the thyroid capsule; (b) maximum diameter of BTNs ≥2 cm; (c) twice fine needle aspiration cytology confirmed benign results; (d) BTNs may compress the trachea or cause aesthetic problem	(1) Fine needle aspiration biopsy-proven benign thyroid nodules; (2) any of the following conditions: hyperfunctional nodules; thyroid nodule-related symptoms (pain, foreign body sensation, neck discomfort; protruding nodules affecting appearance)	Thyroid nodules (1) were benign proven by two fine-needle aspiration biopsies (Bethesda class II at cytologic evaluation of material obtained) within the preceding 3 months and sonograph pattern consistent with low/very low suspicion of malignancy; (2) had a maximum diameter ≥2 cm and continuing to grow; (3) associated with structural symptoms or clinical concern for structural problems; (4) increasing rapidly in volume (more than double in 6 months); (5) patients anxious about malignant transformation
Age of patients (yrs) mean±SD; I vs C	58±3 vs 54±3; p=0.53 *All data presented as mean±SEM	43±5 vs 43±5	45.8±10.2 vs 46.2±11.5	53.61±8.76 vs 52.05±11.95
Sex n (m/f); I vs C	3/11 vs 2/13	NR	8/49 vs 11/40	20/8 vs 14/10
Follow-up (months)	6 months	15 months	48 hours	12 months
Loss to follow-up, n (%)	I: 1 (7); C: 0 (0)	I: 24 (11); C: 27 (12)	Nil	I: 2 (7); C: 6 (20)
Outcomes				
Efficacy				
Nodule volume reduction rate (%), ml mean±SD I vs C	Nodule volume (ml): Baseline: 10.6±2.5 vs 11.2±1.6 6 months: 4.6±0.6 vs 6.3±1.5; p=0.69 Nodule volume reduction rate (%): 1 month: 32.04±5% vs 15.19±12% 3 months: 40.82±5% vs 38.10±13% 6 months: 44±5% vs 47±8%; p=0.73 *All data presented as mean±SEM	Nodule volume reduction rate (%): 1 month: I: RFA- 15.4±7.2%; MWA- 15.3±7.1%; C: NR 3 months: I: RFA- 48.2±11.3%; MWA- 47.9±10.2%; C: NR 6 months: I: RFA- 68.1±8.1%; MWA- 67.8±7.9%; C: NR 12 months: I: RFA- 80.1±1.8%; MWA- 79.3±3.2%; C: NR	NR	Nodule volume (ml): Baseline: I: 17.11±14.41; C: 20.79±14.00 3 months: I: 3.01±2.74 (VRR 75.9%, p<.01); C: NR 6 months: I: 1.70±2.08 (VRR 88.4%, p<.01); C: NR 12 months: I: 0.69±0.89 (VRR 95.2%, p<.01); C: NR Nodule volume reduction rate (ml): Solid nodules (n=5): 3 months: I: 0.34±0.22; C: NR 6 months: I: 0.67±0.20; C: NR 12 months: I: 0.84±0.09: C: NR Cystic nodules (n=23): 3 months: I: 0.84±0.12; C: NR 6 months: I: 0.89±0.12: C: NR 12 months: I: 0.97±0.03; C: NR
Symptom reduction n/N (%)	NR	15 months Peculiar sense in throat: 35/175 (20) vs 19/175 (11); OR 0.31 (95% CI 0.20 to 0.49), p<0.0001 Dysphasia: 9/124 (7) vs 4/142 (3); OR 0.32 (95% CI 0.23 to 0.45), p<0.0001 Compression on trachea: 6/129 (5) vs 1/135 (<1); OR 0.14 (95% CI 0.07 to 0.21), p<0.0001 Hoarseness: 0 (0) vs 1 (<1); OR 0.81 (95% CI 0.32 to 1.59), p=0.87	NR	Nodule-related symptoms at baseline: 10/28 (35.7) vs 11/24 (45.8) Remission of nodule-related symptoms: 10/28 28 (35.7) vs 11/24 (45.8)

Author, year	Dossing 2007 [38]	Jin 2021 [42]	Yan 2018 [47]	Zhi 2018 [44]
Cosmetic appearance improvement n/N (%)	NR	NR	NR	Cosmetic concerns prior to treatment: 28/28 (100%) vs 24/24 (100%) Excellent cosmetic results: 28/28 (100%) vs 20/24 (83.3%)
Thyroid function Median (range) or mean±SD	Serum TSH (mU/ml) at baseline: 0.03 (<0.001-0.20) vs 0.02 (<0.001-0.27); p=0.91 6 months: 0.32 (<0.001-0.82) vs 1.21 (0.43-2.58); p=0.02 Normal/subnormal serum TSH (n) at baseline: 0/14 vs 0/15; p=0.98 6 months: 7/7 vs 15/0; p<0.01 FT4 index (U/l) at baseline: 113±9 vs 137±11; p=0.17 6 months: 109±7 vs 127±14; p=0.37 FT3 index (U/l) at baseline: 2.3±0.2 vs 2.6±0.2; p=0.84 6 months: 2.2±0.2 vs 2.3±0.3; p=0.76 Anti-TPOAb (pos./neg.) at baseline: 0/14 vs 2/13; p=0.51 6 months: 0/14 vs 2/13; p=0.51 *Data presented as mean±SEM Hypothyroidism 6 months after therapy: NR vs 2 (13%)	NR	NR	Serum thyrotropin (µIU/ml) at baseline: I: 1.85±1.17; C: 1.76±0.83 1 month: I: 1.82 (NR); C: 3.94 (NR) 6 months: I: 1.96 (NR); C: 3.59 (NR) 12 months: I: 2.10 (NR); C: 2.81 (NR) Free thyroxine (ng/dl) at baseline: I: 0.92±0.18; C: 0.89±0.17 Anti-TPO and/or anti-TGAb (Y/N) at baseline: I: 1/27; C: 1/23 *"Overall, the volume reduction achieved by MWA did not affect thyroid function, which remained unchanged throughout the 12-month follow-up period"*
Quality of life Mean (SD) or median (IQR), n I vs C	NR	Thyroid-specific QoL scale total score: Baseline: I: 118.9 (64.4 to 195.6), n=218 C: 117.3 (60.2 to 179.2), n=218 15 months: OR 0.34 (95% CI 0.21 to 0.45), p<0.0001 Total physical well being: Baseline: I: 82 (62 to 93), n=202 C: 81 (61 to 92), n=202 15 months: I: 104 (85 to 117), n=178 C: 111 (91 to 117), n=178 OR 1.5 (95% CI 1.32 to 1.89), p=0.0079 Total psychological well being: Baseline: I: 154 (114 to 187), n=218 C: 154 (110 to 187), n=218 15 months: I: 207 (24.7), n=139 C: 183 (24.5), n=136 OR 2.37 (95% CI 1.08 to 3.79), p=0.0018 Total social well being: Baseline: I: 62.9 (13.6), n=218 C: 63 (12.6), n=218 15 months: I: 119 (98 to 126), n=178 C: 112 (91 to 126), n=178 OR 1.49 (95% CI 1.13 to 1.86), p=0.0056	NR	SF-36: 6 months: Physical function: I: 88.15 (NE); C: 87.69 (NE) Role-physical: I: 92.40 (NE); C: 91.95 (NE) Bodily pain: I: 92.86 (NE); C: 95.14 (NE) General health: I: 66.57 (NE); C: 65.20 (NE) Vitality: I: 70.97 (NE); C: 70.67 (NE) Social functioning: I: 94.07 (NE); C: 92.71 (NE) Role-emotional: I: 93.71 (NE); C: 92.71 (NE) Mental health: I: 76.60 (NE); C: 74.92 (NE) 12 months: Physical function: I: 88.61 (NE); C: 87.82 (NE) Role-physical: I: 92.56 (NE); C: 92.09 (NE) Bodily pain: I: 92.72 (NE); C: 94.94 (NE) General health: I: 66.61 (NE); C: 65.35 (NE) Vitality: I: 71.04 (NE); C: 70.89 (NE) Social functioning: I: 93.67 (NE); C: 92.56 (NE) Role-emotional: I: 93.35 (NE); C: 92.56 (NE) Mental health: I: 77.06 (NE); C: 75.47 (NE) *"Compared to patients who underwent surgery, those who underwent MWA had better general health and mental health scores"*

Author, year	Dossing 2007 [38]	Jin 2021 [42]	Yan 2018 [47]	Zhi 2018 [44]
Quality of life Mean (SD) or median (IQR), n, I vs C *(continuation)*		Total spiritual well being: Baseline: I: 31.0 (9.3), n=219; C: 30.6 (8.8), n=219 15 months: I: 66 (48 to 76), n=178 C: 66 (48 to 78), n=178 OR 1.09 (95% CI 0.67 to 2.82), p=0.24		
Nodule recurrence rate	NR	NR	NR	NR
Safety				
SAEs, n (%) I vs C	NR	I: n=208 vs C: n=209 Any: 6 (3) vs 8 (4) Infection: 1 (<1) vs 1 (<1) Pain: 1 (<1) vs 1 (<1) Drainage required >72 hours: 0 (0) vs 1 (<1) Readmitted for investigation of shortness of breath: 1 (<1) vs 1 (<1) Prolonged admission for observation: 2 (1) vs 2 (1) Recurrent laryngeal nerve injury: 0 (0) vs 1 (1) Total= I: 5 vs C: 7	NR	NR
AEs, n (%) I vs C	Pain during procedure: 1 (7) vs NR Pain post-treatment: 5 (33) vs NR Tenderness post-treatment: NR vs 1 (7) Hemithyroidectomy 6 months after therapy: NR vs 1 (7) Median duration of pain or tenderness: 2.5 days (range 0-5.0) vs NR Total= I: 6 vs C: 2	I: n=208 vs C: n=209 Cough: 4 (2) vs 5 (2) Consultation for pain: 1 (<1) vs 1 (<1) Haematoma: 1 (<1) vs 1 (<1) Blood loss >50 ml: 1 (<1) vs 1 (<1) Trachea injury: 0 (0) vs 1 (1) Pyrexia requiring antibiotics: 1 (<1) vs 1 (<1) Blood transfusion: 0 (0) vs 0 (0) Further operation by 15 months: 2 (1) vs 4 (2) Total= I: 10 vs C: 14	Hypercalcaemia: 0 (0) vs 1 (2) Tetania: 0 (0) vs 1 (2) Cervical haematoma: 0 (0) vs 0 (0) Recurrent laryngeal nerve injury: 0 (0) vs 0 (0) Secondary open surgery: 0 (0) vs NR Total= I: 0 vs C: 2	Any: 1 (4) vs 4 (17) Numbness: 0 (0) vs 2 (8) Hoarseness: 1 (4) vs 2 (8) Postoperative pain: 2 (28) vs 22 (24) Postoperative fever: 0 (0) vs 0 (0) Postoperative infection: 0 (0) vs 0 (0) Skin burn: 0 (0) vs 0 (0) Neck damage: 0 (0) vs 0 (0) Total= I: 3 vs C: 26

Abbreviations: AEs – adverse events, Anti-TGAb – anti-thyroglobulin antibody, Anti-TPOAb – anti–thyroid peroxidase antibody, BTNs – benign thyroid nodules, C – comparator, CI – confidence interval, FT3 – free triiodothyronine, FT4 – free thyroxine, I – intervention, IQR – interquartile range, MWA – microwave ablation, m/f – male/female, n – number, NE – not estimable, NR – not reported, OR – odds ratio, pts – patients, QoL – quality of life, RFA – radiofrequency ablation, SAEs – serious adverse events, SD – standard deviation, SEM – standard error of the mean, SF-36 – short-form 36, TSH – thyroid stimulating hormone, US – ultrasound, USA – United States of America, VRR – volume reduction rate, W – watts, yrs – years, Y/N – yes/no.

Note: Blue text represents data digitized via Webplot

Table A-2: Thermoablation: Results from NRSI with propensity score matching (part 1)

Author, year	Bo 2022 [37]	Jin 2018 [41]
Country	China	China
Sponsor	This work was funded in part by the National Natural Science Foundation of China, Shanghai Municipal Health Commission, the Science and Technology Commission of Shanghai Municipality, Shanghai 'Rising Stars of Medical Talent' Youth Development Program, and Shanghai Tenth People's Hospital Climbing Talents Program-Excellent Young Doctors Program.	Nil
Intervention/Product	Thermoablation: The selection of RFA or MWA was based on the experience of the operator and the technical conditions of the hospital at the time of surgery; thransisthmic approach and moving shot technique was used. MWA: ECO-100 multi-functional microwave therapeutic instrument (Changcheng Microwave System Engineering Co. Ltd., Nanjing, China) and disposable microwave antennas (17 G) with active tip lengths of 3 or 5mm were applied for MWA. For MWA, the output power setting was 30 or 35 W, the output frequency was 2450 MHz, and an internally cooled microwave antenna with normal saline for cold fluid circulation was used. RFA: RF generators (RF150 and RF300, Apro-Korea, Gyeonggi, Korea) and straight-type modified internally cooled electrodes (18 G) with active tip lengths of 5 or 7mm (Well-Point RF Electrode, STARmed, Gyeonggi, Korea; CoATherm electrode, Apro-Korea, Gyeonggi, South Korea) were applied for RFA. The generator had an output of 30W or 35W.	Percutaneous MWA: Microwave system (MTI-5DT, Changcheng Medical Instruments Cooperation, Nanjing, China, YZB National 7534-2013) and MWA antenna (Z16.100)
Comparator	Conventional/open thyroidectomy: A 3-5cm transverse arc incision was made on the second transverse finger above the sternum; a high-frequency electric knife was used to incise the white line of the neck to expose the thyroid gland and remove the nodules and surrounding tissues. Endoscopic thyroidectomy: A 0.5-1cm incision was made in the left and right areolae; The troca was inserted, and the operation cavity was established after inflation. The white line of the neck was cut under endoscopy. The surgeon lifted the affected thyroid lobe and used an ultrasonic knife to remove the affected thyroid nodule and surrounding tissues carefully and completely.	Conventional thyroidectomy: The thyroid goiter was dissected with an US knife (Johnson&Johnson Inc., New Brunswick, NJ, USA).
Study design	Retrospective study, propensity score matching	Retrospective study, propensity score matching, double-blinded method
Number of pts	Before propensity matching: n=505 TA: 129; ConT: 320; ET: 56 After propensity matching: TA: 118 vs ConT: 118 TA: 43 vs ET: 43	Before propensity matching: n=280 I: 156; C: 124 After propensity matching: n=212 I: 106; C:106
Inclusion criteria	(1) patients with pressure symptom, cosmetic problem, or discomfort in the neck; (2) patients treated with TA (RFA or MWA), ConT, or ET; (3) the nodule was confirmed as benign via fine-needle aspiration or core-needle biopsy before treatment and in the final resected specimens in the ConT and ET groups; (4) the maximum diameter of the nodule was ≥1.5 cm; (5) more than 12-month follow-up duration.	(a) the thyroid nodule was over 2mm apart from the thyroid capsule; (b) the maximum diameter of the TN ≥2 cm; (c) existence of cosmetic problems or compressive symptoms; (d) cytological conformation of the benign nature of the nodule through US-guided fine needle aspiration cytology; and (e) serum levels of thyrotropine and thyroid hormone within normal levels. Patients who fully complied with all of the inclusion criteria were studied.

Author, year	Bo 2022 [37]	Jin 2018 [41]
Age of patients (yrs) mean±SD; I vs C	TA vs ConT Before propensity matching: 49.4±14.5 (Range: 21-74) vs 56.4±11.0 (Range: 22-79); p<0.001 After propensity matching: 50.9±14.0 (Range: 21-74) vs 52.5±12.7 (Range: 22-78); p=0.350 TA vs ET Before propensity matching: 49.4±14.5 (Range: 21-74) vs 32.9±8.8 (Range: 19-56); p<0.001 After propensity matching: 38.0±10.4 (Range: 21-66) vs 35.3±8.4 (Range: 19-56); p=0.197	Before propensity matching: 36.7±10.3 vs 45.4±11.2 After propensity matching: 39.6±9.3 vs 45.4±11.2
Sex n (m/f); I vs C	TA vs ConT Before propensity matching: 18/111 vs 77/243; p<0.05 After propensity matching: 18/100 vs 15/103; p=0.573 TA vs ET Before propensity matching: 18/111 vs 4/52; p=0.189 After propensity matching: 3/40 vs 4/39; p=0.693	Before propensity matching: 58/98 vs 40/84 After propensity matching: 31/75 vs 28/78
Follow-up (months)	TA: evaluation at 1, 3,or 6 and 12 months, and additional 6 months ConT and ET: 6 months intervals Median: 19 (Range: 12-36) months	MWA: 12.8 months ConT: 12.6 months
Loss to follow-up, n (%)	NA	NA
Outcomes		
Efficacy		
Nodule volume reduction ratio (VRR), I vs C	Volume (ml): Before propensity matching: Baseline: TA: 12.1±15.3 ml (Range: 0.6-118.7 ml) 19 months: TA: 2.6±6.1 ml (Range: 0.0-52.1 ml); p<0.001 VRR (%): 19 months: TA: 80.7±21.1% (Range: -0.0%-100%)	Volume (cm^3); median (IQR): Before ablation: I: 2.50 (0.30-5.00); C: NR 1 month: I: 2.12 (1.21-2.79); C: NR 3 months: I: 1.31 (0.89-1.91); C: NR 6 months: I: 0.82 (0.32-1.21); C: NR 12 months: I: 0.51 (0.00-1.00); C: NR VRR (%): 1 month: I: 15.2±2.3%; C: NR 3 months: I: 47.6±3.6%; C: NR 6 months: I: 67.2±6.8%; C: NR 12 months: I: 79.6±10.2%; C: NR
Symptom reduction, I vs C	Median (IQR) Symptom score: TA vs ConT: Baseline (after propensity matching): 5 (3-6) vs 5 (3-6); p=0.705 After Surgery: 2 (2-2) vs 2 (1.5-2); p=0.826 TA vs ET: Baseline (after propensity matching): 5 (3-6) vs 4 (3-5); p= 0.303 After Surgery: 1 (1-2) vs 1 (0-2); p=0.356 n (%) TA vs ConT Symptom relief: p=0.099 Fully 114 (96.6) vs 108 (91.5) Partially 2 (1.7) vs 5 (4.2) No 2 (1.7) vs 5 (4.2)	Mean±SD Symptom score (10cm VAS): Baseline: Before propensity matching: 4.1±1.4 vs 4.5±1.3, p=0.011 After propensity matching: 4.3±1.4 vs 4.5±1.3, p=0.389 Follow-up: NR

Author, year	Bo 2022 [37]	Jin 2018 [41]
Symptom reduction, I vs C *(continuation)*	Post-operative discomfort: **p<0.05** Yes 6 (5.1) vs 16 (13.6) No 112 (94.9) vs 102 (86.4) Post-operative levothyroxine use: **p<0.001** Yes 1 (0.8) vs 30 (25.4) No 117 (99.2) vs 88 (74.6) TA vs ET: Symptom relief: p=0.632 Fully 40 (93.0) vs 41 (95.3) Partially 2 (4.7) vs 2 (4.7) No 1 (2.3) vs 0 (0) Post-operative discomfort: p=1.000 Yes 2 (4.7) vs 1 (2.3) No 41 (95.3) vs 42 (97.7) Post-operative levothyroxine use: **p<0.01** Yes 0 (0) vs 8 (18.6) No 43 (100) vs 35 (81.4)	
Cosmetic appearance improvement, I vs C	Median (IQR) Cosmetic Score: TA vs ConT: Baseline (after propensity matching): 3 (2-3) vs 3 (2-3); p=0.758 After Surgery: 1 (1-1) vs 1 (1-1); p=0.946 TA vs ET: Baseline (after propensity matching): 3 (1-4) vs 2 (1-4); p=0.903 After Surgery: 1 (1-2) vs 1 (1-1); p=0.196 n (%) TA vs ConT: **p<0.01** Cosmetic relief: Fully 115 (97.5) vs 100 (84.7) Partially 2 (1.7) vs 8 (6.8) No 1 (0.8) vs 10 (8.5) TA vs ET: p=0.317 Fully 42 (97.7) vs 43 (100) Partially 1 (2.3) vs 0 (0) No 0 (0) vs 0 (0)	Mean±SD Cosmetic score: Baseline: Before propensity matching: 3.2±0.8 vs 2.9±0.8, p=0.002 After propensity matching: 3.2±0.8 vs 3.0±1.9, p=0.478 Follow-up: *"A better cosmetic effect in the US-guided MWA group compared to the conventional thyroidectomy group."*
Thyroid function, n (%) I vs C	Postoperative hypothyroidism: TA vs ConT: 1 (0.8) vs 30 (25.4); p<0.001 TA vs ET: 0 (0) vs 8 (18.6); p<0.01 Total = TA: 1; ConT/ET: 38	*"Radionuclide scan of the thyroid showed that the residual thyroid function of all of the subjects in this study was normal."* Total = I: 0 vs C: 0
Quality of life, Mean (SD), I vs C	NR	NR
Nodule recurrence rate n/N (%)	*"Only one nodule (0.8%, 1/129) with regrowth was identified at the final follow-up point. Additional ablation was performed in three nodules (2.3%, 3/129)."*	NR

Author, year	Bo 2022 [37]	Jin 2018 [41]
Safety		
SAEs, n (%), I vs C	NR	NR
AEs, n (%) **I vs C**	Treatment-related complication n (%) TA vs ConT: Any: 4/118 (3.4) vs 8/118 (6.8); p=0.236 Voice Change: 2 (1.7) vs 3 (2.5) Cough while drinking: 1 (0.8) vs 2 (1.7) Hand numbness: 0 (0) vs 2 (1.7) Hematoma: 1 (0.8) vs 1 (0.8) TA vs ET: Any: 1/43 (2.3) vs 0/43 (0); p=1.000 Voice Change: 1 (2.3) vs 0 (0) Total=TA: 5/161 vs ConT+ET: 8/161	Treatment-related complication n (%): 2/106 (1.9) vs 7/106 (6.6); p=0.389 Paralysis of vocal cords: 1 (0.94) vs 7 (6.6) Skin burn: 1 (0.94) vs 0 (0)

Abbreviations: AEs – adverse events, C – comparator, CI – confidence interval, ConT – conventional thyroidectomy, ET – endoscopic thyroidectomy, FT4 – free thyroxine, HIFU – high intensity focused ultrasound, I – intervention, IONM – intraoperative neurophysiological monitoring, IQR – interquartile range, MWA – microwave ablation, m/f – male/female, n – number, NA – not applicable, NR – not reported, OT – open thyroidectomy, pts – patients, RFA – radiofrequency ablation, SAEs – serious adverse events, SD – standard deviation, SF-36 – short-form 36, TA – thermoablation, Ns – thyroid nodules, US – ultrasound, USA – United States of America, VAS – visual analog scale, VRR – volume reduction rate, W – watts, yrs – years.

Note: Blue text represents data digitized via Webplot

Table A-2: Thermoablation: Results from NRSI with propensity score matching (part 2)

Author, year	Lang 2019 [54]	Yan 2023 [48]	Yue 2016 [88]
Country	China	China	China
Sponsor	Nil	Nil	the Shanghai Hospital Development Center (Grant SHDC 12014229), the Science and Technology Commission of Shanghai Municipality (Grants 14441900900 and 16411971100), the National Natural Scientific Foundation of China (Grant 81601502).
Intervention/Product	High-intensity focused ultrasound (HIFU): Commercially available US-guided HIFU device (EchoPulse; Theraclion, Paris, France). Once the treatment head was positioned correctly over the nodule, the device computer (Beamotion v TUS 3.2.2: Theraclion) automatically divided the nodule into multiple subunits for ablation. Each subunit measured approximately 7.3 mm in thickness and 5 mm in width. Each subunit received a continuous, 8-second pulse of HIFU energy followed by 30 seconds of cooling before the beam moved to another subunit. This cycle continued until all subunits received these pulses.	RFA: A bipolar RFA generator (CelonLabPOWER; Olympus Surgical Technologies Europe) and 18-ga bipolar readiofrequency electrodes with 0.9- or 1.5-cm active tips were used (CelonProSurge micro 100-T09; Olympus Surgical Technologies Europe). RFA was performed using recommended ablation techniques, including a hydrodissection technique, a transisthmic approach, and a moving shot technique. The ablation procedure was terminated when the entire nodule had become hyperechoic.	RFA: RFA instrument (Celon AG Medical Instruments, Teltow, Germany). Standard RFA techniques such as "hydrodissection technique" and "moving-shot technique" wre used. The ablation procedures were monitored by real-time US, and ablations were not terminated until the transient hyperechoic cloud caused by the gas covered all units of the nodule. For patients with multiple nodules, only the largest nodule was subject to treatment and those patients formed the RFA group.

Author, year	Lang 2019 [54]	Yan 2023 [48]	Yue 2016 [88]
Intervention/Product *(continuation)*		Contrast-enhanced sonography was performed immediately after RFA to evaluate the ablated area, which was performed after a bolus injection of SonoVue (2.4mL; Bracco), followed by 5mL of normal saline flush. Additional complementary ablation could be performed if any enhancement existed in the ablated area.	
Comparator	Open lobectomy: All patients underwent a standardized lobectomy via the cervical approach by one surgical team. The recurrent laryngeal nerve and external branch of the superior laryngeal nerve on the operated side were carefully sought and mapped out by the intraoperative nerve monitor ([IONM] Medtronic NIM-Response 3.0 system; Medtronic, Dublin, Ireland). An IONM was used to confirm the integrity of the nerves at the end of the lobectomy.	Thyroidectomy: Patients were treated with lobectomy, with or without isthmusectomy, under general anesthesia in the operating room.	Open thyroidectomy: All the operations were carried out by general surgeons with 6 years' clinical experience under general anesthesia according to the standard operation method of hemithyroidectomy.
Study design	Retrospective study, propensity score matching	Retrospective study, propensity score matching	Retrospective study, propensity score matching
Number of pts	Before propensity matching: n=185 I: 97; C: 88 After propensity matching: n=154 I: 77; C: 77	Before propensity matching: n=230 I: 49; C: 181 After propensity matching: n=98 I: 49; C: 49	Before propensity matching: n=404 I: 137; C: 267 After propensity matching: n=216 I: 108; C:108
Inclusion criteria	Only patients who were unwilling to undergo lobectomy were considered for HIFU ablation. To be eligible for ablation, patients had to meet the following criteria: (1) The nodule had to be benign (i.e. Bethesda class II on fine- needle aspiration cytology) and to have a low/very low suspicion pattern on ultrasonography; (2) The nodule (which may be a solitary nodule or a dominant nodule in a multinodular gland) had to be causing local pressure with or without cosmetic symptoms. Patients were asked to rate their pressure symptoms by using a visual analogue scale; (3) The index nodule had to have all three orthogonal dimensions ≥10mm but ≤50mm on US; (4) The index nodule had to be solid or predominantly solid (<30% cystic areas) on US; (5) The index nodule had to be within the treatable ablation depth (i.e. 5-30 mm between the skin and the nodule center); (6) Patients had to have normal serum free T4 and thyroid- stimulating hormone.	(1) 60 years of age or older; (2) nodules confirmed as benign on 2 separate fine-needle aspiration or core-needle biopsy procedures before treatment; (3) maximum diameter of >2.0 cm; (4) no suspicious malignant features on US, such as marked hypoechoic, irregular margins, taller-than-wide shape, or microcalcifications; (5) solid (≤10% of fluid component) or predominantly solid nodules (11%-50% of fluid component); (6) cosmetic and/or symptomatic problems reported; (7) serum thyroid hormone and thyrotropin levels within normal ranges; and (8) a follow-up period of >12 months.	RFA or OT was considered if a patient with TN(s) reported of compressive symptoms or cosmetic problems or anxiety about a malignancy. For RFA there was an additional requirement that cytologic confirmation of benign nature of the nodule with US-guided fine needle aspiration cytology examination according to the American Bethesda System for Reporting Thyroid Cytopathology and nodule without changes on US at least 12-month. Also, for the patient ineligibility to undergo surgery for high thyroid surgical risk (poor surgical candidates, falling general anaesthesia due to a medical condition, repeated neck dissection), RFA would be required. Further, for a patient that was suitable for both RFA and OT, the definitive treatment modality was "self-selecting" after a full explanation of the differences between two procedures. The RFA patients were diagnosed cytologically and the OT patients were diagnosed by surgical pathology.
Age of patients (yrs) mean±SD; I vs C	Before propensity matching: 48±12 vs 54±15.17, p=0.009 After propensity matching: 49±13 vs 51±14, p=0.191	Before propensity matching: 65.0 (5.5) vs 64.0 (6.0) After propensity matching: 65.0 (5.5) vs 64.0 (5.0)	Before propensity matching: 48.3±12.9 vs 52.4±12.7 After propensity matching: 50.8±11.9 vs 49.8±13.6
Sex n (m/f); I vs C	Before propensity matching: 12/85 vs 25/63, p=0.006 After propensity matching: 12/65 vs 17/60, p=0.303	Before propensity matching: 9/40 vs 59/122 After propensity matching: 9/40 vs 9/40	Before propensity matching: 38/99 vs 129/138 After propensity matching: 36/72 vs 39/69
Follow-up (months)	6 months	RFA: 27.30 (36.3) months ConT: 35.7 (25.9) months	6 months

Author, year	Lang 2019 [54]	Yan 2023 [48]	Yue 2016 [88]
Loss to follow-up, n (%)	NA	NA	NA
Outcomes			
Efficacy			
Nodule volume reduction ratio (VRR), I vs C	Nodule shrinkage (%): 3 months: I: 50±22%; C: NR 6 months: I: 64±26%; C: NR	Volume (ml); median (IQR): Before ablation: I: 7.4 (10.1); C: 18.6 (22.0) 1 month: I: 4.3 (4.0); C: 0 3 months: I: 2.5 (3.5); C: 0 6 months: I: 1.2 (2.2); C: 0 12 months: I: 0.7 (2.5); C: 0 24 months: I: 0.3 (1.4); C: 0 VRR (%): 1 month: I: 55.0% (35.9); C: 100% 3 months: I: 75.9% (18.8); C: 100% 6 months: I: 84.6% (26.2); C: 100% 12 months: I: 92.7% (27.5); C: 100% 24 months: I: 94.1% (15.0): C: 100%	Volume (ml); median (IQR): Baseline: Before propensity matching: I: 5.7 (3.9-9.1); C: 5.2 (1.4-11.2); P=0.026 After propensity matching: I: 5.6 (3.9-8.7); C: 5.3 (2.2-10.4); P=0.104 Follow-up: NR
Symptom reduction, I vs C	Symptom improvement score at 6 months (% of patients): 0 (no improvement): I: 4 (5); C: 10 (13) 1 (slight improvement): I: 20 (26); C: 15 (20) 2 (moderate improvement): I: 30 (39); C: 33 (43) 3 (significant improvement): I: 23 (30); C: 19 (25)	Median (IQR) Symptom score: Baseline: 3 (IQR 2)[39] vs 5 (IQR 4)[40] 12 months: 1 (IQR 1)[39] vs 2 (IQR 2)[40]	NR
Cosmetic appearance improvement, I vs C	NR	Median (IQR) Cosmetic score: Baseline: 3 (IQR 1.5)[39] vs 4 (IQR 2)[41] 12 months: 1 (IQR 1)[39] vs 0 (IQR 0)[41]	NR
Thyroid function, n (%) I vs C	Hypothyroidism: 0 (0.0) vs 4 (5.2)	Hypothyroidism: Before propensity matching: 0 (0.0) vs 50 (27.6), p<0.001 After propsensity matching: 0 (0.0) vs 10 (20.4), p=0.001	NR
Quality of life Mean (SD) I vs C	NR	NR	SF-36 dimension scores: After propensity matching: Baseline: Physical function: I: 87.5±10.8; C: 87.1±13.2 Role-physical: I: 91.7±12.8; C: 90.3±10.2 Bodily pain: I: 92.9±12.8; C: 94.1±11.1 General health: I: 65.3±15.6; C: 64.9±16.2 Vitality: I: 69.4±15.3; C: 69.1±17.4

[39] RFA change from baseline to 12 months (P=.001)

[40] ConT change from baseline to 12 months (P<.001)

[41] ConT change from baseline to 12 months (P=.001)

Author, year	Lang 2019 [54]	Yan 2023 [48]	Yue 2016 [88]
Quality of life **Mean (SD)** **I vs C** *(continuation)*			Social functioning: I: 92.5±17.8; C: 92.5±16.7 Role-emotional: I: 91.7±15.8; C: 91.0±15.5 Mental health: I: 75.3±16.3; C: 76.0±15.7 6 months: Physical function: I: 89.17; C: 87.92 Role-physical: I: 93.47; C: 93.06 Bodily pain: I: 94.44; C: 94.31 General health (p=0.029): I: 68.5[42]; C: 66.7 Vitality (p<0.001): I: 71.3; C: 67.5 Social functioning: I: 93.89; C: 93.33 Role-emotional: I: 96.6[43]; C: 94.4[44] Mental health (p=0.038): I: 80.9[45]; C: 79.3[46] EQ-5D-3L (n [%]): Baseline (n= I: 137, C: 229) Mobility (p=0.09) No problems (1): 108 (78.8) vs 229 (85.5) Some problems (2): 29 (21.2) vs 38 (14.2) Confined to bed (3): 0 (0) vs 0 (0) Self-care (p=0.095): No problems (1): 131(95.6) vs 263 (98.5) Some problems (2): 6 (4.4) vs 4 (1.5) Unable to (3): 0 (0) vs 0 (0) Usual activities (p=0.042) No problems (1): 110 (80.3) vs 188 (70.4) Some problems (2): 27 (19.7) vs 79 (29.6) Extreme (3): 0 (0) vs 0 (0) Pain discomfort (p=0.054): None (1): 86 (62.8) vs 193 (72.3) Moderate (2): 51 (37.2) vs 74 (27.7) Extreme (3): 0 (0) vs 0 (0) Anxiety/depression (p=0.004): None (1): 85 (62) vs 119 (44.6) Moderate (2): 50 (36.5) vs 144 (53.9) Extreme (3): 2 (1.5) vs 4 (1.5) Patients in perfect health state (all levels = 1): 40 (29.2) vs 61 (22.8)

[42] Significantly improved from baseline (p=0.012)

[43] Significantly improved from baseline (p=0.007)

[44] Significantly improved from baseline (p=0.049)

[45] Significantly improved from baseline (p=0.002)

[46] Significantly improved from baseline (p=0.011)

Author, year	Lang 2019 [54]	Yan 2023 [48]	Yue 2016 [88]
Nodule recurrence rate n/N (%)	NR	*"Nodule regrowth was not detected. Six ablated nodules (12.2%) disappeared during the follow-up."*	NR
Safety			
SAEs, n (%), I vs C	NR	NR	NR
AEs, n (%) I vs C	Treatment-related complication n (%): Any: 4/77 (5.2) vs 4/77 (5.2) Vocal cord palsy: 3 (3.9) vs 3 (3.9) Horner's syndrome: 1 (1.3) vs 0 (0) Bleeding: 0 (0) vs 1 (1.3) Infection: 0 (0) vs 0 (0)	Treatment-related complication n (%): Before propensity matching: Any: 0/49 (0) vs 16/181 (8.8), p<0.001 Transient recurrent laryngeal nerve palsy: 0 (0) vs 4 (2.2) Transient hypoparathyroidism: 0 (0) vs 3 (1.7) Fever: 0 (0) vs 3 (1.7) Wound infection: 0 (0) vs 4(2.2) Respiratory dysfunction: 0 (0) vs 1 (0.6) Loss of consciousness: 0 (0) vs 1 (0.6) After propensity matching: Any: 0/49 (0) vs 3/49 (6.1), p<0.001 Transient recurrent laryngeal nerve palsy: 0 (0) vs 1 (2) Transient hypoparathyroidism: 0 (0) vs 1 (2) Fever: 0 (0) vs 1 (2) Wound infection: 0 (0) vs 0 (0) Respiratory dysfunction: 0 (0) vs 0 (0) Loss of consciousness: 0 (0) vs 0 (0)	NR

Abbreviations: AEs – adverse events, C – comparator, CI – confidence interval, ConT – conventional thyroidectomy, ET – endoscopic thyroidectomy, FT4 – free thyroxine, HIFU – high intensity focused ultrasound, I – intervention, IONM – intraoperative neurophysiological monitoring, IQR – interquartile range, MWA – microwave ablation, m/f – male/female, n – number, NA – not applicable, NR – not reported, OT – open thyroidectomy, pts – patients, RFA – radiofrequency ablation, SAEs – serious adverse events, SD – standard deviation, SF-36 – short-form 36, TA – thermoablation, Ns – thyroid nodules, US – ultrasound, USA – United States of America, VAS – visual analog scale, VRR – volume reduction rate, W – watts, yrs – years.

Note: Blue text represents data digitized via Webplot

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [2] and in the Guidelines of EUnetHTA [3].

Table A-3: RoB2 of RCTs comparing thermoablation versus thyroidectomy or radioiodine

Trial	Endpoints	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Dossing 2007 [38]	Study-level	Low	Some concerns	Low	Low/High*	Some concerns/High§	High
Jin 2021 [42]	Study-level	Low	High	High	Some concerns/High†	High	High
Yan 2018 [47]	Study-level	Low	High	High	High	High	High
Zhi 2018 [44]	Study-level	Low	High	High	Low/High‡	High	High

Abbreviations: RCT – randomised controlled trial, RoB2 – Cochrane Risk Of Bias 2

Notes:

** AEs/SAEs assessed as having a high risk of bias; nodule/thyroid volume and thyroid function assessed as having a low risk of bias.*

† VRR assessed as having some concerns; symptom reduction, HRQoL, AEs/SAEs assessed as having a high risk of bias.

‡ Nodule volume, VRR and thyroid function assessed as having a low risk of bias; symptom reduction, cosmetic appearance improvement, HRQoL and AEs/SAEs assessed as having a high risk of bias;

§ nodule/thyroid volume and thyroid function assessed as having some concerns; AEs/SAEs assessed as having a high risk of bias.

Table A-4: ROBINS-I of NRSI comparing thermoablation versus thyroidectomy

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Bo 2022 [37]	Moderate	Low	Moderate	Low	Low	Serious	Moderate	Serious	Nil
Jin 2018 [41]	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Nil
Lang 2019 [54]	Moderate	Low	Low	Low	Serious	Serious	Moderate	Serious	Nil
Yan 2023 [48]	Moderate	Low	Moderate	Low	Serious	Serious	Moderate	Serious	Nil
Yue 2016 [88]	Moderate	Low	Moderate	Low	Serious	Serious	Moderate	Serious	Nil

Abbreviations: ID – identification, NRSI – non-randomised studies of interventions, ROBINS-I – Risk Of Bias In Non-randomised Studies of Interventions

Table A-5: Evidence profile: efficacy and safety of thermoablation compared to radioiodine for adults with benign thyroid nodules (RCT)

Quality assessment							Summary of findings				
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect		Certainty
							intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
Nodule volume reduction rate (%) (follow-up: 6 months)											
1 **[38]**	Randomised trial	Very serious[a]	Not serious	Not serious[b]	Very serious	None	**Dossing 2007 [38] – 6 months – VRR (%):** I: 44±5%, C: 47±8%, p=0.73				⨁◯◯◯ Very low[a,b]
Symptom reduction – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Cosmetic appearance improvement – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Thyroid function – serum TSH (mU/ml) (follow-up: 6 months)											
1 **[38]**	Randomised trial	Very serious[a]	Not serious	Not serious[b]	Very serious	None	**Dossing 2007 [38]** **Baseline:** I: 0.03 (<0.001–0.20), C: 0.02 (<0.001–0.27), p=0.91 **6 months:** I: 0.32 (<0.001–0.82), C: 1.21 (0.43–2.58), p=0.02				⨁◯◯◯ Very low[a,b]
Quality of life – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Nodule recurrence rate – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Adverse events (follow-up: 6 months)											
1 **[38]**	Randomised trial	Very serious[a]	Not serious	Not serious[b]	Very serious	None	6/14 (42.9%)	2/15 (13.3%)	RR 3.20 (0.77 to 13.36)	-	⨁◯◯◯ Very low[a,b]

Abbreviations: CI – confidence interval, C – comparator, I – intervention, TSH – thyroid stimulating hormone, VRR – volume rate reduction.

Explanations:

[a] *Dossing 2007 assessed as having a high risk of bias;*

[b] *Very small sample size (between 1-99 participants).*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Table A-6: Evidence profile: efficacy and safety of thermoablation compared to thyroidectomy for adults with benign thyroid nodules (RCT)

Quality assessment							Summary of findings				
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect		Certainty
							intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
Nodule volume reduction rate (%) (follow-up: 12 months)											
2 **[42, 44]**	Randomised trial	Very serious[a]	Not serious	Serious[b]	Not serious	None	**Jin 2021 [42] – 12 months – VRR (%):** I: RFA- 80.1±1.8%; MWA- 79.3±3.2%, C: NR **Zhi 2018 [44] – 12 months – VRR (%):** I: 95.2%±NR (p<0.01), C: NR				⨁◯◯◯ Very low[a,b]
Symptom reduction (follow-up: range 12 months to 15 months)											
2 **[42, 44]**	Randomised trial	Very serious[a]	Not serious	Serious[b]	Not serious	None	**Jin 2021 [42] – 15 months** Peculiar sense in throat: 35/175 (20%) vs 19/175 (11%); OR 0.31 (95% CI 0.20 to 0.49), p<0.0001 Dysphasia: 9/124 (7%) vs 4/142 (3%); OR 0.32 (95% CI 0.23 to 0.45), p<0.0001 Compression on trachea: 6/129 (5%) vs 1/135 (<1%); OR 0.14 (95% CI 0.07 to 0.21), p<0.0001 Hoarseness: 0 (0%) vs 1 (<1%); OR 0.81 (95% CI 0.32 to 1.59), p=0.87 **Zhi 2018 [44] – 12 months** Remission of nodule-related symptoms: 10/28 vs 11/24				⨁◯◯◯ Very low[a,b]
Cosmetic appearance improvement (follow-up: 12 months)											
1 **[44]**	Randomised trial	Very serious[a]	Not serious	Serious[b]	Very serious[c]	None	28/28 (100.0%)	20/24 (83.3%)	RR 1.10 (95% CI 0.73 to 1.67)	-	⨁◯◯◯ Very low[a,b,c]
Thyroid function – serum TSH (mIU/ml) (follow-up: 12 months)											
1 **[44]**	Randomised trial	Very serious[a]	Not serious	Serious[b]	Very serious[c]	None	**Zhi 2018 [44] – Thyrotropin (µIU/ml)** **Baseline:** I: 1.85±1.17, C: 1.76±0.83 **12 months:** I: 2.10 (NR), C: 2.81 (NR)				⨁◯◯◯ Very low[a,b,c]
Quality of life (Thyroid-specific QoL/SF-36) (follow-up: range 12 months to 15 months)											
2 **[42, 44]**	Randomised trial	Very serious[a]	Not serious	Serious[b]	Not serious	None	**Jin 2021 [42] – 15 months – Thyroid-specific QoL scale total score** **Baseline:** I: 118.9 (64.4 to 195.6), n=218; C: 117.3 (60.2 to 179.2), n=218 **15 months:** OR 0.34 (95% CI 0.21 to 0.45), p<0.0001. **Zhi 2018 [44] – 12 months – SF-36** *"Compared to patients who underwent surgery, those who underwent MWA had better general health and mental health scores"* (p<0.05)				⨁◯◯◯ Very low[a,b]
Nodule recurrence rate – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Adverse events (SAEs & AEs) (follow-up: range 2 days to 15 months)											
3 **[42, 44, 47]**	Randomised trial	Very serious[a]	Not serious	Very serious[d]	Not serious	None	18/293 (6.1%)	49/284 (17.3%)	RR 0.41 (0.25 to 0.69)	-	⨁◯◯◯ Very low[a,d]

Abbreviations: AEs – adverse events, CI – confidence interval, C – comparator, I – intervention, MWA – microwave ablation, NR – not reported, QoL – quality of life, RFA – radiofrequency ablation; SAEs – serious adverse events; SF-36 – short-form 36, TSH *– thyroid stimulating hormone, VRR – volume rate reduction.*

Explanations:

[a] *Jin 2021, Yan 2018 and Zhi 2018 assessed as having a high risk of bias;*

[b] *Imprecision downgraded due to study setting (China);*

[c] *sample size = 1-99;*

[d] *Imprecision downgraded due to Yan 2018 only investigating AEs to 48 hours and study setting (China)*

Nomenclature for GRADE table:
Limitations: 0: no limitations or no serious limitations; -1: serious limitations
Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency
Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty
Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Table A-7: Evidence profile: efficacy and safety of thermoablation compared to thyroidectomy/lobectomy for adults with benign thyroid nodules (NRSI)

Quality assessment							Summary of findings				
							Number of patients		Effect		
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	Certainty
Nodule volume reduction (follow-up: range 6 months to 24 months; assessed with: Longest follow-up)											
4 **[37, 41, 48, 54]**	Non-randomised studies	Very serious[a]	NA[b]	Serious[c]	Very serious[d]	None	**Lang 2019 [54] – 6 months – VRR (%):** I: 64±26% vs C: NR **Jin 2018 [41] – 12 months – VRR (%):** I: 79.6±10.2% vs C: NR **Bo 2022 [37] – 19 months – VRR (%):** TA: 80.7±21.1% vs ConT/ER: NR **Yan 2023 [48] – 24 months – VRR (%):** I: 94.1% (15.0) vs C: 100%				⨁◯◯◯ Very low[a,b,c,d]
Symptom reduction (follow-up: range 6 months to 36 months; assessed with: symptom score)											
3 **[37, 48, 54]**	Non-randomised studies	Very serious[e]	NA[b]	Serious[c]	Not serious	None	**Bo 2022 [37] – Median 19 (Range: 12-36) months** TA: Median: 2 (IQR 2-2); ConT: Median 2 (IQR 1.5-2), p=0.826 TA: Median: 1 (IQR 1-2); ET: Median: 1 (0-2), p=0.356 **Yan 2023 [48] – 12 months** I: Median: 1 (IQR 1)[47], C: Median: 2 (IQR 2)[48] **Lang 2019 [54] – 6 months (% of patients)** *0 (no improvement):* I: 4 (5), C: 10 (13) *1 (slight improvement):* I: 20 (26), C: 15 (20) *2 (moderate improvement):* I: 30 (39), C: 33 (43) *3 (significant improvement):* I: 23 (30), C: 19 (25)				⨁◯◯◯ Very low[b,c,e]
Cosmetic appearance improvement (follow-up: range 12 months to 36 months; assessed with: cosmetic score)											
3 **[37, 41, 48]**	Non-randomised studies	Very serious[e]	NA[b]	Serious[c]	Not serious	None	**Bo 2022 [37] – Median 19 (Range: 12-36) months** I: Median: 1 (Range: 1-2), C: Median: 1 (Range: 1-1), p=0.196 **Yan 2023 [48] – 12 months** I: Median: 1 (IQR: 1)[47], C: Median: 0 (IQR: 0)[49] **Jin 2018 [41] – 12.8 months** "A better cosmetic effect in the US-guided MWA group compared to the conventional thyroidectomy group."				⨁◯◯◯ Very low[b,c,f]
Thyroid function (assessed via hypothyroidism) (follow-up: range 6 months to 36 months)											
4 **[37, 41, 48, 54]**	Non-randomised studies	Very serious[a]	Not serious	Serious[c]	Not serious	None	1/393 (0.3%)	52/393 (13.2%)	RR 0.0192 (0.0026 to 0.1383)	-	⨁◯◯◯ Very low[a,c]

[47] RFA change from baseline to 12 months (P=.001)

[48] ConT change from baseline to 12 months (P<.001)

[49] ConT change from baseline to 12 months (P=.001)

Quality assessment							Summary of findings				
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect		Certainty
							intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
Quality of life (SF-36) (follow-up: 6 months)											
1 **[88]**	Non-randomised studies	Very serious[g]	Not serious	Serious[c]	Not serious	None	**Yue 2016 [88] – 6 months – SF-36:** *General health (p=0.029):* I: 68.5[50], C: 66.7 *Vitality (p<0.001):* I: 71.3, C: 67.5 *Role-emotional:* I: 96.6[51], C: 94.4[52] *Mental health (p=0.038):* I: 80.9[53], C: 79.3[54]				⨁◯◯◯ Very low[c,g]
Nodule recurrence rate (follow-up: range 12 months to 36 months)											
2 **[37, 48]**	Non-randomised studies	Very serious[h]	Not serious	Serious[c]	Not serious	None	**Bo 2022 [37]** – *"Only one nodule (0.8%, 1/129) with regrowth was identified at the final follow-up point. Additional ablation was performed in three nodules (2.3%, 3/129)."* **Yan 2023 [48]** – *"Nodule regrowth was not detected. Six ablated nodules (12.2%) disappeared during the follow-up."*				⨁◯◯◯ Very low[c,h]
Adverse events (any) (follow-up: range 6 months to 36 months)											
4 **[37, 41, 48, 54]**	Non-randomised studies	Very serious[a]	Not serious	Serious[c]	Not serious	None	11/393 (2.8%)	22/393 (5.6%)	RR 0.33 (0.16 to 0.67)	-	⨁◯◯◯ Very low[a,c]

Abbreviations: CI – confidence interval, C – comparator, ConT – conventional thyroidectomy, ET – endoscopic thyroidectomy, I – intervention, IQR – interquartile range, NA – not applicable, NR – not reported, QoL – quality of life, RFA – radiofrequency ablation, SF-36 – short-form 36, TA – thermoablation, VRR – volume rate reduction.

Explanations:

[a] *Overall risk of bias is high (Bo 2022, Lang 2019, Yan 2023) and moderate (Jin 2018);*

[b] *Due to the time-varied nature of the outcome, it is not appropriate to evaluate inconsistency because studies reported outcomes at different time points.;*

[c] *Imprecision downgraded due to study setting (China);*

[d] *Large margins (±);*

[e] *Overall risk of bias is high (Bo 2022, Lang 2019, Yan 2023);*

[f] *Overall risk of bias is high (Bo 2022, Yan 2023), and moderate (Jin 2018);*

[g] *Overall risk of bias is high (Yu 2016);*

[h] *Overall risk of bias is high (Bo 2022, Yan 2023).*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

[50] Significantly improved from baseline (p=0.012)

[51] Significantly improved from baseline (p=0.007)

[52] Significantly improved from baseline (p=0.049)

[53] Significantly improved from baseline (p=0.002)

[54] Significantly improved from baseline (p=0.011)

Applicability table

Table A-8: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	**General population (global)** *Gender:* females: 36.5%, male: 23.5% [7] *Age:* <30 years: 10.59%, 30-39: 17.28%, 40-49: 24.89%, 50-59: 33.37%, 60-69: 41.97%, >70 years: 44.66%) [7] *Body weight:* overweight: 36.96%, obese: 40.96%, normal weight: 30.38% [7] *Nodule type:* solid thyroid nodules: 68.39%, mixed: 42.76%, cystic nodules: 6.27% [7] **Study population** *Gender:* ***RCTs:*** Predominately female (approximately n=131 females and n=58 males, one study of 450 participants did not report sex). ***NRSI:*** Predominantly female (approximately n=826 females and n=232 males). *Age:* ***RCTs:*** Average age of participants ranging from 43 and 58 years. ***NRSI:*** Age ranged between 19 and 79 years after propensity score matching. One NRSI only included participants 60 years of age or older. *Nodule type:* ***RCTs:*** No restriction on nodule type. ***NRSI:*** 2 NRSI restricted to only solid or predominately solid thyroid nodules [41, 48] This may be an applicability concern. *Inclusion criteria:* ***RCTs:*** (1) The benign nature of the nodule was required to be confirmed via fine-needle aspiration according to the American Bethesda System for Reporting Thyroid Cytopathology (Bethesda Class II) before treatment. (2) Restrictions on maximum size/diameter of the thyroid nodule and additional feature requirements (e.g. increasing rapidly in volume). (3) Other study-specific clinical features: e.g. hyperthyroidism, thyroid nodule-related symptoms such as compressive symptoms or cosmetic concerns, or anxiety about malignant transformation. ***NRSI:*** (1) Patients were required to have compressive symptoms, cosmetic problems or discomfort in the neck. (2) The benign nature of the nodule was required to be confirmed via fine-needle aspiration or core-needle biopsy examined according to the American Bethesda System for Reporting Thyroid Cytopathology (Bethesda Class II) before treatment. (3) Restrictions on maximum size/diameter of the thyroid nodule and additional feature requirements (e.g. solid or predominately solid nodule, treatable ablation depth between the skin and nodule centre). (4) Participants were required to have serum levels of thyrotropin and thyroid hormone within normal levels.
Intervention	**Thermoablation** Radiofrequency ablation (RFA) Microwave ablation (MWA) High-intensity focused ultrasound (HIFU) Interstitial laser photocoagulation (ILP) Utilisation, techniques, prerequisities and features of the technology are comparable between the intervention employed in the included studies and that used within the clinical setting in Austria and Europe [2, 89].
Comparators	**Surgical thyroidectomy** Conventional thyroidectomy Hemithyroidectomy Lobectomy **Radiotherapy** Radioiodine (RAI) Utilisation, techniques, prerequisities and features of the technology are comparable between the comparators employed in the included studies and that used within the clinical setting in Europe [2].
Outcomes	**Outcomes reported** ***RCTs:*** Thermoablation vs RAI: VRR, thyroid function, AEs Thermoablation vs thyroidectomy: VRR, symptom reduction, cosmetic apearance improvement, thyroid function, QoL, SAEs, AEs ***NRSI:*** Thermoablation vs thyroidectomy: Thermoablation ves thyroidectomy: VRR, symptom reduction, cosmetic apearance improvement, thyroid function, QoL, AEs

Outcomes *(continuation)*	**Outcomes not reported** ***RCTs:*** Thermoablation vs RAI: Symptom reduction, cosmetic appearance improvement, QoL, nodule recurrence rate, SAEs Thermoablation vs thyroidectomy: Nodule recurrence rate ***NRSI:*** Thermoablation vs thyroidectomy: SAEs **Follow-up/timepoints** ***RCTs:*** Follow-up durations of the RCTs ranged from 48 hours to 15 months. Most commonly reported timepoints of assessment include 1,3,6,12 months ***NRSI:*** Follow-up durations of the NRSI ranged from 6 months to 36 months. Most commonly reported timepoints of assessment include 1,3,6,12 months Applicability concern: One RCT only reported early onset AEs at 48 hours [47]. This may not be a suffient amount of time to capture all relevant events.
Setting	**General population (Austria)** *Clinical setting:* Hospital-based setting, both inpatient (thyroidectomy) and outpatient (thermoablation); performed by a skilled surgeon trained in thermoablation techniques. **Study population** *Clinical setting:* Hospital-based setting, both inpatient (thyroidectomy) and outpatient (thermoablation); performed by a skilled surgeon trained in thermoablation techniques. *Countries:* China (k=3 RCTs, k=5 NRSI), Denmark (k=1 RCT) Applicability concern: Of the included studies, 9 of 10 have been conducted in China, which is a developing upper middle class country, whereas Austria is a developed high class country.

Abbreviations: AEs – adverse events, NRSI – nonrandomised studies of interventions, QoL – quality of life, RAI – radioiodine, RCTs – randomised controlled trials, SAEs – serious adverse events, VRR – volume rate reduction.

List of ongoing randomised controlled trials

Table A-9: List of ongoing randomised controlled trials of thermoablation

Identifier/ Trial name	Patient population (estimated enrolment)	Intervention	Comparison	Primary Outcome	Estimated completion date	Sponsor
NCT04233398	Benign Thyroid Nodules (n=240)	HIFU ablation	No treatment	Effectiveness evaluation using treatment effective rate, symptoms score improvement, incidence of treatment-emergent adverse events	November 2024	Theraclion
NCT05142904	Solitary autonomous thyroid nodules (n=232)	RFA	RAI	Hypothyroidism	December 2028	Rijnstate Hospital
ChiCTR2100045585	Benign thyroid nodule (n=60)	Microwave ablation	Open surgery	Nodular volume reduction rate, effective rate of treatment	NR	Beijing Friendship Hospital, Capital Medical University

Abbreviations: HIFU – high-intensity focused ultrasound, ILP – interstitial laser photocoagulation, NR – not reported, RAI – radioiodine, RFA – radiofrequency ablation.

Research questions

Table A-10: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-11: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-12: Clinical Effectiveness

Element ID	Research question
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?

Table A-13: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?

Literature search strategies

Search strategy for Cochrane Library

Search Name: Thermoablation of benign thyroid nodules	
Search date: 14.12.2023	
ID	Search
#1	MeSH descriptor: [Thyroid Nodule] explode all trees
#2	(thyroid NEXT nodul*) (Word variations have been searched)
#3	#1 OR #2
#4	(thermo*ablat*) (Word variations have been searched)
#5	(thermo-ablat*) (Word variations have been searched)
#6	MeSH descriptor: [Radiofrequency Ablation] explode all trees
#7	(RFA*):ti,ab,kw
#8	MeSH descriptor: [Laser Therapy] explode all trees
#9	(laser*) (Word variations have been searched)
#10	(PLA):ti,ab,kw
#11	MeSH descriptor: [Microwaves] explode all trees
#12	MeSH descriptor: [Ablation Techniques] explode all trees
#13	#11 AND #12
#14	(micro*wave*) (Word variations have been searched)
#15	(micro-wave*) (Word variations have been searched)
#16	(MWA*):ti,ab,kw
#17	MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] explode all trees
#18	(high-intensity NEXT focus*ed NEXT ultra*sound*) (Word variations have been searched)
#19	(HIFU*):ti,ab,kw
#20	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	((radio*frequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR micro*wave* OR micro-wave* OR ultra*sound*) NEAR ablat*) (Word variations have been searched)
#22	#20 OR #21
#23	#3 AND #22
#24	(conference proceeding):pt
#25	(abstract):so
#26	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#27	#24 OR #25 OR #26
#28	#23 NOT #27
#29	English:la
#30	German:la
#31	#29 OR #30
#32	#28 AND #31
Total hits: 41	

Search strategy for Embase

Search Name: Thermoablation of benign thyroid nodules		
Search date: 14.12.2023		
No.	Query Results	Results
#1	'benign thyroid nodule'/exp	73
#2	'thyroid nodul*'	23,508
#3	#1 OR #2	23,508
#4	'thermal ablation'/exp	747
#5	thermo*ablat*	1,081
#6	'thermo-ablat*'	150
#7	‘radiofrequency ablation'/exp	46,597
#8	rfa*:ti,ab,kw	20,640
#9	'laser therapy'/exp	31,776
#10	laser*	492,464
#11	pla:ti,ab,kw	27,386
#12	'microwave thermotherapy'/exp	6,875
#13	'microwave ablation device'/exp	545
#14	'ultrasound guided percutaneous microwave ablation'/exp	40
#15	micro*wave*	63,802
#16	'micro-wave*'	194
#17	mwa*:ti,ab,kw	5,777
#18	'high intensity focused ultrasound'/exp	6,944
#19	'high-intensity focus*ed ultra*sound*'	8,116
#20	hifu*:ti,ab,kw	5,051
#21	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	640,233
#22	(radio*frequenc* OR 'radio frequenc*' OR thermal OR thermic OR laser* OR micro*wave* OR 'micro wave*' OR ultra*sound*) NEAR/3 ablat*	86,005
#23	#21 OR #22	655,965
#24	#3 AND #23	1,135
#25	#3 AND #23 AND [randomized controlled trial]/lim	34
#26	random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)	2,293,827
#27	#24 AND #26	94
#28	#24 AND ('case control study'/de OR 'case report'/de OR 'case study'/de OR 'clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'control group'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'feasibility study'/de OR 'intention to treat analysis'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'non inferiority trial'/de OR 'observational study'/de OR 'open study'/de OR 'phase 1 clinical trial'/de OR 'pilot study'/de OR 'prospective study'/de OR 'quasi experimental study'/de OR 'retrospective study'/de OR 'single blind procedure'/de)	779
#29	#25 OR #27 OR #28	806
#30	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de	1,237,134
#31	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,598,455
#32	#30 OR #31	2,668,829
#33	#29 NOT #32	796
#34	#33 AND 'conference abstract'/it	158
#35	#33 NOT #34	638
#36	#33 NOT #34 AND ([english]/lim OR [german]/lim)	587
Total hits: 587		

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) ALL <1946 to December 07, 2023>	
Search date: 14.12.2023	
ID	Search
#1	exp Thyroid Nodule/
#2	thyroid nodul*.mp.
#3	1 or 2
#4	thermo?ablat*.mp.
#5	thermo-ablat*.mp.
#6	exp Radiofrequency Ablation/
#7	RFA*.mp.
#8	exp Laser Therapy/
#9	laser*.mp.
#10	PLA.mp.
#11	exp Microwaves/
#12	exp Ablation Techniques/
#13	11 and 12
#14	micro?wave*.mp.
#15	micro-wave*.mp.
#16	MWA*.mp.
#17	exp High-Intensity Focused Ultrasound Ablation/
#18	high-intensity focus?ed ultrasound*.mp.
#19	HIFU*.mp.
#20	4 or 5 or 6 or 7 or 8 or 9 or 10 or 13 or 14 or 15 or 16 or 17 or 18 or 19
#21	((radio?frequenc* or radio-frequenc* or thermal or thermic or laser* or micro?wave* or micro-wave* or ultra?sound*) adj3 ablat*).mp.
#22	20 or 21
#23	3 and 22
#24	23
#25	limit 24 to randomized controlled trial
#26	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
#27	24 and 26
#28	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
#29	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
#30	28 or 29
#31	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
#32	hi.fs. or case report.mp.
#33	31 or 32
#34	30 not 33
#35	23 and 34
#36	25 or 27 or 35
#37	limit 36 to (english or german)
#38	remove duplicates from 37
Total hits: 392	

Search strategy for HTA-INAHTA

Search Name: Thermoablation of benign thyroid nodules	
Search date: 14.12.2023	
ID	Search
1	"Thyroid Nodule"[mhe]
2	(thyroid) AND (nodul*)
3	((thyroid) AND (nodul*)) OR ("Thyroid Nodule"[mhe])
4	thermo*ablat*
5	"Radiofrequency Ablation"[mhe]
6	RFA*
7	"Laser Therapy"[mhe]
8	laser*
9	PLA
10	"Microwaves"[mhe]
11	"Ablation Techniques"[mhe]
12	("Ablation Techniques"[mhe]) AND ("Microwaves"[mhe])
13	micro*wave*
14	MWA*
15	"High-Intensity Focused Ultrasound Ablation"[mhe]
16	high-intensity focus*ed ultra*sound*
17	HIFU*
18	(HIFU*) OR (high-intensity focus*ed ultra*sound*) OR ("High-Intensity Focused Ultrasound Ablation"[mhe]) OR (MWA*) OR (micro*wave*) OR (("Ablation Techniques"[mhe]) AND ("Microwaves"[mhe])) OR (PLA) OR (laser*) OR ("Laser Therapy"[mhe]) OR (RFA*) OR ("Radiofrequency Ablation"[mhe]) OR (thermo*ablat*)
19	(radio*frequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR micro*wave* OR micro-wave* OR ultra*sound*) AND (ablat*)
20	((radio*frequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR micro*wave* OR micro-wave* OR ultra*sound*) AND (ablat*)) OR ((HIFU*) OR (high-intensity focus*ed ultra*sound*) OR ("High-Intensity Focused Ultrasound Ablation"[mhe]) OR (MWA*) OR (micro*wave*) OR (("Ablation Techniques"[mhe]) AND ("Microwaves"[mhe])) OR (PLA) OR (laser*) OR ("Laser Therapy"[mhe]) OR (RFA*) OR ("Radiofrequency Ablation"[mhe]) OR (thermo*ablat*))
21	(((radio*frequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR micro*wave* OR micro-wave* OR ultra*sound*) AND (ablat*)) OR ((HIFU*) OR (high-intensity focus*ed ultra*sound*) OR ("High-Intensity Focused Ultrasound Ablation"[mhe]) OR (MWA*) OR (micro*wave*) OR (("Ablation Techniques"[mhe]) AND ("Microwaves"[mhe])) OR (PLA) OR (laser*) OR ("Laser Therapy"[mhe]) OR (RFA*) OR ("Radiofrequency Ablation"[mhe]) OR (thermo*ablat*))) AND (((thyroid) AND (nodul*)) OR ("Thyroid Nodule"[mhe]))
22	((((radio*frequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR micro*wave* OR micro-wave* OR ultra*sound*) AND (ablat*)) OR ((HIFU*) OR (high-intensity focus*ed ultra*sound*) OR ("High-Intensity Focused Ultrasound Ablation"[mhe]) OR (MWA*) OR (micro*wave*) OR (("Ablation Techniques"[mhe]) AND ("Microwaves"[mhe])) OR (PLA) OR (laser*) OR ("Laser Therapy"[mhe]) OR (RFA*) OR ("Radiofrequency Ablation"[mhe]) OR (thermo*ablat*))) AND (((thyroid) AND (nodul*)) OR ("Thyroid Nodule"[mhe]))) AND (English OR German)[Language]
Total hits: 3	

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