

2020 European Thyroid Association Clinical Practice Guideline for the Use of Image-Guided Ablation in Benign Thyroid Nodules

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Keywords

Thyroid nodule · Thermoablation · Laser ablation · Radiofrequency · High-intensity focused ultrasound · Microwaves · European Thyroid Association

Abstract

Standard therapeutic approaches for benign thyroid lesions that warrant intervention are surgery for cold and either surgery or radioiodine for autonomously functioning thyroid nodules (AFTN). Image-guided thermal ablation (TA) procedures are increasingly proposed as therapy options for selected clinical conditions. Due to mounting scientific evidence and widening availability, ETA considered it appropriate to develop guidelines for the use of TA in adult patients. TA procedures are well tolerated, but a dedicated training of the operators is required and information on possible complications needs to be shared with the patients. The following factors should be considered when weighing between observation, surgery, and TA for benign thyroid nodules. In solid non-hyperfunctioning nodules, TA induces a decrease in thyroid nodule volume, paralleled by improvement in symptoms. Nodule re-growth is possible over time and may necessitate repeat treatment, or surgery, in a dialogue with the patient. In AFTN, radioactive iodine is the first-line treatment, but TA may be considered in young patients with small AFTN due to higher probability of restoring normal thyroid function and avoidance of irradiation. In

cystic nodules, ethanol ablation (EA) is the most effective and least expensive treatment. TA may be considered for cystic lesions that relapse after EA or have a significant residual solid component following drainage and EA. TA should be restricted to benign lesions that cause symptoms or cosmetic concern. Presently, laser and radiofrequency ablation are the most thoroughly assessed techniques, with similar satisfactory clinical results. Microwaves and high-intensity focused ultrasound therapy options remain to be fully evaluated.

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Scope of the Document

Thyroid nodules are common in the adult population with a prevalence at ultrasound (US) examination of up to 50% in adult females and 30% in males [1–3]. Most lesions are cytologically benign and neither cause local symptoms nor warrant treatment. However, a non-negligible number of patients experience pressure symptoms, complain of cosmetic concerns, or develop subclinical or overt hyperthyroidism due to an autonomously functioning thyroid nodule (AFTN) [1–3]. The above leads, in European countries, to thousands of patients undergoing surgical treatment despite evidence of a benign nodule, most of whom have not been offered any non-surgical therapy options [4, 5].

In such cases, initially, ethanol ablation (EA) and, then, image-guided thermal ablation (TA) procedures, usually performed under US guidance, have been proposed as non-surgical treatment options for around 3 decades. Currently, due to their predictable tissue destruction, TA procedures have superseded, with the exception of pure cysts, the use of EA for thyroid lesions [6–8]. TA, based on the irreversible nodule damage induced by increase in tissue temperature [6–8], selectively destroys a predictable area of the nodule, while sparing the surrounding normal tissue. TA techniques are considered cost- and risk-effective in accomplishing the patients' demand for shrinking benign nodules and improving local symptoms less invasively than with surgery and, most importantly, generally without causing hypothyroidism. These non-surgical techniques are implemented over large parts of Europe and the Far East and are used in several thyroid centers. Despite this, there is little guidance, besides a few national consensus papers [9–12], on the appropriate use of TA in clinical practice. While US-guided diagnostic procedures are widely employed by European endocrinologists, routine use of US-guided therapeutic procedures is still limited to specialized thyroid centers [13]. The ETA survey on minimally invasive treatments demonstrated that, besides the limited access to dedicated training opportunities, the major cause of this only partial implementation was the absence of official statements about their use and indications from the Scientific Societies [13]. For these reasons, the present document offers a list of recommendations for a state-of-the-art use of TA in the management of benign thyroid lesions.

In order to compensate for current non-homogeneous data reporting and trial terminology, the text has been standardized according to the “Image-Guided Thyroid Ablation Procedures: Proposal for Standardization of Terminology and Reporting Criteria” recommendations [14]. In view of this being an ETA guideline, the focus has been on the highest possible level of evidence derived from studies carried out in a European setting.

These guidelines address the optimization of the use of innovative therapeutic tools in clinical management of benign thyroid nodules. They address the vast majority of the thyroid nodule population but are not intended for pediatric cases. While TA is covered, in extenso, EA and radioactive iodine ablation procedures for thyroid nodules are only mentioned in passing. How the diagnosis of a benign nodule is reached is not described in detail; for this, we refer to the pertinent thyroid nodule guidelines [15, 16]. The use of TA in malignant nod-

ules, whether primary or metastatic, is not part of this document.

Importantly, the recommendations always need to take local legislation, clinical setting, medical expertise, available technical resources, and patient preference into consideration.

The ETA GL recommendations for image-guided thyroid ablation are summarized in Table 1.

Methodology for Grading of Evidence and Strength of Recommendations

The Executive Committee of the European Thyroid Association (ETA) commissioned development of this guideline. In consultation with the Guideline Board of the ETA, a task force led by a chairperson (L.H.) was assembled. This team of European clinicians authored the present article. Selection to the panel was based on clinical experience, scholarly approach, being an ETA member, and willingness to participate. The relevant literature was taken into consideration using a systematic PubMed search. We employed an evidence-based approach and incorporated both the knowledge and the practical experience of the panelists to develop the manuscript and the specific recommendations. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [17], was used when rating the strength of the recommendations and the quality of evidence behind each of these.

In accordance with previous guidelines, we used the following coding system: (a) strong recommendation indicated by 1, and (b) weak recommendation, or suggestion, indicated by 2. The evidence grading is given as follows: very-low-quality (∅∅∅∅), low-quality (∅∅∅∅), moderate-quality (∅∅∅∅), and high-quality evidence (∅∅∅∅).

Following discussions and after the task force had reached consensus, the draft was sent to the Guideline Board for comments and thereafter posted on the ETA website for 4 weeks for critical evaluation by the ETA members. All received comments were evaluated by the guideline team, and the resulting changes were incorporated into the final document.

Recommendation 1. In adult patients with benign thyroid nodules that cause pressure symptoms and/or cosmetic concerns and decline surgery, image-guided TA should be considered as a cost- and risk-effective alternative option to surgical treatment or observation alone (1, ∅∅∅∅).

Recommendation 2. We recommend against the use of TA for asymptomatic lesions (1, ∅∅∅∅).

Table 1. Summary of recommendations

Recommendation 1	In adult patients with benign thyroid nodules that cause pressure symptoms and/or cosmetic concerns and decline surgery, image-guided thermal ablation (TA) should be considered as a cost- and risk-effective alternative option to surgical treatment or observation alone (1, ØØØØ)
Recommendation 2	We recommend against the use of TA for asymptomatic lesions (1, ØØØØ)
Recommendation 3	Before TA of thyroid lesions, a benign cytological diagnosis is needed; a repeat FNA is suggested for cytologically benign nodules with the exception of spongiform nodules and pure cystic lesions (EU-TIRADS Class 2); we recommend against TA for nodules with high-risk US features (EU-TIRADS Class 5; 1, ØØØØ)
Recommendation 4	Patients should be carefully informed before the procedure, orally and in writing, about the TA treatment options, their potential efficacy and side effects, the therapeutic alternatives, and the necessity of being compliant (1, ØØØØ)
Recommendation 5	Before the TA procedure, thyroid and vocal cord function, comorbidities, and contraindications to TA treatment should be evaluated; laryngoscopy is recommended in patients with hoarseness, previous neck surgery, or with nodules close to critical structures (“danger areas”; 1, ØØØØ)
Recommendation 6	Local subcutaneous and pericapsular anesthesia is recommended before TA procedures; Mild conscious sedation may be considered, especially in case of HIFU treatment (1, ØØØØ)
Recommendation 7	At the end of the procedure, clinical and US evaluation is recommended in order to rule out potential early adverse effects and define the extent of the ablated area; patients should be instructed to present for clinical and US assessment if severe pain, local swelling, or fever occur within the first week after TA (1, ØØØØ)
Recommendation 8	Early-term (e.g., 3 months) and intermediate-term (e.g., 6 and 12 months) clinical, biochemical, and US evaluations are recommended; long-term follow-up monitoring is suggested, in the absence of symptoms every 1–2 years, in order to reveal regrowth (1, ØØØØ)
Recommendation 9	Based on direct comparison studies, and balance between efficacy and side effects, LTA and RFA are recommended as the first-line TA treatment modalities (1, ØØØØ)
Recommendation 10	Based on studies to date, MWA should at present be considered a second-line TA procedure in patients who are not suitable for or decline other TA procedures, or for participants in protocolled clinical studies (1, ØØØØ)
Recommendation 11	Based on its lower efficacy, higher cost, and limited reported trial evidence, as compared to RFA and LTA, HIFU should be considered only for selected nodules in patients who are not suitable for or decline other TA procedures, and for participants in protocolled studies (1, ØØØØ)
Recommendation 12	In multinodular goiters, due to lack of evidence of efficacy and the expected need of repeat treatment, TA should be restricted to patients with a well-defined dominant nodule or those who are not candidates for thyroid surgery or radioactive iodine treatment, as a palliative therapy option (1, ØØØØ)
Recommendation 13	Because of higher cost and complexity, as compared to aspiration and EA, TA procedures are not recommended as a first line treatment for pure or dominantly cystic thyroid lesions (1, ØØØØ)
Recommendation 14	LTA and RFA should be considered therapeutic options for cystic lesions that relapse after EA and for those that would remain symptomatic due to a large residual solid component (1, ØØØØ)
Recommendation 15	We recommend against TA as first-line treatment for large AFTN; due to the low rate of restoration of normal thyroid function, TA should be considered only for patients who decline or are not candidates for RAI therapy or surgery (1, ØØØØ)
Recommendation 16	TA should be considered in young patients with small AFTN and incomplete suppression of perinodular thyroid tissue due to the higher probability of normalization of thyroid function and the advantage of avoiding irradiation and restricting risk of late hypothyroidism (1, ØØØØ)
Recommendation 17	Treatment with a combination of LTA or RFA and RAI may be considered in selected patients with large AFTN that cause local pressure symptoms in order to achieve a more rapid volume reduction and use of a lower RAI activity (2, ØØØØ)

ØØØØ, very-low-quality evidence; ØØØØ, low-quality evidence; ØØØØ, moderate-quality evidence; ØØØØ, high-quality evidence.

Table 2. Modalities, technical characteristics, and estimated costs of thermoablation treatment

	Laser	RFA	HIFU	MWA
Disposables, G	21	15–18		14–16
Active tip, mm	5	5–20		20–40
Mean power, W	3–7 per fiber	35–60	30–40	30–50
Duration, min	15–30	15–40	45–60	10–20
Average price in EUR (excl. tax)				
Device	30,000	17,000–25,000	>250,000	20,000–25,000
Disposables	1 fiber ~300–500	Electrode 700–900	Kit ~500	Antenna 1,000–1,250
Contraindications, besides clotting disorders		Pacemaker Pregnancy	Cystic component	
Comments	Two operators No need for moving-shot	Experience in moving-shot or multiple overlapping technique	Management of movements and pain Long duration	Limited experience in Europe

G, gauge; RFA, radiofrequency; HIFU, high-intensity focused ultrasound, MWA, microwaves.

Thermal Treatment: Currently Available Techniques

Among the currently available TA techniques for benign thyroid nodules, laser thermal ablation (LTA), radiofrequency ablation (RFA), microwave ablation (MWA), and high-intensity focused ultrasound (HIFU) have been tested in clinical practice and will be addressed in the present document. The devices employed by the different technologies are also defined as applicators [14].

Laser

Laser is a focused beam of light energy, usually generated by a diode or a Nd:YAG source, delivered through an optical fiber into the target tissue [6–8]. In LTA of thyroid nodules, 1–4 optical fibers are inserted at a 10-mm distance from each other, along the longitudinal axis or with a trans-isthmus approach, into the target nodule through thin and flexible 21-gauge (G) needles. The heat-induced changes of the tissue are visible through the appearance of hyperechoic signals due to the formation of gas microbubbles. The backward re-positioning (“pull back”) of the fiberoptics during the procedure allows the destruction of large portions of the thyroid nodule. The mean applied power of LTA is the lowest between the various TA techniques. The procedure is performed in an outpatient setting and requires 15–30 min [6–8].

In Europe, the cost of a disposable kit with a single fiber for LTA ranges from EUR 300 to 500. A diode laser source, without the US equipment, costs around EUR

30,000. Importantly, the price of laser and of the other TA devices may differ widely between the different European countries (Table 2).

Radiofrequency

An electric field, produced by a radiofrequency generator connected to an internally cooled electrode needle, leads to frictional agitation at the ionic level and to heat generation (Joule effect). Monopolar electrodes, with collecting pads, and bipolar devices, without pads, are available [6, 10, 18]. Shorter (7–10 cm length) and thinner (17–19 G) devices, appropriate for use in the neck region, have substituted multi-hook expandable needles. The electrode is introduced under US guidance into the target nodule, and a continuous repositioning of the applicator (“moving shot” or “multiple overlapping shot” technique) results in an ellipsoidal necrotic area [19]. As with LTA, the appearance of hyperechoic signals close to the electrode tip indicates the development of tissue changes, while a steep rise in tissue impedance demonstrates the achievement of tissue necrosis [6, 10, 18].

In Europe, the cost of a disposable applicator ranges from EUR 500 to 1,000. The treatment is performed in an outpatient clinic setting and requires 15–40 min (Table 2).

Microwaves

The equipment consists of a microwave generator, a flexible low-loss coaxial cable, and an internally cooled antenna corresponding to a 14- to 16-G needle [20–22].

Smaller and less invasive MWA applicators are currently under development. The antenna is inserted into the nodule under US guidance, usually using a trans-isthmus approach, and the procedure is then performed according to a “moving-shot technique” until hyperechoic changes cover the entire nodule or a large part of it [20–22].

The cost of MWA applicators is about EUR 600 in Europe. Treatment is performed on an outpatient basis and lasts 10–20 min (Table 2).

High-Intensity Focused Ultrasound

With HIFU, sparing of extranodular tissues is achieved by a computer-assisted planning of the procedure [23, 24].

Heat is generated by the conversion of acoustic into thermal energy. A US diagnostic receiver and a generator of US waves are combined in a single cooled probe. A computerized mapping of the targeted tissue on the US screen provides safety margins for the skin, trachea and large neck vessels [23, 24]. The US beam is automatically delivered to the target tissue through multiple shots, and the procedure is performed without needle insertions. Repositioning of the patient is needed when patient motions are detected by a laser control, in order to avoid treatment of critical areas [23, 24]. The cost of a HIFU machine is over EUR 250,000, and the cost of disposables is around EUR 500. The procedure is performed in an outpatient setting, and treatment duration ranges from 40 to 60 min, but large-size (>5 cm) nodules usually require multiple treatments (Table 2).

Patient Eligibility and Preparation

A benign cytological diagnosis is needed before planning TA of thyroid nodules, in order to minimize the risk of overlooking malignant lesions and thereby postponing their treatment. Thus, confirmation with a repeat FNA is appropriate in case of cytologically benign lesions, because follicular tumors and follicular variants of papillary thyroid carcinoma may not exhibit high-risk sonographic findings [25, 26] and have a non-negligible risk of false negative cytology [27, 28]. Repeat FNA may be omitted in cytologically benign spongiform and pure cystic lesions (EU-TIRADS class 2) [15]. TA should never be performed on nodules with high-risk US features (EU-TIRADS Class 5) due to their considerable risk of harboring malignancy [15, 29]. Since medullary thyroid cancer may not display suspicious sonographic features or unambiguous cytological findings, a single calcitonin determina-

tion should be considered, together with TSH, in the initial biochemical evaluation [2, 11].

The treatment of asymptomatic lesions is discouraged, implying that TA should be restricted to benign lesions that cause local pressure symptoms or cosmetic concerns. Defining a nodule volume cut-off for offering TA is not straightforward because symptoms and cosmetic problems are influenced by the location of the thyroid lesions and the cervical circumference, in addition to a number of factors which cannot be objectively assessed [1, 10, 26]. Female patients and subjects with a thin neck may present early cosmetic concerns, and the majority of subjects with nodules >30 mm, especially if in the isthmus area, may complain of pressure symptoms [30]. Thus, partly in accordance with other guidelines [10], TA should be mainly considered for patients with nodules with a maximum diameter ≥ 30 mm that keep growing steadily during US follow-up and who start complaining of local discomfort. In patients with compressive multinodular goiter, TA should not be used as a substitute for surgery due to the inadequate efficacy in such cases and the need of multiple treatments. In these patients, a careful evaluation with CT or MR imaging should be performed to rule out the presence of intra-thoracic extension or potentially threatening compression of the vital structures [31]. In these cases, if used at all, TA should be restricted to patients with a dominant nodule who are not candidates for thyroid surgery, as a palliative therapy option [11, 14, 20]. Vocal cord function should be carefully considered before TA and laryngoscopic examination is warranted in patients with hoarseness, previous thyroid surgery, or with nodules close to the trachea or nerve structures [32]. After obtaining a thyroid function status, a dedicated US examination should be performed by the operator to confirm the indication for therapy, to exclude potential anatomic contraindications, and to plan the procedure. In case of hyperfunctioning thyroid nodules, hyperthyroidism should primarily be controlled with antithyroid drugs, and the advantages and disadvantages of radioiodine (RAI) treatment should be considered and discussed with the patient [33]. Graves' disease and toxic multinodular goiter are not suitable for TA procedures.

Clotting disorders, relevant comorbidities, and pregnancy status should be evaluated before TA treatment.

The patient needs to be carefully informed, orally and in writing, about:

- The various available management options, including observation, TA or surgery, and their respective advantages and limitations
- The modalities of TA treatment

- The necessary compliance during the procedure
- The potential complications
- The expected decrease in nodule size, usually not associated with complete disappearance
- The possible regrowth over time with need of additional TA or surgery
- The need of long-term follow-up.

Recommendation 3. Before TA of thyroid lesions, a benign cytological diagnosis is needed. A repeat FNA is suggested for cytologically benign nodules with the exception of spongiform nodules and pure cystic lesions (EU-TIRADS Class 2). A calcitonin determination should also be considered. We recommend against TA for nodules with high-risk US features (EU-TIRADS Class 5) (1, ØØØØ).

Recommendation 4. Patients should be carefully informed before the procedure, orally and in writing, about the TA treatment options, their potential efficacy and side-effects, the therapeutic alternatives, and the necessity of being compliant (1, ØØØØ).

Recommendation 5. Before the TA procedure, thyroid and vocal cord function, comorbidities, and contraindications to TA treatment should be evaluated. Laryngoscopy is recommended in patients with hoarseness, previous neck surgery, or with nodules close to critical structures (“danger areas”) (1, ØØØØ).

Procedure and Post-Procedural Management

Procedure

The operators performing thyroid TA need appropriate experience in cervical US anatomy and US-guided diagnostic procedures and a dedicated training in image-guided therapeutic procedures.

During the TA procedure, frequent swallowing and head movements should be avoided. Hence, a mild conscious sedation (e.g., midazolam, 1–3 mg intravenously) may be helpful for keeping the patient relaxed throughout the procedure [9–12]. Local subcutaneous and pericapsular anesthesia is usually recommended when the TA technique requires large bore needles; in case of HIFU, although no invasive devices are required, local anesthesia may help diminish the pain caused by the mechanical injury to the skin and thyroid capsule by the US beam [9–11, 18, 19, 23, 24]. Local anesthesia is usually performed by injecting 2% lidocaine, or mepivacaine solution, into the skin, neck muscles, and thyroid capsule along the expected needle tract. Monitoring of blood pressure, heart rate, and pO₂ is required and is mandatory in case of conscious sedation [10–12].

Real-time US monitoring of the device’s position during the TA procedure is strictly reinforced [6–8, 10, 18–21]. Especially for nodules located close to the thyroid capsule, trachea and/or carotid artery, attention should

be paid to preventing damage to the vital neck structures. In selected cases, local infusion of saline, or 5% glucose, solution forming a liquid barrier of at least 5 mm is required to isolate the target area from nearby critical structures [34]. Patients should be asked to communicate the onset of neck pain, which usually indicates heating of the thyroid capsule and requires discontinuation of treatment followed by repositioning of the TA applicator.

With HIFU, sparing of extranodular tissues is achieved by a computer-assisted planning of the procedure [23, 24].

Post-Procedural Management and Follow-Up

Mild compression of the neck with an ice pack may be useful for preventing local bleeding and thermal injury to the skin. After treatment, clinical and US evaluation is needed for detection of potential early adverse effects of the procedure (e.g., hematoma, burns, or damage to the thyroid capsule) and the assessment of the area of ablation. The treated area appears as a mildly hypoechoic and inhomogeneous zone, with scattered hyperechoic spots due to tissue vaporization [7, 10]. Color-Doppler mapping improves defining the treated area, which appears as devoid of vascular signals. Contrast-enhanced US provides a more accurate assessment of the loss of small vessel signals and better depicts the incompletely treated peripheral areas [14, 35–40]. Notably, in a few European countries, thyroid nodular disease is not among the licensed indications for the use of US contrast agents.

After the procedure an anti-inflammatory (e.g., ketoprofen 100 mg) may be given parenterally in case of pain, followed by a painkiller given orally (e.g., paracetamol 1,000 mg twice/day) during the following 24 h. Patients should be instructed to present for clinical and US assessment in case of severe pain, local swelling, or fever occurring within the first week following TA [12].

Clinical trials have reported varying schedules for clinical and US short- and long-term monitoring [9–12]. Clinical, biochemical (with at least TSH determination), and US examinations are recommended as follows: (a) early: at 3 months, for assessment of initial effects of TA and thyroid function analysis; (b) intermediate: at 6 and 12 months, as above, for the assessment of nodule volume reduction and presence of remaining viable areas, because the maximum nodule shrinkage is nearly always achieved by this time. Subsequent US monitoring on a 1- to 2-year basis is useful to evaluate further nodule volume and structural changes [41–45]. Prolonged regular biochemical follow-up is generally not warranted for non-hyperfunctioning lesions, while protracted thyroid

function monitoring is needed for AFTN. Long-term US follow-up is appropriate because part of the treated lesions regrow after 3–5 years and need additional TA or surgery [46–48]. Different criteria have been used to define nodule regrowth after TA, resulting in a variable 3-year recurrence rate that approximately ranges from 5.0 to 24.0%. Currently, regrowth after treatment should be defined as a nodule volume increase >50% over the smallest recorded volume [11, 12, 14]. Main predictive factors for recurrence appear to be large initial size, functional autonomy, low applied energy, and incomplete ablation of the marginal areas of the nodules [36–38]. Therefore, during follow-up, demonstration of initial regrowth in untreated peripheral areas should prompt a second targeted TA to prevent further volume increase and recurrence of symptoms over time [39]. Notably, a repeat cytological assessment should be considered before retreatment, as nodule regrowth could be a potential sign of overlooked malignancy [11, 28].

Physicians who perform thyroid US examinations during follow-up after TA procedures should be aware of the timing and characteristics of structural modifications induced by the intervention. This is to avoid misinterpretations of late, potentially worrisome, morphological changes (e.g., development of a hypoechoic lesion with intranodular calcifications) [12].

Recommendation 6. Local subcutaneous and pericapsular anesthesia is recommended before TA procedures. Mild conscious sedation may be considered, especially in case of HIFU treatment (1, ØØØØ).

Recommendation 7. At the end of the procedure, clinical and US evaluation is recommended in order to rule out potential early adverse effects and define the extent of the ablated area. Patients should be instructed to present for clinical and US assessment if severe pain, local swelling, or fever occur within the first week after TA (1, ØØØØ).

Recommendation 8. Early-term (e.g., 3 months) and intermediate-term (e.g., 6 and 12 months) clinical, biochemical, and US evaluations are recommended. Long-term follow-up monitoring is suggested, in the absence of symptoms every 1–2 years, in order to reveal regrowth (1, ØØØØ).

Thyroid Phenotypes and TA Outcomes

When interpreting the data, whether using the same or different TA techniques, major limitations are due to the inhomogeneity of the studies concerning a number of parameters (e.g., patient and nodule selection, description of technique efficacy [generally defined for benign solid nodules as a volumetric reduction $\geq 50\%$ of the initial nodule volume], modality of treatment and follow-up, as

well as treatment variables, including applied energy per mL of nodule tissue) [12, 14].

Solid Nodules

Lasers

Short- and long-term technique efficacy of LTA have been documented in a number of single-center randomized trials [41, 42], and confirmed by a multicenter randomized study of 101 patients showing a 59% mean volume reduction at 12 months [43]. A multicenter study of 1,531 patients reported a 72% mean volume reduction at 12 months [44], and a 12-month trial demonstrated an 84% mean volume reduction [45]. LTA efficacy seems stable, with a 51–58% mean volume reduction at 36 months [27, 43]. Accordingly, only a minority (5–9%) of treated nodules exhibit significant re-growth within a 3-year follow-up [43–46]. The results of LTA in benign non-functioning thyroid nodules have been synthesized in a recent meta-analysis which reported a 48, 52, 45, and 44% mean volume reduction rate (VRR) at 6, 12, 24, and 36 months, respectively [49].

As for the other TA techniques, nodule structure (completely vs. mostly solid, and well delineated vs. coalescent) may influence long-term results but is not systematically reported in clinical trials. Outcomes are generally described as more favorable in spongiform and mixed than in completely solid nodules [48].

LTA results in amelioration of cosmetic concerns and local symptoms in the majority of patients. In a prospective multicenter study, only 8% of patients still complained of pressure symptoms at their final evaluation, compared to 38% at baseline [43]. Similarly, in a randomized study, symptom improvement was achieved in 81% of patients treated by LTA versus 0 and 13% in the placebo- and LT4-treated groups, respectively [42]. In addition, in a retrospective multicenter study, the rate of pressure and cosmetic symptom relief after LTA was 48 and 86%, respectively, versus 10 and 8%, respectively, in control subjects [44].

Major complications, defined as unexpected events which may result in severe morbidity and disability increasing the level of assistance [14, 50], are rarely observed after LTA. In a large multicenter study, a 0.5% rate of major complications was reported, with temporary vocal cord palsy documented in 8 out of 1,531 patients [44]. Notably, in 6 of the 8 patients, the target nodule was located in a “danger area,” close to the infero-medial portion of the thyroid lobe. Therefore, this paratracheal thyroid zone should be carefully avoided in case of benign lesions [44]. Minor complications (sub-capsular and

peri-thyroidal hematomas and skin burns) were reported in 0.5% of patients. A single case of “nodule rupture” has been described but pseudocystic transformation and fasciitis represent more frequent complications and need to be better defined [44]. The tolerability of LTA seems good, although self-limiting side effects (mostly transient neck pain) have occurred in 12–30% of LTA sessions. Post-treatment, thyroid function abnormalities have only been anecdotally reported.

Data from validated benign thyroid disease-specific questionnaires, such as the ThyPRO [51, 52] assessing quality of life (QoL) changes are still limited. In a prospective study, both a visual analogue scale, which rated discomfort in the neck, and a validated 13-scale QoL questionnaire demonstrated significant improvement after LTA [53].

Radiofrequency

RFA is an effective TA treatment for thyroid nodules [54, 55]. Mean volume reduction in randomized controlled trials, which did not always differentiate complex from solid nodules, ranged from 69 to 78% at 12-month follow-up [56, 57], and a 5-year retrospective study demonstrated long-term clinical efficacy with a median 67% volume reduction [58]. In the previously quoted meta-analysis, RFA was associated with a 68, 75, and 87% mean VRR at 6, 12, and 24 months, respectively [49]. As a general rule, the smaller the treated nodule the higher the volume reduction (78–82% in ≤ 10 - to 12-mL nodules vs. 62–65% in > 20 - to 30-mL nodules) [56, 57]. As tissue structure affects the alternating current flow, compact tissues are more resistant than soft tissues and, as for LTA, spongiform and mixed nodules respond better to RFA than solid lesions [58, 59]. RFA treatment has been shown to ameliorate pressure as well as cosmetic symptom scores [58, 60].

In a retrospective multicenter study of 1,543 nodules, major complications were recorded in 1.4% of patients, 15 of whom complained of voice changes [61]. A meta-analysis provided similar results, with a 1.3% rate of major complications in a population of over 2,400 patients; again, voice changes were permanent only in 4 (0.16%) of the treated patients [62]. A rather rare complication has been “nodule rupture,” characterized by breakdown of the anterior thyroid capsule and formation of a fluid collection in the anterior neck, which may potentially require surgical drainage [61]. Horner’s syndrome and spinal accessory nerve injury are extremely rare but have been reported. Hematomas, skin burns, persistent pain, vaso-vagal reactions, and vomiting are the minor complications or side effects described [61, 62].

Data on patient satisfaction are limited, and head-to-head prospective studies of RFA versus surgical treatment are lacking. In a cross-sectional study, patients were significantly more satisfied with cosmetic results in the RFA-treated than in the surgical group, but no significant differences were demonstrated in overall satisfaction [63]. In a study of 404 patients, RFA resulted in significantly better HRQoL scores than thyroidectomy, and quality-adjusted life years following RFA were higher than following surgery [64].

Microwave Ablation

High-quality evidence using MWA is limited. Retrospective studies describe a 74.6–90.0% mean volume reduction after 1 year [22], and in 2 meta-analyses volume reduction was 74% at 6 months and 89% at 12-month follow-up [65, 66]. However, in a prospective study comparing the performance of cooled versus uncooled MWA applicators, the mean reduction rates at 3 months were only 40 and 29%, respectively [67]. As with LTA and RFA, this variability in technique efficacy could be due to the heterogeneous structure of the nodules of the patients enrolled in the studies. Currently, MWA appears associated with a higher risk of major and minor complications than LTA and RFA, probably due to a poorer control of the applied energy and to the larger bore of the applicators [66].

A randomized trial in 52 patients demonstrated that MWA was followed by better general health and mental scores than thyroid surgery at 12 and 24 months [68]. In another randomized trial in 108 patients, MWA resulted in a lower visual analogue scale post-procedural pain score, and lower mean cortisol level, as a measure of stress, compared to surgery [69].

High-Intensity Focused Ultrasound

Controlled studies using HIFU are few, are from few institutions, and offer no data from prospective randomized trials. In a 2017 review [70], which included 6 retrospective and prospective studies with a follow-up ranging from 3 to 12 months, the mean volume reduction after HIFU ranged from 48.8 to 68.8%. Similar results were obtained in 2 retrospective non-controlled studies reporting a 43% and a 70% volume decrease at 24-month follow-up [71, 72]. An inverse correlation between the initial nodule volume and the percentage shrinkage of the lesion was reported, and a $> 50\%$ volume decrease was seen only in small-size (≤ 3.0 mL) nodules [73].

No major complications, such as permanent recurrent laryngeal nerve palsy or skin burns, were reported in the above studies. Common side effects were pain, usually

rapidly subsiding after treatment, skin redness, and protracted subcutaneous swelling [70–72]. In a retrospective study, however, unilateral vocal cord palsy was reported in 4 out of 103 (4%) cases [74] and the complications were related to a <1.1 cm distance between the HIFU focus point and the trachea-esophageal groove [74]. Thyroid function appears unaffected by the HIFU treatment [75].

Studies addressing QoL changes are limited. In a retrospective non-randomized trial, HIFU treatment, as opposed to surgery, was associated with shorter hospital stay, lower cost and better post-procedural quality of the voice [76].

Comparison of Outcomes of Different TA Techniques for Benign Solid Non-Functioning Thyroid Nodules

Studies comparing RFA and LTA suggest a nearly similar clinical efficacy and safety of the 2 techniques. Notably, the outcomes of these operator-dependent techniques are markedly influenced by the specific skill and the training period of the physicians who perform minimally invasive procedures. A retrospective multicenter study compared data obtained from 138 patients treated by LTA and 138 patients treated by RFA, after propensity score matching [77]. Mean volume reductions at 6 and 12 months were not statistically different between the RFA- and the LTA-treated group [77]. Two systematic reviews covering a total of 184 and 1,186 patients, respectively, showed a moderate superiority of RFA in terms of nodule volume reduction. In the first study, a greater 6-month mean volume change (77.8 vs. 49.5%) was reported after RFA as compared to LTA [78]. Similarly, in the other meta-analysis, at 12 and 24 months RFA showed a greater VRR than LTA (75 vs. 52% and 87 vs. 45%, respectively) [49]. In a paper based on a direct comparison of RFA and LTA, both performed by the same skilled operators, the techniques demonstrated similar technique efficacy and rate of complications [79]. Finally, a recent single-use, randomized, open-label, parallel trial compared the outcomes of RFA and LA groups. Six months after treatment, the nodule volume reduction was 64.3% in the RFA group and 53.2% in the LTA group, while no significant difference was observed between RFA and LTA for the improvement of compressive symptoms and cosmetic score [80].

In a prospective non-randomized multicenter study of 1,252 patients treated with MWA or RFA, the 2 techniques appeared similarly effective, with a non-significantly greater nodule VRR at 6 months in the RFA group (65 vs. 58%). MWA was also associated with a slightly higher complication rate than RFA (7 vs. 5%, respective-

ly) [81]. These results have been confirmed by a retrospective study of 108 patients after propensity score adjustment [82].

There are neither prospective randomized nor propensity score-matched trials evaluating the efficacy and tolerability of HIFU in comparison with the other TA techniques. In a small uncontrolled series of patients, HIFU, RFA, and MWA showed a comparable nodule volume reduction at 3 months (48, 50, and 44%, respectively) [83]. However, the results were partly biased by differences in baseline volume of the nodules, which were significantly smaller in the HIFU group [83].

Recommendation 9. Based on direct comparison studies, and balance between efficacy and side-effects, LTA and RFA are recommended as the first-line TA treatment modalities (1, ØØØØ).

Recommendation 10. Based on studies to date, MWA should at present be considered a second-line TA procedure in patients who are not suitable for or decline other TA procedures, or for participants in protocolled clinical studies (1, ØØØØ).

Recommendation 11. Based on its lower efficacy, higher cost, and limited reported trial evidence, as compared to RFA and LTA, HIFU should be considered only for selected nodules in patients who are not suitable for or decline other TA procedures, and for participants in protocolled studies (1, ØØØØ).

Recommendation 12. In multinodular goiters, due to lack of evidence of efficacy and the expected need of repeat treatment, TA should be restricted to patients with a well-defined dominant nodule or those who are not candidates for thyroid surgery or radioactive iodine treatment, as a palliative therapy option (1, ØØØØ).

Cystic Nodules

EA is recommended as the first-line treatment for benign cystic thyroid nodules [2], based on retrospective and prospective studies having shown nodule volume reduction after EA ranging from 50 to 98%, paralleled by improvement in local symptoms [84, 85]. These favorable outcomes persist 5 years post-treatment [85]. The main factors negatively influencing the technical efficacy of EA are the number of previous interventions, increasing size of the solid as well as the cystic component, multilocularity, initial nodule volume >10 mL, and increasing vascularization of the lesion [85]. Based on the aforementioned, TA is considered as a potential treatment only for selected predominantly cystic nodules.

Laser

LTA, as well as RFA and MWA, demand to be applied after drainage of the fluid component of the cystic lesion, usually performed during the same session [86]. Studies specifically dedicated to LTA treatment of cystic thyroid nodules are limited. In a prospective randomized trial in 44 patients [86], LTA achieved remission, defined as the

reduction of cyst volume to ≤ 1 mL, in 68% of patients vs. 18% in the control group. LTA treatment also achieved a significant reduction of the solid part of the nodules, while the solid component was unchanged in the control group. The combined use of ethanol and LTA has been demonstrated to be effective in very large cystic nodules [87]. Long-term follow-up demonstrated a maintained efficacy of this approach in the majority of treated patients [88].

Radiofrequency

Most series employing RFA include both solid and cystic nodules, while only few studies specifically address the use of RFA in cystic nodules. In a trial in 57 patients either treated with EA or RFA, the latter resulted in a significantly higher reduction of thyroid nodule volume and symptom scores [89]. Two prospective randomized trials comparing the effects of ethanol versus RFA treatment in 50 patients with predominantly cystic nodules, showed similar technical efficacy, with a 93 and 87% volume reduction in RFA- and EA-treated nodules, respectively, at 6-month follow-up [90, 91]. In all the above-quoted studies, EA and RFA demonstrated nearly similar efficacy, reinforcing EA as the first-line therapy for benign cystic nodules due to its lower cost. However, EA and RFA may be effectively combined to implement an otherwise incomplete treatment [92].

Microwave Ablation

As for RFA, the majority of studies using MWA include both cystic and solid nodules, and no trials have been specifically devoted to cystic thyroid lesions. In 474 benign thyroid nodules undergoing MWA, VRR in predominantly cystic nodules (95% at 12 months) was significantly higher than in solid nodules [22]. This has been confirmed in a prospective study reporting a 92% volume reduction at 12 months [68].

High-Intensity Focused Ultrasound

HIFU is based on a non-invasive approach that does not allow the drainage of fluid collections. There are no relevant studies reporting on fluid removal followed by HIFU treatment as, even after drainage, a liquid component that may hamper US efficacy usually persists within the solid component of the cystic lesion.

Recommendation 13. Because of higher cost and complexity, as compared to aspiration and EA, TA procedures are not recommended as a first line treatment for pure or dominantly cystic thyroid lesions (1, $\emptyset\emptyset\emptyset$).

Recommendation 14. LTA and RFA should be considered therapeutic options for cystic lesions that relapse after EA and for those that would remain symptomatic due to a large residual solid component (1, $\emptyset\emptyset\emptyset$).

Benign Autonomously Functioning Thyroid Nodules Laser Thermal Ablation and Radiofrequency Ablation

Data on TA in AFTNs are mostly based on LTA [38, 93, 94] and RFA [95, 96] treatment. Overall, the mean technical efficacy, defined for AFTN as restoration of normal thyroid function associated with a $\geq 80\%$ reduction of initial volume, is around 50% at 12 months, but the larger the nodule the poorer the likelihood of achieving durable control of thyroid function. Based on the available data, TA may achieve near-complete normalization of serum thyroid hormones in small size (e.g., ≤ 10 mL) AFTN, accompanied by a substantial ($>80\%$) volume reduction, while thyroid function is controlled only in a small fraction of larger AFTN [94, 97]. Thus, TA may be best employed for patients with small AFTNs who decline or are not suitable – due to iodine repletion, comorbidities or pregnancy – for RAI therapy or thyroid surgery.

In a prospective trial, patients with large (>10 mL) hyperfunctioning thyroid nodules, treated either with RAI alone or with LTA followed after 1 month by RAI, demonstrated a greater and more rapid improvement of local symptoms after the combined treatment [98]. Moreover, nodule volume reduction was more pronounced, and the dose of administered RAI was significantly lower [98]. Therefore, TA could be used for selected large-size AFTNs to obtain a volume reduction prior to RAI treatment [94, 98].

A prospective study employing a 12-item Short Form Health Survey questionnaire demonstrated a comparable improvement in HRQoL in patients with AFTN offered either lobectomy or LTA followed by RAI [99].

High-Intensity Focused Ultrasound

HIFU is less effective than RAI for control of hyperfunctioning nodules. A prospective trial in 2 cohorts treated either with HIFU or RAI demonstrated that euthyroidism at 12 months was obtained in 94% of the RAI-treated versus 53% of the HIFU-treated patients [100].

Microwave Ablation

There are no relevant studies specifically addressing the efficacy and safety of MWA for the treatment of AFTN.

Recommendation 15. We recommend against TA as first-line treatment for large AFTN. Due to the low rate of restoration of normal thyroid function, TA should be considered only for patients who decline or are not candidates for RAI therapy or surgery (1, $\emptyset\emptyset\emptyset$).

Recommendation 16. TA should be considered in young patients with small AFTN and incomplete suppression of perinodu-

lar thyroid tissue due to the higher probability of normalization of thyroid function and the advantage of avoiding irradiation and restricting the risk of late hypothyroidism (1, 0000).

Recommendation 17. Treatment with a combination of LTA or RFA and RAI may be considered in selected patients with large AFTN that cause local pressure symptoms in order to achieve a more rapid volume reduction and use of a lower RAI activity (2, 0000).

Concluding Remarks

Currently, US-guided TA procedures may be considered for selected cases as alternative options to the well-established treatments. TA can change the natural history of benign thyroid lesions that keep growing over time in order to prevent or control symptoms without causing hypothyroidism and to reduce risk of surgical complications. Notably, after nearly 20 years of clinical use, there is no evidence of TA techniques causing thyroid neoplasia [101, 102].

In the frame of a patient-tailored approach, the following factors need consideration when contemplating the use of a TA procedure for thyroid nodules in young and adult patients:

- Risk of malignancy should be reliably ruled out and the advantages and disadvantages of all available options weighed in a dialogue with the patient.
- TA procedures should not be used for decreasing the volume of asymptomatic thyroid nodules, unless there is documented and clinically significant growth over time.
- In case of cystic (or predominantly cystic) symptomatic nodules, EA is to be preferred as the most effective, rapid, and least expensive treatment. TA may be considered for cystic lesions that relapse after EA or for those with a residual solid nodule following EA.
- TA should aim at the most complete destruction of the targeted nodule in order to alleviate symptoms and prevent regrowth while maintaining safe procedures and minimizing the risk of side effects. In general, spongiform and complex nodules are better candidates for TA compared to solid compact nodules.

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- TA is associated with a low rate of major and minor complications, but adverse effects are potentially severe. Therefore, the operators need a dedicated training in image-guided thyroid therapeutic procedures.
- TA effects may be stable for years. However, nodule re-growth may occur, and a decision to repeat treatment or offer a different treatment option, for example surgery, needs to be reached together with the patient.
- Among the available TA techniques, LTA and RFA have long been used by several centers, providing robust and consistent clinical results. MWA has only recently been used for treatment of thyroid nodules and needs further validation, as does HIFU.

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Statement of Ethics

This work was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. According to Danish law, this type of research does not need Ethical Committee approval.

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