Annales d'Endocrinologie 83 (2022) 423–430

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SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules

# SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules: Thermal ablation

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ARTICLE INFO

*Keywords:*
Thyroid nodule
Thermal ablation
Radiofrequency
Laser
Ethanol ablation
Consensus

ABSTRACT

The SFE-AFCE-SFMN 2022 consensus deals with the management of thyroid nodules, a condition that is a frequent reason for consultation in endocrinology. In more than 90% of cases, patients are euthyroid, with benign non-progressive nodules that do not warrant specific treatment. The clinician's objective is to detect malignant thyroid nodules at risk of recurrence and death, toxic nodules responsible for hyperthyroidism or compressive nodules warranting treatment. The diagnosis and treatment of thyroid nodules requires close collaboration between endocrinologists, nuclear medicine physicians and surgeons, but also involves other specialists. Therefore, this consensus statement was established jointly by 3 societies: the French Society of Endocrinology (SFE), French Association of Endocrine Surgery (AFCE) and French Society of Nuclear Medicine (SFMN); the various working groups included experts from other specialties (pathologists, radiologists, pediatricians, biologists, etc.). This section deals with thermal ablation, which may constitute an alternative to thyroid surgery in selected patients.



## 1. Introduction

Surgery is the gold standard treatment for symptomatic benign thyroid nodules. However, its risk-benefit ratio needs to be reassessed due to improvements in the reliability of diagnostic procedures and the contribution of alternative techniques: percutaneous ethanol injection and thermal ablation (TA). These are becoming increasingly important for patients seeking to avoid the risk of postoperative hypothyroidism and reduce the risk of complications inherent in surgery, and to benefit from simpler post-operative follow-up. Quality-of-life studies support the use of TA versus surgery in selected patients [1].

## 2. Indications, feasibility consultation, further investigations, multidisciplinary team meeting and consent [2,3]

### 2.1. What are the indications for thermal ablation treatment of a benign nodule?

Indications for thermal ablation are the same as the general indications for the treatment of benign nodules: solitary or dominant nodule, causing functional or esthetic concerns, mild hyperthyroidism (pre-toxic adenoma) or proven hyperthyroidism (toxic adenoma), growing, and of significant size. Decision to treat should involve at least two different specialties and at best be referred to a multidisciplinary team meeting.

### 2.2. What are the contraindications?

Absolute contraindications are: EU-TIRADS 5 nodules > 10 mm in size, cytologically indeterminate or malignant (Bethesda class III, IV, V or VI), toxic multiheteronodular goiters, Graves' disease, multinodular goiters without a dominant nodule.

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https://doi.org/10.1016/j.ando.2022.10.011
0003-4266/

Relative contraindications are: cardiac pacemaker (if bipolar radiofrequency, microwave or laser are not available), pregnancy, nodules with a retrosternal extension.

### 2.3. What are the objectives of pre-procedural examination?

Preoperative examination should preferably be carried out by the practitioner who will perform the procedure, and its purpose is to confirm the indication, exclude contraindications, specify the feasibility of each technique (specific indications or contraindications, specific requirements, advantages and disadvantages), present the various therapeutic options adapted to the patient's context in order to guide them in a shared decision, detail the course of assessment, procedure and follow-up, and obtain informed consent and deliver a document presenting all these elements.

### 2.4. What elements should be collected?

A clinical assessment precedes and guides the investigations and must in particular specify the existence of a link between nodule and symptomatology.

The biological work-up includes: TSH, calcitonin, anti-TPO antibodies, calcium, complete blood and platelet count, and coagulation.

An expert cervical ultrasound scan, in addition to standard analysis, enables study of the neurovascular anatomical relationships.

Nodule samples must include two ultrasound-guided fine-needle aspiration biopsies (FNAB) or core-needle biopsies with a benign result and quantitatively satisfactory material. Only one FNAB or core-needle biopsy is allowed for EU-TIRADS 2 nodules. In the case of autonomous nodules, FNAB is not systematic but at discretion of the medical team. If it is performed, the cyto-pathologist must be informed of the functional status of the nodule.

Other examinations are not systematic: thyroid scintigraphy may be performed according to the usual indications. ENT and digestive explorations or cross-sectional imaging are indicated in case of a nodule close to at-risk areas, dysphonia, symptoms for which the responsibility of the nodule is in doubt or history of cervical surgery.

Clear and fair information should be given to the patient on the possible side-effects and complications and the risk of regrowth, and an informed consent form must be provided.

Recommendation 8.1

Prior to any non-surgical treatment of a thyroid nodule, a dedicated consultation assessing the indication and feasibility of treatment and informing the patient of the benefits, harms and risks compared to surgery should be carried out. Level of evidence: expert opinion, Grade A

Recommendation 8.2

Two ultrasound-guided fine-needle aspiration biopsies or core-needle biopsies should be performed for EU-TIRADS 3 and 4 nodules, and a single FNAB or core-needle biopsy for EU-TIRADS 2 nodules. The result should be in favor of benignity. Level of evidence +++ Grade A

Recommendation 8.3

In autonomous nodules, FNAB is not systematic but at the discretion of the medical team. If it is performed, the functional status of the nodule should be reported to the cytopathologist. Level of evidence: expert opinion, Grade B

Recommendation 8.4

The operator must have experience in thyroid ultrasound and interventional procedures for diagnostic (FNAB, core-needle biopsy) and therapeutic purposes (aspiration and removal, percutaneous ethanol injection). The operator must have received specific training and have assisted a trained operator in several procedures. He or she must be supervised for the first procedures. Level of evidence: Expert opinion, Grade A

## 3. Percutaneous ethanol ablation of benign nodules

### 3.1. What is the place of percutaneous ethanol injection in the treatment of thyroid nodules?

In 2018, the Korean Society of Thyroid Radiology issued recommendations on the use of ethanol to treat thyroid nodules [4]. It concluded that ethanol should be the first-line treatment for cystic and predominantly cystic nodules. A review of the literature supports this view [5–8]. It is a very effective technique, providing 85-95% volume reduction for purely cystic nodules, and 60-90% for mixed nodules with cystic predominance [9,10]. The risk of recurrence is low, at between 7% and 38% at 10 years [6,7], whereas it is higher, at between 10% and 90% [9,11], after simple aspiration without ethanol injection (randomized prospective study [9]). Between 5% and 25% of cystic nodules are refractory to ethanol treatment [6,9,12]. Iterative injection has been proposed, with variable success. In the non-responding mixed nodules finally operated on, a small proportion of differentiated thyroid carcinomas was found on histological analysis (15%) [7].

Complications are rare: transient pain/burning sensation at the injection site due to ethanol effusion outside the nodule, the risk of which can be reduced by pre-procedure local anesthesia and simply rinsing the tubing and needle with sterile saline; hematoma (< 1%); transient dysphonia (1-3%); and hematocele.

In nodules with thick colloid that cannot be aspirated with standard-gauge needles, ethanol treatment is still possible, but several successive procedures are usually necessary.

### 3.2. Are there still indications for ethanol treatment of autonomous nodules?

The technique shows a certain short-term but not very long-lasting efficacy as far as biological results are concerned [8,13], probably because of the uneven diffusion of the ethanol and therefore necrosis that is not easily predictable. Evaluation at 5 years showed normal TSH in only 60% of patients treated for autonomous nodules, and detectable TSH with normal FT3 and FT4 in 35% of patients treated for toxic nodules [8]. Therefore, if an alternative to surgery and iodine-131 is sought, thermal ablation is to be preferred.

### 3.3. How is ethanol treatment performed?

The procedure is performed on an outpatient basis and is described in Appendix 2.1.

### 3.4. What follow-up should be scheduled after ethanol ablation?

Follow-up cervical ultrasound scan is recommended 3-6 months after ethanol treatment, or sooner in case of complications or symptomatic recurrence [4], and then adapted according to progression, with follow-up at 1 year in general. If remission is complete, further ultrasound monitoring is unnecessary. Long-term monitoring of thyroid hormone levels is necessary after ethanol treatment of a hyperfunctioning nodule because of the high risk of recurrence.

**Table 1**
Literature review - Technical effectiveness (percentage volumetric reduction) of radiofrequency thermal ablation of benign thyroid nodule.

| Report | Nodules/Patients | % volume reduction |
|---|---|---|
| Jeong Eur Radiol 2008 | 302/236 | 84% (13-100) > 50%: 91% |
| Baek AJR 2010 | 15 versus observation | 80% (52-96) |
| Faggiano JCEM 2012 | 20/20 (10 hyperthyroid) | 85% |
| Lim Eur Radiol 2013 | 126/111 | 93% at 4 years |
| Ugurlu World J Surg 2015 | 65/33 | 74% |
| Cesareo JCEM 2015 | 42/42 versus surveillance | 69% |
| Deandrea Thyroid 2015 | 40/40 versus surveillance | 71% |
| Aysan Langenbecks 2016 | 100/100 | 85% |
| Ahn Ultrasonography 2016 | 22/22 | 91% |
| Mauri Int J Hyperthermia 2017 | 59 | 74% |
| Cesareo Arch Endocrinol Metab 2017 | 48 | 71% |
| Pacella Int J Hyperthermia 2017 | 152 | 62% |
| Jung Korean J Radiol 2018 | 345 multicenter prospective | 95% at 5 years |
| Dobnig Thyroid 2018 | 150 | 82% |
| Ben Hamou Int J Hyperthermia 2019 | 108/107 including 12 autonomous nodules | 75% at 18 months |
| Deandrea EJE 2019 | 337 solid cold nodules | 70% |
| Deandrea JCEM 2019 | 215 | 67% at 5 years |
| Bernardi Thyroid 2020 | 216 multicenter | 77.1% at 5 years |

Recommendation 8.5
Percutaneous ethanol injection is the first-line treatment for symptomatic cystic and predominantly cystic nodules that recur after aspiration, whether fluid or thick. Level of evidence +++ Grade A

Recommendation 8.6
The effectiveness of ethanol injection should be assessed clinically and by cervical ultrasound 3-6 months after the procedure, and then as appropriate according to progression. Level of evidence +++ Grade A

## 4. Thermal ablation of benign thyroid nodules

Thermal ablation (TA) of benign thyroid nodules is a minimally invasive alternative to thyroid surgery, and is now considered effective and safe. Numerous Korean, Italian and, more recently, French series demonstrated efficacy in terms of nodule volume reduction ratio (VRR) and safety in terms of major adverse events. VRR is defined as (initial volume–residual volume)/initial volume. Depending on the series and technique (radiofrequency ablation (RFA), laser ablation (LA), microwave ablation (MWA)), VRR ranges from 48% to 85% for a single session and the complications rate is between 1% and 3%. The technique is used for non-functional or functional (autonomous, pre-toxic or toxic), solid or mixed nodules.

### *4.1. What are the indications for and results of thermal ablation?*

TA is a technique for treating mostly solid benign nodules. It can sometimes be used for mixed nodules, in combination with ethanol injection. Indications obviously take account of context: general condition of the patient, possible contraindications to surgery under general anesthesia, and the patient's wishes.

The therapeutic objective is the disappearance of the indication(s) by durably reducing the volume of the nodule: esthetic and/or functional issues, dysthyroidism, and/or significant growth of an asymptomatic nodule > 4 cm or 8–10 $cm^3$ [2,14–16].

A distinction is made between

- benign non-functional nodules, where the indication is volume reduction, to resolve the functional and/or esthetic complaint;
- and autonomous nodules: toxic or pre-toxic adenomas, where the indication is normalization of thyroid function, but may also be volume reduction.

#### *4.1.1. What are the indications for benign non-secreting nodules?*

Indications are for symptomatic nodules regardless of volume. There is no definable lower threshold volume. Concerning minimal volume, symptomatology depends not only on the volume of the nodule but also on its topography and the morphology of the patient. Recommendations are therefore based on symptoms rather than nodule volume.

Regarding maximum volume, one study showed no difference in efficacy for volumes greater or less than 30 ml [17]. However, the risk of complications seems to increase with volume [17], and durability decreases with the volume of solid nodules. Large-volume nodules, especially >30 ml, may therefore require iterative treatment [18,19].

Indications are also for asymptomatic nodules larger than 4 cm and with proven significant growth [20].

#### *4.1.2. What are the indications for benign secretory nodules?*

Radioactive iodine (RAI) therapy and surgery are effective and safe but carry a significant risk of secondary hypothyroidism: 10–20% and 10–44%, respectively. This is particularly the case for pre-toxic adenomas. Meta-analyses suggest that TA may be an option regardless of nodule size. However, the efficacy of treatment is inversely proportional to volume and TSH normalization is achieved, according to some series, only in 75% of nodules smaller than 10 ml [21]. Therefore, Italian and Austrian guidelines do not recommend TA alone for nodules larger than 15–20 ml and/or in case of multifocal involvement [22].

TA can be considered to treat hyperthyroidism in autonomous, preferably single, nodules (TSH < 0.3 μIU/ml) [23] in the following cases:

- RAI is contraindicated (young patient, desire for pregnancy);
- persistent uptake in the remaining thyroid parenchyma;
- patient refusal, or contraindications to RAI treatment and surgery;
- in first line for nodules of volume less than 5–10 ml.

The patient should be informed of the risk of failure requiring second TA treatment, especially if the nodule is large.

#### *4.1.3. Outcomes*

- Symptomatology: a volume reduction of 50% is sufficient to improve pressure symptoms. Functional complaints disappeared in 87.5% of patients and esthetic complaints in 61.5%, after the learning period [18].

- Reduction in nodule volume: published data show volume reductions of 62–95% [14,16,19,24–38] (see Table 1). At 5 years, the results remained permanent in the majority of cases, with a progressive regrowth rate of approximately 20% [38].

### 4.2. Thermal ablation techniques and procedure

#### 4.2.1. Which technique should be preferred?

Radiofrequency ablation (RFA) is the most widely used technique in France, South Korea and the United States, with a long track record and good evidence-based studies, and is the first-line technique in all international guidelines.

Laser ablation (LA) was one of the first techniques, used by pioneering Italian teams. There is also a significant background of literature. It provided 55–60% volume reduction in most large prospective and comparative series. The risk of regrowth is significant as of 15 ml and with laser power below 600 J/ml. Clinical efficacy is comparable to RFA, but volumetric efficacy is lower and the risk of recurrence is higher.

LA was also shown to be effective in small autonomous nodules with collapsed TSH that are not accessible to RAI therapy [39] and in thyroid cancers. It has been the subject of specific recommendations by the European Thyroid Association, where it is listed, along with RFA, as a first-line technique [2].

LA and RFA have been compared [36,40]: results varied, but tended to favor RFA in terms of volume reduction and risk of recurrence, although similar in terms of treatment efficacy. Operator experience is an important factor [41]. Considering these results and the lower cost of a single laser fiber, LA is applicable in patients with pacemakers, for small nodules that are troublesome in the isthmic position, for autonomous nodules smaller than 5 ml, and for spongiform nodules.

High-intensity focused ultrasound (HIFU) is not currently recommended for the ablation of thyroid nodules. This procedure has not been proved to be effective [42,43].

Microwaves are the most recently developed and therefore the least widely used technique. However, published series (prospective, retrospective, meta-analyses and comparative versus RFA or lobectomy) have shown its efficacy and safety. Prevalence of complications was comparable to that of RFA, with a non-significant trend for higher prevalence of recurrent nerve palsy.

#### 4.2.2. Description of the thermal ablation procedure

The procedure is usually performed on an outpatient basis. Anticoagulants should have been stopped (with appropriate relays if necessary), as well as antiplatelets when possible [3].

Radiofrequency ablation

RFA can be performed under either local anesthesia or conscious sedation with local anesthesia. Strict extensive antisepsis of the anterior cervical region must be performed. Local anesthesia is performed on the puncture site, and around the thyroid capsule on the side of the nodule.

The RF electrode is cooled. It should be small in diameter (usually 18G). The puncture should generally be carried out via a transisthmic approach. TA sequentially uses the "moving-shot" technique (as opposed to the fixed technique used for liver masses), in order to carry out multiple small (7 or 10 mm) elementary ablations, starting with the most posterior and medial regions of the nodule, then continuing toward the more anterior and lateral parts. In some cases, a feeding artery to the nodule may be identified on Doppler, usually deriving from the superior thyroid artery. Selective arterial destruction can then be performed by radiofrequency ablation, leading to ischemic nodular necrosis ("artery first ablation" (AFA) technique). The anatomical relationships at risk, and in particular the regions where the recurrent nerve, esophagus, vagus nerve and sympathetic ganglion are located and the zones close to the trachea or the skin, will have been identified during the preprocedural feasibility assessment, and sufficient safety margins must be conserved in order to protect them. Having one or more hydro-dissection zones, using refrigerated glucose serum, can be useful, as it protects the structures at risk, and can sometimes limit the margins: thermal ablation of the nodule must be as complete as possible, while conserving safety margins. After removal of the needle, compression of the puncture site is recommended. Ultrasound control of vocal cord mobility should be performed when technically possible.

Laser ablation

One to four 21G Chiba needles with laser fibers are introduced under ultrasound guidance. The recommended power is between 3 and 5 W and illumination of each area uses a recommended delivered energy of 600–800 J/ml. Once the area has been treated, the fibers are moved back 1 cm (pull-back technique). Use of the moving-shot technique has also been described.

### 4.3. Evaluation of efficacy, tolerance and post-procedure follow-up

#### 4.3.1. What are the criteria used to assess the effectiveness of TA?

Five main efficacy criteria are relevant:

- Regression of compressive symptoms and/or of esthetic complaint, which can be assessed qualitatively on a 3-point scale as unchanged, improved or resolved, and/or by dedicated quality of life questionnaires.
- Nodule volume reduction: calculated using the following formula: (initial volume (ml) − final volume (ml) × 100)/initial volume (ml). Technical efficacy is defined by VRR ≥ 50% 6 months after the procedure (intermediate follow-up).
- Ablation ratio (AR): total tissue destroyed as a percentage of nodule volume on the day of treatment, or AR = (initial volume − residual volume + residual destroyed volume)/initial volume. It quantifies the percentage of tissue actually destroyed and predicts risk of recurrence.
- Durability of volume reduction over time and the absence of nodular regrowth.
- Normalization of thyroid function tests (when hyperthyroidism due to an autonomous nodule was the indication for treatment).

#### 4.3.2. What are the complications?

Major complications are few and far between, and not found in all series. No cases of death have been reported. Minor complications are rare (1–3%) and are most frequently classifiable as adverse events.

*4.3.2.1. Major complications.* Tracheal lesion: 1 case was reported with fistulation to the skin, during a procedure under general anesthesia, secondary to electrode malpositioning. The lesion resolved within 4 weeks under antibiotics and packing [44].

Compressive hematoma was reported in 0.8% of cases in 1 series [45].

Permanent recurrent laryngeal nerve palsy: permanent paralysis of the inferior laryngeal nerve is very rare (1/500) [46].

*4.3.2.2. Minor complications.* Transient dysphonia (1–4%) is related to thermal, compressive or chemical (local anesthetic) damage to the recurrent laryngeal nerve or, more rarely, to the external branch of the superior laryngeal nerve. It may be accompanied by false fluid routes and coughing. It is transient in the majority of cases,

lasting from a few hours to a few months [47]. Risk factors comprise operator learning curve and lesions close to the "danger zone". The risk of recurrent laryngeal nerve palsy is reduced with the moving-shot technique (described above), due to the transisthmic approach [48,49]. Specialist management including speech therapy may be required.

Nodule rupture (1–2%) is the extra-nodular outcome of liquefied necrotic contents resulting in a constantly aseptic inflammatory reaction of the subcutaneous and muscular tissue. It occurs mostly between 5 and 60 days after the procedure. It is quite unpredictable but 3 risk factors have recently been reported: volume > 20 ml, proximity to the thyroid capsule, and rich vascularity [48]. Treatment varies according to the situation: simple monitoring, oral corticosteroid therapy, or drainage.

Horner's syndrome (0.1%) is related to damage to the cervical sympathetic pathway by thermal or compressive injury [45]. It is almost always transient and regresses in 7 to 180 days.

*4.3.2.3. Adverse events (AEs).* The most common AEs are: cervical edema (10%), pain, superficial hematoma (5%), fever, and reaction to lidocaine (confusion, muscle contractions, tachycardia).

No cases of clinically significant long-lasting hypothyroidism have ever been reported. Occasional flare-ups of Graves' disease and thyroiditis have been described.

*4.3.3. What is the post-procedure follow-up?*

Immediate post-procedure phase: interview and physical examination to assess pain, checking for the absence of laryngeal (dysphonia, false routes, coughing) and sympathetic involvement. Ultrasound monitoring with Doppler and micro-Doppler evaluation of nodular vascularization assesses the remaining viable and necrotic areas and, if possible, the mobility of the vocal cords.

In the 6 months following the procedure: interview and physical examination assess clinical effectiveness (evolution of initial complaints), pain, recurrent nerve (dysphonia, fluid false routes) and sympathetic plexus damage or nodule rupture (pain, swelling, signs of laryngeal or sympathetic nerves irritation). TSH assay is proposed within a timeframe appropriate to the initial indication.

Clinical and ultrasound follow-up is recommended at least at 6 and 12 months and then annually for at least 5 years. The aim is to assess symptom regression, nodule volume reduction (VRR, ablation ratio), nodular regrowth, and need for second treatment. Clinical evaluation follows up the evolution of esthetic and functional complaints (possibly by questionnaire) and the general satisfaction. Ultrasound follow-up evaluates volume, vascularization, VRR, AR and overall thyroid status. TSH assay is proposed within a timeframe adapted to the initial indication.

Recommendation 8.7

Thyroid thermal ablation is indicated for the treatment of certain symptomatic benign thyroid nodules and/or those with documented ultrasound volumetric progression. Level of evidence +++ Grade A

Recommendation 8.8

Thermal ablation is a treatment option for selected cases of autonomous nodules. Level of evidence ++ Grade B

Recommendation 8.9

Thyroid nodule thermal ablation, regardless of the technique used (radiofrequency, microwaves or laser), should be performed by a trained operator within a dedicated care pathway. Level of evidence ++ Grade A

Recommendation 8.10

Clinical, ultrasound and biological monitoring after thermal ablation is recommended at 3–6 months and then at 12 months and annually for the first 5 years. Level of evidence ++ Grade A

Recommendation 8.11

Nodule reduction < 20% and/or rapid significant regrowth should prompt discussion of repeat FNAB to ensure that a carcinomatous lesion is not overlooked. Level of evidence: expert opinion, Grade A

## 5. Combined treatments

### 5.1. Definition of combination therapy

Combined treatments associate thermal ablation to another therapeutic modality: RAI for certain autonomous nodules, or chemical sclerosing agents for mixed nodules.

### 5.2. Indications and outcomes

*5.2.1. Radioactive iodine and thermal ablation*

If iodine-131 alone does not ensure sufficient efficacy in an outpatient setting and in the event of contraindications or refusal of surgical treatment, certain large autonomous nodules may be treated sequentially by thermal ablation and iodine-131.

Iodine-131 has also been proposed in combination with laser ablation to treat large toxic nodular goiters [50]. The combined treatment resulted in faster resolution of compressive symptoms, more pronounced volume reduction and lower iodine dose. Similar results were shown with microwave therapy [51].

*5.2.2. Ethanol injection and thermal ablation*

The combined use of a chemical sclerosing agent (usually 96% ethanol, more rarely polidocanol) and thermal ablation may be indicated for non-autonomous nodules and nodules of mixed composition when the solid part is > 10–20% of total volume [52–54].

Mixed nodules for which thermal ablation is indicated and in which there are $\geq 1$ significant cystic cavities may be treated by prior or, more rarely, concomitant percutaneous ethanol injection, or if a hematocele occurs during thermal ablation.

### 5.3. Methods, procedure planning and patient information

Ethanol injection and thermal ablation can be combined:

- Sequentially with prior ethanol injection followed a few weeks to months later by thermal ablation. This is the most common modality. The technique and risks of ethanol injection and thermal ablation are unchanged and the patient must be informed. The procedure is scheduled during the feasibility and information assessment prior treatment.
- Concomitantly when intra-nodular bleeding occurs during thermal ablation [52].
- In special cases, when a significant cystic cavity persists after thermal ablation, selective ethanol injection can be performed [52].

Recommendation 8.12

Mixed nodules with a solid component > 10–20% of total volume may be treated sequentially by ethanol injection and thermal ablation. Level of evidence + Grade B

## 6. Minimally invasive treatments for thyroid cancer

### 6.1. Background and indications

Given the indolent weakly progressive nature and excellent prognosis of papillary microcarcinoma, and the cost, operative risks and psychological consequences of surgery, active surveillance is now commonly proposed as an alternative to surgery in selected cases. It is not always well accepted by patients, and thermal ablation is used successfully in this indication by several teams on patients selected according to the criteria of active surveillance. Metastatic cervical lymph-node involvement, multifocal disease suspected on ultrasound, suspicion of macroscopic extra-thyroidal invasion or the patient's wish are, of course, formal surgical indications. While FNAB is not recommended for EU-TIRADS 5 nodules < 10 mm, it is clear that cytological evidence (Bethesda class VI) is essential before considering TA of a suspected micronodule.

### 6.2. Procedure

The pre-therapeutic anatomical ultrasound study is identical to that for benign nodules (see Part III). In addition, it is recommended to assess the size of the cancer, its location (distance to the capsule, inferior laryngeal nerve and trachea, and isthmic location), and to screen for macroscopic extra-thyroidal extension, suspicious lymph nodes (which must be negative), according to the same criteria as for active surveillance. Radiofrequency, microwaves and laser ablation are the three preferred techniques.

### 6.3. What results can be expected?

#### 6.3.1. Tumor destruction, persistence, recurrence, survival and complications

The most recent meta-analysis included 15 studies; 1822 tumors were treated with RFA. Mean follow-up was 33.0 months. The complete destruction rate was 79%. The overall progression rate was 1.5%, with tumor remnants in the ablation region in 0.4% of cases, a new tumor location in 0.9% and cervical metastases during follow-up in 0.2%. No distant metastases were observed. Three major complications occurred: 1 arrhythmia and 2 persistent dysphonias [55].

No statistically significant differences in tumor destruction or recurrence were found between RFA, MWA and LA. However, complete tumor destruction (76.2%) and the lowest recurrence rate (0.01%) were observed with RFA. The complications rate was lower with LA (0.9%) than with RFA (1.7%).

In the study by Zhang et al., histological control by core-needle biopsy of the carcinoma treated with RFA confirmed the absence of residual or recurrent tumor [56].

#### 6.3.2. Comparison with surgery [57,58]

Recurrence frequency and recurrence-free survival were similar between TA and surgery at 4–5 years. The complications rate, hospital stay and cost were significantly lower for TA [59].

The risk of voice disorder, hypothyroidism and postoperative pain was significantly lower compared to surgery. The esthetic result was more satisfactory with TA [60].

#### 6.3.3. Comparison with active surveillance (AS) [61]

There are no randomized controlled studies.

## 7. Conclusion

Thermal ablation is a treatment option to be considered in microcarcinomas without lymph-node involvement or macroscopic local invasion [62]. It has fewer complications and adverse effects than surgery but lacks long-term assessment. It limits the patient's anxiety related to disease presence and progression observed during active surveillance, which may eventually lead to conversion surgery. The indications for thermal ablation may be revised in future according to advances in molecular biology and the results of follow-up studies.

Recommendation 8.13

Thermal ablation (radiofrequency, microwave or laser) of papillary microcarcinoma (WHO definition ≤ 1 cm) may be considered in selected cases as an alternative to surgery or active surveillance. The case should be discussed in a multidisciplinary consultation meeting. Level of evidence +++ Grade B

Recommendation 8.14

After thermal ablation (radiofrequency, microwave or laser) of papillary thyroid microcarcinoma, regular ultrasound monitoring should be performed. Level of evidence ++ Grade A

## Disclosure of interest

The authors declare that they have no competing interest.

## Acknowledgements

Thanks to the reviewers: Emmanuelle Lecornet-Sokol, Françoise Borson-Chazot, Sophie Leboulleux, Claire Bournaud, Marc Klein, Bernard Goichot, Marie-Christine Vantyghem, and Jean-Louis Wemeau.

## Appendix A. Appendix

### A.1. Appendix 1

Effectiveness of laser thermal ablation
Benign euthyroid nodules

| | *N* patients | Initial volume | Delivered energy (J) | Sessions | Follow-up (months) | Volume reduction | Clinical results |
|---|---|---|---|---|---|---|---|
| Achille (2015) [63] | 45 | 24.2 | – | 1 | 12 | 84 | Esthetic: 96%<br>Compressive: 88% |
| Papini (2014) [64] | 1534(8 centers) | 27 | 1,500 | 1,2 | 67 | 72 | Esthetic: 90%<br>Compressive: 80% |
| Mauri (2017) [34] | 31 | 20.3 | 3,000-7,000 | 1 | 12 | 70 | Laser session longer than RF |
| Negro (2016) [65] | 56 | 15.4 | 600¥J/ml | 1 | 48 | 55.5 | Efficacy on spongiform nodules |
| Bernardi(2020) [66] | 190 | 12.2 | 600¥J/ml | 1 | 60 | 57 | Efficacy: 63%<br>Regrowth: 28%<br>Multiple treatments: 18% |

Autonomous nodules

| | *N* patients | Initial volume | Sessions | Follow-up (months) | Volume reduction | Euthyroidism |
|---|---|---|---|---|---|---|
| Gambelunghe (2018) [39] | 95 | 12 (1-118) | 1 | 36 | 58% | <Y5: 100%<br>5-15: 90%<br>15-25: 61%<br>>Y25: 28% |

### *A.2. Appendix 2*

How to perform ethanol injection?

The procedure is performed on an outpatient basis. Strict antisepsis must be performed. Local anesthesia with 2% lidocaine is sometimes performed along the puncture route.

For cystic lesions, a needle is inserted if possible through the isthmus to prevent leakage during the ethanol injection. The cyst should be drained as completely as possible. If the fluid is thick, an injection of isotonic saline to reduce viscosity or a larger gauge needle may be used, or the ethanol injection may be performed in several sessions. The operator then carefully injects an appropriate amount of 95-99% ethanol under constant ultrasound guidance to ensure that the needle is correctly positioned and that there is no extra-nodular leakage. There is no clear consensus on the minimum or maximum amount of ethanol that should be injected, whether it should be re-aspirated or not, or how long the ethanol should be left (2-10 minutes) if it is to be re-aspirated. After removal of the needle, careful compression of the puncture site is performed.

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