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To cite this article: Enrico Papini, Claudio Maurizio Pacella, Luigi Alessandro Solbiati, Gaetano Achille, Daniele Barbaro, Stella Bernardi, Vito Cantisani, Roberto Cesareo, Arturo Chiti, Luca Cozzaglio, Anna Crescenzi, Francesco De Cobelli, Maurilio Deandrea, Laura Fugazzola, Giovanni Gambelunghe, Roberto Garberoglio, Gioacchino Giugliano, Livio Luzi, Roberto Negro, Luca Persani, Bruno Raggiunti, Francesco Sardanelli, Ettore Seregni, Martina Sollini, Stefano Spiezia, Fulvio Stacul, Dominique Van Doorne, Luca Maria Sconfienza & Giovanni Mauri (2019) Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT) group, *International Journal of Hyperthermia*, 36:1, 376-382, DOI: [10.1080/02656736.2019.1575482](https://doi.org/10.1080/02656736.2019.1575482)

To link to this article: <https://doi.org/10.1080/02656736.2019.1575482>



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Published online: 26 Mar 2019.



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## Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT) group

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### ABSTRACT



Benign thyroid nodules are a common clinical occurrence and usually do not require treatment unless symptomatic. During the last years, ultrasound-guided minimally invasive treatments (MIT) gained an increasing role in the management of nodules causing local symptoms. In February 2018, the Italian MIT Thyroid Group was founded to create a permanent cooperation between Italian and international physicians dedicated to clinical research and assistance on MIT for thyroid nodules. The group drafted this list of statements based on literature review and consensus opinion of interdisciplinary experts to facilitate the diffusion and the appropriate use of MIT of thyroid nodules in clinical practice. (#1) Predominantly cystic/cystic symptomatic nodules should first undergo US-guided aspiration; ethanol injection should be performed if relapsing (level of evidence [LoE]: ethanol is superior to simple aspiration = 2); (#2) In symptomatic cystic nodules, thermal ablation is an option when symptoms persist after ethanol ablation (LoE = 4); (#3) Double cytological benignity confirmation is needed before thermal ablation (LoE = 2); (#4) Single cytological sample is adequate in ultrasound low risk (EU-TIRADS ≤3) and in autonomously functioning nodules (LoE = 2); (#5) Thermal ablation may be proposed as first-line treatment for solid, symptomatic, nonfunctioning, benign nodules (LoE = 2); (#6) Thermal ablation may be used for dominant lesions in nonfunctioning multinodular goiter in patients refusing/not eligible for surgery (LoE = 5); (#7) Clinical and ultrasound follow-up is appropriate after thermal ablation (LoE = 2); (#8) Nodule re-treatment can be considered when symptoms relapse or partially resolve (LoE = 2); (#9) In case of nodule regrowth, a new cytological assessment is suggested before second ablation (LoE = 5); (#10) Thermal ablation is an option for autonomously functioning nodules in patients refusing/not eligible for radioiodine or surgery (LoE = 2); (#11) Small autonomously functioning nodules can be treated with thermal ablation when thyroid tissue sparing is a priority and ≥80% nodule volume ablation is expected (LoE = 3).

### ARTICLE HISTORY

Received 13 December 2018  
Revised 11 January 2019  
Accepted 23 January 2019

### KEYWORDS

Statement; thyroid gland; thyroid nodule; ultrasonography; minimally invasive treatments; percutaneous thermal ablation

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## Introduction

Benign thyroid nodules are a common occurrence in the general population and usually do not require treatment unless symptomatic [1]. In this case, patients generally report local compressive symptoms or esthetic concerns, due to the enlarging size of the nodule. Treatment options currently include open or minimally invasive surgery, aspiration with or without ethanol injection for cystic nodules, and thermal ablations. In autonomously functioning thyroid nodules (AFTNs), thyroid function is also affected and in these cases, pharmacological therapy and/or radioiodine ablation are also traditionally indicated [2].

Over the last years, ultrasound (US)-guided minimally invasive treatment (MIT) (including chemical ablation and energy-based ablations) gained an increasing role in the management of benign thyroid nodules [3]. They have proven efficacy and safety for the management of compressive symptoms and the improvement of esthetic concerns [4–9] and are also demonstrating a promising role in the treatment of selected AFTNs [10–14].

In February 2018, a meeting involving different specialists with specific expertise in the use of MIT for thyroid nodules was held in Milan, Italy [15]. It included dedicated radiologists, endocrinologists, nuclear medicine physicians, pathologists, and surgeons who founded the Italian MIT Thyroid (MITT) Group. This interdisciplinary group had the purpose of creating a network between Italian and international physicians who are dedicated to clinical research and care in the field of MIT of thyroid nodules [15].

The purpose of this document drafted by the Italian MITT Group was to provide a series of statements based on literature review and consensus opinion of interdisciplinary experts to facilitate both the diffusion and the appropriate use of MIT for the management of thyroid nodules in clinical practice.

## Materials and methods

### Expert selection

For this consensus, an interdisciplinary board of 29 physicians with specific expertise in the management of thyroid nodules was appointed by the Italian MITT Group for their proven experience in clinical practice and research on the topic. The panel included radiologists, endocrinologists, nuclear medicine physicians, pathologists, and surgeons.

### Literature search and evaluation

After a thorough review of current literature, two authors (GM and LMS) drafted a list of statements addressing the most relevant questions on the use of MIT for thyroid nodules. For each statement, literature evidence was assessed, with a search on major online databases (MEDLINE, Web of Science, EMBASE, and Google, with search terms (thyroid ablation) OR (thyroid radiofrequency) OR (thyroid ethanol) OR (thyroid laser) OR (thyroid microwave) OR (thyroid high-intensity focused ultrasound) OR (thyroid radioiodine) OR

(thyroid fine-needle aspiration and their expansions), and levels of evidence were assigned according to the criteria proposed by the Oxford Center of Evidence-Based Medicine in 2011 [16].

### Consensus process

The Delphi method was used for the consensus process on the clinical use of MITT. This system consists of a sequence of structured group rounds designed to survey the expert opinion on potentially controversial topics and to reach a final shared agreement [17,18]. Thus, in this process, each participant was asked to agree, disagree, or abstain with the proposed statements and the contributors had also the opportunity to provide comments on each topic to appropriately improve the statements. Finally, the AGREE II instrument (a specific tool for assessing the quality and reporting of practice guidelines) was used to verify the minimum quality requirements of the produced document [19,20]. An electronic questionnaire was built on the Google Forms platform (Google LLC, CA) and was disseminated to all the participants.

Two Delphi rounds were initially performed and a final document was prepared to be submitted for publication. After the manuscript was sent back for revisions, the referees' comments were evaluated, the text was modified accordingly, and a third Delphi round was performed. The detailed consensus process is represented in Figure 1.

### Statistical analysis

For each statement, the consensus opinion was established at the end of the Delphi process. The consensus was considered as strong when >95% participants agreed, while it was considered as broad when >80% but less than 95% agreed on each statement [21].

The paper was then prepared based on the results of the Delphi process and circulated via email among all participants for its final approval.

### Statements

**Statement #1.** Predominantly cystic (51–90% of fluid component) or cystic (>90% of fluid component) thyroid nodules that become symptomatic should first undergo US-guided percutaneous aspiration for both diagnostic and therapeutic purposes, and image-guided ethanol ablation in case of relapse

Summary of evidence. Predominantly cystic or purely cystic thyroid nodules are a common clinical finding that does not require treatment unless symptomatic. In case of compressive symptoms or cosmetic concerns, the use of MIT can provide a clinically significant benefit. Simple aspiration, US-guided ethanol ablation, and thermal ablation have been proposed for the management of cystic nodules. Current evidence demonstrates that the outcomes of ethanol ablation are superior to both conservative treatment [22] and simple aspiration [4,23–25], while are nearly equivalent to thermal



**Figure 1.** Flowchart of the Delphi consensus process used in the present document.

ablation [26,27], a procedure that is more complicated and expensive. Thus, US-guided ethanol ablation is the most appropriate procedure for relapsing cysts in terms of efficacy, invasiveness, rapidity, and costs [28].

Level of evidence: 2

Level of agreement: strong (agree,  $n = 28$ ; abstain,  $n = 1$ ; disagree,  $n = 0$ )

**Statement #2.** In symptomatic predominantly cystic thyroid nodules, image-guided thermal ablation should be considered as an option when local symptoms persist after ethanol ablation.

Summary of evidence. A similar efficacy of ethanol ablation and thermal ablation has been reported in the

treatment of predominantly cystic thyroid nodules [26,27]. However, thermal ablation should be considered as a further therapeutic option in cystic lesions that relapse after ethanol ablation or that would remain symptomatic due to the residual solid component [29–31]. Thus, the use of thermal ablation as a second line of treatment seems to be appropriate in selected patients with symptoms persistence after ethanol ablation.

Level of evidence: 4

Level of agreement: strong (agree,  $n = 28$ ; abstain,  $n = 1$ ; disagree,  $n = 0$ )

**Statement #3.** A double cytological confirmation of benignity should be obtained prior to image-guided thermal ablation of thyroid nodules.

Summary of evidence. Generally, a double cytological confirmation should be obtained in thyroid nodules prior to thermal ablation to rule out the risk of missing malignancy [28,32]. A low rate (<3%) of false negative results has been reported after a single fine needle aspiration, so generally, a repeated aspiration after benign report is suggested, unless US appearance of low risk of malignancy. However, as concerns remain regarding a possible higher rate of false negative results, particularly in large nodules, double aspiration is suggested before image-guided thermal ablation of a thyroid nodule [33–35].

Level of evidence: 2

Level of agreement: strong (agree,  $n = 29$ ; abstain,  $n = 0$ ; disagree,  $n = 0$ )

**Statement #4.** A single cytological sample can be considered adequate to confirm nodule benignity if the US appearance is at low risk of malignancy (EU-TIRADS  $\leq 3$ ) and in AFTN.

Summary of evidence. Risk stratification at US is a crucial predictive factor for thyroid nodule management. In this setting, the EU-TIRADS system has been proven to be a valuable tool. Thyroid nodules classified as EU-TIRADS 3 have been proven to have a low risk of malignancy, which ranges between 2% and 4% [36,37]. In nodules that demonstrate both cytological and US low-risk features, the risk of a false negative result at cytology is definitely low, probably ranging from 1% to 3%. Similarly, the risk of malignancy in AFTNs is low in the adult population [38]. Therefore, in these low-risk nodules, a single negative cytological examination may be sufficient to candidate patients for thermal ablation [39–42]. Conversely, MIT management of AFTNs with TIR 3 A cytology is still unsettled.

Level of evidence: 2

Level of agreement: strong (agree,  $n = 29$ ; abstain,  $n = 0$ ; disagree,  $n = 0$ )

**Statement #5.** Thermal ablation may be proposed as a first-line treatment for solid nonfunctioning thyroid nodules that are benign at cytology when they become symptomatic.

Summary of evidence. Traditionally, open thyroidectomy is the standard of care for benign thyroid nodules presenting with cosmetic and/or compressive issues, even though benign at cytology [43]. Limitations of surgery are the frequent need for replacement therapy, the risk of

complications, and the elevated costs [28]. Thermal ablation is an effective outpatient procedure, with high technical feasibility [6], elevated clinical success rate [7,8], low frequency of minor (0.5–4%) [7,9] and major complications (less than 3.9%) [6], and outcomes sustained up to five years [7,44–47]. A few comparative studies between thermal ablation and open thyroidectomy showed that the former resulted in shorter operation time, no need of hospitalization, and absence of post-treatment scar [48], less complications and side effects, no functional changes, higher patients' satisfaction [48–53] and, as a whole, lower direct and long-term costs.

Level of evidence: 2

Level of agreement: strong (agree,  $n = 28$ ; abstain,  $n = 0$ ; disagree,  $n = 1$ )

**Statement #6.** Thermal ablation may be proposed as a treatment for nonfunctioning benign multinodular goiter only in patients who refuse or who cannot undergo surgery.

Summary of evidence. Currently, a single paper reported about the use of thermal ablation in multinodular goiter, showing that sequential treatment in the same session is effective and safe even if with longer procedure time and less tolerable pain in the day after treatment [54]. Due to the limited evidence and the burdensome modality of treatment, thermal ablation should be considered as a possible therapeutic option only in patients with well-defined dominant nodules who refuse or cannot undergo surgery [4].

Level of evidence: 5

Level of agreement: strong (agree,  $n = 28$ ; abstain,  $n = 0$ ; disagree,  $n = 1$ )

**Statement #7.** Thyroid nodules treated with thermal ablation should be routinely followed-up with clinical and US examination.

Summary of evidence. US is the most reliable method to evaluate thyroid nodules, both in the pretreatment setting and after thermal ablation [7,9,45,55,56]. Contrast-enhanced US provides a clear representation of parenchymal vascularization immediately after thermal ablation, when the presence of gas bubbles generated by ablation may impair the assessment of the treated area [57,58]. During follow-up, simple B-mode US nodule evaluation is generally not adequate to distinguish between the still vital part of the nodule and the area of ablated tissue. So, the use of other modalities such as color-Doppler or contrast-enhanced US may be considered for the detection of the still vital part of the treated nodule [4,52,59].

Level of evidence: 2

Level of agreement: strong (agree,  $n = 27$ ; abstain,  $n = 1$ ; disagree,  $n = 1$ )

**Statement #8.** In case of incomplete symptom resolution, symptom relapse, or nodule regrowth, a re-treatment with thermal ablation may be considered.

Summary of evidence. The clinical purpose of thermal ablation is the improvement of local symptoms and signs due to thyroid nodule pressure. If symptoms persist after initial therapy [60–62], an additional treatment may be performed, which usually results in symptom improvement.

Re-treatment after thermal ablation is reported as required in a minority of cases [60,63,64]. The proper timing of re-treatment is presently unsettled.

Level of evidence: 2

Level of agreement: strong (agree,  $n = 29$ ; abstain,  $n = 0$ ; disagree,  $n = 0$ )

**Statement #9.** In case of nodule regrowth, a new cytological assessment is suggested before the second ablation

Summary of evidence. No papers specifically addressed the risk of malignancy in nodules regrowing after image-guided thermal ablation. However, as nodule regrowth (defined as  $\geq 50\%$  nodule volume increase compared to the minimum recorded volume during whatever previous follow-up time point [3]), maybe a potential sign of malignancy a further cytological assessment is suggested before re-treatment.

Level of evidence: 5

Level of agreement: strong (agree,  $n = 29$ ; abstain,  $n = 0$ ; disagree,  $n = 0$ )

**Statement #10.** Thermal ablation may be proposed as a treatment option for AFTN in patients who refuse or cannot undergo traditional treatments with radioiodine or surgery.

Summary of evidence: Thermal ablation treatment of AFTN has been reported to result in volume reduction, symptom amelioration, and improvement or normalization of hyperthyroidism [10–12,47]. However, the success rate of thermal ablation in AFTN appears variable and is influenced by the baseline volume and severity of hyperfunction [13]. Thus, thermal ablation can be proposed as an alternative treatment only in patients with large AFTN or overt hyperthyroidism who refuse or who cannot undergo standard treatment (i.e., radioiodine or surgery) [11,14,28].

Level of evidence: 2

Level of agreement: strong (agree,  $n = 27$ ; abstain,  $n = 1$ ; disagree,  $n = 1$ )

**Statement #11.** Small size AFTN can be treated with thermal ablation when the preservation of normal thyroid tissue function is a priority and it is reasonable to expect at least 80% nodule volume ablation.

Summary of evidence. In case of AFTN, the higher the ablated volume, the better the functional outcome. Patients with AFTN are reported to have a higher probability of symptom resolution and normalization of thyroid function after thermal ablation if the treatment results in the ablation of at least 80% of nodule volume [12,14,65–67]. Thus, a favorable outcome may generally be expected in small AFTN [66], while in larger nodules a combined treatment with thermal ablation and radioiodine may be planned, as it is reported resulting in a more rapid volume reduction and in a lower irradiation than with radioiodine alone [68]. Due to the lack of changes in the function of the surrounding parenchyma and the absence of irradiation, thermal ablation is specifically appealing in young patients or patients with subclinical hyperthyroidism and incomplete suppression of normal thyroid tissue [69].

Level of evidence: 3

Level of agreement: strong (agree,  $n = 27$ ; abstain,  $n = 1$ ; disagree,  $n = 1$ )

## Discussion

This paper represents the first consensus statement of the Italian MITT Group regarding the MIT of benign thyroid nodules. For all statements, strong agreement among the members of the Group was achieved after the third round of Delphi process.

Both a robust literature evidence and an ample consensus among the experts indicated ethanol ablation as the first treatment modality in case of relapse of cystic nodules after the aspiration, due to its low-cost, rapidity, and safety. So, thermal ablation should be reserved only to prevalently cystic lesions that are not controlled by a prior treatment with ethanol ablation.

Strong agreement was found among the participants about the need of two consistently benign cytological samples prior to undergo MIT, as a general rule. Similarly to what reported in the Korean guideline [38], we evaluated the opportunity of considering as sufficient a single benign cytological report. This issue was extensively discussed and the initial statement was modified, as most experts recommended a second cytological sampling regardless the US appearance of nodules. Thus, even though at the end of the process a satisfactory agreement was achieved, we point out the necessity of controlled studies to better clarify this relevant issue due to the weakness of the available evidence.

Regarding the proposal of MIT as the first treatment option for benign thyroid nodules, a robust evidence demonstrates clinically significant and sustained results in most cases with a very low complication rate. Even though well conducted comparative studies on the direct and indirect costs of the two therapeutic approaches are limited, thermal ablation has the advantage of an outpatient procedure and lower expenses in comparison with surgery when a single application is needed. Thus, there is a strong consensus that MIT should be considered as a first-line treatment for symptomatic solid nonfunctioning benign thyroid nodules that become symptomatic. So, at variance with former recommendations, MIT should not be reserved only for patients refusing or who are not suitable for surgery. According to all experts, MIT represents only a second-line therapeutic option in multi-nodular goiter and should be reserved only to patients who are not suitable for surgery.

Regarding follow-up after thermal ablation, there was strong agreement on the crucial role of ultrasound, which should be considered as the imaging method of choice. Other modalities such as color Doppler or contrast-enhanced ultrasound offer complementary information for better differentiation of the ablated area from the still vital part of the nodule tissue, but the evidence is still not robust enough to recommend their routine use in clinical practice.

Strong agreement was achieved on the opportunity of a repeated treatment for benign thyroid nodules in case of incomplete symptoms resolution, or if symptoms relapse after thermal ablation. Presently, there is a lack of studies

specifically addressing the issue of the risk of malignancy in nodules that re-growth over time after thermal ablation. In these cases, however, a strong agreement was achieved on the opportunity of performing a further cytological assessment before a second thermal ablation to rule out the possibility of an underlying malignancy.

The appropriateness of the use of MIT for the management of ATFN has been one of the most debated topics during the Delphi consensus. Although evidence on the topic is fair, the clinical role of MITT in clinical practice is still argued. Specifically, the potential advantages and disadvantages of MITT versus radioiodine ablation are still not well established and further controlled studies on this topic are warranted to better define the appropriate role of MIT in ATFN. Thus, at present, MIT should be proposed as a treatment option only in patients who refuse or cannot undergo traditional treatments (i.e., radioiodine ablation or surgery). A strong agreement, however, was reached on the use of thermal ablation for small ATFN in which the majority of nodule volume (at least 80%) may be expected to be ablated, as the available data demonstrate satisfactory results in small size lesions. Notably, a complete consensus was reached about the preferential use of thermal ablation in young patients or patients with subclinical hyperthyroidism and incomplete suppression of normal thyroid tissue in order to spare the function of surrounding normal thyroid tissue.

In conclusion, this consensus document is based on the assessment of the best available evidence and on the combined opinion of an interdisciplinary group of specialists with specific interest in thyroid nodules and their minimally-invasive management. After this first proposal for the appropriate use of MIT in clinical practice, future updates are warranted on the basis of the improvement of the available evidence.

## Disclosure statement

No participant declared competing or conflicting interests regarding the development of the present statements.

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