European Thyroid Association Survey on Use of Minimally Invasive Techniques for Thyroid Nodules

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Keywords
Thyroid nodules · Thyroid cysts · Thyroid cancer · Questionnaire · Laser ablation · Radiofrequency ablation · Ethanol ablation · Thermal ablation · European thyroid association

Abstract
Objective: Image-guided interventional ultrasound (US) techniques represent diagnostic and therapeutic tools for non-surgical management of thyroid nodular disease. We sought to investigate the attitude of European Thyroid Association (ETA) members towards the use of minimally invasive techniques (MIT) in diagnosis/therapy of symptomatic nodular goitre. Methods: ETA members were invited to participate in an online survey investigating the use of MIT in benign and malignant thyroid nodular disease. Of 865 invited members, 221 (25.5\%) completed the survey. The respondents were from 40 countries; 139 (74.7\%) were from European countries. Results: Respondents personally performed thyroid US (91.6\%), Fine needle aspiration (FNA; 75.3\%), ethanol ablation (EA; 22.1\%), core needle biopsy (CNB; 11\%) and thermal treatments (4.8\%). When skills and/or technology were unavailable, only 13.4\% referred patients “often” or “always” to other centres with specific expertise in this field. Surgery was the preferred first option in patients with recurrent cysts, 4.0 cm benign nodules, local (radioiodine-avid or non-avid) lymph node metastases, or papillary cancers < 1.0 cm. For autonomously functioning nodules radioactive iodine treatment was the preferred choice, followed by surgery. Thermal ablation (TA) was the preferred option only for a 4 cm benign nodule in old patients with comorbidities. Conclusions: US, US-guided FNA and surgery were available to nearly all respondents, while MIT was not. CNB and EA were employed only by about 1/3 of the respondents and TA procedures were available and personally performed only by a minority. For most thyroid lesions, surgery was the preferred option versus thermal therapies. The ETA needs to develop guidelines and establish teaching to overcome geographic inequality and promote the use of MIT as a valid therapy option in appropriate cases.

Introduction
In the thyroid field, image-guided interventional ultrasound (US) techniques have globally been recognised and increasingly employed over the last 4 decades. Their
The use of minimally invasive techniques (MIT), such as laser ablation (LA) and radiofrequency ablation (RFA), has been successfully used to treat thyroid cysts and benign nodules associated with symptoms of compression, and are currently routinely used in some European countries as well as in the Far East [1, 3, 7].

Recently, TA of thyroid tissue, that is destruction by heating and subsequent coagulative necrosis and fibrosis, was proven effective for the local control of papillary thyroid microcarcinomas (PTMC) and metastatic lymph nodes in patients at surgical risk [8, 9]. Furthermore, a few centres have used TA for palliative purposes in thyroid cancer, neither amenable to surgical resection nor radioiodine ablation (RAI), with promising results [10, 11]. In addition to LA and RFA, other techniques, like high intensity focused US (HIFU) and microwave ablation (MWA), are being tested for ablation of benign and malignant thyroid nodules [12, 13].

Although there is a growing body of evidence to support the use of these procedures, we have very little information on their current dissemination into the clinical practice of European thyroidologists. Hence, we carried out a survey among European Thyroid Association (ETA) members aimed at investigating the attitude of ETA members towards the use of MIT in diagnosis/therapy of symptomatic nodular goitre. Imitating well-recognizable clinical situations, despite using virtual patients for illustration, our survey intended to cover MIT of some of the most common thyroid nodule phenotypes.

### Methods

We utilized a web-based survey based on a questionnaire comprising 27 questions. A total of 865 ETA members were sent an initial e-mail between April 1st and 30th 2019, including an electronic link to the questionnaire, followed by 2 reminders with a 2-week interval. Survey responses were collected and electronically stored by the survey service where they were accessible by password. The survey service automatically blocked repeat submissions from the same IP address. The entire survey is available (online suppl. Appendix 1; see online Supplementary Materials).

### Statistical Analyses

Summary statistics were prepared for responses to each question. We considered valid for statistical evaluation only those questionnaires with complete demographic data from the respondents. Pearson’s χ² test or Fisher’s exact test were used to compare frequencies (percentages) between categorical variables. A two-sided p value of < 0.05 was considered statistically significant. Data was analysed using IBM SPSS Statistics version 19 software (SPSS, Chicago, IL, USA).
Results

Sample Characteristics

510 of 865 (59%) ETA members opened the survey, 261 (30.2%) started the survey and 221 (25.5%) scrolled entirely the questionnaire; the mean number of respondents for the 26 questions was 178 ± 22. Characteristics of respondents are presented in Table 1 (Questions 1–6).

Of the respondents, 155 (80.3%) treated thyroid patients on a daily, and 30 (15.5%) on a weekly basis. 127 (66.1%) treated >100 patients/year with nodular thyroid disease, 33 (17.2%) treated 50–100 patients/year, and 24 (12.5%) 10–50 patients/year (Questions 7, 8). The respondents were from 40 countries; 139 (74.7%) were from European countries, with the majority of them being from Italy (31; 16.5%), Denmark (13; 6.9%) or France (10; 5.3%; online suppl. Appendix 2; Question 9).

Diagnostic and Therapeutic Modalities

US, FNA and surgery of the thyroid were virtually available in every hospital/clinic of the respondents (99.5, 97.4, 82.5% respectively), while minimally invasive diagnostic and therapeutic procedures like CNB and EA were available for 33.9 and 36.5%, respectively, and thermal treatments to even fewer (RFA: 23.3%; LA: 12.7%; HIFU: 13.8%; MWA: 2.6%; Question 10). Thus, the combination of US, FNA and surgery was, in European centres usually dealing with thyroid diseases, significantly more available and used than the minimally invasive diagnostic and therapeutic tools (p < 0.01).

In all, 91.6% of the respondents personally performed thyroid US, 75.3% performed FNA, while percentages were much lower concerning the interventional treatment options (EA: 22.1%; thermal treatments: 4.8%; Question 11). Performance of US and FNA was thus much more commonly carried out than the other interventional diagnostic and therapeutic modalities (p < 0.01). In the hospitals of the respondents, but not by them personally, 80% were able to offer US, FNA and thyroid surgery. However, this figure was reduced to between 10 and 33% concerning ability to offer MIT (US, FNA and thyroid surgery versus MIT; p < 0.01; Question 12). When skills and/or instruments in the institutions of the respondents were not available for performing MIT, 13.4% referred their patients “often” or “always” to other centres with specific expertise in this field, whereas 86.6% referred “sometimes,” “rarely” or “never” to institutions that routinely perform these procedures (sometimes/rarely/never versus often/always; p < 0.01; Question 13). The reasons for physicians being reluctant to refer pa-

Fig. 1. Reasons given for physicians never, or rarely, referring patients to MIT (Question 14). The sum exceeds 100% because >1 option could be selected by the respondents. MIT, minimally invasive techniques.
tients to minimally invasive treatments included the absence of dedicated guidelines, uncertainty about clinical outcomes, concern of potential complications and fear of overlooking a thyroid cancer. Notably, 14.4% stated that they did not know exactly what is meant by minimally invasive treatments, and 22.7% believed in the superiority of surgery (Fig. 1; Question 14).

Subsequent questions aimed at investigating the clinical management of patients, that is, when and how MIT was offered.

**Core Needle Biopsy**

CNB was used by 52.0% for thyroid nodules with repeated non diagnostic FNA cytology and by 53.7% when there was suspicion of anaplastic carcinoma, metastasis or lymphoma. In contrast, it was used by 15.4% for nodules initially diagnosed as atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda Class III) and by 13.0% for nodules initially diagnosed as follicular neoplasm or suspicion for follicular neoplasm (Bethesda class IV) [14]. The aggregate exceeds 100% because >1 option could be selected by the respondents (inadequate FNA cytology, suspected anaplastic carcinoma, metastasis or lymphoma vs. Bethesda Class III–IV; \(p < 0.01\); Question 15).

**Cystic Lesion**

For a 25-year-old woman with a 4.0 cm spongiform nodule (EU-TIRADS 2 with a benign FNA) causing symptoms of compression (Question 19), a Choice of therapy for a 25-year old female with a 4.0 cm spongiform nodule (EU-TIRADS 2 with a benign FNA) causing symptoms of compression (Question 19). b Choice of therapy for a 75-year old male patient with a similar thyroid nodule, but now suffering from diabetes, cardiovascular disease and renal failure (Question 20). HIFU, high intensity focused US.
vs. surgery; \( p = \text{NS}; \) Question 17). Less frequent recommendations were levothyroxine treatment (1.1%), aspiration of cystic fluid only (15.6%), liquid drainage followed by TA (6.5%). On the other hand, the rate of those who would refer the patient to surgery fell to 4.3% for elderly patients with cardiac comorbidity, in which case 91.5% of respondents would offer MIT as primary treatment (MIT vs. surgery; \( p < 0.01; \) Question 18).

**Solid Nodule**

For a 25-year-old woman with a 4.0 cm spongiform nodule (EU TIRADS class II at US) [15], the majority of respondents would offer surgery and only a minority TA (Fig. 2a; \( p < 0.01; \) Question 19). For a nodule with the same characteristics in a 75-year-old patient with cardiovascular co-morbidity, the relative percentages markedly changed as TA was preferred to surgery (\( p < 0.01 \)). However, about 20% of the specialists still chose a wait and see strategy (Fig. 2b; Question 20).

For a euthyroid middle-aged woman with a 4.0 cm. thyroid nodule (EU TIRADS class IV at US), 70.7% of ETA members suggested surgery, and only 20.4% suggested TA (\( p < 0.01; \) Question 21).

**Hyperfunctioning Nodule**

For a 65-year-old woman with a 4.0 cm autonomously functioning thyroid nodule (AFTN) causing subclinical hyperthyroidism and compressive symptoms, RAI was suggested by the majority, with surgery as the second, and TA as the third option (Fig. 3a; use of RAI vs. surgery or Anti-thyroid drugs

\[ \begin{align*}
\text{Radioiodine} & \quad 57.9 \\
\text{Surgery} & \quad 24 \\
\text{MIT} & \quad 6.5 \\
\text{MIT + RAI} & \quad 5.4 \\
\text{Anti-thyroid drugs} & \quad 4.9 \\
\text{Wait and see} & \quad 1.1 \\
\end{align*} \]

\[ \begin{align*}
\text{Radioiodine} & \quad 41 \\
\text{Wait and see} & \quad 21.3 \\
\text{Surgery} & \quad 18 \\
\text{MIT} & \quad 12.1 \\
\text{Anti-thyroid drugs} & \quad 3.8 \\
\text{MIT + RAI} & \quad 3.2 \\
\text{EA} & \quad 0.5 \\
\end{align*} \]
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Fig. 4. a Choice of therapy for a 75-year-old female patient who underwent thyroidectomy with lateral and central compartment neck dissection for differentiated cancer and afterwards developed local non radioiodine-avid lymph node metastases (Question 24). b Choice of therapy for a 25-year-old female patient who underwent thyroidectomy with lateral and central compartment neck dissection for differentiated cancer and afterwards developed local lymph node metastases and considered at high surgical risk (Question 25). c Choice of therapy for a 78-year-old female patient harbouring a cytologically confirmed 8 mm intra-thyroidally located papillary thyroid cancer (Question 26). HIFU, high intensity focused US.
For a 20-year-old female with a 2.5 cm AFTN, RAI was again considered the first option, followed by a wait-and-see strategy and, only thereafter, by TA (Fig. 3b; RAI vs. wait and see; $p < 0.05$; RAI vs. TA or surgery; $p < 0.01$; Question 23).

Thyroid Cancer and Lymph Node Metastases

For a 75-year-old female patient who had undergone thyroidectomy with lateral and central compartment neck dissection for differentiated thyroid cancer (DTC), and who afterwards developed cervical non radioiodine-avid metastases, the majority of respondents (55.7%) suggested surgery and a minority (14.2%) wait-and-see or RFA/LA (16.9%; Surgery vs. RFA/LA or vs. wait and see; $p < 0.01$; Fig. 4a; Question 24). Conversely, if the above patient was a 25-year-old female, who had undergone thyroidectomy with lateral and central compartment neck dissection for DTC and afterwards developed local lymph node metastases, surgery was recommended by 35%, a wait-and-see approach by 7.2% (none of the above: 26.7%) and TA by 31.1% of respondents (TA vs. surgery; $p = \text{NS}$; Fig. 4b; Question 25).

Finally, for a 78-year-old female harbouring a cytologically confirmed 0.8 cm intra-thyroidally located papillary thyroid cancer and considered at high surgical risk, thermal therapies represented the third most common recommendation (7.6%), after surgery (45.9%) and a wait-and-see strategy (41%; TA vs. surgery or vs. wait and see; $p < 0.01$; Fig. 4c; Question 26).

Discussion

The widespread use of neck and thyroid US examinations currently result in the diagnosis of nodular thyroid disease in a substantial proportion of the adult population [4, 5]. About 10% of such thyroid lesions exhibit progressive growth over time, in general most relevant for nodules already detectable at physical examination [16]. Unfortunately, due to the absence of effective medical treatments [4, 16], lesions that cause pressure symptoms or cosmetic concerns, also independent of risk of thyroid malignancy, are generally managed with surgical removal [17, 18]. This leads to a high frequency of thyroidectomy performed for benign lesions, as demonstrated by recent comprehensive studies in Europe and the United States [19, 20]. The direct and societal costs of surgery, the low but inevitable risk of complications, and the aesthetic damage induced, represent relevant concerns [21]. Notably, in order to decrease the cosmetic consequences of neck surgery, novel time-consuming and expensive surgical approaches, such as transoral robotic thyroidectomy, requiring specific skills and dedicated tools and carrying risk of further complications, have been proposed [22]. The above considerations, combined with the potential influence on quality of life (QoL), need for thyroid hormone substitution, as well as cosmetic concerns, bring the need of alternative therapeutic options for thyroid lesions that keep growing over time into focus [23].

Various image-guided ablation techniques, with different modes of action, are available for the management of symptomatic benign thyroid nodules [24, 25]. EA for cystic, and TA techniques for solid lesions, have been thoroughly evaluated and considered both safe and effective when used by operators with specific expertise [26]. In the light of the above, and in order to better characterize the diffusion of MIT procedures into current European clinical practice, the ETA conducted a survey among its members. The sample size was thought to be representative, and as previous surveys originated from the responses of approximately 40–50% of the clinically active members of the ETA [27]. Most important, nearly all the respondents declared a specific expertise in the management of thyroid nodules. This statement was confirmed by the fact that the respondents personally performed thyroid US as well as US-guided FNA. At variance with these data, the use of MIT appears to be limited, with the partial exception of EA, to a minority of thyroid centres in Europe. Moreover, the vast majority of the endocrinologists who did not themselves perform EA, or TA procedures for symptomatic benign thyroid lesions, referred their patients to surgery and did not consider referral to centres with specific expertise in non-surgical TA techniques.

Finally, the interest in using thermal therapies in the management of PTMC or cervical recurrences of DTC was definitely limited. TA was rarely considered an alternative option to a simple wait-and-see approach for elderly persons with PTMC, while the use of TA for neck recurrences of DTC occurring after previous cervical dissection was taken into account only by a minority of respondents.

The present survey showed that physicians familiar with thyroid disease management, and the approach to symptomatic well-defined thyroid phenotypes, only partially embrace the use of MIT, even when supported by robust evidence. Currently available evidence on MIT can be compared to the European survey findings, which is discussed in detail in the following sections.
Core Needle Biopsy

US-guided CNB usually provides diagnostic results in cases of thyroid nodules or lymph-node lesions with repeatedly inadequate cytological sampling [18]. In large series of nodules with initially non diagnostic FNA, CNB was proved to offer a significantly higher percentage of diagnostic samples, thus reducing the number of surgical interventions [28]. For anaplastic thyroid tumours, lymphomas and metastatic lymph nodes, CNB may also provide preoperative complementary information for the clinical management [29]. The use of CNB for distinguishing benign nodules from follicular neoplasms, in lesions with indeterminate cytology, is not supported by adequate evidence, although some authors suggest that CNB has the potential to be the first-line alternative diagnostic tool in nodules initially diagnosed as atypia/follicular lesion of undetermined significance [30, 31]. Therefore, it is understandable that, in the present survey, more than half of the ETA members considered CNB to be a complementary diagnostic tool in order to limit diagnostic surgery for nodules with inadequate FNA, and for lesions suspected of being anaplastic or other rare thyroid tumours.

Cystic Lesions

EA is presently recommended by the major thyroid nodule guidelines as the first-line treatment for benign cystic thyroid nodules [18, 32], based on the safety of the technique and the nodule volume decrease after EA, ranging from 50 to over 90%. Volume changes are associated with improvement in pressure symptoms and persist in the long-term [33, 34]. Diminishing efficacy of EA is primarily related to higher baseline volume, the occurrence of rapid haemorrhagic refilling, or the presence of a relevant solid component [33]. Even if trials with TA of cystic thyroid nodules are limited, LA and RFA achieve a significant reduction also of the solid part of complex thyroid nodules and usually control the regrowth of cysts relapsing after EA [35].

Notably, in conflict with the robust evidence on MIT efficacy and safety, >1/3 of the ETA respondents indicate surgery as their preferred choice for a young patient with a recurrent benign thyroid cyst. This finding clearly indicates that ETA respondents are insufficiently familiar with MIT (EA in this case), as about 80% of them do not personally perform EA, and since for about 80% of respondents EA is unavailable as interventional procedure in their institutions. The lack of personal experience and limited availability of such techniques are probably the main reasons driving physicians to refer patients towards surgery instead of MIT.

Solid Nodules

Both LA and RFA induce clinically significant nodule volume reduction and improvement of both cosmetic concerns and pressure symptoms in the majority of patients. Short- and long-term efficacies of the TA procedures have been demonstrated in several single [36] and multicentre randomized trials [37, 38]. Results are stable over time, with a >50% volume reduction at 36 and 60 months and low rate of long-term re-growth. Long-term results appear more favourable in spongiform and complex than in solid nodules [39]. TA procedures are rapid and well-tolerated, effectively performed in out-patient clinics, major complications are rare, and minor complications are reported only in a minority of patients. Most important, post-treatment thyroid function changes are very uncommon [36–38]. Data from validated thyroid disease specific questionnaires assessing QoL changes are limited but a few prospective studies showed significant improvement after TA [24, 36–38].

The body of evidence on the use of MWA is smaller than that for LA and RFA. However, the published retrospective trials, meta-analyses and multicentre prospective studies demonstrated encouraging results (12-month volume reduction ratio of 75–90%), although the treated nodules were usually small (<10 mL) [13, 40, 41].

Prospective randomized trials using HIFU for thyroid nodule ablation are lacking. Volume decrease after HIFU is reported as 50–70% in single-centre studies [42]. Due to the need of a careful nodule selection, the cost and the limited experience, HIFU is at present considered mainly for patients who decline or are not suitable for other TA options.

We conclude that the minority of respondents who consider the use of TA for symptomatic thyroid nodules focus more on avoiding the risks of surgical intervention in elderly patients than on preventing the life-long adverse influence of surgery on the QoL in younger patients.

Hyperfunctioning Nodules

Data from controlled trials with LA [43, 44] and RFA [45, 46] demonstrated the attainment of euthyroidism in about 50% of the AFTN patients after 12 months. TA was followed by a >75% volume decrease and normalization of thyroid function in the majority of small size (e.g., ≤10 mL) hyperfunctioning nodules. In contrast, thyroid function was normalized only in a small fraction of larger lesions [46]. Thus, TA appears appropriate for patients with small AFTN who decline, or are not amenable to RAI therapy or thyroid surgery. HIFU appears as less effective than RAI since thyroid function normalization

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Eur Thyroid J 2020;9:194–204
DOI: 10.1159/000506513

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was obtained at 12-months in 94% of the RAI-treated versus 53% of the HIFU-treated subjects [47]. Data concerning the efficacy of MWA is presently considered insufficient.

Notwithstanding the favourable data concerning LA and RFA, the current survey demonstrates therapeutic inertia in dealing with small AFTN in young patients, as 21% of respondents indicated a wait-and-see strategy instead of TA, a therapeutic option that could control subclinical hyperthyroidism and prevent further nodule growth with low risk of late hypothyroidism.

**Thyroid Cancer and Lymph Node Metastases**

TA as well as EA have been reported to offer promising results in the treatment of local recurrent and and/or persistent DTC [48]. The results of the present survey are, to some extent, controversial. While TA was considered an option as valuable as surgery for cervical recurrences of DTC in young patients, it would be adopted only by a small minority of respondents in the elderly.

Despite the growing evidence, even in the absence of randomized controlled trials offering evidence of efficacy of TA for small and low-risk PTMCs [49, 50], the use of TA is currently considered only by a small minority of the responders, and is deemed as a less appropriate management alternative than watchful waiting without any intervention.

The main scope of our survey was to test the attitude of ETA members towards the use of MIT in benign thyroid nodules and cysts. A survey dedicated to the use of MIT for thyroid malignancies, and addressed to clinicians committed in their practice to thyroid oncology, is needed to provide more accurate results on the perceived role of MIT in that specific field.

A strength of this survey is that respondents were from European countries, albeit we acknowledge that about one of four respondents were from outside Europe. The exact number of European ETA-members who clinically manage thyroid patients is unavailable; as a consequence, we cannot generalize our findings to all European thyroidologists. The number of analysed responses is somewhat small to draw firm conclusions and the small number of thyroidologists from each single country made any comparison between countries unreliable. The high proportion of ETA members who did not open the questionnaire, the number of who did not answer all the questions, and the lack of both content and construct validation of the questionnaire are other limitations to the interpretation of the data. In surveys, self-selection of respondents is an unavoidable bias that may distort conclusions from gathered data. However, it most likely that our data represent a best scenario, as for availability of MIT to thyroid patients, in view of the representation of specialized centres and the fact that the vast majority of respondents routinely treated thyroid patients. It is unlikely that a real-world scenario, interrogating an unselected group of physicians, globally seeing the majority of thyroid patients, would have demonstrated a higher implementation of MIT in this patient group.

**Overall Conclusions and Perspectives**

Up-to-date management of nodular thyroid disease demands availability of several diagnostic and therapeutic modalities in order to obtain a correct diagnosis and offer appropriate treatment options. The present ETA survey shows that while US, US-guided FNA and surgery are widely available, other well-established techniques such as CNB and EA are performed personally by only about 10 and 20% of respondents respectively. Importantly, TA procedures are, on average, available to only 16% of the respondents. A worrying finding, that requires action, is the fact that the overwhelming majority of ETA-members are unfamiliar with MIT, which is performed, on average, by only about 5% of respondents. Even less acceptable is the lack of referring patients, whatever their phenotype, to centres with ability to perform these procedures.

Several reasons may explain why therapeutic techniques, some, in this case MIT, available for decades, have not to a higher degree been implemented. Among these, the absence of dedicated training courses and the lack of an appropriate and consistent reimbursement policy by the National Health Services are possibly the most relevant. As a wake-up call to the ETA the most common explanation provided by the respondents was lack of adequate information and the absence of guidelines from the major Endocrine Societies. As a consequence, the ETA has appointed a panel of experts, with dedicated expertise in MIT, in order to provide clear and evidence-based recommendations for the use of MIT. In the near future, the availability of authoritative guidelines, and the establishment of and access to dedicated courses for training, are intended to improve this still unsatisfactory use of nonsurgical procedures for clinically relevant thyroid lesions, and thereby address the current geographic inequality in therapy options.
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Acknowledgement
There are no acknowledgments to declare.

Statement of Ethics
Not applicable.

Disclosure Statement
The authors have nothing to disclose.

References

Funding Sources
There are no funding sources to declare.

Author Contributions
All authors conceived of the presented idea, supervised the findings of this work, discussed the results and contributed to the final manuscript. E.P. and L.H. developed the questionnaire; R.N. evaluated data.

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Eur Thyroid J 2020;9:194–204
DOI: 10.1159/000506513

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