

Minimally Invasive Ablative Treatments for Benign Thyroid Nodules Current Evidence and Future Directions

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Most thyroid nodules are benign, normo-functioning, and asymptomatic¹⁻². A minority of them grow over time, become locally symptomatic, and require intervention³. Yet, due to the high prevalence of nodular goiter⁴, many patients are referred for surgery without being offered non-surgical alternatives⁵. Surgery, for nodular thyroid disease, is effective and generally safe but is expensive, requires hospitalization, and causes loss of working days⁶. Risk of hypothyroidism, voice changes, and cosmetic damage may have been underestimated in the past but are now an overriding concern for patients with benign thyroid disease⁷. These are among the reasons for nonsurgical management – either with radioiodine⁸ or with image-guided procedures⁹ - being developed and proposed over the last three decades.

Percutaneous ethanol injection was the first ultrasound-guided minimally invasive procedure (MIT) employed in 1990 for hyperfunctioning thyroid nodules¹⁰. While given up for solid nodules, due to limited efficacy, risk of recurrence, and potential side-effects¹¹⁻¹², it has become the standard treatment in cystic nodules because of the efficacy and safety of ethanol injection into a cavity¹³⁻¹⁴. Accepting the limitations of EA in the management of solid thyroid lesions, laser ablation therapy (LTA) was proposed in the early 2000's as the first method for the reduction of nodule volume by means of locally delivered thermal energy¹⁵⁻¹⁶. Since then, moving-shot radiofrequency ablation (RFA)¹⁷, introduced in 2006, high-intensity focused US (HIFU)¹⁸, and microwaves (MWA)¹⁹ have broadened MIT options. During the last twenty years, MITs have consistently documented therapeutic efficacy in prospective randomized trials²⁰⁻²³, large retrospective real-world series²⁴⁻²⁸, and various meta-analyses²⁹⁻³¹. Thus, US-guided TA procedures are now established alternative options to surgery based on robust evidence demonstrating significant decrease of benign thyroid nodule volume and control of local symptoms without causing hypothyroidism or cosmetic damage, with a low risk of complications and no need of hospitalization. The increasing number of publications from several continents as well as guidelines from major international societies, including endocrine, surgical, and radiological associations have undoubtedly accelerated interest in, and implementation of, MITs³²⁻³⁸. Importantly, some issues remain unclarified³⁹ and need further study to better define the appropriate everyday use of MITs.

In the present issue of *Thyroid*, Chorti A et al. provide a timely review of the efficacy and safety of the different MITs employed for the management of symptomatic thyroid nodules in comparison to thyroidectomy⁴⁰. Their network meta-analysis integrates both direct and indirect evidence, to offer a global estimate of the outcomes of the various treatments. The evaluation of 3 RCTs and 13 comparative case series, including 4112 patients, demonstrates the absence of statistically significant differences between RFA, LA, MWA and HIFU regarding nodule volume reduction rate (VRR), improvement of local symptoms, and cosmetic score. The largest VRR was, unsurprisingly, obtained by surgery but the improvement of local symptoms was similar to that achieved by MITs. Thermal ablation techniques, on the other hand, resulted in a significant reduction of the risk of recurrent laryngeal nerve damage, hypothyroidism, and post-operative complications. The results of this study confirm, once more, that MITs are effective therapeutic procedures which should be considered as valid alternatives to surgery, especially for patients who are at surgical risk and for those who do not accept the risk of surgical complications, including cosmetic considerations and hypothyroidism. Use of MITs also, typically, infer a substantial reduction of cost as well as days of in-hospital stay⁴¹.

Our enthusiasm needs to be tempered by the following issues. The quality of the available studies is heterogeneous and mainly based on retrospective data. Most available trials have enrolled nodules of widely different volume and structure. It is now well established that MIT outcomes are more favorable in spongiform and complex lesions than in completely solid nodules; also, that the attained VRR is generally lower in large than in small, presumably asymptomatic, thyroid lesions^{28, 42}. These potentially confounding variables, to some extent present in most studies, may undoubtedly influence the results and thereby the interpretation of systematic reviews and meta-analyses. The follow-up, post-MIT, is, with a few exceptions, short-term for a slowly evolving condition. This latter consideration is of great importance because nodule regrowth is reported to be as high as 15% at 5 years⁴²⁻⁴³ stressing the need of long-term follow-up to evaluate the consequences, including that of cost and compliance, in case of re-treatment⁴¹. Importantly, MIT trials frequently have not used a well-standardized methodology for defining the treatment modalities and the clinical and imaging outcomes of TA procedures⁴⁴. Finally, head-to-head studies of MIT versus

surgery are, most often, not prospective and have not considered lobectomy alone as the only appropriate surgical comparator⁴⁵.

In view of the available solid evidence, we do not need further retrospective or uncontrolled studies evaluating the efficacy of MIT for reduction of nodule volume and amelioration of cosmetic concerns. Similarly, trials addressed establishing a hierarchy of efficacy between the various MIT procedures are of limited interest, because MITs are strongly operator-dependent, non-standardized, and outcomes therefore influenced by the specific local expertise. Notably, the devices employed for RFA, LTA, and MWA are undergoing a continuous technical evolution that improves their efficacy while decreasing the invasiveness of the procedure. Thus, we recommend using the MIT option that is available (potentially also used for non-thyroid indications) and where local expertise offers optimal cost-effectiveness, taking side effects and health-related quality of life (HRQoL) into consideration⁴⁶⁻⁴⁷. What primarily remains to be studied, is well-designed prospective head-to-head studies of the various MITs versus surgery (performed only as lobo-isthmusectomy) and include HRQoL evaluation using validated questionnaires, which can also ascertain minimal important change in HRQoL, e.g., the ThyPRO,⁴⁸⁻⁴⁹ induced by any MIT procedure. Long-term prospective follow-up trials should clarify whether MITs represent a definitive intervention, obviating repeat treatments. Finally, the global long-term costs of the different approaches and their accessibility, currently poor, should be uncovered and improved⁴¹.

Much has happened over the past couple of years and multidisciplinary documents from relevant societies have been published^{32-38, 50}. Therefore, the major challenges extend beyond: “Not if, but why, when, and how”⁵¹. Currently, the major challenges relate to making MITs globally available, avoiding competition over which specialty takes command of MITs, secure multidisciplinary evaluation in the needy, and establish education and training modalities⁵². Structured academic courses and training opportunities under the supervision of tutors with specific expertise should be offered to the operators who are approaching the use of MIT for thyroid nodules. This means a close collaboration between endocrinologists, interventional radiologists, neck surgeons, and nuclear medicine physicians. We consider it advantageous to incorporate the management of benign and

malignant thyroid nodules in the same multidisciplinary organizational structure, accepting that our knowledge regarding the latter⁵⁰ is not as advanced as that of the former³⁵⁻³⁶.

Author Contributions

Both authors contributed equally to the manuscript and approved the final version.

Disclosures

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