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LETTER TO THE EDITOR



Is there a role for minimally invasive thermal ablations in the treatment of autonomously functioning thyroid nodules?

Despite the explosive interest in US-guided thermal ablations for percutaneous treatment of benign symptomatic thyroid nodules, there is still no consensus for their use in functioning nodules. While the Korean Society of Radiology recommended the use of radiofrequency ablation in 2012 for 'patients with autonomously functioning thyroid nodules (AFTN) causing problems related to thyrotoxicosis' [1], the recent update of the AACE-ACE-AME guidelines does not include AFTN among the indications to thermal ablations [2].

AFTN account for up to 10% of cases of thyroid nodular disease. Malignancy is extremely rare, surgery rarely necessary, and radioiodine (^{131}I) is considered as the first-line therapy in the majority of patients, whether affected by hyperthyroidism or not, and whether pre-treated with antithyroid drugs or not [3–6]. Several studies have reported normalization of thyroid function in 75–95% of patients within 3–12 months following ^{131}I therapy, reduction of nodule volume by 30–45% within 1–2 years and long-term (≥ 5 years) risk of hypothyroidism of no more than 10–20% [3,4,7]. Given that some patients might have contraindications to radiation exposure and that late hypothyroidism may occur, minimally invasive therapies (MITs) have been used to treat AFTN. Percutaneous ethanol injection (PEI), laser ablation technique (LA) and radiofrequency ablation (RFA) have been to be successful in the treatment of AFTN.

In a study by Monzani et al., 132 patients with AFTN were treated with 2–16 PEI treatment sessions. The authors reported that all 47 patients with pretoxic adenomas and 60 of the 85 patients (70.6%) with toxic adenomas were completely cured, while partial cure was observed in 11 cases (12.9%), and failure in 14 (16.5%). Patients were followed for up to 8.5 years (median 76 months). However, with PEI treatment, about 40 of the 132 patients reported mild to moderate therapy-related pain [8]. Furthermore, in the case of nodules with a high solid component, PEI has limited efficacy due to the fact that ethanol does not easily diffuse into compact tissue and therefore does not induce widespread, sustained coagulative necrosis. Thus, this technique has now been abandoned by most and it is only recommended as first-line therapy in recurrent benign purely cystic nodules or in those with a high cystic component.

The use of LA for AFTN has been tested in a few small series of patients [9–17], with multiple LA sessions generally needed to normalize serum TSH levels in solitary AFTN or in multinodular goitres [11,13,16,17]. In a randomized trial, LA and ^{131}I treatments both resulted in a similar reduction of AFTN volume but LA achieved normalization of serum TSH levels in far fewer patients [14]. Similar outcomes were obtained in some non-controlled series of AFTN treated with RFA [18–23].

Some authors have reported that sustained, extensive destruction of the functioning tissue is necessary to achieve not only the improvement of symptoms but also their effective remission, with restored euthyroidism [17,24]. In their 2011 study [17], Amabile et al. reported excellent results treating hyperfunctioning nodules with volumes exceeding 40 ml by delivering a high amount of energy in multiple treatment cycles (up to three) with multiple LA sessions (up to three for each cycle). The serum FT3 levels of all 26 patients with hyperfunctioning thyroid nodules were normalized, and in 23 of the 26 (88.5%) patients, a normalized serum TSH level was observed. It seems important to note that none of the patients developed hypothyroidism following LA. The more favorable therapeutic outcome observed in this series (88.5% of cured patients as compared to 50% in the study by Dossing et al. [14]) is likely due to the different mean percent reduction of nodular volume (77.3%) as compared with 44% in the study by Dossing et al. [14]. ROC curves identified the percentage of volume reduction as the best parameter predicting a normalized serum TSH (area under the curve 0.962; $p < .0001$). According to the ROC curves, the cut-off of percent nodular volume reduction able to guarantee the normalization of serum FT3 and TSH was 79.3%.

The recent retrospective study by Gambelunghe et al. [25] on 82 patients with three years of follow up published in the February 2018 issue of IJH seems to confirm Amabile's data. Gambelunghe et al. conclude that it is possible to restore euthyroidism when high percentages of coagulative necrosis are obtained. These authors achieved a high percentage of recovery in small nodules using a single treatment of LA; results were progressively worse as nodule size increased. Indeed, baseline nodule volume was significantly associated with the treatment's success; the percentage of patients who discontinued methimazole therapy was inversely related with the initial volume of the toxic nodules. All patients who had nodules with a volume less than 5 ml were able to suspend methimazole, while 90.2% of patients with nodules with a volume 5–15 ml, 61.1% of those with a volume of 15–25 ml and 28.5% in nodules larger than 25 ml suspended the therapy.

Bernardi et al. also highlighted that a large reduction in the volume of nodules treated with a single session was important to restoring euthyroidism in hyperthyroid patients [24]. In their study, the authors correlated volume reduction at the twelfth month to therapeutic response. These authors highlighted that a single RFA session reduced thyroid nodule volume by 51%, 63%, 69% and 75% after 1, 3, 6 and 12 months, respectively, and that a single RFA session allowed 50% of the patients with AFTN to suspend

antithyroid medication; these patients remained euthyroid afterwards. The patients that went into complete symptom remission had an average volume reduction of 81%, compared to those patients that had only partial symptom improvement, who had a 68% reduction.

In the January 2018 issue of IJH, Cesareo's study [26] confirms these results obtained with a single session of RFA in nodules with a volume ≤ 12 ml. This was a 24-month prospective monocentric open parallel-group trial in which 29 patients with AFTN were divided into 2 groups based on thyroid volume: 15 patients with small nodules (<12 ml) in group A and 14 patients with medium nodules (>12 ml) in group B. All patients were clinically, biochemically, and morphologically evaluated at baseline and at 1, 6, 12 and 24 months after treatment. After RFA, there was greater nodule volume reduction in group A than in group B ($p < .001$ for each follow-up point). There was a greater increase in TSH levels in group A than in group B at 6 ($p = .01$), 12 ($p = .005$) and 24 months ($p < .001$). At 24 months, the rate of responders was greater in group A than in group B (86 vs 45%; $p < .001$). In group A, 86% of nodules converted from hot to cold compared with 18% in group B ($p < .001$). The authors thus conclude that a single session of RFA was effective in restoring euthyroidism in patients with small AFTN and state that nodule volume seems to be a significant predictive factor of the efficacy of RFA in treating AFTN.

Thermal ablations can also be used in combination with radioiodine ablation to accelerate the recovery process and to reduce the radiation dose, as reported by Chianelli et al. [27]. In their 24-month pilot prospective study in a population of large toxic goiters (27.7 ± 17.0 vs 29.4 ± 10.6 ml at baseline), these investigators compared a group of 15 patients with functioning nodules treated with laser technique followed by radionuclide therapy (combined therapy) with a group of 17 patients with matched clinical, demographic, and instrumental findings treated only with ^{131}I . Combined treatment determined faster control of hyperthyroidism. At 1 month, normalization of TSH levels was observed in the group treated with combined therapy. LA resulted in a reduction in administered ^{131}I activity (lower than 600 MBq). In three patients with nodule size <5 cm, LA induced normalization of TSH without any need for subsequent administration of radioiodine. Therefore, complete ablation determines rapid recovery of thyroid function. Finally, it should be emphasized that no patient in this series progressed to hypothyroidism.


In conclusion, we think image-guided thermal ablations might have a relevant application in the treatment of AFTN. In this scenario, similarly than what happens in the treatment of non-functioning thyroid nodules, LA and RFA seems to provide similar clinical results [28–30]. Thus, more than the used technique, the percentage of volume ablation seems to play a crucial role in the treatment of AFTN with MITs. In conclusion, in patients with nodules with volumes contained around 13 ml in which the functional and non-compressive problem prevails, it is possible to solve the problem with a single treatment in a high percentage of cases. In patients with larger volume, thermal ablation can be used before

radioiodine ablation in order to fasten the recovery process and to reduce the radiation dose to the patient.

Disclosure statement

No potential conflict of interest was reported by the authors.

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