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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 ($\geq$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 $\leq$12 ml. This was a 24-month prospective monocentric open parallel-group trial in which 29 patients with AFTN were divided into 2 groups based on thyroid volume: 15 patients with small nodules (<12 ml) in group A and 14 patients with medium nodules (>12 ml) in group B. All patients were clinically, biochemically, and morphologically evaluated at baseline and at 1, 6, 12 and 24 months after treatment. After RFA, there was greater nodule volume reduction in group A than in group B ($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 happen 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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References

[1] Na DG, Lee JH, Jung SL, et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J Radiol. 2012;13:117–125.

[2] Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for clinical practice for the diagnosis and management of thyroid nodules–2016 update. Endocr Pract. 2016;22:622–639.

[3] Hegedus L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. Endocr Rev. 2003;24:102–132.

[4] Bonnema SJ, Hegedus L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocr Rev. 2012;33:920–980.

[5] Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract. 2011;17:456–520.

[6] Haugen BR, Sawka AM, Alexander EK, et al. American Thyroid Association Guidelines on the management of thyroid nodules and differentiated thyroid cancer task force review and recommendation on the proposed renaming of encapsulated follicular variant papillary thyroid carcinoma without invasion to noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Thyroid. 2017;27:481–483.

[7] Nygaard B, Hegedus L, Nielsen KG, et al. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. Clin Endocrinol. 1999;50:197–202.

[8] Monzani F, Caraccio N, Goletti O, et al. Treatment of hyperfunctioning thyroid nodules with percutaneous ethanol injection: eight years' experience. Exp Clin Endocrinol Diabetes. 1998;106:S54–S58.

[9] Dossing H, Bennedbaek FN, Hegedus L. Ultrasound-guided interstitial laser photocoagulation of an autonomous thyroid nodule: the introduction of a novel alternative. Thyroid. 2003;13:885–888.

[10] Spiezia S, Vitale G, Di Somma C, et al. Ultrasound-guided laser thermal ablation in the treatment of autonomous hyperfunctioning thyroid nodules and compressive nontoxic nodular goiter. Thyroid. 2003;13:941–947.

[11] Pacella CM, Bizzarri G, Spiezia S, et al. Thyroid tissue: US-guided percutaneous laser thermal ablation. Radiology. 2004;232:272–280.

[12] Gambelunghe G, Fatone C, Ranchelli A, et al. A randomized controlled trial to evaluate the efficacy of ultrasound-guided laser photocoagulation for treatment of benign thyroid nodules. J Endocrinol Investig. 2006;29:RC23–RC26.

[13] Barbaro D, Orsini P, Lapi P, et al. Percutaneous laser ablation in the treatment of toxic and pretoxic nodular goiter. Endocr Pract. 2007;13:30–36.

[14] Dossing H, Bennedbaek FN, Bonnema SJ, et al. Randomized prospective study comparing a single radioiodine dose and a single laser therapy session in autonomously functioning thyroid nodules. Eur J Endocrinol. 2007;157:95–100.

[15] Valcavi R, Bertani A, Pesenti M, et al. Laser and Radiofrequency ablation procedures. In: Baskin HJ, Duick DS, Levine RA, editors. Thyroid ultrasound and ultrasound guided FNA biopsy. 2nd ed. New York: Springer; 2008. p. 191–218.
[16] Rotondi M, Amabile G, Leporati P, et al. Repeated laser thermal ablation of a large functioning thyroid nodule restores euthyroidism and ameliorates constrictive symptoms. J Clin Endocrinol Metab. 2009;94:382–383.
[17] Amabile G, Rotondi M, Pirali B, et al. Interstitial laser photocoagulation for benign thyroid nodules: time to treat large nodules. Lasers Surg Med. 2011;43:797–803.
[18] Spiezia S, Garberoglio R, Di Somma C, et al. Efficacy and safety of radiofrequency thermal ablation in the treatment of thyroid nodules with pressure symptoms in elderly patients. J Am Geriatr Soc. 2007;55:1478–1479.
[19] Deandrea M, Limone P, Basso E, et al. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. Ultrasound Med Biol. 2008;34:784–791.
[20] Spiezia S, Garberoglio R, Milone F, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid. 2009;19:219–225.
[21] Faggiano A, Ramundo V, Assanti AP, et al. Thyroid nodules treated with percutaneous radiofrequency thermal ablation: a comparative study. J Clin Endocrinol Metab. 2012;97(12):4439–4445.
[22] Baek JH, Jeong HJ, Kim YS, et al. Radiofrequency ablation for an autonomously functioning thyroid nodule. Thyroid. 2008;18:675–676.
[23] Baek JH, Moon WJ, Kim YS, et al. Radiofrequency ablation for the treatment of autonomously functioning thyroid nodules. World J Surg. 2009;33:1971–1977.
[24] Bernardi S, Stacul F, Michelli A, et al. 12-month efficacy of a single radiofrequency ablation on autonomously functioning thyroid nodules. Endocrine. 2017;57:402–408.
[25] Gambelunghe G, Stefanetti E, Colella R, et al. A single session of laser ablation for toxic thyroid nodules: three-year follow-up results. Int J Hyperthermia. 2018;22:1–5. doi:10.1080/02656736.2018.1437931
[26] Cesareo R, Naciu AM, Iozzino M, et al. Nodule size as predictive factor of efficacy of radiofrequency ablation in treating autonomously functioning thyroid nodules. Int J Hyperthermia. 2018;6:1–7. doi:10.1080/02656736.2018.1430868
[27] Chianelli M, Bizzarri G, Todino V, et al. Laser ablation and 131-Iodine: a 24-month pilot study of combined treatment for large toxic nodular goitre. J Clin Endocrinol Metab. 2014;99(7):E1283–1286.
[28] Mauri G, Cova L, Monaco CG, et al. Benign thyroid nodules treatment using percutaneous laser ablation (PLA) and radiofrequency ablation (RFA). Int J Hyperthermia. 2016;15:1–5.
[29] Pacella CM, Mauri G, Cesareo R, et al. A comparison of laser with radiofrequency ablation for the treatment of benign thyroid nodules: a propensity score matching analysis. Int J Hyperthermia. 2017;33(8):911–919.
[30] Mainini AP, Monaco C, Pescatori LC, et al. Image-guided thermal ablation of benign thyroid nodules. J Ultrasound. 2017;20:11–22.

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