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THERMO-ABLATIVE THERAPIES: A NEW HORIZON FOR THE ENDOCRINOLOGIST?

Thyroid nodules

Thyroid nodular pathology is very common in clinical practice, because about 50% of the general population has thyroid nodules. Thyroid ultrasound is the "gold standard" for the description of thyroid nodules and also for the choice of lesions that deserve a cytologic in-depth diagnostic analysis using an eco-guided needle-aspirate. Most nodules (95%) are benign in nature. When benign nodules increase in volume, they can cause compressive symptoms in the structures of the neck (dyspnea, dysphagia, sense of constriction) and / or esthetic problems (1,2). Furthermore, every year, 4% of pre-toxic nodules undergo overt hyperthyroidism, which requires treatment.

The role of surgery, radio-metabolic therapy and levo-thyroxine

Often patients with symptomatic thyroid nodules are sent to surgery. Surgical treatment has a risk of complications estimated at 2% to 10%, may require lifetime hormone replacement therapy, is expensive, may not be indicated for patients at high surgical risk or who refuse this therapeutic option. The administration of radio-iodine (131I) is another possible therapeutic option in multi-nodular goiters. In non-toxic ones it can also be used for cyto-reductive purposes. This therapy has some limitations, such as non-usability in pregnancy, during breastfeeding and in the pre-conception period. Furthermore, increased mortality has been described following radio-metabolic therapy. Finally, therapy with levo-thyroxine for the treatment of thyroid nodular pathology is not recommended by the current guidelines of the AACE / AME / ETA of 2010, since only a few patients undergo volumetric reduction of the nodules, while related side effects may appear to iatrogenic subclinical hyperthyroidism (reduction of bone mineral density and atrial fibrillation) (3).

The role of eco-guided thermo-ablative therapies

In the last two decades, for the treatment of benign, hyperfunctioning and non-thyroid nodules, non-surgical, percutaneous, eco-guided, minimally invasive techniques have been proposed, practicable even in patients with contraindications at surgery or in patients who refuse surgery.

Eco-guided alcoholization (**EA, Ethanol Ablation**) was the first ablative (chemical) treatment used in nodular thyroid pathology. It is currently usable in the treatment of cystic nodules and mixed nodules with a predominantly liquid component. It no longer has any indication in solid lesions and hyperfunctioning nodules, both due to the lack of efficacy and the potential risk of uncontrolled alcohol diffusion with possible recurrent nerve damage. Because of these limitations, techniques have been developed for the treatment of solid thyroid nodules that destroy the nodular thyroid tissue by overheating

with various physical means (thermo-ablative techniques). The destroyed tissue first encounters inflammation, then reabsorption with fibrotic-scar tissue repair and conspicuous reduction in volume.

Laser ablation (LA) uses photons released by optical fibers inserted into the tissue to be destroyed (fig. 1). It was introduced in 2000 and since then there have been numerous evidences about the clinical utility of this method in thyroid nodular pathology (2,4,5). Current AACE / AME / ETA guidelines on thyroid nodule management describe the clinical efficacy and safety of LA. Its use is restricted to patients who refuse surgery or are at high surgical risk (3).

Figure 1. Illumination phase of 3 laser fibers inside a thyroid nodule In LA they are inserted in a cranio-caudal direction from 1 to 4 optical fibers using Chiba 21G needles. Since there is no cooling of the laser source, the heat around the fiber causes vaporization of the surrounding tissues, which create cavitations and tissue carbonization ("charring").

Radiofrequency ablation (**RFA, radiofrequency ablation**) (fig. 2) has been used since 2006 in the treatment of thyroid nodules. It uses a high frequency radio wave, which overheats the tissue by ion friction. The still valid recommendation is to use this method only in selected cases (3). A systematic review with meta-analysis in 2014 demonstrated the efficacy and safety of RFA in the treatment of symptomatic thyroid nodules, with reduction of compression, improvement of esthetic discomfort and control of thyroid hyperfunction (6). This coincides with our experience (data being published). A recent systematic review (June 2014) of the Cochrane Collaboration, which took into consideration 5 randomized controlled clinical trials on LA and RFA, highlighted the effectiveness of these two methods in volumetrically reducing thyroid nodules and in improving compressive and esthetic symptoms (7).

Figure 2. Ablation of thyroid nodule with radiofrequency In RFA a needle-electrode with internal cooling of 18G is inserted in trans-isthmic direction, with an active tip of 1 cm. The active tip determines a sphere of coagulative necrosis of thyroid tissue around the needle, termed "ablation unit". The "moving shot" technique involves the movement of the needle-electrode inside the thyroid nodule, so that the whole nodule is ablated.

HIFU (**High-Intensity Focused Ultrasound**) (fig. 3) is a third thermo-ablative method, which allows the treatment of thyroid nodules with a beam of ultrasound concentrated in a small area; the ablation of significant volumes is obtained by the movement of a robotic arm that repeats the elementary ablative unit in several points. It has the advantage of not being operator-dependent and avoiding the insertion of needles into the patient's neck. The first case published is from 2010 and the scientific evidence regarding the effectiveness of the method is constantly increasing.

Fig. 3. Treatment of thyroid nodule by HI-FU The VTU unit (Visual Treatment Unit) is applied on the patient's neck and high frequency ultrasounds determine the hyperthermic damage inside the thyroid nodule.

Micro-wave ablation (MWA) has only recently been introduced and further studies are needed to verify its clinical impact.

Current and future perspectives of thermo-ablative techniques in the treatment of benign nodules

The interest in minimally invasive ablative therapies of benign thyroid nodules is increasing. The major thyroidologists and authors of guidelines recommend continuing studies on this topic by conducting high-quality scientific work (RCT), with strong

end-points (quality of life), long follow-up and comparison of mini-methods invasive among them and vs surgery (1,2). Soon the new AME-AACE guidelines on thyroid nodule management will be released: given the robust scientific evidence of recent years, it is expected that minimally invasive thermo-ablative therapies will be given a much more important clinical role than in 2010.

The role of thermo-ablative techniques in thyroid malignant pathologies

The potential of thermo-ablative treatments also extends to malignant diseases: local tumor recurrences not surgically treatable, primitive papillary micro-carcinoma (MPTC). An application that is recently emerging with great potential is the treatment with these MPTC techniques. In about half the cases the dimensions of papillary thyroid carcinoma are <1 cm (micro-carcinoma). The primary treatment of the MPTC was tested by us with LA in 2013 with a positive outcome (8). The possibility of treating this type of tumor with LA had been advanced by Papini et al in 2011. In 2012 Fukunari et al reported the resolving treatment of 9 patients with MPTC by RF, while in 2013 Hay et al treated 3 patients with MPTC by PEI. In 2014, Yue et al treated 21 patients with MPTC using MW. Finally, Callender et al are currently conducting a clinical trial with which they intend to compare thyroidectomy vs PEI in the treatment of MPTC (clinicaltrials.gov NCT01974284). LA or RFA have been successfully used in the metastasis isolated from papillary carcinoma (9).

Conclusions

Current indications for the treatment of thyroid pathologies with thermo-ablative techniques The thermo-ablative eco-guided techniques can be used as an alternative to surgery in patients of both sexes with thyroid nodules that cause esthetic problems or compressive problems in the neck . The thyroid nodule to be treated must be benign at the needle-aspirate for at least 2 times, the last of which no more than 3 months before. Nodular lesions with a solid or mixed eco-structure can be ablated. The nodules that respond better to hyperthermic treatment appear to be spongiform ones, followed by mixed and compact ones.

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