Review Article on Interventional Radiology in Glands

Interventional radiology of the thyroid gland: critical review and state of the art

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Abstract: Thyroid nodules are a common incidental finding during a routinely ultrasound (US) exam unrelated to the thyroid gland in the healthy adult population with a prevalence of 20–76%. As treated before with surgery, in the last years new minimally invasive techniques have been developed as an alternative to surgery. The aim of this review, based on newly revised guidelines, is to provide some information regarding the basic principles, indications, materials, techniques, and results of mini-invasive procedures or treatments for thyroid nodules. We performed a narrative review including both newest and representative papers and guidelines based on the different procedures of ablation techniques developed in the last years for the diagnosis and the treatment of thyroid nodules. All examined papers referred very good results in term of volume nodule reduction, improvement in related symptoms and cosmetic problems, with a very low rate of complications and side effects for all the minimally invasive technique analyzed. Obviously, some differents between technique based on different kind of thyroid nodules and different indication were found. In conclusion, many thyroid nodules nowadays could be treated thanks to the advent of new mini-invasive technique that are less expensive and present a lower risk of major complications and side effects compared to surgery.

Keywords: Thyroid nodule; ablation technique; ethanol injection; laser; radiofrequency; microwave; high intensity focused ultrasound (HIFU)

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Introduction

Palpable thyroid nodules are found in about 5% of world population in non-endemic areas with right iodine supplement, with a higher correlation with sex (prevalence in women), age, abnormal intake of iodine and ionizing radiation exposure (1-3). Thyroid nodules are a common incidental finding during routinely ultrasound (US) exams unrelated to thyroid gland in the healthy adult population with a prevalence of 20–76%. The majority of thyroid nodules are benign (>95%) and as long as they do not cause associated symptoms like dyspnea, dysphagia, hoarseness, hyperthyroidism or cosmetic problems, they do not need any treatment (1,4). Beside malignant nodules, treatment should be considered even for growing or large nodules (>4 cm) and in presence of clinical symptoms or cosmetic problems. Surgical procedures such as radical thyroidectomy or hemithyroidectomy have been considered as the gold standard, even though associated with high, sometimes

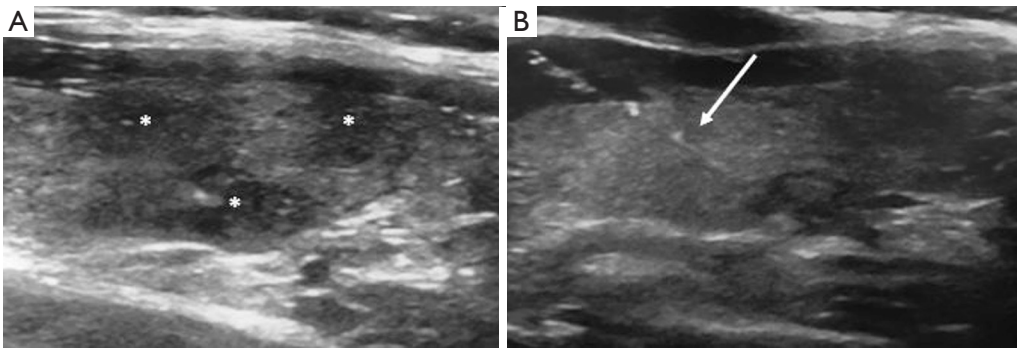

Figure 1 FNAB procedure in a patient with multinodular goitre. (A) US images of thyroid show three hypo-echogenic nodules (*); (B) US-guided FNAB of one nodule. The needle (white arrow) with its tip perfectly inserted inside the lesion is shown. FNAB, fine-needle aspiration biopsy; US, ultrasound.

permanent, risks of complications (bleeding, infection, lesion of recurrent laryngeal nerve, large neck scar, and hypothyroidism), leading patients to a long-term drug treatment with controversial efficacy. In addition, due to the request of general anesthesia, surgery may not be indicated for all patients (2,5-7). More recently, in the radiological field, new non-invasive procedures have been developed as alternative to surgery (8-19). The aim of this review, based on newly revised guidelines, is to provide some information regarding the basic principles, indications, materials, techniques and results of mini-invasive procedures or treatments for thyroid nodules.

Thyroid fine-needle aspiration biopsy (FNAB)

Today, FNAB represents the gold standard for the diagnosis of the nature of thyroid nodules due to its safety, reliability, low costs and high tolerability by the patients (3,20). According to the newly reviewed guidelines for thyroid nodules (<5 mm), US monitoring is always recommended. FNAB is indicated in presence of large nodules (≤5–10 mm), with dubious US features associated to pathologic lymphnodes, extrathyroidal growth, personal or familiar history of thyroid cancer, and dubious clinical or imaging findings. In addition, FNAB should be performed in case of (I) nodules (>10 mm) showing frankly benign features; (II) nodules (≥20 mm) with spongiform, iso-hyperechoic or predominant (>50%) cystic aspect in absence of suspicious US findings; (III) in presence of progressive increase in size. Exclusion criteria include presence of hot nodules on scintigraphy and/or patients with severe coagulation disorders. US guidance makes FNAB safer and is now considered mandatory, allowing real-time control of the tip of the needle when approaching the target areas avoiding the vascular structures (1,3,21-23). Five cytologic diagnostic categories are considered for the diagnosis of thyroid nodules (1): nondiagnostic, benign, indeterminate, suspicious for malignancy, and malignant.

Technique and complications

For all interventional procedures on the thyroid gland, the patient is on the prone position, with a pillow under the shoulders allowing hyperextension of the neck. The neck is cleansed with betadine or alcohol. Subsequently, local anesthetic is administered. FNAB is performed using needles of variable caliber (ranging from 21 to 27 G) usually attached to a 10 cc syringe. In rare cases of cystic nodules, where the colloid content is too dense, thicker needles are employed (up to 18 G). While entering into the nodule, the tip of the needle is continuously visualized by the operator under US-guidance. With or without aspiration, depending on the structure and vascularization of the nodules, the needle is moved to and fro of some millimeters to remove cells and, in the end, the material extracted is fixed in alcohol or dried air and sent to the cytopathologist (1-3) (*Figure 1*). Low rates of complications are described in literature, when the procedure is performed by expert operators, and include bleeding with risk of cervical hematoma, local infections and vasovagal syncope. Proper use of antiseptics, US assistance (for identification of intra and extra-gland vascular structures) and the manual compression of the entry site may help reduce the likelihood of complications (3,24-29). Still controversial is the use of antithrombotic agents to reduce the risk of post-procedural bleeding. The cause is that the

antithrombotic agents can probably lead to major cardiac and cerebrovascular accidents (3,27-29). Severe coagulative deficits may represent a contraindication to FNAB. Despite Abu-Yousef *et al.* reported only 2 hematomas in 593 patients submitted to antithrombotic therapy *vs.* 4 events of bleeding in 449 patients not taking antithrombotic medications, it is suggested, whenever applicable, to suspend or modify the antithrombotic medication after consulting with the clinician (3,26,27).

Results

The superiority of US-guided FNAB in terms of adequacy of the cytological material obtained, possibility of false negative results, sensitivity and specificity has been demonstrated in several studies. In 9,683 patients, Danese *et al.* found low rates of cytologically inadequate material (3.5% *vs.* 8.7%) using US-guided FNAB, experiencing an increase in the percentage of sensitivity, specificity, and global diagnostic accuracy (97.1% *vs.* 91.8%, 70.9% *vs.* 68.8% and 75.9% *vs.* 72.6%, respectively). They reported only 1% of false-negative results *vs.* 2.3% without US assistance (30). Another study carried out by Can *et al.* demonstrated a statistically relevant low rate of inadequate cytologic material after US-guided FNAB (P<0.01). In fact they observed 27.2% of inadequate cytologic results in nodules aspirated by palpation (in 202 patients) *vs.* 12.5% in those aspirated under US-guidance (184 patients) with a sensitivity of 100% for both procedures (31). In their experience, Deandrea *et al.* demonstrated that 52% of histologically malignant nodules could be detected only thanks to US assistance, concluding that manually guided FNAB is not feasible in non-palpable nodules and not so accurate in a multinodular goiter (32). Another study conducted by Wu presented satisfying results in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (100% *vs.* 96%, 86% *vs.* 50%, 97% *vs.* 98, 100% *vs.* 33% and 97% *vs.* 94%, respectively). The author reported 1% of non-diagnostic material *vs.* 7% in 100 patients submitted to US-guided FNAB *vs.* 100 patients who underwent manual FNAB. All procedures had been performed by the same pathologist (33). Overall, US-guided FNAB provides satisfying results in terms of sensitivity, specificity, PPV, NPV and accuracy with low rates of complications, particularly when performed by expert operators (20,21,23-35). Moudgil *et al.* performed US-FNAB on 86 thyroid nodules in 70 children. Ninty point seven percent of the diagnostic procedures showed good correlation between cytopathology and pathology in patients undergoing surgery (93.1%), without false positive or false negative results for malignancy. These results are quite satisfying when we consider that the rates of malignant nodules in children are higher than in adults (35).

Percutaneous ethanol injection (PEI)

PEI is a mini-invasive technique consisting in the introduction of ethanol into the tissues. The consequence is a thrombosis of small vessels associated at inflammatory reaction. The resulting coagulative necrosis followed by fibrosis leads to reduction of the dimension of the treated lesion (36-38). According to the new guidelines, PEI represents the first-line treatment for relapsing and symptomatic benign cystic lesions and for nodules with an important fluid component. This is due to its safety, tolerability, effectiveness in volume reduction, cost effectiveness, low rates of recurrence, and short- and long-term complications (1,36,39-43). PEI was initially used also to treat hyper-functioning nodules or nodular goiters. However, compared to surgical treatment or radioiodine therapy, high recurrence rates of hyperthyroidism, increase in complications, and risk of progressive regrowth make this technique indicated only for the treatment of hot nodules that cause compressing symptoms. PEI is also used in those patients presenting contraindications to or no benefits from more effective alternative treatments (1,36,44,45). The nodule decrease in volume, albeit of lower entity than in cystic nodules, is also described in literature. However, the need of repeat treatments brings the potential risk of fibrosis of the cervical structures surrounding the treated area due to the diffusion of ethanol, making a possible surgery treatment more difficult. For all these reasons, PEI should be considered for the treatment of benign solid nodules only when alternative and more effective modalities are not applicable (1,36,46-48).

Technique and complications

A unique protocol to perform PEI has not been defined, yet. Still under way are the studies of the right amount of ethanol to be injected, the number of repeat treatments and the time lapse between them, to achieve maximum positive effects with minor number of complications (40). The patient positioning is the same as during FNAB. After skin sterilization, variable size needles (usually ranging from

20 to 25 G) are inserted in the center of the lesion under US-guidance with or without previous injection of local anesthesia at the entrance site. The cyst or the fluid parts of the nodule are almost completely drained by aspiration. Ethanol (usually with a concentration ranging from 95% to 99%) is slowly injected in the residual cavity through a syringe, filling up about 30–50% of the previously aspired volume. The procedure lasts about 2 minutes and is always monitored with US (ethanol shows an intense echogenicity). The solid part of the nodule is avoided. The procedure stops in case ethanol leakage is observed out of the nodule or if the patient refers severe pain. Some authors inject a saline solution or lidocaine during final withdrawal of the needle at the end of the procedure (36,40-50). Usually, PEI is a well-tolerated and safe technique. Diffusely described and not common complications are represented by local pain, dizziness, local hematoma, or complications related to ethanol extravasation from the nodule (recurrent laryngeal nerve palsy, peri-glandular fibrosis). More severe but rare complications include ethanol-related larynx or skin necrosis, Graves' disease, Graves' orbitopathy, Horner's syndrome. One case of Plummer adenoma has also been described in literature (36,40,50-53).

Results

The effectiveness of PEI in the treatment of symptomatic cystic or relapsing cystic lesions and of mixed nodules with a predominant fluid content has been largely described, so much to be considered by the guidelines the first-line option due to its safety, cost-effectiveness (1,36,39-43) and low potential risk of impairing the thyroid function. In a preliminary randomized trial (including 20 patients with predominantly cystic thyroid nodules divided into two groups) and in a prospective study (including 32 patients with the same nodule characteristics), Verde *et al.* demonstrated significant effectiveness in nodule volume reduction (>50%), at 12-month follow-up, in 80% patients treated with ethanol injection after fine needle aspiration of the fluid component, without relevant side effects (54). Zingrillo *et al.* treated 43 patients with relapsed cyst after two aspirations or patients with an inefficient aspiration procedure due to the viscosity of the fluid material. They showed an impressive reduction in the volume of the cyst (91.9%±11.4%) in 93% of patients at 5-year follow-up with an additional 5% increased rate of success after one retreating procedure. The patients reported disappearance of related symptomatology and only mild pain was described as complication (42). Also Bennedbaek *et al.* described "curative" volume reduction in recurrent thyroid cyst treated with PEI equal to 82% (*vs.* 48% treated only with cyst aspiration and isotonic saline solution). They reported a lower number of sessions (single session in 64% *vs.* 18%) and low rates of side effects consisting only in moderate/severe pain and one case of transient dysphonia (48). Several studies correlate the number of PEI sessions with the dimension of the cystic volume. For example, a recent work by Negro *et al.* demonstrates a significantly ($P<0.05$) higher number of PEI in the group with larger cystic lesions (>30.0 mL) with the smallest percentage in volume reduction after the first treatment ($P<0.05$). Conversely, the smallest cystic lesions (<10.0 mL) had a significant volume reduction only after one PEI session in a high number of cases (85.7%). Even in these cases, the rate of side effects consisting of mild/moderate pain was very low (17.4% and 4.1%, respectively) (50,55,56). Baek *et al.* did not find significant differences in volume reduction, symptomatology and cosmetic scores comparing the treatment with PEI and radiofrequency ablation (RFA) in cystic nodules, and considered the first as a better technique due to cost-effectiveness and low risks of major complications (40). The same considerations are shared by other authors (Sung *et al.*) and can be found in the revised guidelines (1,39,56,57).

Concerning the treatment of solid thyroid nodules, though many non-randomized and a few randomized trials demonstrate a decrease in nodule volume after PEI treatment, an increased rate of complications is described, with only a limited improvement observed for repeated treatments (44,58,59).

Using PEI, Kim *et al.* found statistically significant differences ($P<0.01$) between nodule volume reduction in cystic lesions and solid lesions (59). For this reason, PEI is not the first choice in the treatment of solid thyroid nodules and is reserved to those patients who present contraindications to other more effective treatments (1,44,46-48,60-62).

PEI can find indication in hyperfunctioning or goitre thyroid nodules. As secondary treatment choice, it is employed in patients with solid lesions, due to short-term volume reduction and thyroid-stimulating hormone (TSH) serum suppression in many cases, with an high rate of recurrence (1,44,61,62).

Some authors conducted meticulous search on the effectiveness of PEI in the treatment of recurrent papillary thyroid carcinoma, but their investigations are limited by too short-term follow-up studies. A recent research

published in the current year by Kim *et al.*, based on the treatment with PEI of 41 recurrent lesions that could not undergo repeat surgery, and long-term follow-up (minimum 60 months), shows a good rate of size reduction (58.5%) and statistically significant index of no-response lesions depending on age and size. Finally, the authors conclude considering PEI as a secondary treatment option with some limitations, to be used for patients who cannot be submitted to or refuse repeat surgery, and in lesions with a diameter >10 mm (51).

Laser thermal ablation (LTA)

LTA is a quite new mini-invasive technique that, causing coagulative necrosis, can significantly reduce thyroid nodule volume as well as symptoms and cosmetic problems. The technique uses heat generated from laser light. The resulting increase in local temperature (>60 ℃) leads to necrosis, followed by fibrosis and consequent reduction of the lesion size. The new guidelines provide evidence of the effectiveness, safety and well tolerability of this technique as alternative to surgery. LTA reduces large benign nodules that cause symptoms or cosmetic problems without determining changes in thyroid function or autoimmunity (1,35,63-67).

Technique and complications

After putting the patient in the typical position for thyroid procedures (hyperextension of the neck with a pillow under the shoulder), skin disinfection is performed, followed by local anesthetic injection into the subcutaneous tissue and the thyroid capsule. Silica optical fibers are inserted, under US-guidance, into the lesion through one to four 21 G needles positioned along the longitudinal major nodule axis, at a distance of 10–15 mm from each other depending on the nodule size. Energy is generated by Nd:YAG (neodymium: yttrium aluminum garnet) or by laser diode and delivered into the lesion for 5–15 minutes, until an inhomogeneous hyperechogenic area appears in place of the nodule. In case of large nodules, the "pull back technique" is employed; consisting in the retraction of the fibers of 1.0–1.5 cm. LTA is a safe procedure with low rate of side effects. Minor complications include cervical swelling and pain, local bleeding, hematomas and fever. More rarely, major side effects were observed such as changes in thyroid function or autoimmunity, laryngeal dysfunction, vocal cord palsy, recurrent nerve lesion or cervical structure injuries (1,35,45,65-75).

Results

In agreement with the guidelines in endocrinology, non-randomized, randomized and multicentre retrospective studies confirm the effectiveness, safety and clinical efficacy of LTA in the treatment of symptomatic cold thyroid nodules in terms of volume reduction and improvement in symptoms and cosmetic problems (1,35,62,64,65,72). Valcavi *et al.* reported a reduction of about 50% (47.8%) in nodule volume at 3-year follow-up studies in 122 patients. Changes in thyroid function were not observed and symptoms and cosmetic signs improved in 73.0% and 71.3%, respectively, with a worsened condition for both inferior to 5%. Only 9% of nodule regrowth and low rates of side effects were observed (2 patients showed delayed laryngeal dysfunction; alterations of the thyroid function were observed in 4 patients) (68). Similar results were reported also in a randomized trial work by Døssing *et al.* carried out in 78 euthyroid patients at 1 year follow-up, with a 51% rate of decreasing nodules, disappearance of symptoms and cosmetic complaints in 84% and 72% of patients. Only moderate pain, lasting 4 days, was reported as side effect with no modification in thyroid function (69). Gharib *et al.* produced two prospective randomized studies where patients with cold thyroid nodules, treated with two different kinds of laser source (Nd:YAG and diode), showed similar and significant reduction in nodule volume (44% and 43%, respectively). They also observed reduction of local symptoms in most of the patients at 6- and 12-month follow-up. These studies were compared with LT4 suppression therapy and with a control group and both did not present significant changes in nodule diameters and symptoms (46). A recent study conducted by Pacella in 1,871 patients showed statistically relevant ($P<0.001$) improvement after LTA treatment in terms of volume reduction (mean 72.11%, more significant in mixed nodules where it reached 79.7%), related symptoms (from 49% to 10%) and cosmetic signs (from 86% to 8%). The complication rate was low (only 0.9%) and no thyroid function or autoimmunity changes were reported (64). Concerning hyperfunctioning thyroid nodules and multinodular goitre, LTA does not represent the first choice treatment because radioiodine therapy and surgery provide better results. Although some investigations carried out on small series observed recovery of the physiological thyroid function and disappearance of hyperfunctioning areas at radioisotope scan in patients treated with LTA, in other

studies the use of this technique was deemed unsatisfactory. Repeat treatments were necessary to normalize the TSH serum levels and the technique did not prove as cost-effective as radiation therapy (35,44,62,69,73-75). In a randomized trial, Døssing *et al.* compared the results between a single LTA treatment and radioiodine therapy on 30 solitary hot nodules. Even though LTA showed similar volume nodule reduction, the normalization of serum TSH was obtained in 50% of patients alone (73). In conclusion, LTA may be considered as a therapeutic option in small, solitary and small hyperfunctioning nodules in patients with contraindication or pharmacological interaction to radioiodine therapy (1,35,44,62). Several studies compared LTA to RFA and provided different results on their efficacy in the treatment of benign thyroid nodules. In favour of LTA is a recent study performed by Pacella *et al.* where in 601 nodules (449 treated with LTA and 152 with RFA), a slightly superior nodule shrinkage was observed in the LTA group, particularly in large nodules. The same incidence of complications was observed (74). The treatment of unresectable or recurrent malignant thyroid cancer is poorly described in literature. The few investigations available are based on low numbers of patients and short-term follow-up studies. Radioiodine therapy and surgery remain the gold standard in these cases. LTA can be considered as palliative in primary thyroid carcinoma and as an alternative in the local control of small recurrent papillary carcinoma (44). Zhou *et al.* have recently published a work where 27 recurrent papillary carcinoma lesions (with diameter <15 mm) were treated with LTA. In their experience, the lesions showed great reduction in volume (7.5±2.8 mm and 105.4±114 mm^3 to 0.4±1 mm and 0.8±2.4 mm^3 at the final follow-up). Three patients needed a second treatment session due to incomplete ablation detected by contrast-enhanced ultrasound (CEUS). No patients presented vascular signals at color-Doppler exam. Absence of vascularization was also appreciated at CEUS examination. No major complications were described (75).

RFA

RFA is a new minimally invasive technique developed in the last years. Applied also for the treatment of bone and abdominal tumors, RFA is based on the movement of ions determined by an electric field, which in turn is produced by an external radiofrequency generator. The latter is connected to an electrode needle that determines an increase in local temperature (between 60 and 100 ℃). The result is a coagulative necrosis of the area around the needle. RFA can be performed in the treatment of benign thyroid nodules which cause symptomatology and cosmetic problems. It can also be applied in patients with recurrent thyroid cancers who present contraindications or simply do not acconsent undergoing surgery (1,2,4,35,44,76-81). At present time, this technique is not recommended for the treatment of primary thyroid cancer because so far there is not scientific evidence on its effectiveness (1,4,82,83).

Technique and complications

With the patient in the supine position and hyperextended neck, the skin is disinfected and local anesthesia performed. The latter is preferred to general anesthesia because the patient must be constantly monitored. Onsets of pain or voice alterations, in fact, are events that require interruption of the procedure. Local anesthesia is injected in sub-cutaneous tissues and under the thyroid capsule. RFA can be carried out with two different techniques both under US-guidance, using two different types of needles. The "fixed ablation technique" consists in the introduction of a 14 G multitined expandable needle (with 4–9 expandable hooks) along the long axis of the nodule (cranio-caudal approach). The "moving shot technique" consists in the introduction of an internally cooled needle with variable diameter (17–19 G), length (7–15 cm) and active tips (ranging from 0.5 mm to 2 cm). The needle is inserted through the isthmus (trans-isthmic approach), starting from the middle to the lateral direction, to reach the nodule which is divided in different small hypothetical zones, each ablated by moving the tip of the needle from the deepest position upwards to the most superficial part of the nodule. The "moving shot technique" presents some advantages over the "fixed ablation technique". The latter provides a spheroidal ablation area, while the "moving shot" technique allows treatment of ellipsoidal areas (that represent the most likely form of thyroid nodule in routine practice). Moreover reduces the risk of complications and side effects, due to the minor exposure and the constant US monitoring of the laryngeal recurrent nerve that runs in the "danger triangle" situated between trachea, esophagus and thyroid gland. In addition, the trans-isthmic approach allows stability of the needle and prevents its involuntary movement even if the patient talks or coughs. Finally, the ablation of the lesion is confirmed by the US appearance of a hyperechogenic area associated to a sudden increase of impedence registered by the external generator (1,4,35,44,84-90) (*Figure 2*).

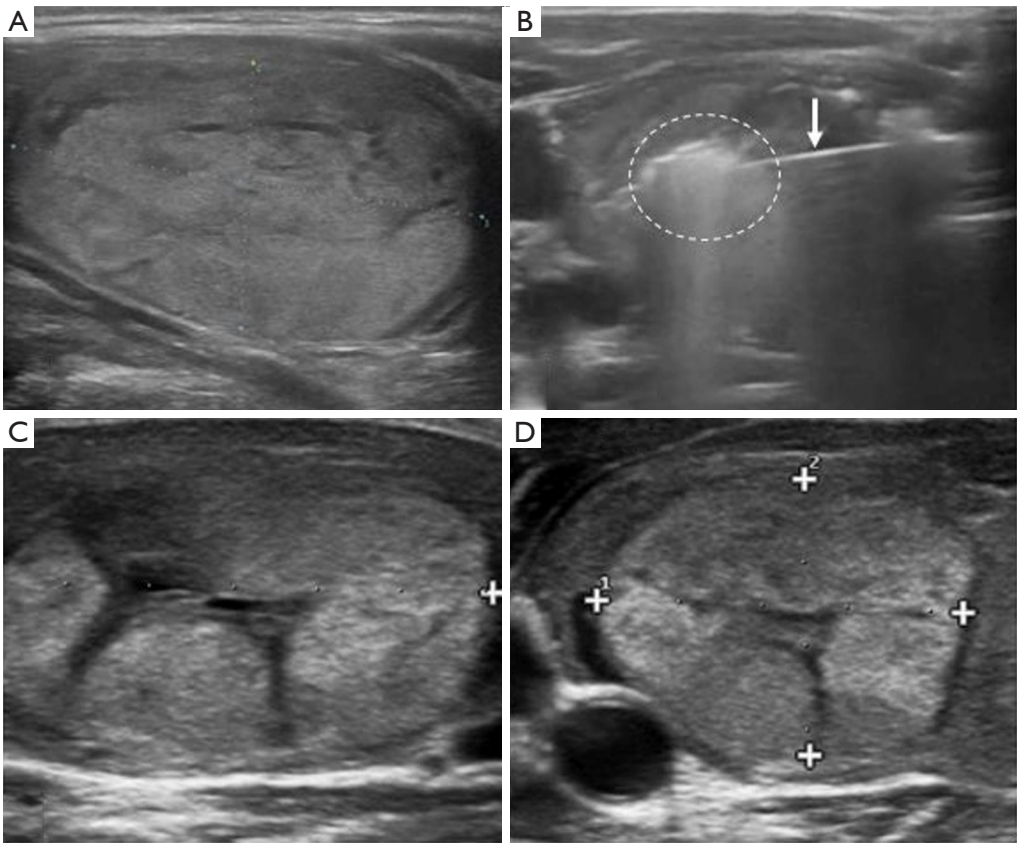

Figure 2 RFA procedure of a benign thyroid nodule. (A) US image of a thyroid nodule of the right lobe in a 47-year old woman; (B) RFA of the nodule: the needle inside the lesion (white arrow) with the appearance of a hyper echogenic area represented the ablated area; (C) US appearance of thyroid nodule after RFA treatment at 1 month follow-up. Reduction in nodule volume can be appreciated; (D) US image shows a significant shrinkage of the benign nodule compared to image (A) and (C) at 6-month follow-up study. +, the cursors to measure the lesion diameter. US, ultrasound; RFA, radiofrequency ablation.

Complications and side effects are similar to those observed during other interventional procedures. Low rates of major complications are described when the procedure is performed by an expert team. Several sensitive structures surround the thyroid gland: recurrent laryngeal and vagus nerve, cervical ganglion, esophagus, trachea and important vessels. However, so far, no injury of vessels, esophagus and trachea has been described in literature. Hydrodissection, consisting of 5% dextrose solution injection between the peripheral nodule area and surrounding critical structure, has been demonstrated effective to reduce clinical complications (91). Major complications were represented by voice changes determined by an injury of the laryngeal or vagus nerve (usually transient and not lasting more than 3 months), brachial plexus damage, nodule rupture and rare changes in thyroid function (above all transient). Minor complications included bleeding and subsequent hematoma (lasting few weeks and reduced by post-procedural neck-compression), pain (it is the most frequent side effect and was generally controlled by stopping the ablation or using pain-killers for 2–3 days post-treatment), skin burns around the puncture sites, and infection (for this reason, antibiotics must always be administered before RFA), cough and vomiting (4,60,91-94).

Results

Several studies demonstrate the effectiveness, safety and clinical efficacy of RFA in terms of nodule volume reduction, improvement in symptoms and cosmetics in the treatment of both benign cold and hyperfunctioning thyroid nodules (resolving thyrotoxic status in hot nodules). The newly

reviewed guidelines also confirm RFA as an alternative to surgery and radioiodine therapy. A systematic review carried out by Fuller *et al.* in 2014 analyzed nine studies inclusive of 292 nodules (both cold and hot) in 284 patients with a mean of 1.05 session treatment performed for each nodule. The reviewed studies included 3 single arm observational investigations employing RFA alone, 2 single arm observational studies performing RFA before or after PEI, 2 randomized controlled trials comparing RFA to a control group, 1 randomized prospective trial comparing the effectiveness of one to two RFA sessions treatments and 1 randomized, prospective trial confronting RFA to PEI. The longest follow-up was 12 months. These studies demonstrated a statistically significant important reduction in mean volume of cold (–9.67 mL, ranging from –15.04 to –4.30 mL) and autonomously functioning nodules (–16.14 mL, ranging from –24.28 to –7.99 mL) after RFA. After the treatment, symptoms and cosmetic problems had a statistically significant improvement as well. Four trials using VAS for symptoms showed a mean improvement of –2.89 points (ranging from –2.51 to –3.28 points) and five trials presenting objective four-point scale for cosmetic problems showed a mean improvement of –2.02 points (ranging from –1.69 to –2.35 points). Even in those studies, using a combined symptom-cosmetic 0 to 6 point scale, changes were statistically significant, with a mean improvement of –2.96 points (ranging from –2.66 to –3.25 points) (95). In benign hyperfunctioning thyroid nodules, improvement in gland function was also appreciated and associated to reduction of antithyroid medication. These studies showed low rate of complications and side effects (3.9%). Two major complications (1 vocal cord palsy lasting 1 month after treatment and 1 diffuse glandular haemorrhage) and 11 minor complications (hematoma, slight-moderate pain, fever, edema and low-grade skin burn at the site of electrode insertion) were noticed (4,57,88-90,92-97) and were comparable to the rate of complications observed in another large study performed by Baek *et al.* (3.3%) (91). Lim *et al.* showed an important shrinkage of nodules with a mean of 93.5%±11.7% in 111 patients at longer follow-up series (about 4 years) with a mean session treatment of 2.2±1.4. They noticed a faster and better reduction in volume in predominantly cystic, compared to solid nodules, and obtained a statistically significant improvement in symptoms and cosmetics (P<0.001) (96). The rate of regrowth superior to 50% was low (5.6%) depending on an undertreating of the peripheral nodule portion that could lead to more sessions of treatments and a relapse of increase in thyroid function (according to other authors) (85,98,99). Deandrea *et al.* (98) showed at 6-month follow-up study, a significant volume reduction in patients treated with RFA (15.1±3.1 *vs.* 4.2±2.7 mL; P<0.0001), compared to patients who underwent observation alone (14.4±3.3 *vs.* 15.2±3.5 mL). Furthermore, both cosmetic and compressive symptoms had a statistically significant (P<0.001) improvement (3.6±0.5 *vs.* 1.7±0.4 and 3.6±1.9 *vs.* 0.4±0.7, respectively) compared to the other group without reporting any complications or changes in thyroid function (100). In a recent study in 108 patients with single or multiple nodules, Tang *et al.*, showed a statistically significant decrease in nodule volume (P<0.05) after RFA with volume reduction ratio (VRR) at 1- and 3-month follow-up of 64.12% and 85.54%, respectively (2). Sung *et al.* treated 44 hot nodules (23 with a toxic nodule and 21 with a pretoxic nodule) that refused or presented contraindication to surgery or radioiodine therapy (99). The mean follow-up was 19.9±12.6 months. They observed an important shrinkage of nodules already at 1 month and even greater during the last follow-up passing from a mean volume of 18.5±30.1 mL to a mean volume of 4.5±9.8 mL (P<0.001). A significant improvement of thyroid serum hormon was also observed and, at scintigraphy, 35 nodules showed loss of overall uptake. Nine nodules showed decreased uptake at the last follow-up. Related symptoms and cosmetic problems were also found significantly improved during the last follow-up study. No major side effects were found. Different studies compared RFA with LTA resulting in higher efficacy of RFA in providing nodule volume decrease (1,100,101). However, recent studies performed on a number superior to 1,500 patients reported that both techniques had similar uptake decrease (1,98). RFA can be used for locoregional control of cancer or improvement of cancer-related symptoms in patients with recurrent thyroid cancer who present high surgical risk and refuse repeat surgery. RFA of recurrent thyroid cancer in the neck resulted in a mean volume reduction of 56% to 93% with 42% to 58% of nodules completely disappearing and 64% of patients experiencing symptom improvement and serum thyroglobulin concentration decrease. Long-term follow-up data have not been published, yet (88,102,103). According to the Korean Society of Thyroid Radiology and confirmed by a 2015 Italian report, even in absence of long-term follow-up studies, RFA is indicated in the treatment of recurrent thyroid cancers in patients with high surgical risk or refusing repeat surgery. In literature, the mean

tumor volume reduction described presented a variable rate ranging from 50.9% to 8.4%. The rate of tumor complete disappearance ranged from 25% to 94% of cancers with an improvement in therapeutic success and symptoms ranging from 75% to 97% and 64%, respectively. Moreover, in many patients a decrease in serum thyroglobulin concentration was described (88,102-111). A recent meta-analysis made by Suh *et al.* compared the effectiveness and safety of RFA and PEI for the treatment of total sample size of recurrent thyroid cancers in 270 patients with a VRR ≥50% rate of 100.0% after RFA and of 89.5% after PEI associated to a rate of complete disappearance of the nodules of 68.8% and 53.4%, respectively. The RFA rate of recurrence of 0.0% and 2.4% concerning PEI and also the number of sessions were lower in patients treated with RFA (less than 1.3 *vs.* greater than 2 in PEI). All this rates were however no statistically significant (110). Based on the guidelines, RFA is not indicated as first-line therapeutic option due to a low number of evidence (1,92). Despite this, a recent study by Zhang *et al.* reported no residual or recurrent tumor after RFA at 12- and 18-month follow-up in 92 patients with low-risk papillary thyroid micro-carcinomas (PTMC). In addition, no suspicious metastatic lymphnodes were detected and US-guided biopsy confirmed the absence of residual or recurrent cancer areas. No major complications were described during this study (111).

Percutaneous microwave ablation (PMWA)

PMWA is a new technique used to treat thyroid nodules. Due to its novelty, the technique is still scarcely described in literature. Used for the treatment of tumors of other nature, it uses the rotation of molecules produced from microwave energy to increase the local kinetic energy thus producing a rapid increase of local temperature inside the tissues. The result is the ablation of the target tissue (112-119).

Technique and complications

The patient is in the supine position with neck extension. The material needed is a microwave generator, a flexible low-loss coaxial cable and a cooled shaft antenna. The generator produces 1–100 W of power at 2,450 MHz, releasing energy in pulse or continuous way. The antenna is a 16 G needle and is composed by polytetrafluoroethylene. It is 3–5 mm long. Distilled water is conveyed inside the antenna shaft to cool it. After skin disinfection and local anesthesia the needle antenna is positioned along the long axis of the nodules under US-guidance. Delivered energy usually ranges from 30 to 50 W and the ablation zone appears like a hyperechoic area, similarly to RFA. The complete ablation is obtained moving the tip of the needle. Several authors recommend compression of the neck to avoid the formation of hematoma. Hydrodissection techniques can also be used to increase the distance between the target lesions and the critical structures surrounding the thyroid (112,113). Complications and side effects are the same as in the other ablation techniques and include hematomas, different degrees of pain intensity, transient voice changes, recurrent laryngeal nerve injury, skin burns and thyroid dysfunction (115-119).

Results

Only a few studies report the effectiveness of PMWA in the treatment of benign solid thyroid nodules. The described volume reduction rate ranges from 45% to 65% in follow-up studies lasting up to 12 months. Improvement of symptoms and cosmetic problems and no significative changes in thyroid function were observed (116,117). Recent studies included an important number of patients. Liu *et al.* treated with PMWA 474 benign thyroid nodules in 435 patients and observed a significant decrease in volume (90% is the mean rate of final volume reduction at 1-year follow-up). No major complications were described (112). Wu *et al.* treated 121 benign thyroid nodules and observed statistically significant ($P<0.001$) improvement in the decrease of nodule volume, symptoms and cosmetic problems at 1-year follow-up with a low number of complications (2 patients had hoarseness recovered within 2 months; 2 patients showed a slight skin burns; 1 case developed Horner syndrome, recovered within 2 months) (113). Yue *et al.* reported a significant shrinkage of nodules treated with PMWA in 110 patients at 1 year (ranging from 12.6±15.1 to 3.2±5.7 mL). Sixteen patients had recurrence 12 months after treatment and the authors put this in relation to initial large volume of the nodule, presence of more irregular blood vessels and lower energy delivered (116). Only one study describes the use of PMWA in the treatment of 17 patients with 23 recurrent thyroid cancers with high rate of mean tumour volume reduction (91%) at 18-month follow-up. Thirty point four percent of patients showed complete disappearance of tumors and 52.2% residual small scar-like lesions (119).

High intensity focused ultrasound (HIFU)

HIFU is a new mini-invasive technique that induces

thermal coagulative necrosis inside the tissues due to high intensity US beam focalized into a target lesion, without skin penetration by devices. Several significations are required to perform the complete ablation of the lesions considered the small ablative volumes provided by each single sonication. This may lead to prolonged duration of the treatment (120-126).

Technique and complications

Under conscious sedation, the patient is placed in a supine position with hyperextended neck. According to literature, only one US-guided device for the treatment of thyroid nodules is commercially available, namely the EchoPulse® (Theraclion SA, Malakoff, France). This device has two independent US systems, one for US-guidance and the other attached to the transducer generating the focalised US beam. The focal point is always put in the centre of the US image where the target area always appears as hyperechoic. The device is setted to limit automatically its power when approaching the sensible structures around the nodule. Maintenance of safety margins is always recommended to avoid complications as described in literature. The lesion is divided into different voxel areas of treatment. Each sonication lasts from 4 to 8 seconds with 20 to 40 seconds of cooling interval (7,123-126).

Results

A low number of patients were treated with HIFU and a recent systematic review presented by Lang *et al.* identified five original studies which showed nodule volume reduction rate ranging between 45% and 68%, after a single session of HIFU ablation, with varying results depending on nodule size and length of follow-up (7). An investigation carried out in 2017 by Sennert *et al.* on 19 benign nodules showed volume reduction rate of 58% at 3-month follow-up, with 10 out of 19 patients showing therapeutic success (defined as a volume reduction ≥50%) (126). No studies have been published, yet, describing the treatment of primary of recurrent thyroid cancer.

Conclusions

Treated by surgery alone during the past decades, many thyroid nodules nowadays can be treated by means of new mini-invasive techniques that are less expensive and present lower risks of major complications and side effects over surgery. In particular, PEI is in presence of cystic thyroid nodules, LTA and RFA in the treatment of both cold and hyperfunctioning benign nodules in patients who refuse or have contraindications to surgery or radioiodine therapy. In presence of recurrent papillary thyroid cancer, PEI, LTA and above all RFA can be considered as a valid option in patients who cannot undergo surgery. PMWA and HIFU show less evidence of effectiveness in the treatment of this kind of nodules even if the results published so far are encouraging. During the last years, PMWA has importantly developed and the last studies have demonstrated similar effects compared to RFA. So, PMWA can be considered as a valid alternative to the other ablation techniques. Further studies are needed instead to confirm the effectiveness of HIFU as treatment of choice. At present, the complication rate of HIFU is lower than in other techniques, but the rate of volume reduction of the nodules is lower. There are also less therapeutic indications which represent a limit to its employment.

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Footnote

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