Radiofrequency ablation for benign thyroid nodules

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Abstract

Benign thyroid nodules are an extremely common occurrence. Radiofrequency ablation (RFA) is gaining ground as an effective technique for their treatment, in case they become symptomatic. Here we review what are the current indications to RFA, its outcomes in terms of efficacy, tolerability, and cost, and also how it compares to the other conventional and experimental treatment modalities for benign thyroid nodules. Moreover, we will also address the issue of treating with this technique patients with cardiac pacemakers (PM) or implantable cardioverter-defibrillators (ICD), as it is a rather frequent occurrence that has never been addressed in detail in the literature.

Keywords: radiofrequency ablation, thyroid nodule, pacemaker, implantable cardioverter-defbrillator, ultrasound-guided procedure, minimally invasive nonsurgical techniques

Introduction

Benign thyroid nodules are an extremely common occurrence (1). Radiofrequency ablation (RFA) is a minimally invasive nonsurgical technique that can reduce thyroid nodule size with the thermal injury caused by high-frequency alternating electric current. This is a procedure that is performed under local anesthesia, by the ultrasound-guided insertion of a radiofrequency electrode into the thyroid nodule (2-6).

Although some of the most authoritative guidelines on thyroid nodules touch on RFA only as an alternative to surgery for the treatment of recurrent thyroid cancer in high risk surgical patients or in those refusing additional surgery (7-9), there is accumulating/growing evidence that RFA is also a valid alternative to surgery for the treatment of symptomatic benign thyroid nodules. Consistent with it, in the first Italian opinion statement on this topic, Garbergoglio and colleagues agreed on the use of RFA for treating benign nodular thyroid disease when surgery is contraindicated or declined (10).

Based on the existing literature and on our experience (11-13), here we review what are the current indications to RFA, its outcomes in terms of efficacy, tolerability, and cost, and also how it compares to the other conventional and experimental treatment modalities for benign thyroid nodules. Moreover, we will also address the issue of treating with this technique patients with cardiac pacemakers (PM) or implantable cardioverter-defibrillators (ICD), as it is a rather frequent occurrence that has never been addressed in detail in the literature.

1. Indications to the procedure in case of benign thyroid nodules

Radiofrequency ablation (RFA) is a minimally invasive nonsurgical technique that can reduce thyroid nodule size with the thermal injury caused by high-frequency alternating electric current. There is abundant literature suggesting that RFA could be used to treat benign thyroid nodules. Since 2006 (14), several studies have proved RFA efficacy and safety on symptomatic benign thyroid nodules (15-19). Based on this ground, in 2012, the Korean Society of Thyroid Radiology published a consensus statement where RFA was indicated for the treatment of benign thyroid nodules causing local symptoms or cosmetic concerns, as well as for the treatment of autonomously functioning nodules causing hyperthyroidism-related problems (20).

According to this consensus statement, RFA ideal target is a single, benign thyroid nodule that has become symptomatic (6). Now, assuming we had to advise on the best treatment modality a patient with a benign thyroid nodule, we would consider RFA only if they complained of nervousness, weight loss, palpitation, or neck discomfort. Otherwise, if this patient had no symptoms, we would generally recommend observation by repeating thyroid ultrasonography in about 1 to 2 years (21). On the other hand, if a patient presented with a symptomatic or hyperfunctioning thyroid nodule, RFA could be taken into consideration once the nodule had been confirmed cytologically benign by at least two separate fine needle aspirations (20). Cytologically benign thyroid nodules correspond to the Thy2/Tir2 category of the British/Italian system (22) and/or to the Bethesda category II of the Bethesda system for reporting thyroid cytopathology (23).

The rationale for obtaining two fine needle aspiration biopsies before RFA is to reduce the likelihood of false negative cytological reports (24). To date, there is no evidence in supporting the treatment benefit of RFA as a first line therapy for thyroid carcinomas, nodules suspicious for malignancy, follicular neoplasms, and follicular lesions of undetermined significance. The procedure, which has

been found inadequate as a cure for thyroid carcinoma (25), will inevitably delay surgery, which is the recommended curative approach in this case (12). As for follicular neoplasms or follicular lesions of undetermined significance, where malignancy rate is between 14% and 48% (24), there is not only a significant/considerable risk of treating a nodule which is a cancer, but also the concern as to whether RFA might facilitate the transformation of follicular lesions to follicular carcinomas (12).

Nevertheless, it is noteworthy that one RFA session does not seem to affect subsequent thyroid surgery. In particular, we have shown that in two patients who had undergone RFA, the subsequent surgical removal of thyroid nodules was not impacted by one RFA session, and that the patients could be successfully operated on with no complications (12). This outcome was attributed to the fact that the RFA had not altered the capsule, possibly because we are used to keeping the active tip of the needle within the nodule all through the procedure, which allowed us to undertreat the areas adjacent to the capsule (4). Therefore, one RFA session should not exclude the possibility that the same patient undergoes thyroid surgery in the future.

2. Special precautions to take in patients with cardiac pacemakers or implantable cardioverter-defibrillator

There are no absolute contraindications to RFA for the treatment of a symptomatic benign thyroid nodule. Nevertheless, the Korean Society of Thyroid Radiology (20) advises to take special care in patients with serious health problems, pregnant women, and patients with contralateral vocal cord palsy. Here we will address the issue of treating with thyroid RFA patients with cardiac pacemakers (PM) or implantable cardioverter-defibrillators (ICD), as it is a rather frequent occurrence that has never been addressed in detail in the literature (2-5).

RFA is a procedure that may cause electromagnetic interferences (EMI), as it induces thermic injury to the tissue by an alternating electric field produced by a unipolar electrode, which is connected to an external radiofrequency generator. RFA-induced EMI could prevent cardiac PM or ICD from functioning properly (26-31). In general, EMI may lead to the following responses in the cardiac devices: (*i*) temporary or permanent resetting to a backup, reset, or noise-reversion pacing mode; (*ii*) temporary or permanent inhibition of pacemaker output; (*iii*) an increase in pacing rate due to activation of the rate-responsive sensor; (*iv*) ICD firing due to activation by electrical noise (26).

So far, there have been no reports of such responses in the cardiac devices of patients treated with thyroid RFA. It has to be noted that the automatic reset of the programming that can be observed when a cardiac device is positioned within an intense electrical field is rarely observed even during cardiac RFA. Therefore, this is very unlikely to happen in patients treated with thyroid RFA. Anyway, while patients that are not PM-dependent are unlikely to experience any problem due to EMI, major problems could be observed in PM-dependent patients (i.e. those without spontaneous ventricular activity when the pacemaker is switched off or programmed in VVI 30/min) or in patients with ICD. In these patients, for example, EMI can be erroneously considered as a cardiac high rate activity by the device,

which in turn triggers or inhibits ventricular stimulation and -in case of an ICD- activates antitachycardia therapies.

In general, in order to minimize EMI it is recommended to administer RFA in brief and intermittent bursts at the lowest possible energy levels (27). This can help avoid the false recognition of sustained tachyarrhytmias or minimize the effect of potential inhibition of pacing even in PM dependent patients. Secondly, it is recommended to maximize the distance between the radiofrequency electrode and the cardiac device (30). Moreover, the radiofrequency current path (electrode tip to current return pad) should be kept as far away as possible from the pulse generator and lead system, in order to avoid a possible "antemna effect" due to the heating of the electrode tip. Last, it is recommended to monitor peripheral pulse by a non-electrocardiographic method (i.e. pulse oximetry) throughout the procedure and to perform an ECG as soon as the treatment has finished.

In Trieste, patients undergoing RFA are followed by a dedicated team, which includes endocrinologists, interventional radiologists, pathologists and surgeons, as well as other specialists, when there are specific issues that need to be addressed, such as the treatment of patients with cardiac devices. So, when treating patients with PM or ICD, we follow a protocol that has been endorsed by the Cardiovascular Department of the Azienda Ospedaliero-Universitaria di Trieste (**Table 1**), which is largely based on the Heart Rhythm Society Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors published in 2011 (31).

Basically, prior to the procedure, patients with PM should be assessed as to whether they are PM-dependent. If they are not PM-dependent, a spontaneous rhythm is evident at the ECG either spontaneously or during PM interrogation, when the device is transiently programmed at a rate < 30-40 bpm. In these cases, EMI are considered unlikely to be clinically significant, and therefore special

precautions are not needed during the procedure. In PM-dependent patients, on the other hand, either the cardiac device should be reprogrammed to an asynchronous mode or a magnet should be placed over it during the procedure. The magnet placed over the device can in fact transiently modify PM programming, allowing it to stimulate the heart at a fixed rate, which is not inhibited by any false cardiac activity due to EMI. In general, the use of a magnet positioned over the device is safer than any device reprogramming, as it allows an immediate restoration of the cardiac device functions after the procedure.

Patients with ICD should have their tachyarrhythmia treatment algorithms programmed off before the procedure, in order to prevent unwanted shocks due to spurious signals that the device might interpret as ventricular tachycardia or fibrillation. Once the ICD has been inactivated, patients should be monitored continuously for life-threatening arrhythmias by ECG and by pulse oxymetry. Moreover, temporary pacing and defibrillation equipment should be available (if emergency cardioversion were required, the paddles should be placed as far from the implanted device as possible in an orientation likely to be perpendicular to the orientation of the device leads). Straight after RFA, the ICD should be programmed back to its original settings, with the antitachycardia function restored to its active status. Although a magnet positioned over an ICD disables its antitachycardia function, it does not modify its PM function. Therefore, if patients with ICD are PM-dependent, the magnet does not protect them from the risk of asystole due to EMI. In these patients, it is recommended to reprogram the device before the procedure, particularly if long continuous RFA applications are scheduled.

3. RFA efficacy, complications, and cost

3.a Efficacy

RFA efficacy is based on the ability of hyperthermia to induce tissue coagulative necrosis and to reduce thyroid nodule volume, whereby local symptoms, cosmetic concerns improve, and thyroid function normalizes. In order to get more precise ablations and to improve both efficacy and safety, thyroid RFA has evolved almost immediately from the use of multitined "fixed" expandable 14-G electrodes (15, 16) to that of straight, internally cooled electrodes that are sequentially moved within the nodule, ablating/destroying it unit by unit (14). The ablation usually starts from the deepest layer, and the electrode is slowly withdrawn towards the surface (17). While the first type of electrodes and technique have been used mainly in Europe (15, 16, 18, 32) the second approach, also called moving-shot technique, was initially proposed by the Korean Authors (14, 17) and has now been adopted in Italy too, being more precise but less invasive (11, 33, 34). This approach allows for a better control of the needle. Therefore, it minimizes normal tissue injury and help tailoring the extent of the treatment according to nodule shape and features.

All the studies that have evaluated the efficacy of RFA for the treatment of benign thyroid nodules are summarized in **Table 2**. When looking at the series where the moving-shot technique was used, the first prospective study comparing RFA efficacy to observation, showed that RFA was superior to observation as it significantly reduced thyroid nodule volume by 80% after 6 months (19). In this study, the procedure did not only reduce nodule volume as compared to observation, but it was also therapeutically successful, as it achieved a volume reduction greater than 50% in all the patients. This data has been recently confirmed by an Italo-Korean work where thyroid nodules were reduced by 77% in Korea and 66% in Italy after 6 months from one RFA session (33). Consistent with it, another recent study has shown that one RFA session reduced nodule volume by 55% and 80% at 6 and 24 months

(34), and we have found that one session of RFA significantly reduced thyroid nodule volume by 50%, 64%, 70%, 71%, 67% after 1, 3, 6, 12, and 24 months (12), as shown in **Figure 1**. Interestingly, these results seem to be maintained at least for 48 months – which is the longest follow-up that has been published so far (35).

Most importantly, in all these studies (12, 19, 33, 34), nodule volume reduction was paralleled by a significant improvement of local symptoms and cosmetic concerns. In addition to that, Valcavi and colleagues demonstrated that RFA-induced nodule volume reduction was also associated with an improvement of health-related quality of life (HRQL). HRQL refers to the well-being of a person, and its assessment derives from the score of both physical and mental well-being statuses. Interestingly, in this paper patients with thyroid nodules had lower scores of mental well-being status as compared to healthy controls, which significantly improved and normalized after RFA (34).

Overall, the factors that seem to affect treatment response include initial solidity, as purely cystic nodules are usually reduced by 90% (36-38), nodule volume (18, 19), vascularity (39), and functionality (3). Moreover, the technique used, the training of the operators (33), and the energy delivered per nodule volume (19) should all be taken into account. Among these factors, the energy delivered per nodule volume has been advocated as the most important for long-term shrinkage (33). Consistent with the concept that initial nodule volume affects treatment response, Lim and colleagues showed that larger nodules required more treatment sessions than the smaller ones to achieve similar volume reductions. In particular, patients with nodules whose volume was between 0-10 mL underwent 1.7 ± 0.9 RFA sessions, those with nodules measuring between 10-20 mL underwent 2.8 ± 1.7 RFA sessions, and those with nodules with a volume greater than 20 mL underwent 3.8 ± 1.5 RFA sessions (35). In this study, undergoing more than one RFA session was feasible and safe, and the volume reduction achieved was maintained for 48 months. Although the final volume reduction achieved by

RFA seems to be greater in the patients that have undergone more than one RFA session (17, 35), we believe that the decision of performing more than one RFA session should be based on patient's complaints (symptoms and cosmetic concerns) rather than the percentage of nodule volume reduction achieved after the first procedure. This is in line with what was concluded by Huh and colleagues who compared the efficacy of one and two RFA sessions, finding that there was no significant difference between the two groups, and who suggested that additional RFA sessions should be limited to patients with a large nodule (> 20 mL) or unresolved clinical problems (40).

Another circumstance that might require more RFA sessions is the treatment of a hyperfunctioning nodule. The studies available have shown that, although RFA improves thyroid hyperfunction, it allows medication withdrawal in no more than half of the patients (11, 16, 18). Therefore, it seems to be less effective for thyroid hyperfunction than it is for treating local symptoms and cosmetic issues. This could be due to insufficient ablation of the external border of the hyperfunctioning nodule, which could in turn lead to nodule regrowth and relapse/worsening of hyperthyroidism (4, 5).

3.b Complications

It is abundantly clear that RFA is safe and well tolerated. For this reason this technique was initially advocated as a useful treatment modality for weak or elderly patients, or for those with challenging hemostasis, comorbidities, and other clinical or social issues not conducive to surgery (15). This is also the reason why in 2015 Garberoglio and colleagues recommended the use of RFA for symptomatic or hyperfunctioning benign thyroid nodules in patients where surgery/or radioiodine were either contraindicated or declined (10).

Nevertheless, RFA has some side effects and can cause also some complications. Side effects include postoperative cervical pain, vomiting, coughing, fever, vasovagal reactions, and hematoma formation.

Postoperative pain, which is the most common side effect, occurred at a variable rate, from 2.6% of patients in (41), to 5.2% in (11), to 5.5% in (17), and to 17.5% in (34). The most likely mechanisms underlying this side effect are parenchymal edema and thyroid capsule thermal damage. In our experience, pain was generally mild, it required only oral analgesics (such as paracetamol) to be relieved and ceased within 2 weeks from the procedure. As for hematomas, they usually disappear within a couple of weeks. To avoid their formation it is generally recommended not only to interrupt antiplatelet drugs and to switch patients that are on anticoagulants to low molecular weight heparin (20), but also to evaluate by Doppler ultrasonography the presence of any vessel along the approach route prior to the procedure (33).

The incidence of major complications is relatively low. Baek and colleagues (41) observed 48 complications in 1459 patients (3.3%). These complications included voice changes, brachial plexus injury, tumor rupture (42), permanent hypothyroidism, skin burn, and vomiting. This is consistent with what we reported last year (13). In 107 patients treated by RFA the complication rate was 3.7% (13). These complications included voice changes (n=2), a late-onset painless thyroiditis with transient thyrotoxicosis (n=1), and a full-thickness skin burn (n=1) (13). In our experience, voice changes were treated by oral prednisone and resolved within one month and one and a half months. Voice changes have been generally attributed to thermal nerve injury. To avoid this occurrence it is suggested undertreating the area adjacent to the nerve, also called the danger triangle (2). As for the late-onset painless thyroiditis that we have reported (11), it developed 3 months after the procedure and resolved spontaneously within 30 days, without causing hypothyroidism. The onset of a thyroiditis with thyrotoxicosis could be attributed to the inflammatory process that might take place after needle entry to the thyroid, which could trigger the release of thyroid hormones (11), which reminds of the postaspiration thyrotoxicosis (43).

The most serious complications that we have encountered so far is a full-thickness skin burn caused by thermal injury, which required the help of plastic surgeons to heal. The details of this case have already been presented (13). Here we would like to remind that in order to prevent skin burns, it is important to reach the nodule with the transisthmic approach, such that the electrode passes through the isthmus. It is also important to inject cold fluid (e.g. lidocaine) in the subcutaneous layers under the puncture site, which will increase the distance between the nodule and the skin. In addition, some Authors suggest to apply an ice bag on the skin next to the puncture site during the ablation (41). As already mentioned, when a skin burn develops, in order to achieve a satisfactory esthetic result, specific care will facilitate the wound healing process (13).

3.c Cost and time consumption

The cost of a radiofrequency generator is about $25000 and the cost of an electrode is about $750-1500 per session (4, 5). Treatment may be performed on outpatients, with a time expenditure of about 30 minutes (4). Two years ago we compared RFA cost and time consumption to those of surgery in patients who had undergone a hemithyroidectomy (11). Overall, the length of one RFA session was 45 minutes and its cost was about $1800. On the other hand, the mean operative time for hemithyroidectomies performed in a standard inpatient regimen was 80 minutes, the length of the hospital stay was 2.33 days and their mean cost was about $5000. In the group of patients requiring short-stay surgery, mean operative time was 82.5 minutes, hospital stay was 1 day, and the cost was about $4500. Therefore, RFA compares extremely favorably to surgery in terms of cost, as it costs roughly 2.6 times less than surgery, without including the fact that sick-leave is significantly shorter and social costs are significantly lower.

4. How does RFA compare to the other treatment modalities?

4.a Conventional techniques

Surgery and radioiodine remain the conventional and established treatments for thyroid nodules (5). So far, only two studies have compared RFA to surgery. In the first one (11), 37 patients who underwent RFA were retrospectively compared to 74 patients who underwent emithyroidectomy, which was performed either in a standard inpatient or in a short-stay surgical regimen. RFA reduced nodular volume by 70% after 12 months and it was an effective method for treating nodule-related clinical problems, but it was not as effective as surgery for the treatment of autonomously functioning thyroid nodules. In particular, while RFA was able to relieve from nodule-related symptoms in 85% of patients, hyperthyroidism was completely resolved only in 33% of patients. This data was in line with previous studies, where hyperfunction was fully controlled in 24% of patients after 6 months from RFA (16), and in 40% of patients after 12 months from RFA (32). Therefore, this study indicated that the best approach to treat autonomously functioning nodules remained surgery and not RFA. Nevertheless, in the same study RFA was found safe and extremely well tolerated, while surgery caused hypothyroidism in 25% of patients and had a higher complication rate than RFA.

The greater tolerability of RFA was also proved in a larger population by the second study (44), where the efficacy and safety of RFA were compared to those of surgery (including both thyroidectomy and lobectomy). This second study demonstrated that the incidence of complications was significantly higher in the surgery group than in the RFA group, being 6% and 1% respectively. Moreover, hypothyroidism was detected in 71.5% of patients after surgery and in none after RFA (44).

Although in these studies the population who underwent RFA was comparable to that who was surgically treated, we believe that RFA and surgery are not overlapping but complementary techniques,

and therefore their ideal target is not the same thyroid nodule. Taking into account RFA efficacy and tolerability, and the fact that it is easier, faster, more tolerable, and gives even more effective results if pretreatment nodule volume is not too large (i.e nodule volume < 20 mL), in our view RFA represents a valid therapeutic strategy for patients with symptomatic nodules that are perceived "too little" to undergo surgery, but still "too much" to keep with the observation. On the other hand, in patients with large nodules (> 20 mL), who will probably require more than one session to satisfactorily reduce thyroid nodule volume, surgery should remain the first-line treatment option in light of its efficacy and safety. However, if surgery was contraindicated or declined, RFA could be a valid therapeutic alternative also for large nodules.

As for radioiodine therapy, it is effective to treat autonomously functioning thyroid nodules, as it normalizes thyroid function and significantly reduces thyroid volume. For instance, a single dose of ^{131}I aiming at a level of 100 Gy normalized thyroid function in 75% of patients and reduced nodule volume by 40% in 12 months (45, 46). To date, there are no comparative studies between RFA and radioiodine. Nevertheless, based on the existing literature, RFA does not cause hypothyroidism, which occurs in up to 60% of patients several years after ^{131}I treatment (47), and does not require the use of contraceptives in fertile women (48). Moreover, it can be inferred that RFA is probably superior to radioiodine in terms of nodule volume reduction, while it is likely to be inferior to it in terms of thyroid function normalization. On this basis, the possible usefulness of a combined treatment (RFA + radioiodine) has been recently proposed for large hyperfunctioning nodules (49), where RFA could produce faster and more marked nodule shrinkages, coupled with a lower-radioiodine-administered activity as compared to radioiodine alone. Otherwise, RFA has been recommended in patients where radioiodine is either contraindicated or declined (10),

Also levothyroxine therapy has been used for the treatment of cold thyroid nodules. However, its use should not be recommended routinely in patients with benign thyroid nodules (50). Although suppressive levothyroxine therapy may decrease nodule size and prevent the appearance of new nodules in iodine deficient regions (51), its effect is modest, with most studies suggesting an average 5-15% reduction of nodule volume after 6-18 months (52-54). In addition, suppressive levothyroxine therapy increases the risk of adverse consequences related to iatrogenic thyrotoxicosis (50). On the other hand, the efficacy of non-suppressive levothyroxine therapy remains unproven (8), as it is supported only by non-blinded, non-randomized trials, such as (55). Taken together, these results explains why the choice of this treatment has declined (56). Moreover, in a recent Cochrane Collaboration systematic review, levothyroxine was found not as effective as minimally invasive therapies for the reducing the volume of benign thyroid nodules (57).

4.b Nonsurgical, image-guided, minimally invasive techniques

In addition to RFA, nonsurgical, image-guided, minimally invasive techniques include percutaneous ethanol injection (PEI), laser ablation (LA), microwave ablation (MWA), and high-intensity focused ultrasound (HIFU). Among these techniques, PEI, LA, and RFA are gaining ground in the daily management of thyroid nodules and cysts, while MWA and HIFU are presently under investigation.

PEI is the oldest image-guided, minimally invasive technique that can be used for the treatment of benign thyroid nodules. The first documented use of PEI dates back to 1989 (58), when the sclerotizing properties of ethanol were used to treat thyroid cysts after aspiration. Then, in the 90s, PEI was used on solid nodules without much success despite multiple sessions, and with limitations related to ethanol causing serious side effects. Today, this technique is considered the first line therapy for large and/or symptomatic thyroid cystic lesions (8). On average, PEI can reduce the volume of thyroid cysts by 64-

93%, with a 69-95% rate of successful treatments, defined as a reduction of thyroid cyst volume greater than 50 % (59).

Although RFA is effective for the treatment of predominantly cystic nodules, PEI remains the first line therapy for thyroid cystic lesions, as it is simpler and more cost effective. When RFA was compared to PEI for the treatment of benign thyroid cysts, PEI resulted to be superior to RFA in terms of number of treatment sessions required (37) and mean volume reduction (38). In a retrospective study, Sung and colleagues showed that PEI was superior to RFA in terms of number of treatment sessions required, which were between 1 and 2 for PEI, which was successful in 94.4% patients, and between 1 and 3 for RFA, which was successful in 95.2% of patients (37). In a prospective study comparing the volume reduction achieved by one session of PEI to that achieved by one session of RFA, PEI reduced thyroid cystic nodules by 96.9%, while RFA reduced them by 93.3% after 6 months (38).

LA is another thermal ablation method that can be used for the treatment of benign thyroid nodules. Laser, which is an acronym for Light Amplified Stimulated Emission of Radiation, directs collimated, monochromatic, coherent, and powerful light energy to a well-delimited area of tissue in a predictable, precise, and controlled way. Light energy is applied via optical fibers connected to a laser energy generator, and in order to increase the lesion size multiple fibers are usually inserted simultaneously in an array around the tumor. These fibers consist of 300 μm-diameter plane-cut optic fibers that are inserted through the sheath of a 21-gauge Chiba needle, with 5 mm of the bare fiber being in contact with thyroid tissue. Since the introduction of LA for the treatment of symptomatic thyroid nodules in 2000, several studies have reported its efficacy (5). Nodule shrinkage ranges from 36 to 82%. In particular, patients with spongiform nodules seem to be the best candidates for LA (59). Based on this ground, LA has been recommended as a possible option for the treatment of benign thyroid nodules by

the guidelines of the American Association of Clinical Endocrinologists, the Italian Association of Clinical Endocrinologists, the European Thyroid Association (50).

Although there are no studies directly comparing the two procedures, in a recent Bayesian meta-analysis evaluating RFA and LA, RFA was found to be more effective at decreasing nodule volume after 6 months from the procedure, as it achieved a larger pooled percentage mean change and absolute mean change as compared to LA (77.8% vs 49.5%, respectively) (60). Moreover, looking at long-term follow-up studies, like those with more than 2 years of follow-up, it seems that the volume reduction achieved by RFA (up to 90-92%) is superior to that achieved by LA (around 50%) (35, 61).

In addition to that, when looking at RFA and LA procedures from a technical point of view, RFA is performed via a moving shot technique, based on the concept of moving the electrode during the procedure. The nodule is divided into several conceptual units and ablated unit by unit, starting from its deepest layer and then moving sequentially the tip of the electrode to the left and the right, while slowly withdrawing it toward the surface. This approach allows tailoring the procedure to every nodule. It maximizes the ablation of the entire nodule margins, while avoiding injury of the recurrent laryngeal nerve, trachea, and esophagus. As compared to RFA approach, LA requires 2 to 4 fibers inserted simultaneously in the center of the nodule for the ablation. Laser firing is started from the bottom part of the nodule and then needles and fibers are pulled back. The duration of laser illumination ranges from 6 to 30 minutes, depending on the nodule size. Light irradiation is continuous and it is shortly suspended for fiber repositioning. This approach, which is a bit more complicated and time-consuming (60), would not achieve treatment of the nodule margins, which could then regrow, as seen with long-term follow-up studies (61). Therefore, RFA is emerging as the ablation procedure of choice for solid nodules (6).

Conclusion

Based on the existing literature, the greatest shift in the future routine management of benign thyroid nodules will probably be determined by the availability of nonsurgical, minimally invasive techniques, such as RFA. This technique has shown the potential to help in the daily management of thyroid nodules, particularly when they are single, cold, and symptomatic, where it has been proven safe and effective. In our view, RFA does not overlap with the conventional and established treatments for thyroid nodules, namely surgery and radioiodine, but it is complementary to them. RFA could in fact represent the solution for a need that has remained unanswered for years, helping those patients that perceive their nodule as something too small to be conventionally treated (or which cannot be conventionally treated), but too big to keep with the simple clinical follow-up.

Figure legends

Figure 1. Thyroid nodule volume reduction at 24 months. Representative transverse and longitudinal B-mode ultrasound images showing RFA effects at baseline (A-B), 1 month (C-D), 6 months (E-F), 12 months (G-H), and 24 months (I-J) from the procedure. The treated area of the nodule appears reduced in size and hypoechoic.

Conflict of interest disclosure

The authors declare that they have no conflicts of interest

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Figure 1

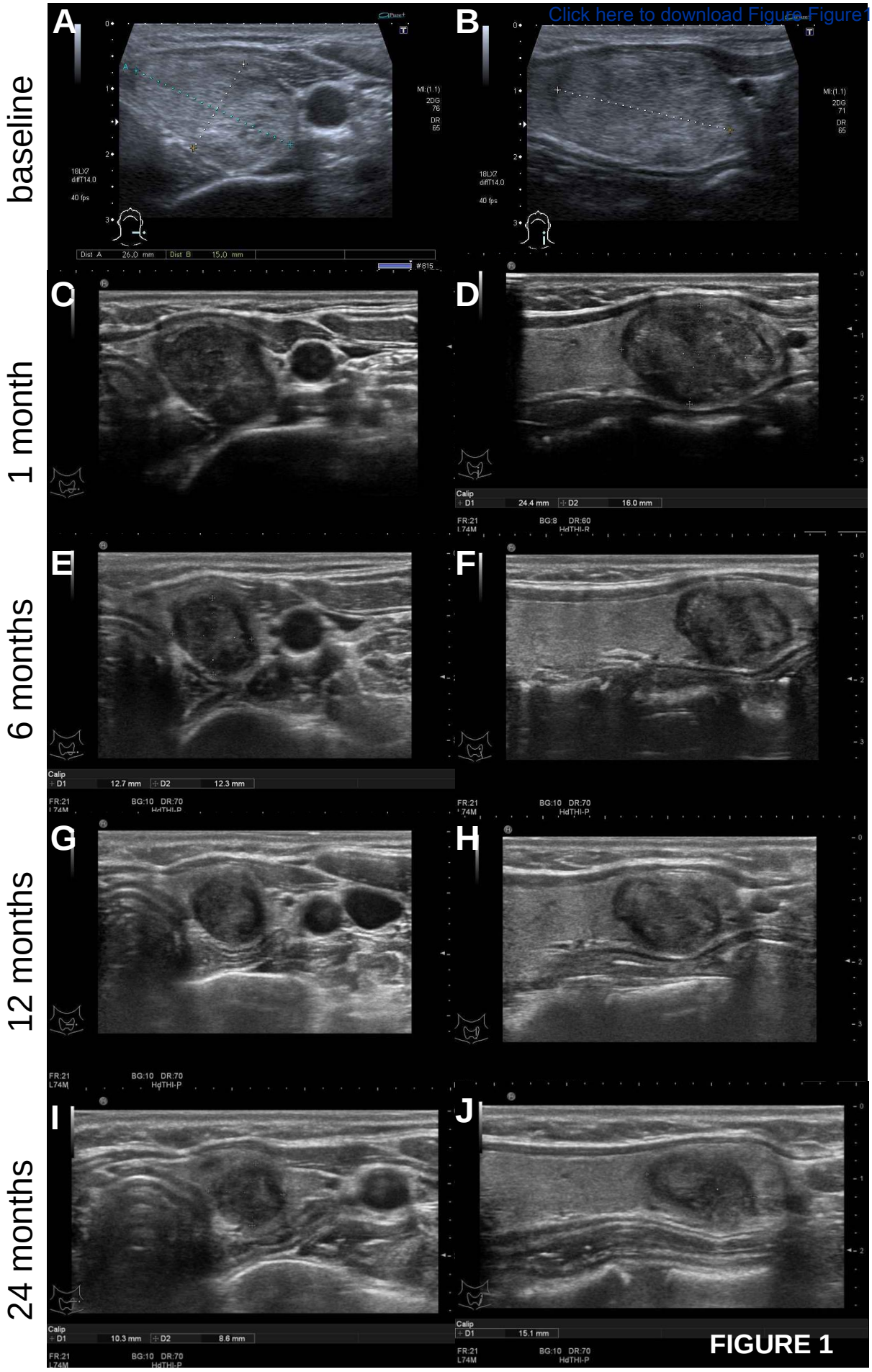

FIGURE 1

Table 1. Management of patients with implanted pacemakers (PM) or implanted cardioverter-defibrillators (ICD)

	non PM dependent	**PM dependent**
PM	*Before the procedure*: special precautions are not needed *During the procedure:* peripheral pulse monitoring *After the procedure*: special precautions are not needed	*Before the procedure*: either reprogram the device to asynchronous mode and suspend rate-adaptive functions / or place a magnet over the device *During the procedure:* peripheral pulse monitoring *After the procedure*: either program back the device to its original status / or remove the magnet
ICD	*Before the procedure*: suspend tachyarrythmia treatment algorithms *During the procedure*: 1. ECG and peripheral pulse monitoring 2. temporary pacing and external cardioversion-defibrillation equipment available *After the procedure*: program back the device to its original status	

Table 2. Thyroid nodule volume reduction achieved by RFA

	No of nodule/pts	Electrode type	Solid component	Nodule function cold/hot nodules	Mean initial volume	No of sessions	Follow-up duration	Volume reduction at last follow-up	Ref
Kim et al. 2006	35/30	17-G internally cooled	0-100%	Cold nodules	6.3 mL	1	6 mo (15 nodules)	63.8%	14
Spiezia et al. 2007	39/39	14-G Multitined expandable	n/a	Cold nodules	24 mL	1-3	6 mo	74%	15
Deandrea et al. 2008	33/31	14-G Multitined expandable	50-100%	10 cold/23 hot	27.7 mL	1	6 mo	50.7%	16
Jeong et al. 2008	302/236	17-G internally cooled	0-100%	Cold	6.1 mL	1-6	6 mo (140 nodules)	84.79%	17
Baek et al. 2009	9/9	17 and 18-G internally cooled	10-100%	Hot nodules	14.98 mL	1-4	6 mo	70.7%	39
Spiezia et al. 2009	94/94	14-G Multitined expandable	70-100%	66 cold/28 hot	24.5 mL	1-3	24 mo	79.4%	18
Baek et al. 2010	15/15	18-G internally cooled	50-100%	Cold nodules	7.5 mL	1	6 mo	79.7%	19
Lee et al. 2010	27/27	18-G internally cooled	10-50%	Cold nodules	4.2 mL	1	6 mo	92%	36
Sung et al. 2011	21/21	18-G internally cooled	<10%	Cold nodules	10.19 mL	1-3	6 mo	92.2%	37
Jang et al. 2012	20/20	18-G internally cooled	<50%	Cold nodules	11.3 mL	1-2	6 mo	92%	62
Huh et al. 2012	15/15 15/15	18-G internally cooled	>50% >50%	Cold nodules Cold nodules	13.3 mL 13.0 mL	1 2	6 mo 6 mo	71% 77%	40
Faggiano et al. 2012	20/20	14-G multitined expandable	>70%	10 cold /10 hot	13.3 mL	1	12 mo	86%	32
Ha et al. 2013	14/11	18-G internally cooled	>50%	Cold nodules	9.7 mL	1	43 mo	87.2%	63
Lim et al. 2013	126/111	17 and 18-G internaly cooled	0-100%	Cold nodules	9.8 mL	1-7	48 mo	93.5%	35
Sung et al. 2013	25/25	18-G internally cooled	<10%	Cold nodules	9.3 mL	1	6 mo	93.3%	38
Bernardi et al. 2014	37/37	18-G internally cooled	10-100%	25 cold/12 hot	12.8 mL	1-2	12 mo	70%	11
Dobrinja et al. 2015	64/64	18-G internally cooled	10-100%	46 cold/18 hot	13.8 mL	1	24 mo	67%	12
Che et al. 2015	375/200	18-G internally cooled	nd	Cold and hot nodules	5.4 mL	nd	12 mo (194 nodules)	84.8%	44
Deandrea et al. 2015	20/20 20/20	18-G internally cooled	>70% >70%	Cold nodules	13.9 mL 16.4 mL	1 1	6 mo 6 mo	77% 66%	33
Valcavi et al. 2015	40/40	18-G internally cooled	>80%	Cold nodules	30.0 mL	1	24 mo	80%	34
Sung et al. 2015	44/44	18-G internally cooled	10-100%	Hot nodules	18.5 mL	1-6	6 mo	74.5%	64