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DR ANDREA PALERMO (Orcid ID : 0000-0002-1143-4926)

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Radiofrequency Ablation for the Management of Thyroid Nodules: A Critical Appraisal of the Literature

Cesareo Roberto*[1], Palermo Andrea*[2] Pasqualini Valerio[3], Cianni Roberto[3], Gaspa Gianluigi[4], Manfrini Silvia[2], and Pacella Claudio Maurizio[5].

[1]Thyroid Disease Center, "S. M. Goretti" Hospital, Latina, Italy
[2]Dep. of Endocrinology and Diabetes, University Campus Bio-Medico, Rome, Italy
[3]Dep. of Radiology, "S. M.Goretti" Hospital, Latina, Italy
[4]Dep. of Food Science and Nutrition, University Campus Bio-Medico, Rome, Italy
[5]Past Chief Dep.of Diagnostic Imaging and Interventional Radiology - Regina Apostolorum Hospital, Albano Laziale, Rome, Italy

* These authors contributed equally to this paper

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Corresponding author:
Andrea Palermo, MD PhD
Dep. of Endocrinology and Diabetes,
University Campus Bio-Medico
00128 Rome, Italy
Phone: +39 0622541619
E-mail: a.palermo@unicampus.it

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ABSTRACT

The majority of benign thyroid nodules are asymptomatic, remain stable in size, and do not require treatment. However, a minority of patients with growing nodules may have local symptoms or cosmetic concerns, and thus demand surgical therapy. The timely use of ultrasound-guided, minimally invasive thermal therapies has changed the natural history of benign, enlarging thyroid nodules (TNs). These procedures produce persistent shrinkage of TNs and an improvement of local symptoms. Among the various procedures, percutaneous ethanol injection (PEI) represents the first-line treatment for thyroid cysts, while in solid cold nodules, laser and radiofrequency ablation (RFA) have proven to be very effective and safe techniques in producing significant volume reduction that remains stable over several years. In particular, RFA seems to be suited for the management of small and medium nodules, while larger nodules may require repeated RFA treatments, and could be difficult to treat if they extend into the chest. RFA is performed in outpatient clinics, and has a lower risk of complications compared to surgery. **However, to date, there is still no unanimous consensus on the percutaneous treatment of benign nodules using such minimally invasive thermal techniques. In this review, we critically revise the literature to identify patients who are more likely to benefit from RFA treatment as an alternative to surgery.**

Key terms: Radiofrequency, **Thermal Ablation Therapies,** Thyroid Nodules, Ultrasound.

Introduction

Thyroid nodules (TNs) are typically asymptomatic and are found in 33% to 68% of adults when evaluated by ultrasound[1]. Although TNs are benign and treatment is often not mandatory[2], some patients require treatment due to pressure symptoms or cosmetic complaints[3]. Current guidelines do not recommend routine use of thyroxine suppression therapy in clinical practice as the results are controversial and there is a risk of bone and heart cardiac side effects [4].

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Nonsurgical, minimally invasive treatment options such as percutaneous ethanol injection (PEI), percutaneous laser ablation (LA), and radiofrequency ablation (RFA) are used to treat symptomatic benign TNs[5]. PEI is known to be very successful in treating cystic or predominantly cystic thyroid nodules while most expert centres, to date, have abandoned this technique during the last decade for solid thyroid nodules[6, 7]. LA, primarily investigated for the treatment of solid nodules[8], is successful in reducing the volume of treated TNs by 40% to 80% and clinical outcomes in patients followed for more than 5 years indicate that this procedure results in satisfactory mid- to long-term clinical response in the majority of cases[9, 10]. RFA, introduced in 2006, has been reported to be a safe, effective treatment for benign TNs[11]. **However, to date, there is still no unanimous consensus on the percutaneous treatment of benign nodules using minimally invasive thermal techniques. In this review, we critically revised the literature to identify patients who are more likely to benefit from RFA treatment as an alternative to surgery.**

Patients

Rarely, patients with thyroid nodules complain of pain in the neck, jaw, or ear. If a nodule is large enough to compress the trachea or oesophagus, it may cause difficulty with breathing or swallowing, or cause a "tickle in the throat"**.**

The treatment indications of the Korean Society of Thyroid Radiology (KSThR) include patients presenting with benign thyroid nodules (BTNs) with nodule-related compressive symptoms and/or cosmetic concerns, or with autonomously functioning thyroid nodules (AFTN) (we do not consider here the indications in recurrent thyroid cancer). In this consensus statement, nodule size is not considered a specific criterion for RFA, although the authors declare that "patients with nodules with a maximum diameter >2cm (roughly 4-5 mL) that continue to grow over time, may be considered for RFA, depending on symptoms or cosmetic discomfort, their location, and the patient's feeling"[12]. The experts' panel in the first Italian opinion statement indicate RFA for large (volume>2 0ml) cold nodules in patients with local symptoms or cosmetic complaints and ~~the~~ AFTNs hot/warm at scintiscan, either toxic or pretoxic. The same experts, however, also suggest treatment for ~~also~~ cold nodules with volume <20 mL coupled with early local discomfort that grow significantly over time[13]. In the Italian opinion statement, the above indications are intended for solid or predominantly solid nodules while the Korean group includes solid, mixed and cystic nodules with a variable cystic component. These indications are not yet fully shared in the USA where the

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American Association of Clinical Endocrinologists (AACE) advises caution for use of these minimally invasive thermal techniques - LA or RFA - and recommends their use when patients decline or do not respond to conventional therapies[14]. All the aforementioned guidelines recommend the use of RFA in patients in whom thyroid surgery was either contraindicated due to comorbidity or unacceptable perioperative risks, or it was refused by the patients. On the contrary, their use to treat TNs is not currently endorsed by American Thyroid Association for Differentiated Thyroid Cancer and Thyroid Nodules (ATA)[4]. According to 2015 guidelines of this Association, most asymptomatic nodules demonstrating modest growth should be followed without intervention. Surgery may be considered for growing benign TNs if they are large (> 4 cm) and causing compressive or cosmetic symptoms.

These various recommendations reflect variations in cultural preferences and potential differences in the pathogenesis of multinodular goitre related to the iodine status in S.E Asian, European and U.S. populations. Thus, to date, the nodule size and sonographic component criteria (solid or mixed and their percentage) vary across the above mentioned guidelines and the current indications for RFA remain unclear.

Before undergoing the procedure, TN should be confirmed as benign on at least two separate ultrasound (US)-guided fine needle aspirations and/or core needle biopsies. Because of the high risk of malignancy, the treatment of follicular neoplasms (classified as Thy3 according to the British and Italian reporting system for thyroid cytopathology, which corresponds to Bethesda Categories III and IV nodules) should not be advised[15]. **Some patients might not be good candidates for this procedure if ultasonographic visualization of the nodule is poor and access to the nodule cannot be achieved with ease. Thus, RFA treatment should be avoided in large multinodular goitre or in retrosternal TNs.** Caution should be taken in performing RFA of benign TNs with ultrasound characteristics of malignancy. **Finally, the patients, before the procedure, should be correctly informed about the goals to be achieved using this technique. In case of large nodules, the operator should alert the patient about the possibility of retreatment.**

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Procedure

Radiofrequency is mostly performed in an outpatient clinical setting, after local anaesthesia, in patients under conscious sedation. The term radiofrequency (RF) refers to an alternating electric current oscillating between 200 kHz and 1200 kHz. Application of RF agitates tissue ions as they attempt to follow the changes in direction of the alternating current, thus creating frictional heat around the electrode. Although heat creates immediate damage to tumour tissue, this is significant only in regions very close to the electrode (a few mm). In other words, in the widely used monopolar mode, the patient is part of a closed-loop circuit that comprises a radio frequency generator, an electrode needle, and a large dispersive electrode (ground pads). The RFA ablation setup can be thought of as an electrical circuit wherein the current loop includes a generator, electrodes, wiring, and tissue as the resistive element. An alternating electric field is created within the tissues of the patient. Tissues are imperfect conductors of electricity (electrical impedance) so current flow leads to frictional agitation at the ionic level and to heat generation, known as the *Joule effect*. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads concentrates the generated heat around the needle electrode. Tissues nearest to the electrode are heated most effectively, while peripheral areas receive heat by thermal conduction[16]. Ablative heating leads to tissue dehydration and water vaporization, with a rapid increase in circuit impedance. Methods to improve the circuit impedance such as expanding the electrode surface area, pulsing the input power, or injecting saline solution are used to augment RFA current flow in these circumstances. Several electrode types are available for clinical RFA, including internally cooled electrodes and multiple-tined expandable electrodes with or without perfusion[17].

So far, two electrode types have been used for thyroid RFA: a straight, internally cooled electrode, and multi-tined expandable electrode. These have been used in Korea and Italy, respectively. Today, the “moving-shot technique” represents the most used procedure. Jeong et al. have described a trans-isthmic approach[18]. The electrode needles, calibre ranging from 17G to 19G, are inserted under US guidance into the TN along its short axis by the aforementioned approach, and different zones of the target are sequentially ablated by moving the position of the electrode tip. The electrode is initially positioned in the deepest part of the nodule and then moved to the central areas, and finally to the superficial areas of the lesion. During the procedure, the output power ranges from 40W to 80W and time exposure is calculated to obtain a transient hyperechoic area in each of the different zones

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undergoing ablation. The number of insertions depends on nodule size. This method has multiple advantages. First, the entire length of the electrode can be visualized on a transverse US view. Furthermore, there is minimal exposure of the danger triangle (which includes the recurrent laryngeal nerve and/or oesophagus) to the heat.

Patients are usually treated with local anaesthesia at the puncture site. We deploy a variant of the aforementioned technique as we use a 60W-radiofrequency output power and, as a sign of effectiveness of ablation procedure, time exposure needed to obtain transient, multiple hyperechoic zones.

Clinical Outcomes

RFA appears to be an effective nonsurgical option to improve pressure and cosmetic symptoms in benign TNs. Several reports and prospective randomized trials have shown significant nodule volume reduction (50% to 80% compared to the baseline volume and according to the single studies)[11, 18-30]. At the moment, a common consensus regarding the definition of small, medium, and large nodule has not been established. **Some authors categorize thyroid nodules with volumes of < 10 ml as small and > 20 ml as large[13, 23, 31]. Others consider nodules with initial volumes between 12.0 to 30.0 ml as medium, and those > 30.0 ml as large[27]. Some authors suggest 12ml as a cut-off level below which no treatment is advisable and only observational follow-up[32] is recomended.** Although RFA is generally effective in reducing TN volume, the best reduction rates appear to be limited to small and, partially, medium nodules[11, 22, 26, 27, 33].

Large nodules require multiple treatment sessions[19,23]. The criteria utilized for repeating RFA (up to 6 procedures in some patients) varied across different studies and include: a remaining portion of the nodule on follow-up[18]; volume-reduction of less than 50%[18]; or patients complaining of incompletely resolved compressive symptoms[23]. In contrast, a prospective evaluation of the efficacy of additional RFA (single session vs two sessions) concluded that a single session RFA showed satisfactory volume reduction and clinical response[34]. Therefore, the indication for repeating RFA remains unclear. The overall rate of regrowth (defined as > 50% increase in nodule volume compared with previous ultrasound) has been reported to be 5.6% in earlier studies[23] and 24.1% in more recent studies[31]. Recurrence (defined as a more than 50% increase compared to the previously reported smallest volume on ultrasonography) has been reported to

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occur in 57.4%[31] These studies concluded that incompletely treated nodules may start to enlarge within the first two years after ablation with recurrences of marginal vital tissue. Vital volume increase tended to occur earlier than regrowth and might be an early sign of regrowth during follow-up after the RFA of benign TNs[31]. **Probably the main explanation for this behaviour is that, in large nodules, RFA could be less effective as the radiofrequency energy may not be evenly distributed to the entire lesion[20]. Other possible explanations for this problem are likely to relate to the number of RFA procedures for the nodule as well as the total energy delivered per procedure. Anyway, robust data** describing the efficacy of RFA on large nodules are lacking[26]. **Thus,** we do not have sufficient data to determine the exact percentage of regrowth, although major regrowth rate is expected in medium or large nodules (> 20 ml). Therefore, in medium and large nodules, it is important to inform the patient about the possibility of recurrence **and regrowth and the necessity of having to carry out multiple treatments**.

The symptom score measured using a 10 cm visual analogue scale (grade 0-10 VAS), adopted by most of the studies is a useful tool to categorize patients clinically but this scale is operator sensitive: there is no accurate correspondence between nodule volume and symptom scores. In fact, in many studies, the symptom score is quite similar but thyroid nodule volume is very different[26, 35, 36] (Table 1 and 2).

Another visual analogue scale was adopted in only two trials but it is quite similar (the authors using one scale from 0 to 6). However, also in this case, small cold thyroid nodules (about 8 ml) had the same symptom score as larger nodules (about 24 ml)[20, 22].

Most of the previous trials have focused on small/medium, cold, benign thyroid nodules that, usually, do not display significant cosmetic or compressive symptoms. Indeed, **the mean value of the symptom score is not so high (3.42±1.97 vs 0.83±0.93) to be sure that RFA should be performed in all the nodules evaluated. (Tables 1 and 2).**

Another parameter, focused on patients' well-being, that has been studied in subjects undergoing RFA, is quality of life (QoL) measured by questionnaires such as SF-36 [37]. In particular, a recent trial compared health-related quality of life (HRQoL) and cost-effectiveness of RFA vs open thyroidectomy (OT) for benign TNs. The authors concluded that patients treated with RFA had significantly better HRQoL than patients

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treated with OT regarding general health (68.5 versus 66.7, p = 0.029), vitality (71.3 versus 67.5, p < 0.001) and mental health (80.9 versus 79.3, p = 0.038)[38]. -A more recent use of this method was made by other authors to explore changes in HRQoL scores during a 2-year follow up using the Short-Form (SF)-12 Health Questionnaire (a reduced form of the more extensive SF-36 questionnaire) in patients with symptomatic TNs of different sizes treated with RFA[28]. However, although QoL measurement may be a good tool to evaluate the post-procedural changes in subjects treated by thermal ablation or surgery, it is not a validated instrument to classify subjects who need to be treated by thermal ablation. In fact, it is a post-procedural analysis.

Ultimately, in light of the above considerations, to date, objective evaluation criteria shared by all researchers on this particular field of study ~~are~~ are lacking.

Data are missing about the improvement of thyroid function in patients with hot nodules, even if a recent multicentre study validated the efficacy of RFA in such cases[29]**. Moreover, a review of previous papers revealed discordant data about the treatment of pre-toxic and toxic nodules.** Several biases may have affected these papers: patients undergoing multiple sessions or treated by more operators[21, 29]. Hence, the evaluation of the actual efficacy of RFA in patients affected by hot nodular goitre appears to be trivial. We do not have sufficient data to consider this procedure cost-effective in light of the fact that the achievement of a euthyroid state might need several treatments (Table 2). Moreover, the patients often did not completely stop antithyroid drug therapies before and/or after RFA and, in those undergoing only one procedure, the percentage of euthyroidism was lower[22, 29, 36].

RFA and other techniques

A recent systematic review argued the superiority of RFA compared to laser (LA) in reducing benign solid TN volume. However, the analysis included only nodules with volumes of <15ml, which does not reflect real clinical practice, where larger nodules are often encountered and treated[39]. **In addition, a more recent paper on a small case series reported direct comparisons between the two techniques highlighting a substantial equivalence. In conclusion, the two procedures might be similarly effective when performed by operators with the same expertise[40, 41]. Up to now, no RCTs have been published on the comparison between radiofrequency and LA for thyroid nodule ablation. In summary, the RFA technique seems to share similar indications to LA.**

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However, regarding problems specific to RFA, the moving shot technique is an effective method to ablate thyroid tissue but it could be considered more operator sensitive compared to LA which, generally, does not require multiple repositionings of the electrode and is performed with small needle guidance[10, 41, 42]. However, this issue should be better addressed with a focused prospective trial.

Some studies aiming to compare surgery (hemithyroidectomy or thyroidectomy) to RFA for the treatment of benign thyroid nodules have recently been published but did not include very large nodules[25, 33]. Up to now, no clinical trials have been performed to evaluate the superiority of RFA vs ~~S~~surgery on the management of large nodules. Moreover, ~~about~~ regarding small and medium nodules, some authors have recently demonstrated that RFA and surgery were both safe, although RFA had fewer complications and seems to be less expensive when only one RFA treatment is performed. Indeed, compared to surgery, this technique allows a shorter treatment period (from 20 minutes to an hour, according to the baseline TN volume[26, 27]), fewer complications (1.0 vs 6.0)[33], preservation of thyroid function, and fewer hospitalization days[25]. We did not consider other emerging forms of thermal ablation because they are not yet thoroughly assessed or well established ablative methods for TNs.

Safety and complications

RFA of TNs is usually considered a safe, well-tolerated procedure. In order to achieve the best results in terms of TN volume reduction and low complication rates in the treatment of benign thyroid nodules, operator experience is very important. Although the complication rate of RFA is low, various complications may occur (Table 3). Regarding major ones, voice change is the most frequent. Other major complications include cases of permanent right paramedian vocal cord palsy and inspiratory stridor without dysphonia [27], and severe autoimmune thyrotoxicosis persisting for a few months after RFA treatment and requiring high dosages of methimazole and cortisone (data not published). The mechanism for causality between these treatments and autoimmune disease is not completely understood. Regalbuto C *et al* [43] suggested a pathophysiological mechanism based on the destruction of thyroid tissue in subjects genetically predisposed to autoimmune reactions, whereby the release of a large quantity of antigenic material from follicular thyroid cells may trigger an autoimmune inflammatory response through thyroid and orbital soft tissues. Among minor complications, pain, coughing and vasovagal reactions can be considered the most frequent

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side effects. Other complications are nodule rupture, hypothyroidism, brachial plexus injury and skin burn[44, 45].

We advise that, before starting RFA, these topics should be stressed and, where appropriate, shared with the patient:

a) Describe major and minor complications.
b) Explain the reduction rate and timing, according to the current literature (the nodule does not disappear!)
c) Describe the possibility of an additional treatment if there is significant regrowth (mainly for larger nodules).
d) The results of at least two fine needle aspirations should be available from the nodule to be treated (Thy 2 according to the British and Italian reporting system for thyroid cytopathology).
e) Avoid treating **substernal TNs and deep, posteriorly located nodules** (there may be not total control of the needle, which could create exposure to more tissue and, sometimes, severe complications)
f) Do not use these procedures in pregnant women or in patients with severe heart disease (there are no evidence-based data about these subjects).
g) Avoid RFA in patients affected by ipsilateral vocal palsy. Perform a laryngoscopy and an otorhinolaryngologist evaluation in case of dysphonia or contralateral vocal palsy.
h) Do not perform RFA in patients with magnetic devices.

Open questions and Conclusions

In our view, some issues remain unclear and should be better addressed in the future. In particular:

- **Which are the nodules that better respond to ~~the~~ RFA treatment? In particular, is it cost-effective to treat large benign non-functioning nodules?**
- **How many small and medium nodules can cause compressive symptoms or cosmetic discomfort?**
- **Is it cost-effective to treat autonomously functioning thyroid nodules with RFA compared to radiometabolic treatment?**

According to literature, this technique should be used in patients with medium-sized, cold, benign thyroid nodules, or by small nodules that lead to cosmetic problems. We need to gather more evidence-based data about the effectiveness of RFA in terms of volume reduction and cost-efficacy for large thyroid nodules. Finally, with regards to hot nodules,

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small-medium, hot, toxic nodules could probably be treated, but only in patients who refuse radioiodine therapy, which remains the gold standard treatment.

In conclusion, RFA can be considered a viable alternative to classic thyroid surgery but available data are still the subject of debate and the proper selection of patients with benign nodules for minimally invasive techniques and subsequent monitoring deserve more extensive investigation.

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Table and figure legends

Table 1. RFA in cold nodules
Table 2. RFA in hot nodules
Table 3. Complications in patients treated by RFA

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Table 1: result of RFA in cold nodules

Study	No. of Patients	Volume At baseline (ml)	Volume reduction %	Follow-up	Design	Sonographic characteristics	Number of sessions	Symptom score reduction	Cosmetic score reduction	Technique	One single/more operators	Year
Kim et al. (11)	30	6.3	64	6.5 months	Not controlled study	Mainly cystic	1	88% reduction complessive symptoms	NA	Free-hand	One single	2006
Jeong et al (18)	236	6.13 ± 9.59	84.1	6 months	Retrospective cohort	Solid/cystic/ mixed	1,4	NA	NA	Internally coole Moving shoot	Two operators (pheraps)	2008
Deandrea et al (19)	10	39.3 ± 27.8	46.3 ± 17.1	6 months	Prospective cohort	Solid/mixed	Retreatment in larger nodules	NA	NA	Multitined expandable	One single	2008
Spiezia et al (20)	66	21.1 ± 1.7	79.4 ± 2.5	24 months	Prospective cohort	Solid component (> 70%)	More treatment in larger nodules	NA	NA	Multitined expandable	NA	2009
Baek et al (35)	15	7.5 ± 4.9	82.6 ± 81	8 months	Controlled study	Solid component (> 50%)	1	3.33 ± 0.90 vs 1.00 ± 0.76	3.60 ± 0.51 vs 1.53 ± 0.52	Internally cooled Moving shoot	Two operators (pheraps)	2010
Faggiano et al (22)	10	About 8	About 82	12 months	Randomized controlled study	Solid component (> 70%)	1	NA	NA	Multitined expandable	NA	2012
Lim et al (23)	126	9.8 ± 8.5	93.5 ± 11.7	49.4 months	Retrospective study	Solid and mixed	2.2 ± 1.4	4.3 ± 1.6 vs 0.8 ± 0.9	3.2 ± 0.8 vs 1.3 ± 0.6	Internally cooled Moving shoot	NA	2013
Turtullici et al (24)	45	13.5 ± 6.7	72.6 ± 11.3	6 months	Retrospective	NA	NA	NA	NA	Internally cooled Moving shoot	NA	2014
Deandrea et al (26)	40	15.1 ± 3.1	72 ± 12	6 months	Randomized controlled study	Solid (> 70%)	Probably one session	3,6 ± 1,9 vs 0,4 ± 0,7	3,6 ± 0,5 vs 1,7 ± 0,4	Internally cooled Moving shoot	At least two operators	2015
Cesareo et al (27)	42	24.5 ± 19.6	68.6 ± 13.5	6 months	Randomized controlled study	Solid (> 70 %)	One session	2.8 ± 3.3 vs 0.4 ± 2.2	2.6 ± 0.9 vs 0.4 ± 2.1	Miltitined expandable	One single	2015
Valcavi et al (28)	45	30.0 ± 18.2	−80.1 ± 16.1	2 years	Retrospective	Solid (> 70%)	One session	5.6 ± 3.1 vs 1.9 ± 1.3	5.7 ± 3.2 vs 1.9 ± 1.5	Internally cooled Moving shoot	One single	2015

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Cesareo et al (30)	48	23.5 ± 18.6	71.1 ± 14.3	1 year	Retrospective	Solid (> 70%)	One session	3.4 ± 3 vs 0.4 ± 0.8	2.8 ± 0.7 vs 1.5 ± 0.7	Multitined expandable	One single	2017

NA = Not Available

Table 2: result of RFA in hot nodules

Study	Number of patients	Volume at baseline (mL)	Volume reduction %	Follow-up	Stopped thyreostatic therapy %	Reduced but continued therapy	Number of sessions	Symptom score reduction	Cosmetic score reduction	Technique	One single/more operators
Deandrea et al (19), 2008	23	22.5±16	52,6±16,3	6 months	22.70%	77.30%	More treatments	NA	NA	Multitined expandable	One single
Spiezia et al (20), 2009	28	32.7±5.4	59,6±37	12 months	SH:100% Toxic: 53%	Toxic: 47%	More treatments †	NA	NA	Multitined expandable	NA
Baek et al (21), 2009	9	14.98±25.53	70.7±22.9	6-17 months	NA	NA	2.2±1.0	2.4±1.7 vs 0.6±0.7	3.1±1.2 vs 1.4±1.0	Moving shoot	NA
Faggiano et al (22), 2012	10	About 18	NA	12 months	40%	40%	1	NA	NA	Multitined expandable	NA
Bernardi et al (25), 2014	12	NA	NA	12 months	33%	67%	1.03	NA	NA	Moving shoot	NA
Sung et al (29), 2015	44	18.5±30.1	81.7±13.6	19.9±12.6 months	60% ‡	2 of 5 patients	1.8±0.9	3.3±2.1 vs 0.9±1	3.8±0.5 vs 1.9±0.9	Moving shoot	More operators
Bernardi et al (36), 2016	30	17.12±2.39	74.78±3.01	12 months	50%	50%	1	2,03±0,11 vs 1.07±0,05	3,08±0,07 vs 1.74 ± 0.12	Moving shoot	One single

† = Thirty-four percent of patients (toxic and non toxic) required more than one RTA treatment
‡ = Before ablation, an anti-thyroid drug was prescribed for five patients. Three of these five patients were able to stop the anti-thyroid drug following ablation
NA = Not Available
SH = Subclinical Hyperthyroidism

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Table 3a: complications in patients treated by RFA

Study	No. of Patients	Hematoma (No. of patients)	Skin Burn (No. of patients)	Middle Pain (No. of patients)	Severe Pain (No. of patients)	Painless thyroiditis with thyrotoxicosis (No. of patients)	Sensation of heat and mild swelling of the neck (No. of patients)	Fever (No. of patients)
Kim et al (11), 2006	30	1	1	2	...	...	...	...
Jeong et al (18), 2008	236	5	...	13	...	...	...	...
Deandrea et al (19), 2008	10	...	...	...	...	...	NA	...
Spiezia et al (20), 2009	66	…	...	13	...	...	NA	5
Baek et al (21), 2009	9	…	...	...	...	...	...	...
Baek et al (35), 2010	15	...	...	NA	...	...	NA	...
Faggiano et al (22), 2012	10	...	...	...	...	...	NA	...
Lim et al (23), 2013	126	1	...	...	...	...	...	...
Turtullici et al (24), 2014	45	...	1	...	...	...	...	...
Bernardi et al (25), 2014	12	…	...	2	...	1	...	...
Deandrea et al (26), 2015	40	...	...	...	...	...	NA	...
Cesareo et al (27), 2015	42	...	...	...	...	...	...	...
Valcavi et al (28), 2015	45	...	...	...	7	...	...	1 Periprocedura (within 30 days)
Sung et al (29), 2015	44	...	...	NA	...	...	NA	...
Cesareo et al (30), 2017	48	...	...	8	1	...	...	...

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Table 3b: complications in patients treated by RFA

Study	No. of Patients	Transient Hyperthyroidism (No. of patients)	Hypothyroidism (No. of patients)	Brachial plexus injury (No. of patients)	Voice Change (No. of patients)	Permanent vocal palsy (No. of patients)	Bleeding intranodular (No. of patients)	Bleeding pericapsular (No. of patients)
Kim et al (11), 2006	30	3	...	...	2	...	...	...
Jeong et al (18), 2008	236	3	...	...	3	...	...	...
De Andrea et al (19), 2008	10	...	...	...	...	...	...	...
Spiezia et al (20), 2009	66	...	...	...	...	...	...	...
Baek et al (21), 2009	9	...	1	...	...	...	...	...
Baek et al (35), 2010	15	...	...	...	...	...	...	...
Faggiano et al (22), 2012	10	...	...	...	...	...	...	...
Lim et al (23), 2013	126	...	...	1	1	...	...	...
Turtullici et al (24), 2014	45	...	...	...	...	...	...	...
Bernardi et al (25), 2014	12	...	...	...	...	...	...	...
Deandrea et al (26), 2015	40	...	...	...	...	...	...	...
Cesareo et al (27), 2015	42	...	...	...	2	1	...	...
Valcavi et al (28), 2015	45	...	...	...	1 (transient voice change)	...	3	1
Sung et al (29), 2015	44	...	...	...	...	...	...	...
Cesareo et al (30), 2017	48	...	...	...	...	...	...	...

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Table 3c: complications in patients treated by RFA

Study	No. of Patients	Vasovagal reaction (No. of patients)	Vomiting (No. of patients)	Cough (No. of patients)	Swelling (No. of patients)	Bruise (No. of patients)	Pseudocystic Transformation (No. of patients)	Nodule rupture (No. of patients)
Kim et al (11), 2006	30	...	...	...	...	...	...	...
Jeong et al (18), 2008	236	...	...	...	...	...	...	...
De Andrea et al (19), 2008	10	...	...	...	...	...	...	...
Spiezia et al (20), 2009	66	...	...	...	...	...	...	...
Baek et al (21), 2009	9	...	...	...	...	...	...	...
Baek et al (35), 2010	15	...	...	...	...	...	...	...
Faggiano et al (22), 2012	10	...	...	...	...	...	...	...
Lim et al (23), 2013	126	...	1	...	...	...	...	...
Turtullici et al (24), 2014	45	...	...	...	...	...	...	...
Bernardi et al (25), 2014	12	...	...	...	...	...	...	...
Deandrea et al (26), 2015	40	...	...	...	...	...	...	...
Cesareo et al (27), 2015	42	...	...	...	...	...	...	...
Valcavi et al (28), 2015	45	1	...	2	4 Immediate postoperatory (within 24 hours)	1 Periprocedural (within 30 days)	1 Periprocedural (within 30 days)	1 Periprocedural (within 30 days)
Sung et al (29), 2015	44	...	...	...	...	...	...	...
Cesareo et al (30), 2017	48	...	...	...	...	...	...	...

NA = Not Available

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