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Comparison between Radioiodine therapy and single-session Radiofrequency ablation of autonomously functioning thyroid nodules: a retrospective study

Running title:

Radioiodine versus RFA to treat AFTN

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Main text

- Nothing to disclose.
- No competing financial interests exist.
  On behalf of all authors, the corresponding author states that there is no conflict of interest.

Abstract:

Objective

To compare the efficacy of Radioiodine (RI) and Radiofrequency ablation (RFA) in the treatment of autonomously functioning thyroid nodules (AFTNs). End points: nodule volume reduction (NVR) and thyroid function normalization.

Design, patients and measurements

Twenty-two patients (2:20 M:F; 51.9±13.9 years) affected by 25 AFTNs, treated by RFA were retrospectively compared with 25 patients (8:17 M:F; 57.2±12.8 years) affected by a single AFTN treated by RI. Both group showed analogous characteristics as to age, gender, toxic/pretoxic phase, and pre-treatment nodule volume (calculated by the ellipsoid formula). Thyroid hormone levels and autoimmune thyroid profile were assessed before treatment. A fixed RI activity of 555MGb (15mCi) was administered. RFA was performed with an 18G, single-tipped electrode, by the 'modified moving shot technique'. Thyroid hormones were assessed and the nodule post-treatment volume calculated 12 months after treatment.

Results

No statistical difference was found between the post-treatment NVR by comparing RI and RFA (p=0.69). The volume reduction rates were 68.4±28.9% and 76.4±16.9% after RI and RFA, respectively. As to the thyroid function, 5/25 patients developed clinical hypothyroidism after RI. After RFA, all the 22 patients silenced their AFTN and normalized the thyroid hormones. Subclinical hypothyroidism was recorded in 2 patients after both RI and RFA. Thus, the functional therapeutic success, defined as the restoration of euthyroidism, was achieved in 18/25 (72%) patients treated by RI and in 20/22 (90.9%) treated by RFA.

Conclusions

No statistical difference in NVR was found between RI and RFA. All patients responded to RI but 5/25 were 'over-treated' developing hypothyroidism. RFA was effective in all patients with no case of post-treatment clinical hypothyroidism. No radiation exposure and lower risk of post-treatment hypothyroidism might make RFA the favorite option especially for young patients.

Introduction

The autonomously functioning thyroid nodule (AFTN), also known as Plummer's adenoma, is a predominantly benign neoplasm presenting as a solitary hyperfunctioning nodule, in an otherwise healthy thyroid gland. It is visualized as a 'hot spot' by thyroid scintiscan, due to the strong concentration of Iodine-131 (^{131}I) used as radiotracer (dose, 50 μCi), compared with the surrounding thyroid tissue. The prevalence of AFTN ranges from 0.9% up to 9% [1,2]. AFTNs can cause a range of functional abnormalities, from euthyroidism to subclinical hyperthyroidism (pretoxic nodule) and overt hyperthyroidism (toxic nodule) [3]. The toxic phase of AFTN is characterized by hormonal abnormalities and clinical hyperthyroid symptoms, whereas in the pretoxic phase free triiodothyronine (fT3) and free thyroxine (fT4) are normal with low/suppressed levels of thyrotropin (TSH). Despite the absence of clinical symptoms, the pre-toxic phase may determine long-term adverse effects, particularly on the skeletal bones and cardiovascular system [4-6]. Thus, treatment may be advised when compression of adjacent structures, cosmetic complaints, hyperthyroid symptoms are present, and, also, to avoid progression of hyperthyroidism or to break off the 'pretoxic state', in order to evade the enlargement of the thyroid nodule together with long-term consequences. Hemithyroidectomy of the affected lobe is the standard treatment option for AFTNs [7]. However, some patients refuse surgical resection and others are unsuitable for surgery because of high anaesthesiologic risks; therefore, alternative therapeutic strategies have been proposed.

Radioiodine (RI) treatment has been increasingly used to solve hyperthyroid states, by applying different schemes of RI doses (low or high fixed dose as well as doses calculated on the basis of the nodule size or RI uptake after ^{123}I administration [8, 9]). The optimal dose of RI to silence the hyperfunctioning nodule, avoiding the development of hypothyroidism, is still a matter of debate. As demonstrated by Allahabadia et al, patients affected by large nodules (both palpable and visible) were associated with higher risk of treatment failure after a single dose of RI, and often required a second treatment session [10]. As a consequence, RI treatment is suited for small- to medium-sized AFTNs. The absolute contraindications to this therapy are breastfeeding and pregnancy, and another disadvantage is radiation exposure. Since the '90s, alternative therapies have been investigated: percutaneous ethanol injection (PEI) [3,11] and later laser ablation (LA) [12] were proposed for the treatment of AFTNs and proved effective techniques and possible treatment options. The PEI main drawbacks are: 1) the low capability to spread into mixed or solid tissues, making the technique less effective in the treatment of solid nodules, and 2) the need of multiple treatment sessions [13]. As to LA, several treatment sessions are required to normalize thyroid hormone levels [14,15]. During the last decade, Radiofrequency ablation was introduced as a reliable, minimally invasive procedure to treat symptomatic benign thyroid nodules in patients unwilling to or ineligible for surgery or RI therapy. Moreover, the Korean Society of Thyroid Radiology [16, 17] suggests using RFA in patients with nodule-related symptoms, or with cosmetic problems, or in patients who are affected by AFTNs both in the toxic and pre-toxic phases. In the Guidelines updated in 2017, the Korean Society stressed the risk of the worsening of pre-existing chronic diseases after surgery or RI therapy, and pointed out the controversy, which remains around the RI effect on childbearing patients. (Rew#1; point 4) At the same time, also the first Italian opinion Statement about indications of RFA, included the AFTNs in the group of nodular thyroid diseases which may benefit from the procedure [18]. In particular,

the Authors stated that the patients with toxic or pretoxic thyroid nodules, who are contraindicated to or refuse surgery and RI therapy, are eligible for RFA. Finally, the American Thyroid Association Guidelines confirm the RFA procedure as 'a welcome novelty in the management of AFTNs' [19].

The aim of this study is to compare the efficacy of RI and RFA in the treatment of AFTNs. End points to evaluate the efficacy of each treatment are: 1) nodule volume reduction and 2) hyperfuntioning thyroid nodule silencing, to solve the hyperthyroid functional state.

Materials and Methods

This study is a retrospective analysis of data collected prospectively. The study was approved by our institutional review board (CEAVNO) on May 19th 2016; an informed consent form to the procedure was signed by all the patients.

From May 2013 to March 2017, 22 consecutive patients (2 males, 20 females; mean age, 51.9 ± 13.9 years; range 26–72 years) affected by a total of 25 AFTNs and treated by RFA were included in our study and compared with 25 patients with a single AFTN treated by the routine practice of RI. To reduce bias in comparing these two therapies, the series of patients included in the RI group were retrospectively selected among the RI treatments performed between January 2015 and January 2017 in our Institution, in order to match them with the RFA group of patients. As a consequence of the matching, it was possible to find out that both groups of patients showed analogous characteristics as to the crucial parameters of age, gender, toxic/pretoxic phases, and pre-treatment volume of the nodules. The volume of the nodule was calculated according to the ellipsoid formula: $a*b*c*\pi/6$; where a, b and c are the diameters measurements. (Rew#1; point 1) The matching was created by using the chi-square test to compare the selected categorical, non-numerical parameters based on the treatment

received (gender, pre-RFA or RI treatment with antithyroid drug therapy, autoimmune thyroiditis, functional phase of the hyperthyroidism). As to the selected continuous numerical parameters (age, pre-treatment TSH value, pre-treatment nodule volume) the "bivariate statistical analysis" was performed to confirm the appropriate comparison of the RI and RFA groups.

Pre-treatment assessment

The thyroid hormone levels (TSH, fT3, fT4) and the autoimmune profile (Thyroid Peroxidase antibody – TPOAb, and Antithyroglobulin antibody – TgAb) were assessed in each patient before the treatment. The TSH normal range was between 0.4-4.0 microUI/mL, and a cut-off of <0.1 microUI/mL was chosen to indicate suppressed TSH levels. The reference normal laboratory values ranged between 2.7-5.7 ng/mL for fT3, 0.7-1.7 ng/mL for fT4, < 30 UI/mL for TPOAb and finally <10 UI/mL for TgAb. If the laboratory tests showed a thyrotoxic phase, the anti thyroid drug (ATD) treatment was administered to in order to restore euthyroidism.

Thyroid Scintiscan

All patients were evaluated by thyroid scintiscan, in order to confirm the strong concentration of the ^{131}I radiotracer into the nodule. The radioiodine scintigraphy with uptake allowed the calculation of the ^{131}I uptake values and the thyroid imaging after the administration per os of 50 μCi of radioiodine. The uptake values were performed on the 3rd and the 24th hour (New Atomlab 950, Biodex Medical System, Urbino, Italy). The thyroid imaging was acquired on the 24th hour using a single-head large field-of-view gamma camera (Omnia TH33, Mediso Ltd., Budapest, Hungary) equipped with high-energy high resolution collimators. In our study the AFTN was assessed as a hyperfunctioning nodule which determines complete

suppression of the surrounding thyroid tissue when the scintigraphic examination showed radiotracer uptake exclusively in the nodule area, whereas when the uptake of the radiotracer was still visible, though slightly sparsely, in the whole thyroid gland the nodule was assessed as hyperfunctioning nodule partially suppressing the remnant thyroid tissue (Figure 1).

Ultrasound evaluation

A B-mode Ultrasound (US) exam (7.5 MHz, MyLab Twice, Esaote, Italy) was performed to define the nodule texture (solid or mixed) and to calculate the volume of each nodule according to the ellipsoid formula: $V = \pi abc/6$ (where V is volume, a is the largest diameter, and b and c the two other orthogonal diameters). In the RFA group, the contrast enhanced ultrasound (CEUS) exam was also performed. The CEUS exam is a useful instrument to evaluate the efficacy of the RFA, because the unenhanced pattern is an indirect index of tissue necrosis [20]. Before treatment a cytological confirmation of the benign nature of all AFTNs was obtained.

RFA Procedure

After conscious sedation and a local lidocaine US-guided injection to achieve thyroid capsular anesthesia, RFA was performed. When the AFTNs showed a mixed (fluid and solid) structure, a preliminary aspiration of the main fluid component was performed to obtain only predominantly solid lesions (solid component > 75%).

All RFAs were performed using a RF generator (VIVA RF generator, STARmed, Korea), an 18-gauge internally cooled straight type electrode (Rew#1; point 8) (10-mm active tip) and by applying the 'modified moving shot technique' [21]. The 'modified moving shot technique' was performed in antero-posterior view of the US-guidance and by using a radial movement of the electrode to create a cone-shaped ablative volume. This technique allowed

selecting the shorter pathway to the central and deepest portion of the nodule and, as a consequence, to reduce the number of insertion points into the skin. During the procedure, RF power was applied in a range from 30 to 45 Watt. The impedance was carefully monitored to avoid tissue carbonization. The efficacy of RFA was evaluated by performing CEUS examination once or twice before ending the procedure. The ablation was stopped only when the CEUS exam showed complete devascularization of the AFTN, with an unenhanced pattern. In fact, differently from the RFA treatment in benign non-functioning nodules, where the aim is cytoreduction, the RFA goal in AFTNs is the complete necrosis of the nodule, which produces an excess of thyroid hormones. The US-guide allowed monitoring procedural complications during or after RFA. Ice was applied on the patient's neck skin at the end of the procedure, to prevent edema of the superficial tissue.

All the RFA procedures were performed by a single operator (S.M.), with more than 5 years' experience in RFA of thyroid nodular diseases and with more than 20 years' experience in percutaneous ablative treatments on liver and kidney. (Rev #1; point 9)

RI ablation

The RI therapeutic activity administered was 15 mCi (555 MBq) of ^{131}I to all patients independently of the pre-treatment nodule volume. It was administered in a 'day hospital regimen'; this management was in accordance with the European Council Euratom Directive 97/43 and the Italian Legislative Decree 187/2000, which define the maximum outpatient dose as 16.2 mCi (600 MBq). RI was administered when the TSH level was almost suppressed as a result of the patient's hyperthyroid state, in order to have it concentrated only in the nodule. In fact, if the patient had been previously treated with ATDs, these were discontinued 21-25 days before the patient's RI treatment.

Follow-up

In both groups of patients showing a pre-treatment 'toxic' phase controlled by ATD, the ATD was discontinued immediately after the chemical or thermal ablation. All patients were asked to repeat TSH and fT3 dosage 30-45 days after treatments to verify the absence of hormonal abnormalities (in particular the absence of the combination of suppressed TSH levels and over range fT3). Moreover, they were invited to contact our Center if they experienced hyperthyroid symptoms in between treatment and laboratory exams.

Twelve months after treatment TSH, fT3, fT4 were assessed. The nodule volume was calculated by B-mode US, according to the ellipsoid formula. In the RF group the US examination of the nodule was completed by performing CEUS, to monitor the 'necrotic' portion of the nodule (Figure 2).

Statistical analysis

All statistical computations were performed with dedicated software packages (JMP statistical software 7.0, SAS; Cary, NC, USA). Continuous variables were reported as means ± standard deviation (SD); categorical variables were reported as frequencies or percentages. Data of the two groups were compared with the appropriate use of the Fisher exact test and the Wilcoxon rank test. A P value less than 0.05 was considered indicative of a significant difference.

Results

Patients' data

The baseline characteristics of the patients and nodules, grouped by the treatment received, are summarized in Table 1. A statistical comparison of these characteristics was performed in order to verify the absence of statistical difference between the two groups, as shown by the p

value. In the RI group 16/25 patients showed AFTN in the toxic phase, and reported symptoms such as palpitation and hand tremor; whereas in the RFA group thyrotoxicosis was present in 12/22 patients. Before RI, the ATD was administered in 13/16 patients in the toxic phase, while before RFA all the 12 patients underwent ATD therapy. The ATD drug administered in all cases was Methimazole and its starting dosage ranged from 5 to 15 mg, according to the severity of the hyperthyroid state. Two out of 25 patients treated by RI and 3/22 treated by RFA were positive for TPOAb or TgAb.

Treatment outcomes

The treatment outcomes for the two groups at the 12-month follow-up are summarized in Table 2. As to the volume reduction end-point, the mean post-RI volume of the nodule was 4.95±8.2 mL, with volume reduction rate (VRR) of 68.4±28.9%; whereas post-RFA volume of the nodule was 2.6±2.1 mL, with VRR of 76.4±16.9%. By comparing RI and RFA, no statistical difference was found either between the post-treatment nodule volume (p=0.62) or the VRR (p=0.63).

As to the thyroid function end-point, after RI therapy, all the 25 patients silenced the hyperfunctioning thyroid nodules. Five patients developed clinical hypothyroidism requiring Levothyroxine (LT4). The remaining 20 patients normalized their fT3 and fT4 values (success rate of 80%); among them 18 showed euthyroidism, whereas in 2/20 patients the THS values were slightly over-range (sub-clinical hypothyroidism). The characteristics of the 5 patients with whom RI determined undesirable effects (clinical hypothyroidism) are reported in Table 3.

After RFA, all the 22 patients silenced their hyperfunctioning thyroid nodule and normalized the fT3 and fT4 values with a success rate of 100%. Two out 22 patients showed sub-clinical hypothyroidism (TSH value of 6.7 microUI/mL and 4.9 microUI/mL, respectively, associated with fT3 and fT4 in the normal range). Both patients were affected by thyroiditis: one of them was diagnosed 'Hashimoto's thyroiditis (with positive TPOAb)', whereas the other suffered from nonspecific thyroiditis, characterized by reduced volume of the thyroid gland, low vascular signal by EchoColor Doppler and hypoechoic texture by B-mode US evaluation. Finally, as to complications, no patients experienced any minor or major complication in both groups.

Discussion

The conventional treatment of AFTNs is the hemithyroidectomy of the affected lobe, which guarantees the preservation of the thyroid function by the contralateral healthy thyroid lobe and decreases the risk of permanent hypocalcemia if the parathyroid glands of the affected side are damaged. However, the risk of permanent unilateral laryngeal nerve injury still remains with a percentage ranging from 0 to 2.1% [7, 21].

The most widely diffused alternative choice of treatment is RI, because of the high percentage of clinical efficacy (thyroid function is normalized in 75–95% of patients after 3-12 months) and to the low cost of the therapy [22]. However, in pregnant or breastfeeding women RI is absolutely contraindicated. Moreover, in women of childbearing age who develop thyrotoxicosis, the management of possible future pregnancy should be discussed in advance: pregnancy should be delayed until euthyroidism is restored [23]. The options for such functional restoration are: thyroid surgery, ablative therapy using RI, or ATDs. Surgery might cause permanent neck scar, which might discourage young patients. The main disadvantage of RI is the conception delayed at least for 6 months; as to ATDs, they resolve

the symptoms, but, when discontinued, the reappearance of the disease is certain. Moreover, due to the ATDs capability to cross the placenta, as well as to modulate fetal thyroid function, the pursuance of this therapy during pregnancy is to be avoided [24, 25]. In both male and female young patients the RI therapy exposes them to radiation; the administered 15 mCi dose of ^{131}I to young men showed a reduced sperm motility, which can, therefore, determine infertility in subjects at risk [26]. Finally, in order to successfully undergo RI therapy, the ATDs should be discontinued for 21-25 days prior to RI therapy, in order to have suppressed levels of TSH, which guarantees the ^{131}I concentration in the AFTNs. However, this management exposes the patients to the risks associated with the symptoms of hyperthyroidism (especially cardiovascular diseases). These disadvantages lead to seeking alternative treatments to RI therapy, especially in these selected groups of patients. The RFA is a possible alternative therapy to RI in the treatment of AFTNs, showing efficacy in restoring euthyroidism, especially in nodules of small dimension [27]. Indeed, in young hyperthyroid patients, both males and females, the RFA can have advantages: 1) rapid efficacy of the therapy without wash-out period in which it is not possible to attempt conception. As demonstrated by Sung et al, no post-procedural aggravation of symptoms was experienced, and, because of the RFA efficacy, the ATDs can be interrupted or significantly reduced immediately after the procedure [6]; 2) low risk of major complications, which include permanent voice change (0-2.3%), nodule rupture (0.1%), Horner syndrome (0.1%), and spinal accessory nerve injury (0-2.3%) [6, 27-29]; 3) finally, the absence of post-procedural scars [30, 31]. At the same time, in patients affected by cardiovascular comorbidities, RFA allows the ATDs administration until the day before the procedure.

In our study, 22 patients with 25 AFTNs treated with a single session of RFA, and 25 patients with a single AFTN treated with a dose of 15mCi of ^{131}I were compared. The two groups were homogeneously selected in terms of age, sex, functional phase of hyperthyroidism,

ATD administered, and pre-treatment volume of the nodule. Both procedures proved to be safe. In particular, in the RFA-treated group of patients no complications were recorded: neither transient nor permanent paralysis of the laryngeal nerve, bleeding or protracted pain (more than 24 hours) were experienced. No patient needed to contact the Center in the 30 days between treatment and the first check because of the appearance of clinical symptoms related to hyperthyroidism. The latter datum was particularly important for the group of RFA-treated patients, where a possible adverse effect might have been the uncontrolled release of free thyroid hormones, as a result of the mechanical cell damage induced by ablative therapy. To monitor this hypothetic effect, the first 5 consecutive patients, who underwent RFA, repeated the TSH, fT3 and Tireoglobulin (Tg) dosage immediately after the procedure, and then 3 and 24 hours after the procedure. In all 5 cases there was no uncontrolled variation of TSH or fT3, while a transient over-threshold increase of the Tg value was recorded.

In our study, the end-points to evaluate the efficacy of each therapy were the volume nodule reduction 12 months after the chemical or thermal ablation, and the solution of the hyperthyroid state. As to volume reduction, both RI and RFA were effective, though the decrease was slightly in favor of RFA (76.4% versus 68.4%). These results were in agreement with the Literature, which reports the average of AFTN volume reduction rate of 35-54% after RI therapy [14, 22, 32] and of 52.1% and 79.7% after RFA [6, 33]. As to RFA, it showed percentage of volume reduction higher than the other minimally-invasive procedures applied on the hyperfunctioning thyroid nodules. In fact, Dossing et al. reported 6-month post-laser ablation VRR of 44% [14], whereas results from a series of hyperthyroid patients treated by PEI (in several sessions) showed VRRs at the 12-month check of 72% and 66% in pre-toxic and toxic nodules, respectively [34].

As to the normalization of the thyroid function after treatment, all patients, both those treated with RFA and those with RI, silenced their AFTN. Despite the majority of patients (72%) treated by RI therapy were restore to euthyroidism, 5 patients developed clinical hypothyroidism (i.e. TSH values over 9.0 microUI/mL or high TSH values associated with fT4 values lower than the range). Among the 5 post-treatment hypothyroid patients, two of them were in a pre-toxic phase when the RI was administered. This condition was characterized by non-suppressed TSH values, which increases the risk of ^{131}I not exclusively concentrating in the AFTN. As a consequence, the ^{131}I may determine damage to the healthy thyroid tissue. Moreover, another of the 5 post-treatment hypothyroid patients had positive TPOAb before RI therapy. High levels of TPOAb can underlay Hashimoto thyroiditis and, as a consequence, can be considered a risk factor for post-treatment hypothyroidism [35, 36]. Finally, 2/5 patients showed a prevalent nodule uptake with only partial suppression of the remaining thyroid parenchyma by thyroid scintiscan (one of them was in a functional pretoxic phase). From the nuclear medicine point of view, this condition might be considered risky since the ^{131}I is taken up by the thyroid tissue surrounding the AFTN, damaging the 'healthy' gland [37]. As to the patients treated by RFA, none developed clinical hypothyroidism. Two patients showed subclinical hypothyroidism, and one of them required the administration of a low dose (225 mcg/week) of LT4. The thyroid gland surrounding the AFTN of both patients was affected by thyroiditis (Figure 3). The patient who needed LT4 was affected by Hashimoto thyroiditis with positive TPOAb level before RFA treatment. The ablation silenced the affected nodule, restoring the functionality of the surrounding thyroid tissue. For the restoration of normal thyroid hormone function, RF could be considered more effective than RI. The percentage of hypothyroidism after RI in our series was 20%, in agreement with the Literature, where the risk of developing post-RI hypothyroidism is 12-32% after a year [38, 38]. This is most likely due to the perinodular uptake of RI. As to RFA

the substitution medical therapy (LT4) was required in only one patient because the procedure was specifically targeted at the nodule, and it was effective independently of the toxic or pretoxic functional phases. Thus, despite the high cost of the electrode used in RFA - ten times more expensive than the cost of the administered dose of RI - the minimally invasive RFA procedure showed two main benefits: the reduction of the risk of hypothyroidism and the absence of exposure of patients to radiation.

One of the limits of our study lies in the retrospective analysis of the data and in the length of the follow-up (1 year) (Rew#1; point 15). In fact, our research was not a randomized trial, despite the fact the series of patients included in each group were statistically homogeneous in terms of gender, age, functional thyroid phase, medical treatment received before RI or RFA, and the pre-treatment nodule volume. Moreover, the series of patients was limited and the operator who performed RFA was the same in all cases. Probably the reliability of the results would increase if the study were a multi-centric one including a higher number of patients. Finally, the post-treatment scintiscan was not performed; all patients were evaluated in the follow-up period, by laboratory tests and US (CEUS in the RFA group) because the goal of the therapy was to solve the hyperthyroid state.

In conclusion, in an era of 'personalized medicine', it would be recommendable to adjust the therapy to the individual patient. Cost-effective RI is good for older patients with no serious cardiovascular comorbidities, though the percentage of hypothyroidism after RI-treatment in our series was still 20%. On the contrary, RFA did not determine clinical hypothyroidism. Moreover, the absence of radiation exposure, the lower risk of post-treatment hypothyroidism, the possibility to continue ATD therapy until the day before the RFA procedure, make RFA the best option for women of childbearing age, young men with moderate to high risk of infertility and patients affected by cardiovascular diseases, for whom a discontinued medical therapy would be risky.

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Table 1. The baseline characteristics of the patients and nodules grouped by the treatment received.

	Pts treated by RI	Pts treated by RFA	P value
Num pts/num nodules	25/25	22/25	
Age [range]	57.2 ± 12.8 yrs [20-76]	51.9 ± 13.9 yrs [26-72]	0.84
Gender (F:M)	17:8	20:2	0.68
Functional phase (Toxic:Pretoxic)	16:9	12:10	0.34
TSH pre-treatment value	0.16 ± 0.18	0.48 ± 0.40	0.97
# pts under antithyroid drugs	13	12	0.64
# pts TPOAb or TgAb positive	2	3	0.44
Pre-treatment nodule volume [range] (mL)	11.0 ± 11.2 [2.23-38.2]	14.3 ± 17.2 [0.3-87.3]	0.68
Pre treatment nodule maximum diameter [range] (mm)	36.6 ± 9.8 [18-58]	38.3 ± 13.9 [11-70]	0.85

TPOAb, Thyroid Peroxidase antibodies; TgAb, Antithyroglobulin antibody.
*The 'p value' shows the absence of any statistical difference when the two groups' parameters are compared.

Table 2. Twelve-month after treatment outcomes.

	Pts treated by RI	Pts treated by RFA	p value
Post-treatment nodule Volume (mL)	4.95 ± 8.20	2.55 ± 2.06	ns
Nodule Volume reduction rate (%)	68.4 ± 28.9	76.40 ± 16.86	ns
Functional therapeutic success			**<0.05**
• # pts euthyroid (%)	18/25 (72%)	20/22 (90.9%)	
Functional therapeutic unsuccess			**ns**
• # pts with persistent hyperthyroidism* (%)	0	0	
Functional undesirable effect			**<0.05**
• # pts with sublcinical hypothyroidism** (%)	2/25 (8%)	2/22 (9.1%)	
• # pts with clinical hypothyroidism*** (%)	5/25 (20%)	0	

* Hyperthyroidism with suppressed TSH values (<0.1 microUI/mL).
** Subclinical hypothyroidism was defined as normal fT3 and fT4 values associated with over range TSH values.
*** Clinical hypothyroidism was defined as TSH values > 9 microUI/mL or over-range TSH value, in association with fT3 and/or fT4 under-range values.
"ns": not significant.

Table 3. Unsuccessful RI-treated patients' characteristic.

	Pts treated by RI				
	#1	**#2**	**#3**	**#4**	**#5**
Age	65	20	30	59	61
Gender	F	M	F	M	F
Functional hyperthyroidism phase	Toxic	Toxic	Toxic	Pretoxic	Pretoxic
Pre-treatment ATD administration	yes	yes	no	no	no
TPOAb and/or TgAb	negative	negative	positive	negative	negative
Thyroid scintiscan nodule uptake of ^{131}I radiotracer	exclusive	partial	exclusive	partial	exclusive
Pre-treatment nodule volume (mL)	10.91	8.83	3.39	4.02	10.16
Post-treatment nodule volume (mL)	3.47	6.82	0.33	2.75	3.45
Volume Reduction Rate (%)	68.19	22.76	90.27	31.59	66.04

Figure legends

Figure 1. (a) Exclusive nodule uptake of the radiotracer, with complete suppression of the remaining thyroid parenchyma. (b) Prevalent nodule uptake with partial suppression of the remaining thyroid parenchyma.

Figure 2. (a) Echo-color-Doppler US exam of the pre-treatment nodule and (b) enhanced vascularization by CEUS. (c) CEUS exam performed at the end of the RFA procedure, which shows the unenhanced pattern as an indirect index of complete tissue necrosis. The lesion margins are indicated by "+".

Figure 3. (a) Echo-colour-Doppler US exam of the pre-treatment nodule and (b) enhanced vascularization by CEUS. (c) B-mode US exam performed 12 months after RFA and (d) the unenhanced pattern showing complete nodule necrosis. The lesion margins are indicated by "+". (e) The contralateral "healthy" thyroid lobe in lateral and (f) anterior-posterior US view. The lobe is slightly hypoechoic, dimensionally reduced and with intra-parenchymal calcification. The thyroid lobe boundaries are indicated by "+".