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Clinical outcomes of thermal ablation retreatment of benign thyroid nodules: A multicenter study from the Italian minimally-invasive treatments of the thyroid group

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Abstract

Background: Thermal ablation (TA) is an established therapeutic option alternative to surgery in patients with solid, benign thyroid nodules causing local symptoms. However, a variable part of thyroid nodules remain viable after these non-surgical treatments, and as many as 15% of nodules treated with TA may require a second treatment over time. This study aimed to evaluate the outcomes of TA retreatment on symptomatic benign thyroid nodules where the volume decreased by < 50% after the first procedure (=technique inefficacy).

Methods: We performed a multicenter retrospective cohort study including patients that underwent retreatment with TA for benign thyroid nodules, whose volume decreased by < 50% after initial treatment. The primary aim was to evaluate volume and volume reduction ratio (VRR) over time and compare the 6- and 12-month VRR after first vs second treatment. The secondary aim was to identify protective or risk factors for technique inefficacy, regrowth and further treatments, expressed as adjusted hazard ratios (HRs) and 95% confidence interval (CI), after adjustment for sex, age, nodule volume, structure and function, nodule regrowth or symptom relapse, technique used and if the same technique was used for the first and second TA and time between them.

Results: We included 135 patients. Retreatment led to VRR of 50% and 52.2% after 6 and 12 months. VRR after retreatment was greater than after first treatment in small and medium size nodules (<30 mL), while there were no differences for large nodules (>30 mL). After retreatment technique inefficacy rate was 51.9%, regrowth rate was 12.6%, and further treatment rate was 15.6%. Radiofrequency ablation (RFA) was protective towards technique inefficacy (HR 0.40; 95% CI: 0.24-0.65) and need of further treatments (HR 0.30; 95% CI: 0.12-0.76). Large nodule volume (>30 mL) was associated with increased risk of retreatment (HR 4.52; 95% CI: 1.38-14.82).

Conclusion: This is the first study evaluating the outcomes of retreatment on symptomatic benign thyroid nodules with a VRR <50% after the initial TA treatment. Best results were seen in small and medium nodules (<30 mL) and after RFA. Prospective confirmatory studies are needed.

Keywords: retreatment, second treatment, thermal ablation, laser, radiofrequency ablation, thyroid nodules

Introduction

In 2022, the Italian National Institute of Health published guidelines for the management of benign thyroid nodules, which recommended thermal ablation (TA) as a therapeutic alternative to surgery in patients with solid, cytologically benign and single thyroid nodules causing local symptoms or cosmetic concerns. Worldwide, in Europe [1-3], Asia [4], and Americas [5], several scientific societies and research groups have embraced these minimally invasive treatments as one of the options to manage symptomatic benign thyroid nodules. This approach follows almost two decades of experience with thermal ablations of benign nodules and robust evidence of their efficacy and tolerability [6,7].

TA is an outpatient procedure performed using different modalities. Technically, either an electrode-needle generating an alternating electric field (in case of radiofrequency ablation, RFA) or one or more optical fibers conveying laser light (in case of laser ablation, LA), are inserted into the nodule under local anesthesia and ultrasound guidance, to induce rapid heating of the target zone. Heating is followed by coagulative necrosis, and, over time, by fibrotic changes and progressive nodule shrinkage. This is associated with symptom improvement or disappearance, as well as with improvement of health-related quality of life [8]. General principles for the safe performance, training and adoption of ablation techniques for benign thyroid nodules have been recently published [9].

Although TA significantly decreases thyroid nodule volume, the thyroid nodule usually does not disappear. Follow-up studies have shown that technique efficacy (i.e. volume reduction ≥50% after 1 year from treatment) is not always achieved, and as much as 20% of nodules might regrow, such that 15% of nodules may require a second treatment [10]. Retreatments are more likely in case of larger baseline nodule volume, lower energy delivered, unsatisfactory 12-month volume reduction (i.e. technique inefficacy) and nodule regrowth [10]. Several papers report the effects of multiple treatment sessions on the same nodules [11], but the effects and outcomes of second treatments remain to be clarified. The aim of this study was to evaluate the effect of retreatment with TA on symptomatic benign thyroid nodules where the volume decreased by < 50% after the first procedure (i.e. technique inefficacy). The primary aim of the present study was to evaluate volume and volume reduction ratio (VRR) over time and compare the 6- and 12-month VRR after initial treatment vs retreatment. The secondary aim was to evaluate the effects of retreatment in terms of technique inefficacy, nodule volume regrowth, and the need for further interventions, as well as to identify protective or risk factors for these outcomes.

Materials and methods

Study design

This is a multicenter retrospective cohort study on benign thyroid nodules that were retreated with TA due to technique inefficacy, as defined by VRR <50% after first treatment. The primary aim of the present study was to evaluate volume and volume reduction ratio (VRR) over time and compare the 6- and 12-month VRR after initial treatment vs retreatment. The secondary aim was to evaluate the effects of retreatment in terms of technique inefficacy, nodule volume regrowth, and the need for further interventions, as well as to identify protective or risk factors for these outcomes.

The study protocol was presented during the conference “Minimally-invasive treatments of the thyroid (MITT) 2023. State of the art in Europe”, held in Milan in February 2023. The Italian Centers belonging to the MITT group were invited with an open call to contribute with patient data and ten centers participated in the evaluation (1 Center in Lecce, 2 in Milano, 1 in Modena, 1 in Napoli, 1 in Perugia, 3 in Torino, and 1 in Trieste).

Patient inclusion criteria were: (i) two separate benign fine-needle aspiration cytology reports prior to first treatment (i.e. Bethesda II) (10, 11); (ii) VRR < 50% after first treatment; (iii) first and second TA performed by the same operator and in the same Center; (iv) 6- and/or 12-month outcome data after retreatment; and (v) consent to use patients’ data for study purposes. Exclusion criteria were: (i) VRR ≥ 50% and no regrowth after the initial treatment; (ii) very large volume thyroid nodules (volume > 100 mL).

This study was conducted in accordance with the declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the Comitato Etico Unico Regionale Friuli Venezia Giulia CEUR FVG CEUR FVG (268_2019 FYTNAB). Patients provided informed consent for the use of their data for this study purposes.

Procedures

RFA was performed with 18-G needles and the moving shot technique [12,13], median energy delivered was 1024 J/ml (190-9182). LA was performed with 1-3 optical fibers and a 1064 nm diode laser source [6,14]. The number of fibers depended on nodule volume and morphology, median energy delivered was 480 J/ml (165-3716).

Definitions

Nodules were classified as small, if their volume was <15 mL; medium, if their volume was between 15 and 30 mL, and large, if their volume was >30 mL and <100 mL [15]. Nodules with a volume > 100 mL were considered as very large nodules [16], and they were excluded from this study. Nodule structure was classified as solid if the fluid component was ≤10%, predominantly solid if the fluid component was between 11-50%, predominantly cystic if the fluid component was between 51-90%, and cystic if the fluid component was >90% [17]. Autonomously functioning thyroid nodules (AFTN) were defined based on TSH <0.4 microU/mL and positive thyroid scintigraphy. Technique efficacy was defined as a volume reduction ≥ 50% after 1 year from the treatment [17]. Technique inefficacy was defined as any volume reduction < 50% after at least 6 months from the treatment. Regrowth was defined as a ≥50% increase compared to the previous smallest volume at US examination [17]. Symptoms refer to local symptoms, such as neck discomfort or pain, cough, foreign body sensation, and cosmetic concerns, and their presence was assessed by clinical record review.

Timeline of patients' follow-up

The timeline of patients' follow-up is shown in **Supplementary Figure 1**. During the pre-retreatment period, $\mathbf{T_{baseline}}$ is the date of patient's first visit before any treatment was performed; $\mathbf{T_{6\ first\ treatment}}$ is the date of the visit performed 6 months after the first treatment; $\mathbf{T_{12\ first\ treatment}}$ is the date of the visit performed 12 months after the first treatment; $\mathbf{T_{last\ visit}}$ is the date of the last visit performed after the first treatment and before retreatment. During the retreatment period, the follow-up visits started at $\mathbf{T_0}$ and ended at $\mathbf{T_n}$, the last visit done by each patient after retreatment. The nodule volume was measured at each visit ($\mathbf{T_x}$), and the VRR after the first procedure and after retreatment were calculated compared to the measurements taken at $\mathbf{T_{baseline}}$ and $\mathbf{T_0}$ respectively.

Statistical analyses

All the statistical analyses were performed using SAS (version 9.4 SAS Institute Inc., Cary, NC, USA). Categorical variables are reported as frequencies and percentages, and continuous variables as mean ± standard deviation (SD) and median stratified by each outcome. Variations over time of nodules' volume and VRR after retreatment, were evaluated applying the Friedman test for repeated measures in the whole cohort. Mean ± SD, median, first (Q1) and third quartiles (Q3) were reported.

The paired difference in volume of nodules (and VRR) between (i) $\mathbf{T_{6\ first\ treatment}}$ and $\mathbf{T_6}$ and (ii) $\mathbf{T_{12\ first\ treatment}}$ and $\mathbf{T_{12}}$ were evaluated with Wilcoxon signed-rank test, both in the entire cohort and stratified according to the nodule's volume category at $\mathbf{T_{baseline}}$ and by technique (primary aim). Mean ± SD, median, first (Q1) and third quartiles (Q3) were reported.

Simple and multiple Cox proportional hazard models were performed to assess the association between retreatment outcomes (technique inefficacy, nodule's volume regrowth, further treatment), and different covariates, in order to identify protective or risk factors (secondary aim). In the Cox multiple proportional hazard analysis, the covariates were automatically selected using the backward selection with a p-value<0.20 according to Wald Chi-Square. The proportional hazard assumptions were verified for each model. Hazard ratio (HR) and 95% confidence interval (95% CI) were reported.

In particular, in the Cox proportional hazard models, the following outcomes were examined: (i) technique inefficacy, defined as VRR<50% between $\mathbf{T_x}$ and $\mathbf{T_0}$, (ii) nodule's volume regrowth, defined as VRR≥50% increase compared to the previous smallest volume at US examination, (iii) a further (third) treatment, defined as any treatment performed after $\mathbf{T_n}$. For each patient included in the study cohort, the period of follow-up started at $\mathbf{T_0}$ and ended with the occurrence of the first of the following event: the event of interest or the last visit $\mathbf{T_n}$. For each patient, person-time was appropriately computed according to each outcome. In addition, in these models, the following covariates were considered: sex; age at $\mathbf{T_{baseline}}$; nodule's volume at $\mathbf{T_{baseline}}$ in categories (small/medium/large); nodule's structure at $\mathbf{T_{baseline}}$ (Solid/Predominantly solid); nodule's function at $\mathbf{T_{baseline}}$ (Non-AFTN/AFTN); nodule's volume regrowth at each $\mathbf{T_x}$ (Yes/No); technique used at retreatment

(LA/RFA); a variable that specifies if the same technique was used at the first treatment (Yes/No); symptom relapse before retreatment (Yes/No); time (in month) elapsed between the first treatment and the last visit before retreatment.

Results

Description of the patients and treatments

Data from 193 patients with symptomatic benign thyroid nodules that were retreated with thermal ablation were collected. We excluded: 48 nodules with a satisfactory response to first treatment (VRR > 50% and no regrowth); 3 patients whose data were incomplete, and 7 very large thyroid nodules (>100 mL). Our final cohort was comprised of 135 patients with symptomatic benign thyroid nodules where the volume decreased < 50% after first procedure, and who underwent a retreatment with thermal ablation (**Figure 1**). As shown in **Table 1**, median age of patients was 54 years (IQR 18) and 75.6% (102/135) were women. As for nodule characteristics, 28.2% (38/135) of patients had a small nodule, 31.9% (43/135) had a medium nodule, and 40% (54/135) had a large nodule. Nodules were solid in 62.2% (84/135) of patients, and the remaining 37.8% (51/135) were predominantly solid. Nodules were non-functioning in 91.1% (123/135) of patients.

The earliest time point at which retreatment was considered was 6 months after the first treatment. The median time elapsed between the first treatment and the last visit before retreatment was 24 months (IQR 36). Before retreatment, nodule regrowth was recorded in 23% (31/135) of patients, presence or relapse of symptoms was recorded in 74.8% (101/135) of patients, thyrotoxicosis was recorded in 6.7% (9/135) of patients (=75% [9/12] of patients in the AFTN subgroup). In 50 patients (mostly those with nodule regrowth) a new cytological assessment was performed before retreatment and the results were consistent with Bethesda II cytology in 92% of them (46/50), Bethesda I in 4% of them (2/50), and Bethesda III in 4% of them (2/50).

In 66.7% (90/135) of patients, the technique of retreatment was RFA, while in 33.3% (45/135) of patients it was LA. In 92.6% (125/135) of patients, the technique used for retreatment corresponded to the same technique used for the first procedure. In the remaining few cases, the technique was changed from LA to RFA, mostly because LA had been the first TA technique that was introduced in clinical practice, followed by RFA. After retreatment, the number of patients for each time-point of follow-up and length of follow-up are reported in **Figure 2A-B**.

Nodule volume and VRR after 6 and 12 months from first procedure and retreatment.

After retreatment, nodule volume and VRR changed over time (as shown in **Figure 2A-B**). We compared the nodule volume and VRR measurements obtained at $\mathbf{T_{6\ first\ treatment}}$ and at $\mathbf{T_{12\ first\ treatment}}$ to those obtained at $\mathbf{T_6}$ and at $\mathbf{T_{12}}$ after retreatment. Significant paired differences were found in the whole cohort (as shown in **Figure 3A-B** and Supplementary Table 1). In particular, retreatment was more successful than first treatment in terms of nodules' volume reduction. In the whole cohort, the VRR was 39.2% (25.0-50.4) at $\mathbf{T_{6\ first\ treatment}}$ as compared to 50% (32.0-61.8) at $\mathbf{T_6}$ after retreatment, $p<0.001$ for paired analysis. Likewise, the VRR was 36.7% (20.2-51.4) at $\mathbf{T_{12\ first\ treatment}}$ as compared to 52.2% (32.9-66.1) at $\mathbf{T_{12}}$ after retreatment, $p<0.001$ for paired analysis.

After stratification for nodule volume at $\mathbf{T_{baseline}}$, retreatment led to greater VRR than first treatment in small and medium nodules (<30 mL) at $\mathbf{T_6}$ and at $\mathbf{T_{12}}$, but not in large nodules (>30 mL) where the VRR did not differ between first treatment and retreatment (**Figure 3B** and Supplementary Table 1). In particular, in small nodules, the VRR was 32.9% (18.5-54.0) at $\mathbf{T_{12\ first\ treatment}}$, as compared to 52.5% (36.4-67.2) at $\mathbf{T_{12}}$ after retreatment, $p<0.001$ for paired analysis. In medium nodules, the VRR was 34.7% (18.5-54.1) at $\mathbf{T_{12\ first\ treatment}}$, as compared to 54.1% (46.4-69.2) at $\mathbf{T_{12}}$ after retreatment, $p<0.001$ for paired analysis. In large nodules, the VRR was 39.1% (24.3-47.1) at $\mathbf{T_{12\ first\ treatment}}$, as compared to 41.8% (27.6-62.1) at $\mathbf{T_{12}}$ after retreatment, $p=0.09$ for paired analysis.

After technique stratification, retreatment significantly reduced nodule volume in both LA+LA and RFA+RFA subgroups (**Figure 3C**). Retreatment led to greater VRR than first treatment at $\mathbf{T_6}$ in the RFA+RFA subgroup and at $\mathbf{T_{12}}$ in both LA+LA and RFA+RFA subgroups (**Figure 3D** and Supplementary Table 2). In particular, LA+LA subgroup, the VRR was 30% (12.3-47.1) at $\mathbf{T_{12\ first\ treatment}}$, as compared to 43.8% (26.4-53.3) at $\mathbf{T_{12}}$ after retreatment, $p<0.037$ for paired analysis. In medium nodules, the VRR was 39.6% (23.8-54.1) at

$\mathbf{T_{12\ first\ treatment}}$, as compared to 58.4% (43.1-69.9) at $\mathbf{T_{12}}$ after retreatment, p<0.001 for paired analysis.

Technique inefficacy, regrowth and further treatments

Technique inefficacy (VRR <50% after retreatment) was observed in 70 patients (51.9%), as shown in **Table 2**. In a Cox proportional hazards model including the variables of [describe variables in model], RFA was independently inversely associated with technique inefficacy (HR=0.4; 95% CI: 0.24-0.65). Regrowth was observed in 17 patients (12.6%) as shown in **Table 3**. There were no variables that were found to be independently associated with regrowth. Further treatments of thyroid nodules were observed in 21 patients (15.6%), as shown in **Table 4**. Large nodule volume at baseline was independently associated with further treatment over time (HR=4.52; 95% CI: 1.38-14.82), and the use of RFA was inversely independently associated with requiring further treatments (HR=0.3; 95% CI: 0.12-0.76).

Histopathologic findings

A total of 16/135 patients (11.8%) underwent thyroid surgery after retreatment. The final histologic diagnosis showed benign pathology in 10/16 patients (62.5%), malignant pathology in 3/16 patients (18.75%), while in 3 patients final pathology went missing (18.75%). Malignant pathology included the following: 1 classic papillary thyroid carcinoma, 1 follicular subtype of papillary thyroid carcinoma, 1 follicular thyroid carcinoma.

Discussion

In this study, we report the effects of TA retreatment on benign thyroid nodules after an initial unsatisfactory procedure, i.e. nodule volume reduction < 50% after the first procedure. Indications to TA retreatment included: nodule regrowth (23%), symptom relapse (75%), persistence of thyrotoxicosis (6.7%). In our study, the earliest time point at which retreatment was considered was 6 months after the first procedure, because the greatest volume reduction is usually observed after the first months from the procedure [11,18]. Nevertheless, based on the fact that the proper timing of retreatment is presently unsettled [1], and that retreatment may address issues that arise during the follow-up (i.e.

nodule regrowth, AFTN), the median time elapsed between the first treatment and the last visit before retreatment was 24 months.

Retreatment led to a median VRR of 50% and 52% after 6 and 12 months from the procedure, and it was more successful than first treatment in terms of nodules' volume reduction. Nevertheless, the effect of TA retreatment appeared to be somewhat limited. For instance, we have previously reported that TA (either with LA or with RFA) was able to reduce nodules' volume by 63%, 67%, 68%, 69%, and 70% at 1, 2, 3, 4, 5 years after the first treatment. Therefore, our data suggest that in nodules with unsatisfactory responses to first treatment, the response to an additional TA might remain somewhat limited as compared to the average volume reduction that has been reported in the literature. Potential factors leading to suboptimal results may be nodule composition, vascularization and/or the biological characteristics of thyroid benign tumors [19] that include not only thyroid follicular nodular diseases but also RAS-driven follicular adenomas and oncocytic adenomas [20,21].

In addition, retreatment led to greater VRR than first treatment in small and medium nodules (<30 mL) but not in large nodules (>30 mL). These data are consistent with the established finding that the smaller is the nodule volume, the better is the response to the TA procedure. For instance, Deandrea et al. reported that nodules with a volume < 15 ml were reduced by 77% as compared to nodules with a volume > 15 ml that were reduced by 67% after RFA [15]. Likewise, also Valcavi et al. observed a trend toward larger effect in the smallest nodules after LA [22]. There are several factors underlying the different response of small and large nodules. The first is related to the amount of energy delivered [10,23] as in large nodules more efforts should be made to reach the required energy threshold to treat them entirely [15]. The second is anatomy [24]. The edges of large (>30 ml) thyroid nodules are usually close to critical surrounding structures, such as the esophagus, trachea, recurrent laryngeal or vagus nerve, and cervical ganglion, and it is cumbersome to perform a safe and complete target ablation [24].

After retreatment, technique inefficacy (VRR <50% after retreatment) was observed in 70 patients (51.9%), regrowth was observed in 17 patients (12.6%), and the need of further treatments was observed in 21 patients (15.6%). Cox multiple proportion hazard regression showed that RFA was protective towards technique inefficacy and the need of further treatments. This is consistent with our previous report that RFA was associated with a significantly lower risk of regrowth and retreatment [10], as well as with other studies [25]. These results may be ascribed to the amount of energy delivered, which is significantly higher in the RFA compared to LA. The energy delivered is associated with treatment outcomes and its amount should be always specified in the procedure report [17]. RFA and LA have specific modalities of production and distribution of thermal energy. In case of LA, energy delivered should be at least 500-600 J/mL [9,26,27], while in case of RFA, the amount of energy delivered should be greater than 1000 J/mL [10,23]. In line with these requirements, in our study we found that the average amount of energy delivered was 480 J/mL for LA and 1024 J/ml for RFA retreatment.

A second technical aspect explaining why RFA was protective towards technique inefficacy and further treatments as compared to LA, is the moving shot technique, whereby it is possible to move the tip of the electrode across the entire nodule area, which allows the tailoring of the procedure to the nodule variables features, maximizing the ablation of its marginal areas [25,28]. Consistent with this, previous studies have shown that the extent of tissue ablation, as assessed by the initial ablation ratio [29], was associated with technique efficacy [29] and reduced likelihood of further treatments [30]. By contrast, LA induces a well-defined area of tissue ablation near the thermal source with rapid energy decay in the surrounding tissue, with the advantage of great precision but the disadvantage of the lack of total tissue ablation, unless multiple fibers are employed [16,19]. Nevertheless, caution should be taken when comparing the various thermal ablation techniques, because RFA, LA, and MWA are strongly operator-dependent techniques and their outcomes are influenced not only by local expertise but also by continuous technical evolution [31].

Be it RFA or LA, the larger is the volume of the nodule the higher is the likelihood of the need of repeated treatments over time [11]. For instance, in a previous study we reported that baseline volume cutoffs associated with retreatment after one procedure were 22.1 mL for RFA and 14.5 mL for LA [10]. In this study we found that large nodule size (>30 mL) was associated with requiring further treatments. It has been argued that thermal ablations may provide higher financial and quality of life values compared to surgery for appropriately selected patients [32]. For example, TA compares extremely favorably to surgery in terms of costs, as it costs roughly 2.6 times less than surgery, and sick-leave is significantly shorter, provided that patients are treated once [18]. On this basis, also from the cost-efficacy perspective [18,32], our data suggest to consider that in thyroid nodules with unsatisfactory responses to first treatment (VRR <50%), the response to additional TA might remain somewhat limited, and that baseline volume > 30 mL is associated with likelihood of further treatments. Second, RFA is protective towards technique inefficacy and likelihood of further treatments as compared to LA. Third, based on the few patients who were operated on (16/135), 18.75% of the thyroid nodules that were surgically removed were found to be differentiated thyroid carcinomas. This rate of malignancy in benign nodules unresponsive to TA is consistent with other studies, indicating a malignancy rate of 19.4-20.8% in nodules whose volume did not decrease by 50% after one procedure or regrew during follow-up [21,33]. In particular, a VRR <20% after 1 year from the first TA should raise suspicion of an underlying malignancy [10] and prompt for repeat fine-needle biopsy/core-needle biopsy [33] or thyroid surgery [10,33].

The main limitations of this study are its retrospective design, the potential selection bias (as all consecutive patients were not screened for the study and the selection of patients was at the discretion of the investigators at each participating site), and the small number of patients with protracted (3-year) follow-up. In addition, being the first study on the outcomes of benign thyroid nodules that have undergone retreatment with TA, it should be considered as a preliminary study. Nevertheless, its strengths are: (*i*) its innovative data, (*ii*) the inclusion of paired analyses (comparing VRR between first-treatment and retreatment) as patients were treated by the same operators, and (*iii*) its multicenter design, providing a real-world assessment of thermal ablation outcomes (including both LA and RFA). Further studies are needed to determine whether 30 mL is the appropriate volume threshold for favoring surgical management, and to confirm the rate of malignancy in nodules unresponsive to TA.

In conclusion, this is the first study evaluating the effects of TA retreatment on symptomatic benign thyroid nodules with unsatisfactory response to initial treatment. Retreatment led to VRR of 50% at 6 months and VRR of 52.2% at 12 months. Best results were seen in small and medium nodules (<30 mL) and after RFA. Further prospective studies are needed to confirm our results.

Authorship contribution statement

Stella Bernardi: conceptualization, data curation, investigation, visualization, writing – original draft. Valentina Rosolen: formal analysis, investigation, methodology, visualization, writing –original draft. Fabio Barbone: methodology, writing- review & editing, supervision. Stefano Borgato: data curation, resources (patients). Maurilio Deandrea: data curation, resources (patients). Pierpaolo De Feo: data curation, resources (patients). Laura Fugazzola: data curation, resources (patients). Giovanni Gambelunghe: data curation, resources (patients). Roberto Negro: data curation, resources (patients), Salvatore Oleandri: data curation, resources (patients). Giampaolo Papi: data curation, resources (patients). Enrico Papini: writing - review & editing. Francesca Retta: data curation, resources (patients). Ruth Rossetto: data curation, resources (patients). Daniela Sansone: data curation, resources (patients). Giuseppe Serra: data curation, formal analysis. Luca Maria Sconfienza: writing - review & editing. Luigi Solbiati: writing - review & editing. Stefano Spiezia: data curation, resources (patients). Fulvio Stacul: data curation, resources (patients). Giovanni Mauri: data curation, resources (patients), writing review & editing.

Authors' disclosure

Authors declare no relevant conflict of interest

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Table 1. Patient characteristics

Characteristics of patients	
Age in years, mean ± SD (median):	53.8 ± 14.1 (54.0)
Sex, n (%):	
Male	33 (24.4)
Female	102 (75.6)
Nodule Volume at baseline, n (%):	
Small (<15 mL)	38 (28.2)
Medium (15-30 mL)	43 (31.9)
Large (30.01-100 mL)	54 (40.0)
Nodule structure, n (%):	
Solid (fluid component≤10%)	84 (62.2)
Predominantly solid (11%≤fluid component≤50)	51 (37.8)
Nodule function, n (%):	
Non-AFTN	123 (91.1)
AFTN	12 (8.9)
Technique used at retreatment, n (%):	
LA (Laser Ablation)	45 (33.3)
RFA (RadioFrequency Ablation)	90 (66.7)
Was the same technique used at the first treatment?, n (%):	
No	10 (7.4)
Yes	125 (92.6)
Time (months) elapsed between the first treatment and the last visit before retreatment, mean ± SD (median):	30.8 ± 22.2 (24.0)
Nodule regrowth before retreatment, n (%):	
No	104 (77.0)
Yes	31 (23.0)
Presence of symptoms, n (%):	
No	34 (25.2)
Yes	101 (74.8)

AFTN: autonomously functioning thyroid nodules.

Table 2. Predictive variables of "technique inefficacy" (VRR<50%) after retreatment.

	VRR<50%							
	No (n=65)	**Yes (n=70)**	**Crude HR**	**95% CI**	**p-value**	**Adjusted HR**	**95% CI**	**p-value**
Person time (in month) from re-treatment to the end of follow-up or unsuccess, mean ± SD (median):	29.2 ± 24.2 (24.0)	6.9 ± 3.8 (6.0)	-	-		-	-	
Age in years, mean ± SD (median):	52.1 ± 14.1 (51.0)	55.4 ± 14.1 (56.0)	1.08	0.92 - 1.28	0.35	-	-	
Sex, n (%):								
Male	12 (18.5)	21 (30.0)	1	-		1	-	
Female	53 (81.5)	49 (70.0)	0.74	0.45 - 1.24	0.25	0.67	0.39 - 1.13	0.13
Nodule Volume at baseline, n (%):								
Small (<15 mL)	18 (27.7)	20 (28.6)	1	-		1	-	
Medium (15-30 mL)	26 (40.0)	17 (24.3)	0.75	0.39 - 1.43	0.37	0.80	0.42 - 1.55	0.51
Large (30.01-100 mL)	21 (32.3)	33 (47.1)	1.17	0.67 - 2.04	0.58	1.60	0.85 - 3.02	0.15
Nodule regrowth before retreatment, n (%):								
No	49 (75.4)	55 (78.6)	1	-		-	-	
Yes	16 (24.6)	15 (21.4)	0.93	0.52 - 1.64	0.79	-	-	
Technique used at retreatment, n (%):								
LA (Laser Ablation)	10 (15.4)	35 (50.0)	1	-		1	-	
RFA (RadioFrequency Ablation)	55 (84.6)	35 (50.0)	0.49	0.30 - 0.78	0.0025	0.40	0.24 - 0.65	0.0003
Was the same technique of first treatment used in retreatment?, n (%)								
No	5 (7.7)	5 (7.1)	1	-		-	-	
Yes	60 (92.3)	65 (92.9)	1,08	0.43 - 2.68	0.8731	-	-	

Nodule structure, n (%):								
Solid (fluid component≤10%)	38 (58.5)	46 (65.7)	1	-		-	-	
Predominantly solid (11%≤fluid component≤50)	27 (41.5)	24 (34.3)	0.85	0.52 - 1.39	0.51	-	-	
Nodule function, n (%):								
Non-AFTN	57 (87.7)	66 (94.3)	1	-		1	-	
AFTN	8 (12.3)	4 (5.7)	0.57	0.21 - 1.56	0.27	0.44	0.16 - 1.25	0.12
Presence of symptoms, n (%):								
No	13 (20.0)	21 (30.0)	1	-		1	-	
Yes	52 (80.0)	49 (70.0	0.78	0.47 - 1.30	0.34	0.64	0.37 - 1.12	0.12
Months between first treatment and retreatment mean ± SD (median)	34.0 ± 20.8 (36.0)	27.9 ± 23.3 (12.0)	0.93	0.81 - 1.06	0.28	-	-	-

AFTN: autonomously functioning thyroid nodules. VRR: volume reduction ratio. HR: Hazard ratio. 95% CI: 95% confidence interval. A p-value < 0.05 was considered significant.

Table 3. Predictive variables of "nodule regrowth" after retreatment.

	Nodule regrowth							
	No (n=118)	**Yes (n=17)**	**Crude HR**	**95% CI**	**p-value**	**Adjusted HR**	**95% CI**	**p-value**
Person time (in month) from retreatment to the end of follow-up or to regrowth, mean ± SD (median):	23.9 ± 20.6 (12.0)	35.3 ± 16.1 (36.0)	-	-		-	-	
Age in years, mean ± SD (median):			0.91	0.62 - 1.34	0.62	-	-	
Sex, n (%):								
Male	30 (25.4)	3 (17.7)	1	-		-	-	
Female	88 (74.6)	14 (82.4)	1.69	0.48 - 5.90	0.41	-	-	
Nodule Volume at baseline, n (%):								
Small (<15 mL)	32 (27.1)	6 (35.3)	1	-		-	-	
Medium (15-30 mL)	38 (32.2)	5 (29.4)	0.85	0.25 - 2.88	0.79	-	-	
Large (30.01-100 mL)	48 (40.7)	6 (35.3)	0.87	0.28 - 2.69	0.80			
Nodule regrowth before retreatment, n (%):								
No	90 (76.3)	14 (82.4)	1	-		-	-	
Yes	28 (23.7)	3 (17.7)	1.31	0.37 - 4.64	0.67	-	-	
Technique used at retreatment, n (%):								
LA (Laser Ablation)	36 (30.5)	9 (52.9)	1	-		1	-	
RFA (RadioFrequency Ablation)	82 (69.5)	8 (47.1)	0.50	0.19 - 1.32	0.16	0.34	0.10 - 1.09	0.07

Was the same technique of first treatment used in retreatment? n (%)								
No	10 (8.5)	0 (0.0)	1	-		-	-	
Yes	108 (91.5)	17 (100.0)	-	-		-	-	
Nodule structure, n (%):								
Solid (fluid component≤10%)	74 (62.7)	10 (58.8)	1	-		1	-	
Predominantly solid (11%≤fluid component≤50)	44 (37.3)	7 (41.2)	1.24	0.47 - 3.26	0.67	2.20	0.67 - 7.27	0.19
Nodule function, n (%):								
Non-AFTN	109 (92.4)	14 (82.4)	1	-		-	-	
AFTN	9 (7.6)	3 (17.7)	0.66	0.17 - 2.56	0.55	-	-	
Presence of symptoms, n (%):								
No	27 (22.9)	7 (41.2)	1	-		-	-	
Yes	91 (77.1)	10 (58.8)	0.70	0.27 - 1.85	0.47	-	-	
Months between first treatment and retreatment mean ± SD (median)	31.5 ± 22.7 (24.0)	25.8 ± 18.5 (24.0)	0.92	0.70 - 1.20	0.52	-	-	

AFTN: autonomously functioning thyroid nodules. HR: Hazard ratio. 95% CI: 95% confidence interval. A p-value < 0.05 was considered significant.

Table 4. Predictive variable of further treatments after retreatment

	Further treatments							
	No (n=112)	**Yes (n=21)**	**Crude HR**	**95% CI**	**p-value**	**Adjusted HR**	**95% CI**	**p-value**
Person time (in month) from retreatment to the end of follow-up or to further treatment, mean ± SD (median):	26.4 ± 21.9 (18.0)	29.7 ± 19.1 (24.0)	-	-		-	-	
Age in years, mean ± SD (median):	53.4 ± 14.5 (52.5)	55.2 ± 11.5 (58.0)	1.01	0.73 - 1.40	0.95	-	-	
Sex, n (%):						-	-	
Male	28 (25.0)	5 (23.8)	1	-		-	-	
Female	84 (75.0)	16 (76.2)	1.10	0.40 - 3.01	0.85	-	-	
Nodule Volume at baseline, n (%):								
Small (<15 mL)	32 (28.6)	6 (28.6)	1	-		1	-	
Medium (15-30 mL)	41 (36.6)	2 (9.5)	0.4	0.08 - 2.00	0.26	0.56	0.11 - 3.01	0.50
Large (30.01-100 mL)	39 (34.8)	13 (61.9)	2.02	0.77 - 5.33	0.15	4.52	1.38 - 14.82	0.01
Nodule regrowth before retreatment, n (%):								
No	87 (77.7)	16 (76.2)	1	-		1	-	
Yes	25 (22.3)	5 (23.8)	1.54	0.56 - 4.25	0.40	2.42	0.74 - 8.00	0.15
Technique used at retreatment, n (%):								
LA (Laser Ablation)	33 (29.5)	12 (57.1)	1	-		1	-	
RFA (RadioFrequency Ablation)	79 (70.5)	9 (42.9)	0.5	0.21 - 1.18	0.11	0.30	0.12 - 0.76	0.01
Was the same technique of first treatment used in retreatment?, n (%)								
No	10 (8.9)	0 (0.0)	1	-		-	-	
Yes	102 (91.1)	21 (100.0)	-	-		-	-	

Nodule structure, n (%):								
Solid (fluid component≤10%)	67 (59.8)	16 (76.2)	1	-		-	-	
Predominantly solid (11%≤fluid component≤50)	45 (40.2)	5 (23.8)	0.54	0.20 - 1.48	0.23	-	-	
Nodule function, n (%):								
Non-AFTN	102 (91.1)	19 (90.5)	1	-		-	-	
AFTN	10 (8.9)	2 (9.5)	0.42	0.10 - 1.88	0.26	-	-	
Presence of symptoms, n (%):								
No	28 (25.0)	5 (23.8)	1	-		-	-	
Yes	84 (75.0)	16 (76.2)	1.56	0.57 - 4.30	0.39	-	-	
Months between first treatment and retreatment mean ± SD (median)	32.1 ± 23.1 (24.0)	21.4 ± 14.1 (12.0)	0.78	0.57 - 1.07	0.12	-	-	

AFTN: autonomously functioning thyroid nodules. HR: Hazard ratio. 95% CI: 95% confidence interval. A p-value < 0.05 was considered significant.

Figure Legends

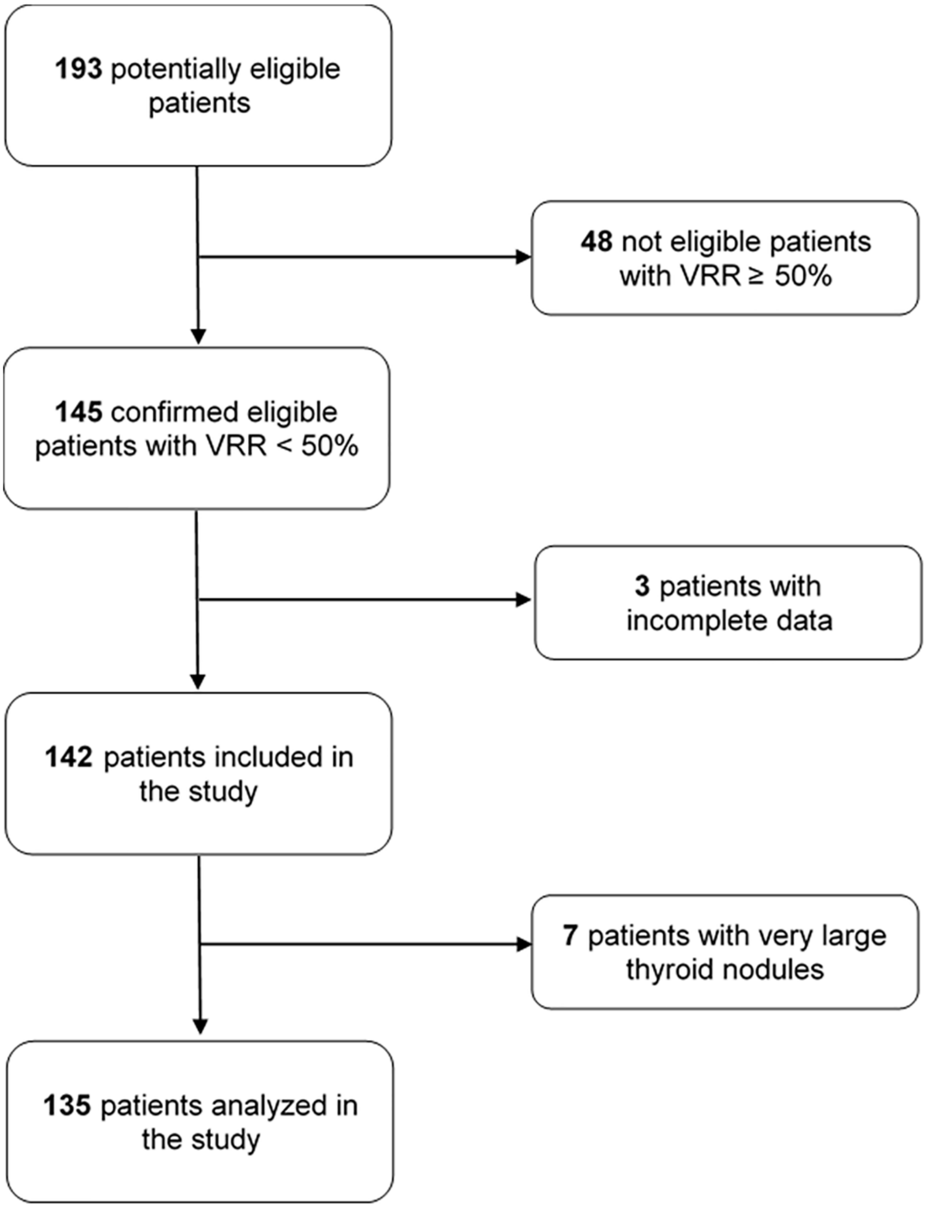

Figure 1. Flow chart. Flow chart of the criteria used for the selection of patients analyzed in the study.

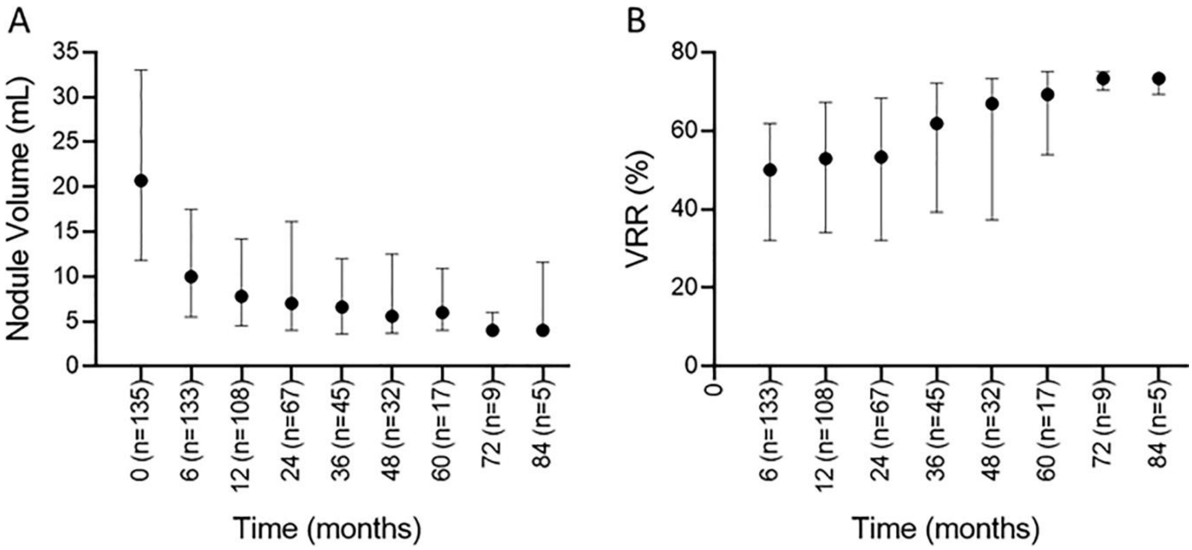

Figure 2. Distribution of nodule volume and VRR after retreatment in the entire cohort. Length of follow-up after retreatment and number of patients are specified for each time point. Data are expressed as first quartile (Q1), median and third quartile (Q3) of Friedman test. (A) Nodule volume; Friedman test p-value <0.0001 with Cochran-Mantel-Haenszel Statistics Based on Rank Scores Controlling for subjects; p-value <0.0001 with Cochran-Mantel-Haenszel Statistics Based on Rank Scores; (B) VRR; Friedman test p-value =0.26 with Cochran-Mantel-Haenszel Statistics Based on Rank Scores Controlling for subjects; p-value <0.001 with Cochran-Mantel-Haenszel Statistics Based on Rank Scores.

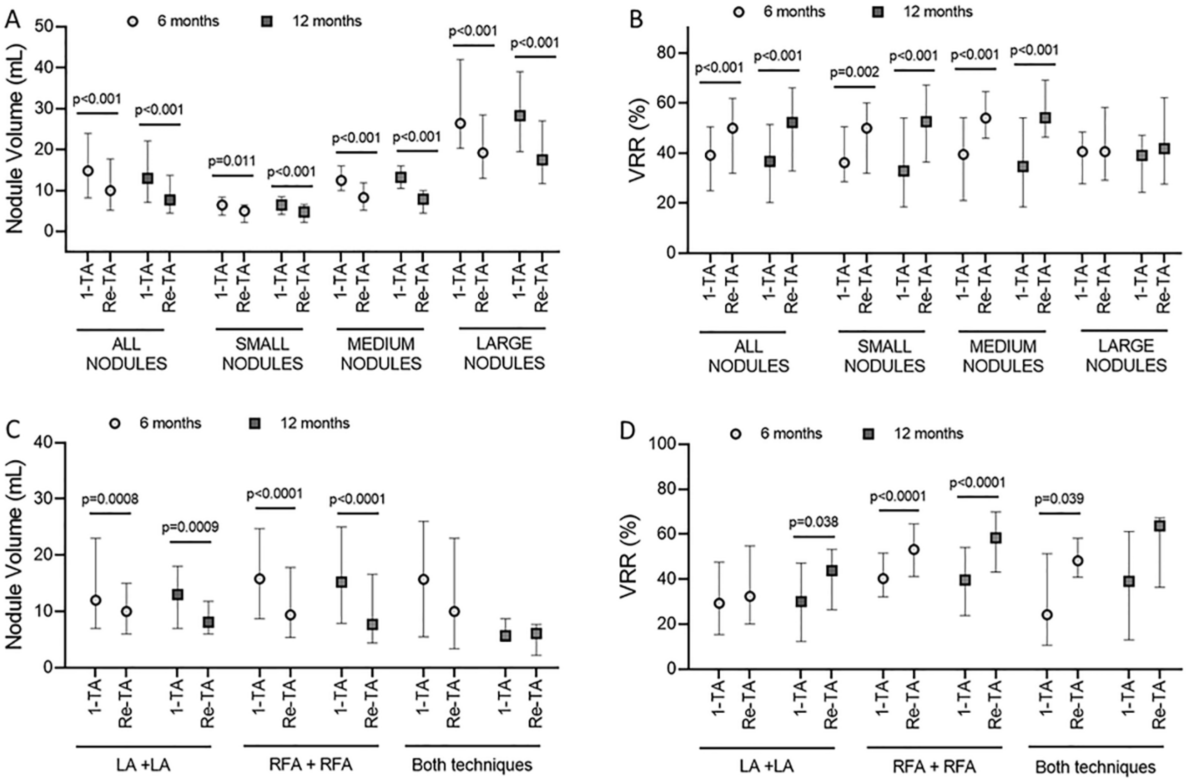

Figure 3. Distribution of 6- and 12-month nodule volume and VRR after first treatment and retreatment. Data are expressed as first quartile (Q1), median and third quartile (Q3). Paired differences were evaluated with Wilcoxon signed-rank test. p<0.05 are reported. (A) Nodule volume in all nodules and nodules stratified into small, medium, and large; (B) VRR in all nodules and nodules stratified into small, medium, and large; (C) Nodule volume in patients treated with LA (LA+LA), RFA (RFA+RFA), or both techniques; (D) VRR in patients treated with LA (LA+LA), RFA (RFA+RFA), or both techniques. 1-TA is for first treatment, re-TA is for retreatment, VRR is for volume reduction ratio; LA is for laser ablation, RFA is for radiofrequency ablation.