Reviews in Endocrine and Metabolic Disorders
https://doi.org/10.1007/s11154-019-09487-y

Efficacy of radiofrequency ablation in autonomous functioning thyroid nodules. A systematic review and meta-analysis

R. Cesareo[1] · A. Palermo[2] · D. Benevenuto[3] · E. Cella[3] · V. Pasqualini[4] · S. Bernardi[5] · F. Stacul[6] · S. Angeletti[7] · G. Mauri[8] · M. Ciccozzi[3] · Pierpaolo Trimboli[9]

Abstract
Whether thermal ablation is effective to treat toxic thyroid nodules (TTN) is still unknown. Aim of this review was to achieve more robust evidence on the efficacy of radiofrequency ablation (RFA) in treating TTN in terms of TSH normalization, thyroid scintiscan, and volume reduction rate (VRR). A comprehensive literature search of PubMed/Medline and Scopus was performed in November 2018 to retrieve published studies. Original papers reporting TTN treated by RFA and later followed-up were eligible. Excluded were: articles not within this field, articles with unclear data, overlapping series, case/series reports. Discordances were solved in a final collegial meeting. Information was collected concerning population features, treatment procedure, follow-up, cases with TSH normalization, cases with scintiscan normalization, VRR of nodules. Pooled prevalence of patients with TSH or scintiscan normalization, and pooled VRR over time were calculated. For statistical analysis, the random-effects model was used. Eight articles published between 2008 and 2018 were included. The overall number of AFTN treated by RFA was 205. Five studies used a single session of treatment. The time of follow-up ranged from six to 24 months. The pooled rate of patients with TSH normalization was 57%. The pooled rate of patients with scintigraphically proven optimal response was 60%. The pooled VRR at 1 year was 79%. Baseline nodules volume was associated with the rate of TSH normalization. In conclusion, a moderate efficacy of RFA in treating TTN was found, and this can represent a solid starting point in this field.

Keywords Radiofrequency ablation · Autonomous functioning thyroid nodules

Abbreviations

AFTN	Autonomously functioning thyroid nodules
LA	Laser ablation
PEI	Percutaneous ethanol injection
RFA	Radiofrequency ablation
TTN	Toxic thyroid nodules
VRR	Volume reduction rate

1 Introduction

Autonomously functioning thyroid nodules (AFTN) are a not rare entity, especially in iodine deficiency regions. Generally, these lesions undergo a progressive development over time with an increase of their function and then clinically manifest as toxic thyroid nodules (TTN). The latter represents the second

R. Cesareo and A. Palermo contributed equally to this work.

✉ Pierpaolo Trimboli
pierpaolo.trimboli@eoc.ch

[1] Thyroid and Metabolic Bone Diseases Center, Santa Maria Goretti Hospital, Latina, Italy

[2] Department of Endocrinology, Univerity Campus Biomedico, Rome, Italy

[3] Unit of Medical statistic and Molecular Epidemiology, University Campus Bio-Medico, Rome, Italy

[4] Departments of Radiology, Santa Maria Goretti Hospital, Latina, Italy

[5] Department of Medical Sciences, Cattinara Teaching Hospital, University of Trieste, Trieste, Italy

[6] Radiology Department, Maggiore Teaching Hospital, ASUITS, Trieste, Italy

[7] UOC Laboratory Medicine, University Hospital Campus Bio-Medico of Rome, Rome, Italy

[8] Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Dipartimento di Oncologia e Emato-Oncologia, Università degli Studi di Milano (La Statale), Milan, Italy

[9] Department of Nuclear Medicine and Thyroid Centre, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Published online: 18 March 2019

most common cause of hyperthyroidism after Graves' disease [1]. Traditionally, radioiodine and surgery have been used as effective and definitive treatment of TTN, while anti-thyroid drugs may be considered when the above therapies are contraindicated or refused by patient [2]. Since complications such as recurrent laryngeal nerve injury and hypoparathyroidism may be observed after surgery, radioiodine is generally worldwide adopted as first-line treatment due to its safety, favorable clinical outcome and relatively low cost [2, 3]. However, the number of patients that may refuse radioactive treatment is not negligible, and radioiodine is not feasible in some clinical conditions (i.e. pregnant or bleeding women, other). Furthermore, of importance, radioiodine is indicated only when scintiscan demonstrates an exclusive uptake in correspondence of the AFTN with complete/almost complete functional suppression of the remaining thyroid parenchyma. On the contrary, AFTN with no functional suppression of remaining thyroid tissue are not eligible for radioiodine. Thus, other alternative options to cure toxic nodule are required, especially in countries where prolonged hospitalization is mandatory for radioiodine administration (e.g. Switzerland, Germany and other).

During the last decade, in order to avoid surgery and its potential complications, several non-surgical therapies of benign thyroid nodules, such as laser (LA), radiofrequency (RFA) ablation, high intensity focused ultrasounds, and percutaneous ethanol injection (PEI) have been proposed and largely diffused. Among these, laser and radiofrequency are the most commonly used [4–7]. While laser and radiofrequency are more frequently used in non-functioning benign thyroid nodules, their use in TTN is less frequently described. In this context, it is interesting to annotate that some international guidelines (e.g. Italian and Korean [8, 9]) suggest this option when both surgery and radioiodine are contraindicated or refused by patient, even if evidence of their efficacy has still not been obtained. On the contrary, only sparse data exist on the use of other thermal therapeutic options [10, 11], and PEI is not recommended due to its recognized poor performance [2]. However, whether thermal treatment can be considered as a valuable alternative to conventional ones is still a matter of debating.

The present study was undertaken to achieve more robust evidence on the efficacy of RFA in treating TTN. Accordingly, here we systematically reviewed the literature on this topic and performed a meta-analysis of available data of serum thyroid function, thyroid function at scintiscan, and volume reduction rate (VRR) of nodules at echographic follow-up.

2 Methods

2.1 Conduct of review

This meta-analysis was conducted according to PRISMA guidelines [12].

2.2 Search strategy

A comprehensive literature search was independently conducted by two investigators (RC, PT) on the online databases of PubMed/Medline and Scopus. Both investigators used the following algorithm of search: (radiofrequency AND thyroid AND (hyperthyroidism OR autonomous OR toxic OR hyperfunction OR adenoma OR autonomously functioning thyroid nodules.). A beginning date limit was not used, the search was updated on November 28, 2018, and no language restriction was used. To try to expand our search, reference lists of the retrieved articles were also screened to identify additional studies.

2.3 Study selection

Articles found by our search were screened. As the major selection criterion, only original papers reporting complete data of AFTN/TTN treated by RFA and later followed-up could be included in this systematic review. Exclusion criteria were: a) articles not within the field of interest of this review; b) articles that did not have clear data; c) studies with overlapping patient or nodule data; d) review articles, editorials, letters, comments, or case/series reports. Two researchers (RC, PT) independently reviewed titles and abstracts of the retrieved articles, applying the above criteria. Then, four authors (RC, PT, AP, GM) independently reviewed the full-text of the remaining articles to determine their final inclusion. Discordances were solved in a final collegial meeting.

2.4 Data extraction

For each included study, the following information was extracted in a piloted form: author, publication year, study period, study design, country, population characteristics, treatment procedure, number, gender and age of patients, number of TTN, follow-up duration, complications, number of patients with normalization of TSH after withdrawal of anti-thyroid drugs, and number of patients with normalization of thyroid scintiscan. Data were cross-checked and any discrepancy fully discussed by all the authors.

2.5 Study quality assessment

The quality of studies was evaluated by analyzing the following issues: selection of patients, type of reference standard, laboratory evaluation, appropriate time of post-treatment follow-up. For each of these issues, the risk of bias of included studies was assessed independently by all the authors and risk of bias was rated as low, high, or unclear.

2.6 Statistical analysis

The prevalence of patients with serum recovery of thyroid function after RFA was calculated in each study (in this context, euthyroid patients and patients with subclinical hypothyroidism were considered as cured by RFA). Then, the pooled rates were obtained. The VRR of each study was searched and the pooled result was calculated. For each study mean, standard deviation, and sample size were extracted to calculate the pooled mean difference of nodules volume before and after RFA. For statistical pooling of the data, Der Simonian and Laird method (random-effects model) was used [13]. In this model, pooled data represent weighted averages related to the sample size of the individual studies. Proportion meta-analysis was performed by StatsDirect software. Mean difference of nodules volume before and after RFA was calculated by Rev.Man software. Mean VRR was calculated by ProMeta 3 software.

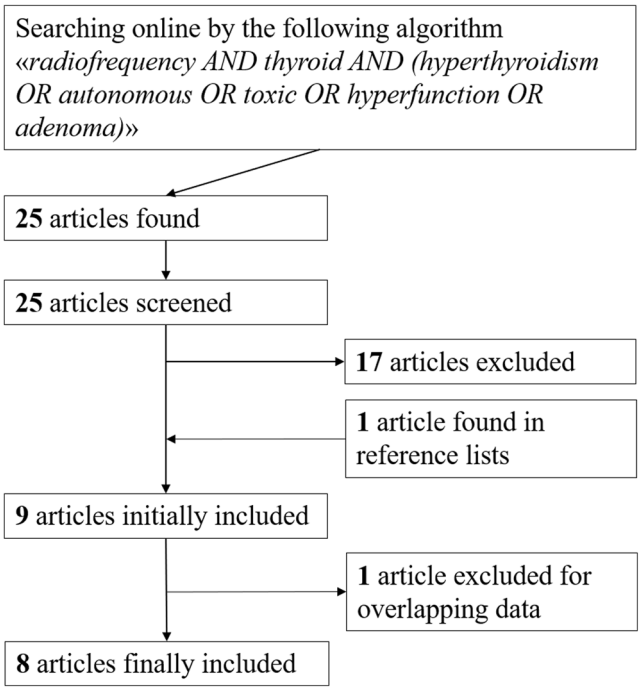

Fig. 1 Flow chart of search of articles

3 Results

3.1 Eligible articles

By using the above algorithm and selection criteria, the online search retrieved 25 papers. All these articles were screened and eight studies [14–21] were initially included in the systematic review. Another paper [22] was found by screening the reference list of the included studies and it was considered as eligible for our review. However, this article was published by the authors of another included study [19] and the period of enrolment of cases was overlapping. Then, this study [22] was excluded. Due to the apparently limited number of articles retrieved by this search algorithm, we further extended our search by a second algorithm, being "(radiofrequency OR RFA AND ablation) AND thyroid". No further articles were eligible for the present meta-analysis. Thus, eight studies were finally included. Flow of search was illustrated in Fig. 1.

3.2 Qualitative analysis (systematic review)

The included articles were published between 2008 and 2018 by authors from Italy, Austria, and South Korea. These articles were reported as prospective in six cases and retrospective in two cases. One trial was registered. The overall number of AFTN treated by RFA was 205. Mean age of patients was comprised between 43 and 72 years. Three studies enrolled only nodules with solid composition while the remaining ones included also solid and mixed nodules. The investigators used the moving shot technique in six studies. Before RFA, patients were frequently under anti-thyroid therapy and only one study included patients with no therapy at baseline. Importantly, four studies used a single session of treatment. The time of follow-up ranged from six to 24 months. Table 1 illustrates the general characteristics of the included studies.

3.3 Quantitative analysis (meta-analysis)

The available data for the meta-analysis is shown in Table 2, and Table 3 details the main results of the meta-analysis. The pooled rate of patients with TSH normalization after RFA in the absence of anti-thyroid drugs was calculated combining all eight articles [14–21] and was 57% (ranging in the studies between 21 and 87%). Figure 2 illustrates the results of the meta-analysis regarding the proportion of patients with normalization of serum TSH at the end of the study. When we considered only those four studies using single session RFA treatment [17, 19–21], this pooled proportion was 61% (ranging from 40 to 88%). The rate of patients with scintigraphically proven optimal response after RFA was calculated combing three studies [15, 17, 20] and was 60%. The pooled VRR was calculated combining five articles [16, 18–21] and was 79%. Mean volume difference of nodules volume 1 year after RFA was calculated combing five studies [16, 18–21] and was 13 mL. Due to the high heterogeneity found in the latter analysis, we explored the correlation

Table 1 Main characteristics of the included studies

First Author, year (ref.)	Country	Study design	Study period	AFTN (n)	Patients age (mean ± SD)	Nodule type (echostructure)	Therapy by MMI	RFA technique	RFA sessions	Last follow-up (months)
Deandrea, 2008 [14]	Italy	Prospective	Apr 2004 - Dec 2005	23	66.8 ± 12.1	Solid/mixed	All	Fixed electrode	More treatmentsduring the same session	6
Baek, 2009 [15]	South Korea	Retrospective	Oct 2006 - Jul 2007	9	47 ± 17	Solid/mixed/cistic	2 cases	Moving-shoot	2.2 ± 1	12
Spiezia, 2009 [16]	Italy	Prospective	Jan 2005 - Jan 2007	28	72.5 ± 0.5	Solid	All	Fixed electrode	More sessions in 34% of patients	24
Faggiano, 2012 [17]	Italy	Prospective (trial regitration number NCT01649206)	Jan 2010 - Jun 2011	10	58.3 ± 4.3	Solid	All	Fixed electrode	Single	12
Sung, 2015 [18]	South Korea	Retrospective	Aug 2007 - Jul 2011	44	43 ± 14.7	Solid/mixed	5 cases	Moving shot	1.8 ± 0.9	19.9 ± 12.6
Bernardi, 2017 [19]	Italy	Prospective	Apr 2012 - May 2015	30	69.1 ± 2.0	Solid/mixed	All	Moving shot	Single	12
Cesareo, 2018 [20]	Italy	Prospective	Jan 2015 - Jun 2015	29	51.41 ± 15.5	Solid	None	Moving shot	Single	24
Dobnig, 2018 [21]	Austria	Prospective	Apr 2014 - Jun 2017	32	52 ± 12.9	Solid/mixed	17 cases	Moving shot	Single	12

Legend. MMI, methimazole

between the volume of nodules at baseline and the rate of TSH normalization at the end of the study. As illustrated in Fig. 3, small basal nodules volume should be associated with high rate of normal TSH after RFA.

3.4 Study quality assessment

Low risk was observed in selection of patients in all included studies. High risk of reporting was present in one study. High risk of reference standard was present in two studies which performed the re-evaluation of thyroid function after RFA during methimazole. Low risk of time of follow-up was present in three studies. Table 4 reports all results of study quality assessment.

4 Discussion

According to the present findings, RFA may represent a valuable option to manage subjects with AFTN/TTN. In the last few decades, there has been a strong boost to avoid thyroid surgery with the exception of those patients in whom it is a mandatory therapy (i.e. cancers and very large goiters with compressive symptoms). This is due to the non-negligible rate of post-operative transient and chronic complications and the high cost of this treatment. Hyperfunctioning lesions account for 5 to 10% of all thyroid nodules [1] and radioiodine is the standard of care to treat patients with AFTN/TTN. In this context, RFA has been reported as a potential reliable tool but, up to now, solid evidence is absent.

The present study aimed to achieve more robust evidence on the effectiveness of RFA to treat AFTN/TTN in terms of normalization of serum TSH, improvement of scintigraphic results, and reduction of nodules volume. As the general result of our systematic review, only nine studies were found to report the efficacy of RFA in AFTN/TTN and one of these was excluded for overlapping data with another series. Importantly, when we calculated the overall proportion of patients with normalization of TSH at the end of the studies, we found 57% of cases. This rate was slightly higher when we pooled only the results from those studies using single session RFA. This difference might be due to the lower baseline TTN volume in studies using single session RFA [19–21] (in one study [17] the basal volume was unclear but reported in a figure as lower than 20 mL) with respect to the other ones using more treatments [14–16, 18], i.e. 12.4 vs. 22.1 mL, respectively. We cannot exclude that this finding should be random and due to the small number of studies. Later, we calculated the pooled proportion of patients with scintigraphically proven cure of TTN and found that 60% of patients showed an improved scintiscan. Finally, a VRR of 79% was observed

Table 2 Main results reported in the included studies

First Author, year (ref.)	Nodules volume at baseline (ml)	Nodules volume at 6 months (ml)	VRR at 6 months (%)	Nodules volume at 12 months (ml)	VRR at 12 months (%)	Scintigraphic recovery of function (n)	Patients with TSH normalization (%)
Deandrea, 2008 [14]	22.5 ± 16.3	11.6 ± 10.7	52.1 ± 16.1	N/A	N/A	N/A	5 (21.7%)
Baek, 2009 [15]	14.9 ± 25.5	8.2 ± 21.2	70.7 ± 22.9	N/A	N/A	4 (44.4%)	4 (44.4%
Spiezia, 2009 [16]	32.7 ± 5.4	N/A	N/A	7.5 ± 1.2	77 ± 6	N/A	15 (53.5%)
Faggiano, 2012 [17]	N/A	N/A	N/A	N/A	N/A	N/A	4 (40%)
Sung, 2015 [18]	18.5 ± 30.1	7.0 ± 14.7	74.5 ± 15.7	4.5 ± 9.8	81 ± 13	35 (79.5%)	36 (81.2%)
Bernardi, 2017 [19]	17.1 ± 2.3	4.6 ± 0.6	65.7 ± 20.2	4.2 ± 0.6	74.7 ± 3.0	N/A	15 (50%)
Cesareo, 2018 [20]	11.5 ± 7.5	3.9 ± 3.7	68 ± 15	3.4 ± 3.2	75 ± 22	14 (48%)	17 (58.6%)
Dobnig, 2018 [21]	8.7 ± 7.0	N/A	86.1 ± 13.4	2.1 ± 4.7	86.1 ± 13.4	N/A	28 (87.5%)

Legend. VRR, volume reduction rate of the nodule. Scintigraphic recovery represents the number of AFTN which showed a resolution of hyperfunction when they were re-evaluated by scintiscan after RFA

1 year after RFA. All these results had a significant heterogeneity probably due to some differences between the studies in the period of follow-up, RFA procedure, and characteristics of nodules at ultrasound and scintiscan [Tables 1 and 3]. Exploring this heterogeneity, we found that smaller nodules had a higher chance to be treated with TSH normalization than larger ones. In a recent study included in this review [20] it was observed that RFA is effective in restoring normal thyroid function in patients with small size autonomous nodule. Baseline nodule volume appears to be a significant predictive factor of the efficacy of RFA in treating AFTN. Further RFA prospective studies should be useful to confirm this result. Other authors confirmed the importance of pre-treatment nodule volume as a variable to determine the response to the thermal treatment. In particular, Gambelunghe and colleagues showed that the smaller the pre-treatment volume, the higher the probability to discontinue methimazole after LA [23]. It's likely that in the context of toxic and pre-toxic nodules, the ablation of most of the nodule area is essential to reduce the risk of recurrence of hyperfunction. As a proof of this concept, Bernardi et al. [19] reported that cured patients had a mean nodule reduction of 81%.

In the past, some authors investigated the role of PEI in AFTN. In particular, Zingrillo et al. [24] compared PEI with radioiodine in patients with uninodular TTN. Follow-up after 36 months, despite a comparable reduction in nodules volume in the two groups, suppressed TSH levels were recorded in 14% of patients receiving multiple PEI while not in those treated with radioiodine. Quite similar results were confirmed by other authors [25] and, currently, PEI is discouraged in AFTN also because the recurrence of hyperthyroidism and the regrowth of the treated nodules are very common [26]. The efficacy of laser on AFTN has also been tested over the last 10 years but the small number of subjects enrolled and low quality of the studies does not allow to draw robust conclusions. Moreover, the efficacy of

Table 3 Overall results of the present meta-analysis

Parameter	Pooled effect size (95% CI)	Inconsistency	Egger test (p)
Rate of patients with normalization of TSH (all studies)	57% (40 to 72)	82.6%	0.056
Rate of patients with normalization of TSH (four studies using single session RFA)	61% (40 to 81)	79.1%	0.119
Rate of patients with scintigraphically proven recovery of function	60% (35 to 82)	78.4%	N/A
Volume reduction rate	79% (75 to 83)	87.63%	$p = 0.138$
Mean volume reduction one year after RFA	13 mL (13 to 19)	98%	N/A

Legend. Inconsistency above 50% indicates the presence of a significant heterogeneity between the studies. Significant Egger test indicates the presence of publication bias (this test cannot be performed for pooled data of less than four series

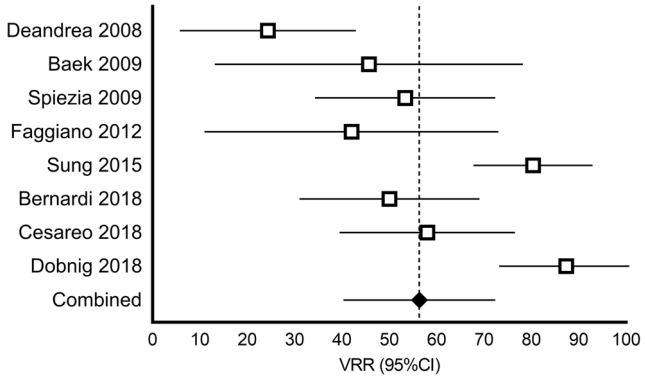

Fig. 2 Pooled results of proportion of patients with TSH normalization after RFA

laser seems to be confirmed mainly in the context of small and mildly hyperfunctioning nodules [27, 28]. Conversely, in larger AFTN the success rate is unsatisfactory and normalization of thyroid function usually requires multiple sessions [29].

A short discussion concerning the tolerability of RFA should be addressed. RFA has been reported as safe and well tolerated procedure. In fact, a recent systematic review found an overall complication rate of 2.38% and major complications were recorded in 1.35%. No patients had any life-threatening RFA-related complications [30]. Then, in 2017 Korean Guidelines the panel quoted that thyroid RFA is associated with a low incidence of complications when performed by experienced operators (strong recommendation, high-quality evidence) [9]. This issue should encourage to use RFA also in AFTN/TTN.

Limitations and strengths of the present meta-analysis should be discussed. First, the durability of RFA efficacy in correcting hyperfunctioning of TTN plays a significant role in evaluating this procedure in this clinical context. In many studies that we retrieved in the literature, the time of follow-up of patients was quite short. A longer follow-up is needed to verify the efficacy of RFA to reach a stable TSH. In fact, hyperfunctioning cells might be persistent within the lesion and then a relapse of overt or subclinical hyperthyroidism should be expected at long follow-up. Second, the true gold standard to evaluate the response of AFTN to the treatment is represented by scintiscan. However, only three studies adopted this approach to verify the efficacy of RFA. Third, in half of the included studies, the authors treated patients in multiple RFA sessions. However, ideally, we should treat thyroid nodules in a single session RFA. Fourth, it has to be underlined that no data on cost-effectiveness of RFA in AFTN exist.

In conclusion, this systematic review found eight studies evaluating the efficacy of RFA to treat AFTN/TTN to be meta-analyzed. The approach used in these studies was significantly different and the pooled results heterogeneous. Overall, the rate of patients with TSH normalization or scintigraphically proven efficacy of RFA was about 60% and this can represent a solid

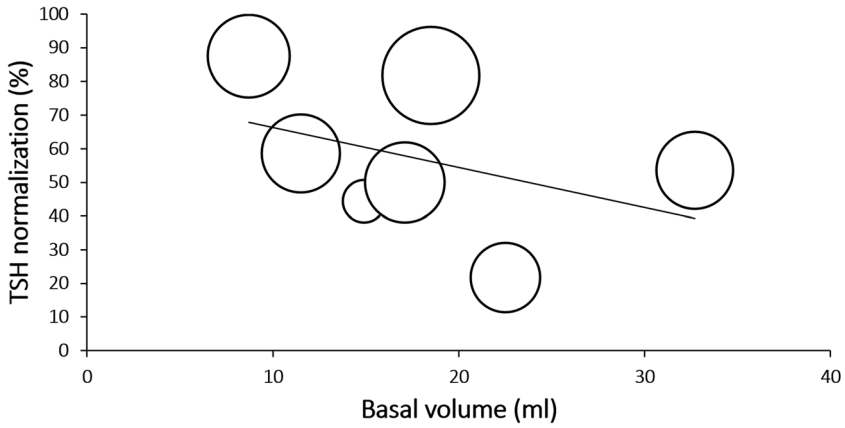

Fig. 3 Metaregression exploring the correlation between baseline nodules volume and TSH normalization at the end of the studies. Size of circle indicates size of study's sample

Table 4 Quality assessment of the studies

First Author, year (ref.)	Cases selection	Reporting	Reference standard	Laboratory evaluation	Follow-up duration
Deandrea, 2008 [14]	U	L	U	L	U
Baek, 2009 [15]	U	L	L	L	U
Spiezia, 2009 [16]	U	U	U	L	L
Faggiano, 2012 [17]	U	H	U	L	U
Sung, 2015 [18]	U	L	L	L	U
Bernardi, 2017 [19]	U	L	H	L	L
Cesareo, 2018 [20]	U	L	L	L	L
Dobnig, 2018 [21]	U	L	U	L	U

Legend. For each category (patients' selection, reporting, reference standard, laboratory evaluation, follow-up duration) the risk of bias was assessed as low (L), high (H), or unclear (U)

starting point in this field. The VRR was 79% at 1 year after RFA. Further original papers, ideally randomized controlled trials with long follow-up, are needed before extending the use of RFA as an option to cure patients with AFTN/TTN.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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