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META ANALYSIS

Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: A systematic review and meta-analysis

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Abstract

Background Image-guided thermal ablations are commonly used in the treatment of thyroid nodules. Radiofrequency ablation (RFA) and laser ablation are the most commonly used. Here we aimed to obtain solid evidence of the long-term efficacy of RFA and laser ablation in benign non-functioning solid thyroid nodules (BNFSTN).

Methods PubMed, CENTRAL, Scopus, and Web of Science were searched until March 2019. Studies reporting the effectiveness of RFA or laser ablation in patients with BNFSTN in terms of volume reduction rate (VRR), compressive symptoms and cosmetic concerns were included. Complications were also assessed.

Results Out of 963 papers, 12 studies on RFA and 12 on laser ablation were included, assessing 1186 and 2009 BNFSTNs, respectively. Overall, VRR at 6, 12, 24, and 36 months was 60%, 66%, 62%, and 53%. VRR of RFA was 68%, 75%, and 87%, respectively. VRR of laser ablation was 48%, 52%, 45%, and 44%, respectively. Baseline volume of nodules undergone RFA was significantly smaller compared to laser ablation (20.1 ± 22.4 versus 24.6 ± 23.6 ml; $p < 0.01$). Nodules smaller than 30 ml obtained better outcomes than larger ones. A significant reduction in compressive symptoms and cosmetic concerns was found after RFA.

Conclusions This meta-analysis showed that both RFA and laser ablation are able to obtain a significant volume reduction in BNFSTNs. A significant volume reduction is already evident at 6 months after thermal ablation and results are stable over the time.

Key words Radiofrequency ablation · Laser ablation · Non-functioning thyroid nodules · Volume reduction rate · Meta-analysis

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Introduction

Thyroid nodule is a common entity. It occurs as a palpable lesion in 5% of women and 1% of men from iodine-sufficient regions [1, 2], while its prevalence in the general population increases to 70% in ultrasound (US) studies [1–3]. The large majority of thyroid nodules is benign. When the malignancy risk is excluded, patients with thyroid nodule(s) can be managed differently. Asymptomatic, benign nodules generally do not require treatment and patients are addressed to clinical follow-up. On the other hand, patients who refer clinical symptoms or discomfort specifically correlated to the goiter, may require a specific treatment [4–6]. Traditionally, surgery has represented the main treatment strategy. However, reducing invasiveness in patients with benign thyroid nodules is a crucial breakthrough of our era. Indeed, while thyroid surgery is widely available in specialized centers, it still carries a 2–10% prevalence of complications, such as neck scarring, hypothyroidism, transient or definitive postoperative hypoparathyroidism, recurrent laryngeal nerve injury, and the recognized risks associated with general anesthesia. Also, surgery is expensive and may not be appropriate for a surgically high-risk individual [4–8].

Relevant advancements have been achieved in the last decades with image-guided thermal ablations, such as radiofrequency ablation (RFA), laser ablation, high-intensity-focus ultrasound (HIFU), and microwave ablation (MWA). Solid non-functioning thyroid nodules with a cytological proof of benignancy determining local compressive symptoms or esthetic/cosmetic concerns have represented the main target of these treatments. On the contrary, other benign thyroid lesions, such as autonomously functioning adenoma, still represent a potential challenge [9]. Among all these thermal options, RFA and laser ablation have been certainly the most largely used, while only preliminary sparse results have been reported for the other therapies. Then, due to relevant observational studies and some randomized controlled trials, international guidelines recommend RFA and laser ablation in selected patients with local symptoms due to benign non-functioning solid thyroid nodules (BNFSTN) [10–13]. Fewer studies have been published on HIFU and MWA which anyway appear as encouraging options [14–17]. More recently, a relevant document quoted that the technical success of image-guided thermal ablations of a thyroid nodule should be defined as a volumetric reduction rate (VRR) ≥ 50% of the initial nodule volume. According to the same document, clinical success should be defined as the ability of treatment to resolve the clinical condition itself [18]. To date, data on results of RFA and laser ablation has been limited to the first few months of follow-up in the majority of papers, also with inhomogeneous definition and reporting of technical and clinical efficacy. Furthermore, stability of the treatment results over time still remain a major issue to be solved. Obtaining more robust evidence on results durability over time could allow to assume image-guided thermal therapies as a consistent alternative to surgery in symptomatic patients with BNFSTN.

With the present study, we aimed to systematically review the literature on the use of RFA and laser ablation in BNFSTNs to obtain solid evidence about their technical and clinical efficacy over time. End-points of this meta-analysis were VRR, compressive symptoms, cosmetic concerns, and complications.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19].

Search strategy

A six-step search strategy was planned. Firstly, we searched sentinel studies in PubMed. Secondly, keywords and MeSH terms were identified in PubMed. Thirdly, in order to test the strategy, the terms “radiofrequency”, “laser”, “thyroid”, and “nodule” were searched in PubMed. This allowed the development of the best strategy to return all identified sentinel studies and the lowest number of non-relevant articles. Fourthly, PubMed, CENTRAL, Scopus, and Web of Science were searched. This allowed the creation of the database of studies to be assessed. Fifthly, studies reporting VRR, compressive symptoms, cosmetic concerns, and complications for RFA or laser ablation in BNFSTN were included. Finally, references of included studies were screened for additional papers. The last search was performed on March 4, 2019. No language neither time restriction was adopted. Three investigators (C.V., M.C., and P.T.) independently and in duplicate searched papers, screened titles and abstracts of the retrieved articles, reviewed the full-texts, and selected articles for their inclusion.

Study selection

Thermal ablation represents a valuable treatment mainly for solid or predominantly solid thyroid nodules. Then, only original papers reporting complete data of BNFSTNs treated by RFA or laser ablation and later followed-up for at least 6 months could be included in this systematic review. Exclusion criteria were: (a) articles not within the field of interest of this review; (b) studies evaluating RFA or laser ablation in malignant, autonomous functioning, or cystic nodules; (c) studies with <6-month follow-up; (d) studies with overlapping patients or nodules data; (e) review articles, editorials, letters, comments, or case/series reports. Three researchers (C.V., M.C., and P.T.) independently reviewed titles and abstracts of the retrieved articles, applying the above criteria. Then, four authors (C.V., G.M., M.C., and P.T.) independently reviewed the full-text of the remaining articles to determine their final inclusion. Discordances were solved in a final collegial meeting.

Data extraction

The following information was extracted independently and in duplicate by three investigators (C.V., M.C., and P.T.) in a piloted form: (1) general information on the study (author, year of publication, country, study type, follow-up duration, number of patients, number, and volume of BNFSTNs); (2) RFA or laser ablation procedure; (3) VRR; (4) compressive symptoms score; (5) cosmetic score; and (6) complications. For cosmetic score, the nodule was classified according to the following scale: 1. no palpable mass; 2. no cosmetic problem but palpable mass; 3. a cosmetic problem only on swallowing; and 4. easily visible mass. For compressive symptoms score, a visual analog scale (scale 0–10) was used, where 0 indicates the absence of compression and 10 an important compression giving serious symptoms and modifying the patient's quality of life. The main paper and supplementary data were searched. Data were cross-checked and any discrepancy was discussed.

Study quality assessment

The risk of bias of included observational studies was assessed independently by two reviewers (M.C. and P.T.) through National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Studies [20]. The risk of bias of included RCTs was assessed independently by the same reviewers through the Cochrane Collaboration's tool for assessing risk of bias for the following aspects: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selecting reporting. For other bias, funding was assessed. Each domain was assigned low, unclear, or high risk of bias [21].

Statistical analysis

The primary outcome was the VRR at 6, 12, 24, and 36 months after RFA or laser ablation. Secondary outcomes included change in compressive symptoms score and cosmetic score from baseline to the last available follow-up. Reported complications were also assessed. The endpoints were analyzed as continuous variables and summarized as weighted mean and weighted mean difference, respectively. If standard deviation was missing in a study for a specific outcome, it was calculated from standard error, 95% confidence interval or from interquartile range; if none of these were available, the largest among the other studies was reported. A subgroup analysis based on the number of sessions and on the baseline nodule volume was planned, with a cut-off of 30 ml. Meta-regressions on VRR based on baseline nodule volume and year of publication were attempted. Pooled data were presented with 95% confidence interval (95% CI). Heterogeneity between studies was assessed by using I^2, with 50% or higher regarded as high. Publication bias was assessed with Egger's test; the trim-and-fill method was used for estimating its effect. Finally, although the objective of the present review was the independent evaluation of RFA and laser ablation in the management of BNFSTN, a comparison between RFA and laser ablation for VRR was attempted through *t*-test. All analyses were carried out using Prometa 3.0 (Internovi) and RevMan 5.3 (The Cochrane Collaboration) with a random-effect model; $p < 0.05$ was regarded as significant.

Results

A total of 963 papers were found, of which 197 on PubMed, 36 on CENTRAL, 371 on Scopus, and 359 on Web of Science. After removal of 435 duplicates, 528 articles were analyzed for title and abstract; 440 records were excluded (guidelines, reviews, on techniques other than RFA or laser ablation [e.g. HIFU, MWA, percutaneous ethanol injection], on lesions other than thyroid solid benign nonfunctioning nodules [parathyroid, thyroid cancer, thyroid cysts, autonomous nodules], case reports, not in humans). The remaining 88 papers were retrieved in full-text and 24 articles were finally included in the systematic review (Fig. 1).

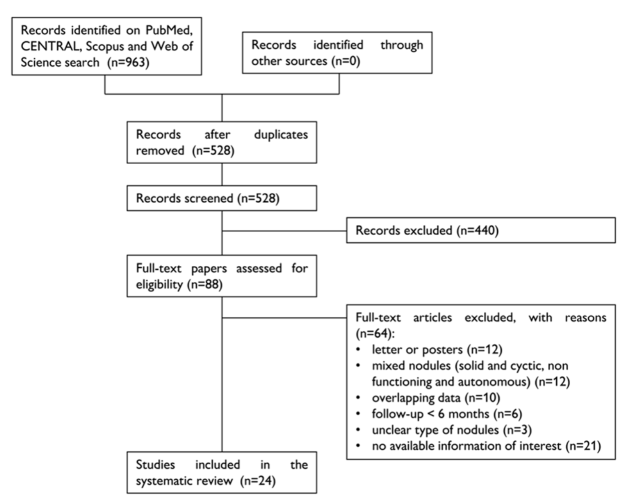

Fig. 1 Flow-chart of the systematic review

Table 1 Characteristic of included studies on radiofrequency ablation and availability of data

First author	Year	Country	Study design	Number of BNFSTN	Solid definition (%)	Study period	6-month assessment	12-month assessment	24-month assessment	36-month assessment
Spiezia [22]	2009	Italy	PCS	66	>70	2005–2007		x		
Huh [23]	2012	Korea	RCT	30	>50	2007–2008	x			
Lim [24]	2013	Korea	RCS	81	>50	2002–2007	x	x	x	x
Cesareo [25]	2015	Italy	RCT	42	>70	2011–2013	x			
Deandrea [26]	2015	Italy, Korea	RCT	40	>70	2010–2012	x			
Valcavi [27]	2015	Italy	RCS	40	>80	2012–2014	x	x	x	
Aysan [28]	2016	Turkey	PCS	51	>80	2013–2015	x			
Yue [29]	2017	China	RCS	102	>50	2012–2015	x	x		
Pacella [30]	2017	Italy	RCS	152	>70	2009–2014	x	x		
Cervelli [31]	2017	Italy	PCS	51	>75	NR	x	x		
Deandrea [32]	2019	Italy	PCS	337	>70	NR	x	x		
Guang [33]	2019	China	RCS	194	>80	2014–2015	x	x	x	

BNFSTN benign non-functioning solid thyroid nodules, *NR* not reported, *PCS* prospective cohort study, *RCS* retrospective cohort study, *RCT* randomized controlled trial, x retrieved data

Qualitative analysis (systematic review)

The characteristics of the included articles are summarized in Tables 1 and 2 [22–45]. The studies were published between 2002 and 2019. Sample sizes ranged from 12 to 1534 BNFTNs. Median post-treatment follow-up was 12 months on both RFA and laser ablation. Mean post-treatment follow-up was 15.5 ± 12.1 and 19.5 ± 14.9 months after RFA and laser ablation, respectively. Six studies were prospective cohort, 10 retrospective cohorts and seven randomized controlled; the study design was not clearly stated in one study [36]. Twelve studies examined RFA and 12 laser ablation. Participants were adult outpatients with a solid thyroid nodule causing compressive symptoms or cosmetic concerns and being ineligible to or refusing surgery. Benignity was defined according to one or two separate fine-needle aspiration cytologies. The nodule was defined as non-functioning if cold on scintigraphy or if the patient was euthyroid. Devices and technical aspects for RFA and laser ablation are reported in Supplementary Data. Overall, 1186 BNFSTN were treated with RFA and 2009 with laser ablation. Nodule volume at baseline was 20.1 ± 22.4 ml in RFA, and 24.6 ± 23.6 ml in laser ablation ($p < 0.01$).

Quantitative analysis (meta-analysis)

The primary outcome was the VRR at 6, 12, 24, and 36 months. Overall, image-guided thermal ablations were associated with a VRR of 60%, 66%, 62%, and 53%. RFA was associated with a VRR of 68%, 75%, and 87%, respectively. There were not enough RFA data for the 36-months follow-up in order to perform a meta-analysis. Laser ablation was associated with a VRR of 48%, 52%, 45%, and 44%, respectively. Similar results were found when assessing only nodules undergone single session treatment. Comparing VRR at each follow-up with the previous one in different ablative modalities, a statistically significant reduction was found only for RFA at 24 months (Table 3 and Fig. 2). A subgroup analysis was performed according to nodule volume at baseline. There were enough data to perform a meta-analysis only for RFA, with nodules smaller than 30 ml achieving a better outcome (Table 4).

Data regarding change in compressive symptoms and cosmetic score from baseline to the last available follow-up were available only for RFA, showing an improvement of both (Figs. 3 and 4). However, most of studies on laser ablation reported an improvement of both outcomes [34–43, 45].

The list of reported complications can be found in Supplementary Data.

Overall, a high heterogeneity was found. In order to investigate this, a meta-regression using nodule volume at

Table 2 Characteristic of included studies on laser ablation and availability of data

First author	Year	Country	Study design	Number of BNFSTN	Solid definition (%)	Study period	6-month assessment	12-month assessment	24-month assessment	36-month assessment
Døssing [34]	2002	Denmark	PCS	16	NR	NR	x			
Døssing [35]	2005	Denmark	RCT	15	NR	NR	x			
Cakir [36]	2006	Turkey	NR	12	NR	NR		x		
Døssing [37]	2006	Denmark	RCT	30	NR	NR	x			
Papini [38]	2007	Italy	RCT	21	NR	2003–2004		x		
Valcavi [39]	2010	Italy	RCS	122	>80	2004–2006	x	x	x	x
Dossing [40]	2011	Denmark	RCS	78	NR	1999–2008		x		
Gambelunghe [41]	2013	Italy	RCS	40	NR	2005–2008	x	x	x	x
Papini [42]	2014	Italy	RCT	101	NR	NR	x	x	x	x
Pacella [43]	2015	Italy	RCS	1534	>60	2004–2013		x		
Negro [44]	2016	Italy	RCS	26	NR	2009–2012	x	x	x	x
Oddo [45]	2018	Italy	PCS	14	>70	2014–2015	x	x		

BNFSTN benign non-functioning solid thyroid nodules, *NR* not reported, *PCS* prospective cohort study, *RCS* retrospective cohort study, *RCT* randomized controlled trial, x retrieved data

baseline as explanatory variable was performed, showing a significant interaction with VRR only for RFA. Publication bias was found for overall analysis of image-guided thermal ablations and for laser ablation VRR at 12 months; the trim-and-fill method did not change the estimate (Supplementary Data).

Study quality assessment

The risk of bias of the included studies is shown in Supplementary Data. Concerning the observational studies, statement of the study question, enrollment of patients, description of intervention, outcome measures, patients flow, and statistical analysis were adequate in all. In three studies, eligibility criteria were not clearly described [31, 34, 36]. A selection bias was found in four: Spiezia, 2009 enrolled only elderly patients; Aysan, 2016, Yue, 2017 and Deandrea, 2019 selected nodules depending on the maximum diameter [22, 28, 29, 32]. To treat very small nodules in order to minimize the risk of complications (i.e. subcapsular, close to trachea, or carotid arteries) was based on clinical decision. There was no sample size calculation in any study. Outcomes were blindly assessed in three [22, 41, 44]. Outcome measure of interest were generally taken multiple times, except in two studies [40, 43]. Concerning the RCTs, we found no attrition or reporting bias; no study was funded by industry. Information on random sequence generation and allocation concealment was not reported in one study [26]. Performance bias was rated as high in all, since an open-label design was used. However, no other study design could have been reasonably used: thermal treatments were compared with observation or levothyroxine in some studies, and single versus multiple sessions in other studies. Finally, outcome assessment was blinded only in two studies [35, 37].

Discussion

This study was conceived as an attempt to achieve robust evidence on the efficacy over time of thermal ablation to reduce volume of BNFSTN and its correlated symptoms. Particularly, the present study focused on RFA and laser ablation, as the most worldwide used thyroid thermal ablation modalities, but it was not undertaken to compare the performance of these two options. To our knowledge, this is the first high-evidence study assessing the durability of both techniques. Twenty-four studies were found, of which 12 on RFA and 12 on laser ablation. The overall results of our meta-analysis showed that both RFA and laser ablation were effective in reducing nodule's size. Results were stable up to 2 years for RFA and 3 years for laser ablation. Improvement in compressive symptoms and cosmetic concerns was demonstrated for RFA. Based on our results, we discuss several considerations.

First, both RFA and laser ablation were effective to reduce the volume of BNFSTNs and their success was maintained up to 2–3 years. In the overall analysis, the 36-month VRR appeared to be smaller than the 24-month one, although not statistically significant. It is worth noting that data for the former outcome were retrieved from one study using RFA and four studies using laser ablation. Thus, a comparison between the two endpoints was biased. Two recent studies with long-term results of RFA [46] and laser ablation [47] were recently published. Both studies showed patients overlap with other included papers and anyway they would have not changed the longest meta-analyzable data. Overall, following the herein recorded results, we are able to consider that when a nodule shows a shrinkage at first visits after RFA or laser ablation its volume will be stable later. This finding achieves high interest for clinical practice, because when a patient is treated using RFA or

Table 3 Volume reduction rate of BNFSTN with all thermal treatments, RFA or laser ablation, according to follow-up and number of sessions

	6-month assessment			12-month assessment			24-month assessment			36-month assessment		
	Number of BNFSTN (number of studies)	VRR (%)	I^2	Number of BNFSTN (number of studies)	VRR (%)	I^2	Number of BNFSTN (number of studies)	VRR (%)	I^2	Number of BNFSTN (number of studies)	VRR (%)	I^2
Overall results of thermal ablation												
All studies	1479 (19)	60	97	2960 (17)	66	99	598 (7)	62	99	370 (5)	53	99
Single session treatment	1123 (16)	57	97	1034 (12)	59	99	323 (5)	51	98	289 (4)	44	94
Radiofrequency ablation												
All studies	1120 (11)	68‡	98	1023 (8)	75‡	98	315 (3)	87†‡	85	–	–	–
Single session treatment	779 (8)	67‡	97	631 (4)	71‡	98	–	–	–	–	–	–
Laser ablation												
All studies	359 (8)	48‡	11	1937 (9)	52‡	97	283 (4)	45‡	96	289 (4)	44	94
Single session treatment	344 (8)	47‡	0	403 (8)	49‡	86	283 (4)	45	96	289 (4)	44	94

†$p < 0.05$ versus previous assessment with the same technique

‡$p < 0.05$ for RFA versus laser ablation at the same follow-up

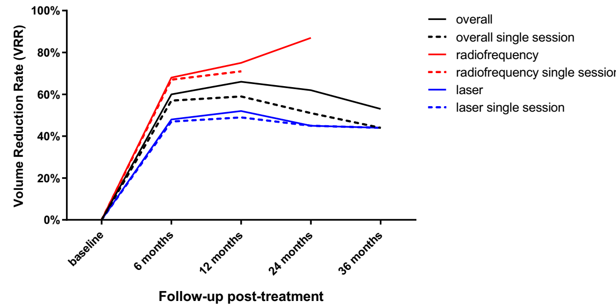

Fig. 2 Pooled results of volume reduction rate of BNFSTN considering RFA, laser ablation, and all studies

laser ablation instead of surgery the optimal results over time shall be guaranteed. The latter issue, together with the low frequency of complications recorded in these studies (see below), represents a high-level evidence which allows us to consider a non-surgical thermal treatment as a real alternative to surgery. Since thermal ablation has been used in patients with esthetic or compressive symptoms related to a single nodule or a dominant nodule in a multinodular goiter especially when smaller than 30 mL, our results have to be interpreted in this clinical context.

Second, the performance of RFA seems to be better than that of laser ablation in terms of VRR achieved. However, several issues have to be discussed on this topic. First of all, several differences are present between studies on RFA and on laser ablation, including significant different nodule volume at baseline, publication period, geographical region, nodule composition, and energy deposition. While most RFA data were published since 2015, the large majority of laser ablation data were reported in a previous time frame (Fig. 5), including the very initial experiences on BNFSTN. This also explained the longer duration of follow-up in studies using laser ablation. Furthermore, the studies on laser ablation were published only by European authors, while RFA data were reported by European and Asian researchers. Moreover, the studies on RFA defined solid nodules when there was a solid composition in at least 50–80% of the lesions, while this definition was not reported in the large part of laser ablation studies. Both different chronology of the publications and diffusion of RFA versus laser ablation might explain the different size of nodules treated by either treatment; the selection of patients has been probably improved over time [48]. Indeed, nodules treated by RFA were significantly smaller than those undergone laser ablation, and the baseline volume was found to be significantly associated with the efficacy of RFA (Supplementary Data). Sparse data on the comparison between RFA and laser have been published and no significant difference have been observed [30]. Notably, no randomized controlled studies were reported until now. Finally, it should be highlighted how the endpoint of the

Table 4 Volume reduction rate of BNFSTN with RFA according to nodule volume at baseline and follow-up

Baseline nodule volume (ml)	6-month assessment			12-month assessment		
	Number of BNFSTN (number of studies)	VRR (%)	I^2	Number of BNFSTN (number of studies)	VRR (%)	I^2
<30	616 (6)	69‡	95	545 (4)	75‡	97
≥30	180 (4)	57‡	62	169 (3)	63‡	61

‡$p < 0.05$ for BNFSTN < 30 ml versus ≥ 30 ml at the same follow-up

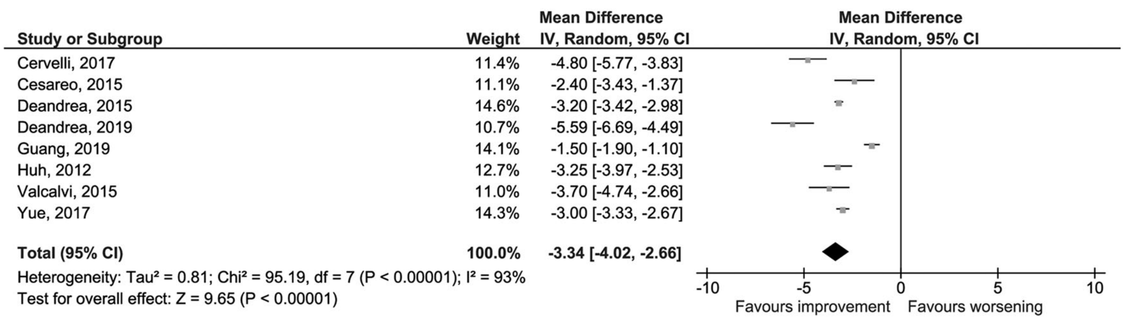

Fig. 3 Change in compressive symptoms score of BNFSTN treated with RFA from baseline to the last available follow-up

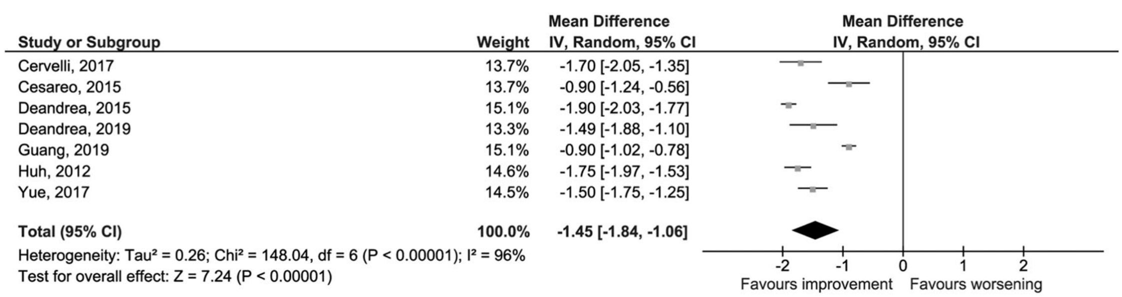

Fig. 4 Change in cosmetic score of BNFSTN treated with RFA from baseline to the last available follow-up

treatment is not to achieve the maximum VRR possible, but to achieve a stable clinical result (e.g. resolutions of compressive symptoms) with the minimum possible rate of complications. On this topic, a great inhomogeneity among studies was found regarding endpoints and reporting criteria. This further highlight what recently reported regarding the need of an higher standardization in terminology and reporting criteria [18].

Third, ideally, patients should be treated in a single session. Seven studies on RFA and 10 studies on laser ablation used this approach. Moreover, two studies were specifically designed to test this hypothesis. In Huh et al. (2012), 30 patients were randomized to one or two sessions of RFA, respectively; no significant difference between the two groups was found for VRR, compressive symptom, or cosmetic score. However, following the first session, three patients in the first group requested an additional treatment because of unsatisfying nodule-related symptoms [23]. In Dossing et al. (2006), 30 patients were randomized to one or three sessions of laser ablation, respectively; a little incremental effect in nodules undergone multiple treatments was reported, without differences in subjective symptoms [37]. This implies that when expected results are not met, retreatment can potentially be considered [24].

Fourth, even if the algorithm search of the study was not designed to evaluate the side effects, a low prevalence of complications with RFA and laser ablation was reported. Recurrent laryngeal nerve injury (including transient voice change) was the most frequent major complication both with RFA and laser ablation. Other major complications included brachial plexus injury ($n = 1$), local infection ($n = 1$), massive colliquative necrosis ($n = 1$), and nodule rupture with fasciitis ($n = 1$) among RFA-treated patients; pseudocyst transformation with fasciitis ($n = 3$) and trachea

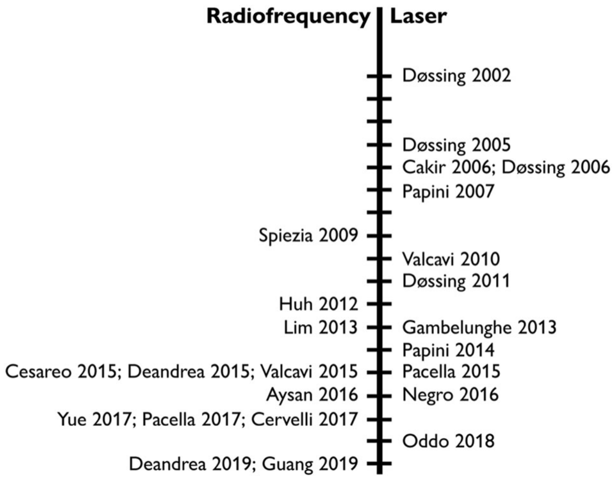

Fig. 5 Timeline of included studies

injury ($n = 1$) were described in laser ablation-treated patients. No analysis was performed on these data, since studies were selected based on the stated efficacy end-points and that analysis should be affected by selection bias. Moreover, reporting differed among studies; a missing data cannot be assimilated to a lack of the event (Supplementary Data).

Limitations and strengths of the present meta-analysis should be discussed. Firstly, even if the duration of follow-up we found was significant, it might be considered as limited compared to the expectancy of life of treated patients. Secondly, data on success rate, defined as VRR > 50%, were often missing, and data on compressive symptoms and cosmetic concerns with laser ablation were unevenly reported (Supplementary Data) [18]. To follow the standardized reporting in future studies should be useful for future reviews [18, 49]. Thirdly, we were not able to assess the difference between single and multiple session treatments. Lastly, a high heterogeneity was found possibly due to: (1) study design; (2) procedure modality and mastering; and (3) patients' characteristics other than the extracted ones.

In conclusion, a significant VRR was recorded in BNFSTN treated by thermal ablation. Available data allowed to show that both compressive symptoms and cosmetic concerns were significantly improved by RFA. As a relevant novelty for clinical practice, these results obtained early were stable over time. With this evidence, both RFA and laser ablation can be considered in patients with BNFSTN.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest G.M. consults for Elesta SrL. The remaining authors declare that they have no conflict of interest.

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References

1. J.B. Vander, E.A. Gaston, T.R. Dawber, The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann. Intern. Med. **69**(3), 537–540 (1968)
2. W.M. Tunbridge, D.C. Evered, R. Hall et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin. Endocrinol. **7**(6), 481–493 (1977)
3. S. Guth, U. Theune, J. Aberle, A. Galach, C.M. Bamberger, Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur. J. Clin. Invest. **39**(8), 699–706 (2009)
4. L. Hegedüs, S.J. Bonnema, F.N. Bennedbaek, Management of simple nodular goiter: current status and future perspectives. Endocr. Rev. **24**(1), 102–132 (2003)
5. L. Hegedüs, Clinical practice. The thyroid nodule. N. Engl. J. Med. **351**(17), 1764–1771 (2004)
6. S. Filetti, C. Durante, M. Torlontano, Nonsurgical approaches to the management of thyroid nodules. Nat. Clin. Pract. Endocrinol. Metab. **2**(7), 384–394 (2006)
7. A. Bergenfelz, S. Jansson, A. Kristoffersson et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch. Surg. **393**(5), 667–673 (2008)
8. B. Nygaard, L. Hegedüs, K.G. Nielsen, P. Ulriksen, J.M. Hansen, Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. Clin. Endocrinol. **50**(2), 197–202 (1999)
9. R. Cesareo, A. Palermo, D. Benevenuto et al. Efficacy of radiofrequency ablation in autonomous functioning thyroid nodules. A systematic review and meta-analysis. Rev. Endocr. Metab. Disord. **20**(1), 37–44 (2019)
10. H. Gharib, E. Papini, J.R. Garber et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules 2016. Endocr. Pract. **22**(5), 622–639 (2016)
11. B.R. Haugen, E.K. Alexander, K.C. Bible et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid **26**(1), 1–133 (2016)
12. G. Mauri, C.M. Pacella, E. Papini, L.M. Sconfienza, L. Solbiati, Proceedings of the first Italian conference on thyroid minimally invasive treatments and foundation of the Italian research group for thyroid minimally invasive procedures. Int. J. Hyperth. **34**(5), 603–605 (2018)
13. J.H. Kim, J.H. Baek, H.K. Lim et al. 2017 Thyroid radiofrequency ablation guideline: Korean Society of Thyroid Radiology. Korean J. Radiol. **19**(4), 632–655 (2018)
14. B.H. Lang, Y.C. Woo, K.W. Chiu, Two-year outcomes of single-session high-intensity focused ultrasound (HIFU) treatment in persistent or relapsed Graves' disease. Eur. Radiol. (2019). https://doi.org/10.1007/s00330-019-06303-8.

15. P. Trimboli, F. Pelloni, F. Bini, F. Marinozzi, L. Giovanella, High-intensity focused ultrasound (HIFU) for benign thyroid nodules: 2-year follow-up results. Endocrine. (2019). https://doi.org/10.1007/s12020-019-01909-w.
16. N. Kotewall, B.H.H. Lang, High-intensity focused ultrasound ablation as a treatment for benign thyroid diseases: the present and future. Ultrasonography **38**, 135–142 (2019)
17. Y.L. Yang, C.Z. Chen, X.H. Zhang, Microwave ablation of benign thyroid nodules. Future Oncol. **10**, 1007–1014 (2014)
18. G. Mauri, C.M. Pacella, E. Papini et al. Image-guided thyroid ablation: proposal for standardization of terminology and reporting criteria. Thyroid. **29**(5), 611–618 (2019)
19. A. Liberati, D.G. Altman, J. Tetzlaff et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann. Intern. Med. **151**(4), W65–W94 (2009)
20. National Heart, Lung, and Blood Institute. Quality assessment tool for observational studies. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed March 2019.
21. J.P. Higgins, S. Green, Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. http://handbook-5-1.cochrane.org/. Accessed March 2019.
22. S. Spiezia, R. Garberoglio, F. Milone et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid **19**(3), 219–225 (2009)
23. J.Y. Huh, J.H. Baek, H. Choi, J.K. Kim, J.H. Lee, Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session—prospective randomized study. Radiology **263**(3), 909–916 (2012)
24. H.K. Lim, J.H. Lee, E.J. Ha, J.Y. Sung, J.K. Kim, J.H. Baek, Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. Eur. Radiol. **23**(4), 1044–1049 (2013)
25. R. Cesareo, V. Pasqualini, C. Simeoni et al. Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules. J. Clin. Endocrinol. Metab. **100**(2), 460–466 (2015)
26. M. Deandrea, J.Y. Sung, P. Limone et al. Efficacy and safety of radiofrequency ablation versus observation for nonfunctioning benign thyroid nodules: a randomized controlled international collaborative trial. Thyroid **25**(8), 890–896 (2015)
27. R. Valcavi, P. Tsamatropoulos, Health-related quality of life after percutaneous radiofrequency ablation of cold, solid, benign thyroid nodules: a 2-year follow-up study in 40 patients. Endocr. Pract. **21**(8), 887–896 (2015)
28. E. Aysan, U.O. Idiz, H. Akbulut, L. Elmas, Single-session radiofrequency ablation on benign thyroid nodules: a prospective single center study: radiofrequency ablation on thyroid. Langenbecks Arch. Surg. **401**(3), 357–363 (2016)
29. W.W. Yue, S.R. Wang, F. Lu et al. Radiofrequency ablation vs. microwave ablation for patients with benign thyroid nodules: a propensity score matching study. Endocrine **55**(2), 485–495 (2017)
30. C.M. Pacella, G. Mauri, R. Cesareo et al. A comparison of laser with radiofrequency ablation for the treatment of benign thyroid nodules: a propensity score matching analysis. Int. J. Hyperth. **33**(8), 911–919 (2017)
31. R. Cervelli, S. Mazzeo, L. De Napoli et al. Radiofrequency ablation in the treatment of benign thyroid nodules: an efficient and safe alternative to surgery. J. Vasc. Interv. Radiol. **28**(10), 1400–1408 (2017)
32. M. Deandrea, F. Garino, M. Alberto et al. Radiofrequency ablation for benign thyroid nodules according to different ultrasound features: an Italian multicentre prospective study. Eur. J. Endocrinol. **180**(1), 79–87 (2019)
33. Y. Guang, W. He, Y. Luo et al. Patient satisfaction of radiofrequency ablation for symptomatic benign solid thyroid nodules: our experience for 2-year follow up. BMC Cancer **19**(1), 147 (2019)
34. H. Døssing, F.N. Bennedbaek, S. Karstrup, L. Hegedüs, Benign solitary solid cold thyroid nodules: US-guided interstitial laser photocoagulation—initial experience. Radiology **225**(1), 53–57 (2002)
35. H. Døssing, F.N. Bennedbaek, L. Hegedüs, Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules—a randomised study. Eur. J. Endocrinol. **152**(3), 341–345 (2005)
36. B. Cakir, O. Topaloglu, K. Gul et al. Effects of percutaneous laser ablation treatment in benign solitary thyroid nodules on nodule volume, thyroglobulin and anti-thyroglobulin levels, and cytopathology of nodule in 1 yr follow-up. J. Endocrinol. Invest. **29**(10), 876–884 (2006)
37. H. Døssing, F.N. Bennedbaek, L. Hegedüs, Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules: one versus three treatments. Thyroid **16**(8), 763–768 (2006)
38. E. Papini, R. Guglielmi, G. Bizzarri et al. Treatment of benign cold thyroid nodules: a randomized clinical trial of percutaneous laser ablation versus levothyroxine therapy or follow-up. Thyroid **17**(3), 229–235 (2007)
39. R. Valcavi, F. Riganti, A. Bertani, D. Formisano, C.M. Pacella, Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. Thyroid **20**(11), 1253–1261 (2010)
40. H. Døssing, F.N. Bennedbæk, L. Hegedüs, Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. Eur. J. Endocrinol. **165**(1), 123–128 (2011)
41. G. Gambelunghe, R. Fede, V. Bini et al. Ultrasound-guided interstitial laser ablation for thyroid nodules is effective only at high total amounts of energy: results from a three-year pilot study. Surg. Innov. **20**(4), 345–350 (2013)
42. E. Papini, T. Rago, G. Gambelunghe et al. Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial. J. Clin. Endocrinol. Metab. **99**(10), 3653–3659 (2014)
43. C.M. Pacella, G. Mauri, G. Achille et al. Outcomes and risk factors for complications of laser ablation for thyroid nodules: a multicenter study on 1531 patients. J. Clin. Endocrinol. Metab. **100**(10), 3903–3910 (2015)
44. R. Negro, T.M. Salem, G. Greco, Laser ablation is more effective for spongiform than solid thyroid nodules. A 4-year retrospective follow-up study. Int J. Hyperth. **32**(7), 822–828 (2016)
45. S. Oddo, E. Felix, M. Mussap, M. Giusti, Quality of life in patients treated with percutaneous laser ablation for non-functioning benign thyroid nodules: a prospective single-center study. Korean J. Radiol. **19**(1), 175–184 (2018)
46. M. Deandrea, P. Trimboli, F. Garino et al. Long term efficacy of a single session RFA of benign thyroid nodules: a longitudinal 5-year observational study. J. Clin. Endocrinol. Metab. (2019). https://doi.org/10.1210/jc.2018-02808
47. R. Negro, G. Greco. Unfavorable outcomes in solid and spongiform thyroid nodules treated with laser ablation. A 5-year follow-up retrospective study. Endocr. Metab. Immune Disord. Drug Targets. (2019). https://doi.org/10.2174/1871530319666190206123156
48. R. Cesareo, A. Palermo, V. Pasqualini et al. Radiofrequency ablation for the management of thyroid nodules: a critical appraisal of the literature. Clin. Endocrinol. **87**(6), 639–648 (2017)
49. E. Papini, C.M. Pacella, L.A. Solbiati et al. Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian Minimally-Invasive Treatments of the Thyroid (MITT) group. Int. J. Hyperthermia. **36**(1), 376–382 (2019)