RADIOFREQUENCY ABLATION (RFA) AS AN ALTERNATIVE TO CONVENTIONAL TREATMENT

EDITED BY: Loredana Pagano, Cosimo Durante and Ralph P. Tufano
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RADIOFREQUENCY ABLATION (RFA) AS AN ALTERNATIVE TO CONVENTIONAL TREATMENT

Topic Editors:
Loredana Pagano, University of Turin, Italy
Cosimo Durante, Sapienza University of Rome, Italy
Ralph P. Tufano, The Johns Hopkins Hospital, Johns Hopkins Medicine, United States

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EDITORIAL
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Editorial: Radiofrequency Ablation as an Alternative to Conventional Treatment

Loredana Pagano[1]*, *Cosimo Durante*[2] *and Ralph Patrick Tufano*[3]

[1] Division of Endocrinology, Diabetology and Metabolism, Department of Medical Sciences, University of Turin, Turin, Italy, [2] Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy, [3] Department Head and Neck Endocrine Surgery, Sarasota Memorial Health Care System, Sarasota, FL, United States

Keywords: radiofrequency ablation (RFA), thyroid nodule, papillary microcarcinomas (PMC), thyroid volume, minimally invasive technique

Editorial on the Research Topic

Radiofrequency Ablation (RFA) as an Alternative to Conventional Treatment

OPEN ACCESS

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Terry Francis Davies, Icahn School of Medicine at Mount Sinai, United States

***Correspondence:**
Loredana Pagano
loredana.pagano@med.uniupo.it

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Ultrasound (US)-guided radiofrequency ablation (RFA) is a minimally invasive treatment modality that may be an alternative to surgery in patients with benign thyroid nodules. In addition, it may serve as an alternative treatment for carefully selected papillary microcarcinomas (PMC) and recurrent thyroid cancers.

In a systematic review on 17 retrospective studies, Monpeyssen et al. provided evidence for the effectiveness of RFA in reducing nodular volume and compressive and cosmetic symptoms in benign thyroid nodules, without causing thyroid dysfunction or life-threatening complications. Indeed, RFA is a percutaneous treatment that results in thermal tissue necrosis and ultimately fibrosis within the target nodule. As a result of this process, the nodules shrink with a 12-month volume reduction rate ranging from 67 to 75% for those lesions undergoing a single procedure. Thermal ablation, however, is an operator-dependent technique and should be performed in centers with RFA specific expertise. Two single center, retrospective studies (Bernardi et al., Bisceglia et al.) found that efficacy should always be evaluated at specific time points (1, 3, 6 and 12 months), with the one-year follow-up visit being generally considered optimal for assessing final outcome. In these cohorts of patients, there was a good association between initial ablation ratio and volume reduction ratio (VRR) 1 and 5 years after the procedure. Proper selection of the patients appears to be a key step with the nodule size (<25ml) and the echotexture (i.e., macrocystic pattern) being the parameters that positively predict the outcome of the treatment.

Moreover, two reviews (Cesareo et al., Pace-Asciak et al.) demonstrated that RFA can be successfully used to treat autonomously functioning thyroid nodules displaying signs or symptoms of compression to adjacent structures, hyperthyroidism, and in pretoxic nodules. Such an approach represents a valuable alternative to therapies that may complicate pre-existing chronic disorders in elderly patients, or that are controversial in young women, like radioactive iodine therapy. Even in

these cases, patient selection is essential to optimize treatment efficacy in terms of volume reduction and thyroid function normalization.

Indications for RFA in treating small primary differentiated thyroid cancers is a hot topic now. Benefits on health-related quality of life (HRQL) have been reported in a large cohort of patients with nonaggressive thyroid malignancies not amenable to surgery due to the presence of co-morbidities (Lan et al.) Mauri et al. reported promising data in properly selected, very low risk thyroid cancer patients, especially in PMC, T1 N0, in whom RFA turned out to be a safe alternative to either surgery or active surveillance. RFA could contribute to reduce the treatment burden of surgery and/or the psychological burden of active surveillance for these patients.

The purpose of discussing these issues in the Research Topic of Frontiers in Endocrinology session is to highlight the current and possible future utility of RFA as an alternative therapeutic approach in treating benign and malignant thyroid diseases.

AUTHOR CONTRIBUTIONS

All authors equally contributed to the composition of this editorial.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Quality of Life in Papillary Thyroid Microcarcinoma Patients Undergoing Radiofrequency Ablation or Surgery: A Comparative Study

Yu Lan[1,2,3], *Yukun Luo*[1,2]*, *Mingbo Zhang*[2]*, *Zhuang Jin*[2], *Jing Xiao*[1,2], *Lin Yan*[2] and *Yaqiong Zhu*[1,2]

[1] School of Medicine, Nankai University, Tianjin, China, [2] Department of Ultrasound, The First Medical Center of Chinese PLA General Hospital, Beijing, China, [3] Department of Ultrasound, The People's Hospital of Liaoning Province, Shenyang, China

Objective: Papillary thyroid microcarcinoma (PTMC) has a good prognosis and a long survival time. Health-related quality of life (HRQoL) is vital for PTMC patients during their survivorship. Ultrasound (US)-guided radiofrequency ablation (RFA), which has high efficacy and safety, is recommended as an alternative treatment to surgery for the patients with low-risk PTMC. However, the assessment of QoL of patients with PTMC has not been specially reported. The purpose of our study was to compare the HRQoL of patients with PTMC who underwent RFA and those who underwent surgery.

Methods: From October 2019 to December 2019, 88 PTMC patients were enrolled in our study, including 54 in RFA group and 34 in surgery group. We used three questionnaires which included the 36-item short form health survey (SF-36), thyroid cancer-specific quality of life (THYCA-QOL), and Fear of Progression Questionnaire-Short Form (FoP-Q-SF) for each patient to evaluate their scores of HRQoL. The scores were compared after adjusting for age, sex, medical expense, and follow-up time.

Results: According to the SF-36, the scores of the domain for the role limitation due to physical problems and emotional problems (RP, RE) as well as Physical Component Summary (PCS) showed a significant negative linear association between the RFA group and surgery group: RP coefficient [coef]−22.613 [confidence interval (CI) −33.504 to −11.723], $p < 0.001$, RE (coef: −21.901 [CI −36.737 to −7.064], $p = 0.004$), and PCS (coef: −8.312 [CI −13.694 to −2.930], $p = 0.003$). The THYCA-QOL showed that the scores of the surgery group were higher than that of the RFA group regarding scars (coef: 10.246 [CI 1.330 to 19.162], $p = 0.025$ according to the multivariate analysis), suggesting a higher level of complaint in the surgery group. There was no statistically significant difference in the scores of FoP-Q-SF between the two groups.

Conclusions: In patients with PTMC, US-guided RFA offers advantage over surgery in terms of HRQoL, which supports the role of RFA as an alternative strategy to surgery.

Keywords: papillary thyroid microcarcinoma (PTMC), ultrasound, radiofrequency ablation (RFA), surgery, quality of life

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Loredana Pagano, University of Turin, Italy

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***Correspondence:**
Yukun Luo
lyk301@163.com
Mingbo Zhang
owsifanduizhe@126.com

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INTRODUCTION

Papillary thyroid microcarcinoma (PTMC), which is papillary thyroid carcinoma (PTC) with a maximum diameter of ≤1 cm (1, 2), has high incidence, low mortality rate, and over 90% 10-year survival rate (3–6). Although it is often referred to as the "good cancer," health-related quality of life (HRQoL) is often reduced by sleep disorders, fatigue, and limited daily activity compared with general people (7, 8). Studies showed that HRQoL of thyroid cancer survivors is negatively affected for up to 20 years after treatment (9). Thus, more attention should be paid to the HRQoL of patients when choosing treatment strategy (10).

The recent American Thyroid Association (ATA) Guidelines also emphasize that physicians should consider long-term quality of life outcomes when making treatment decisions, and recommend active surveillance (AS) for PTMC (2). However, patients who worry about untreated tumors or tumor metastases may experience significant psychological stress (11). Although surgery is a general recommendation of treatment (2, 12–14), it may cause some complications such as permanent recurrent laryngeal nerve paralysis, hypothyroidism, hypoparathyroidism, or an ugly scar (15–19), which may decrease QoL of thyroid cancer survivors and negatively affect their psychological well-being and social function (7, 20).

Ultrasound (US)-guided thermal ablation has become a new treatment strategy for thyroid nodules (21–25). The efficacy and safety of microwave ablation and radiofrequency ablation (RFA) in the treatment of thyroid microcarcinoma have been demonstrated in previous studies (26–28). However, the comparative study of the quality of life for thyroid cancer patients between undergoing surgery and thermal ablation has not been reported yet.

In this study, we sought to make the comparison of HRQoL between the low-risk PTMC patients who underwent US-guided RFA and surgery by using three different and validated questionnaires.

MATERIALS AND METHODS

Patients

The comparative study was approved by the Institutional Review Board at General Hospital of Chinese PLA (S2019-211-01). Informed consent for treatment and questionnaire procedures was obtained from each participant. From October 2019 to December 2019, 88 patients (15 male and 73 female with an average age of 42.09 years ± 10.02 years ranging from 23 years to 64 years) who had undergone RFA or open surgery in our hospital were enrolled in our study (**Figure 1A**).

For the RFA group, patients were enrolled in this study if they fulfilled the following criteria: (1) a solitary suspicious thyroid nodule with a maximum diameter of less than 1 cm was detected by US; (2) low-risk PTMC, which is defined as patients without any evidence of nodal or distant metastases, extrathyroidal extension, or history of radiation exposure (2, 12); (3) core needle biopsy (CNB) confirming PTMC without aggressive histological type (except hobnail, poorly differentiated, or tall cell variants) (29); (4) patients refused surgery or were poor candidates for surgery; and (5) more than 1 month's follow-up.

For the surgery group, patients had undergone surgery and were included in this study if they fulfilled the following criteria: (1) a solitary suspicious thyroid nodule with a maximum diameter of ≤1 cm detected by pre-operative US; (2) low-risk PTMC, which is defined as patients without any evidence of nodal or distant metastases, extrathyroidal extension, or history of radiation exposure (2, 12); (3) surgical pathology confirming PTMC without aggressive histological type and no other aggressive features; and (4) more than 1 month's follow-up.

A total of 54 PTMC patients underwent RFA, two of whom were poor candidates for surgery due to chronic cardiac insufficiency, and 52 of whom subjectively refused open surgery or active surveillance. 34 PTMC patients underwent surgery, with 16 patients who underwent total thyroidectomy and 18 patients who underwent unilateral lobectomy.

All PTC patients who underwent surgery or RFA came to our department for review and filled in the questionnaire, and the questionnaire screening process was completed by the investigator (Y.L.) alone. The characteristics of tumors and surgical methods of the patients were obtained from the electronic medical record system of our hospital, and the questionnaires of the patients meeting the inclusion criteria were enrolled in this study (**Figure 1B**).

Ablation Procedure

In our study, all patients underwent routine US and contrast-enhanced ultrasonography (CEUS) examination before ablation by using a 15L8W linear array transducer and a real-time US System (Siemens ACUSON Sequoia 512, Siemens, Mountain View, CA), a L12-5 linear array transducer and a real-time US System (Philips EPIQ7, Philips Healthcare, Bothell, WA), or a L12-4 linear array transducer and a real-time US System (Mindray M9, Mindray, Shenzhen, China). Routine US characteristics of lesions including location, composition, echogenicity, shape, margin, and echogenic foci (**Table 1**) were assessed and recorded according to the ACR TI-RADS (30). All RFA procedures were performed by the same sonographer (K.Y.L.), who has 20 years' clinical experience in routine and interventional US.

Patients lay in the supine position with their necks extended. Skin sterilization was performed and 1% lidocaine was used for local anesthesia at the intended puncture site. The hydrodissection technique was used with a mixture of 1% lidocaine injected into the anterior capsule space and normal saline injected into the posterior capsule space to protect vital structures (cervical artery, trachea, esophagus, recurrent laryngeal nerve) to prevent thermal injury when the distance between the lesion and the surrounding vital structures was <5 mm. Moving-shot ablation technique was used to perform the RFA. (22, 25). The RFA extends beyond the edge of the lesion to prevent local residue and recurrence. When all the target areas become transient hyperechoic zones, the ablation stops. During the procedure, more attention would be paid to

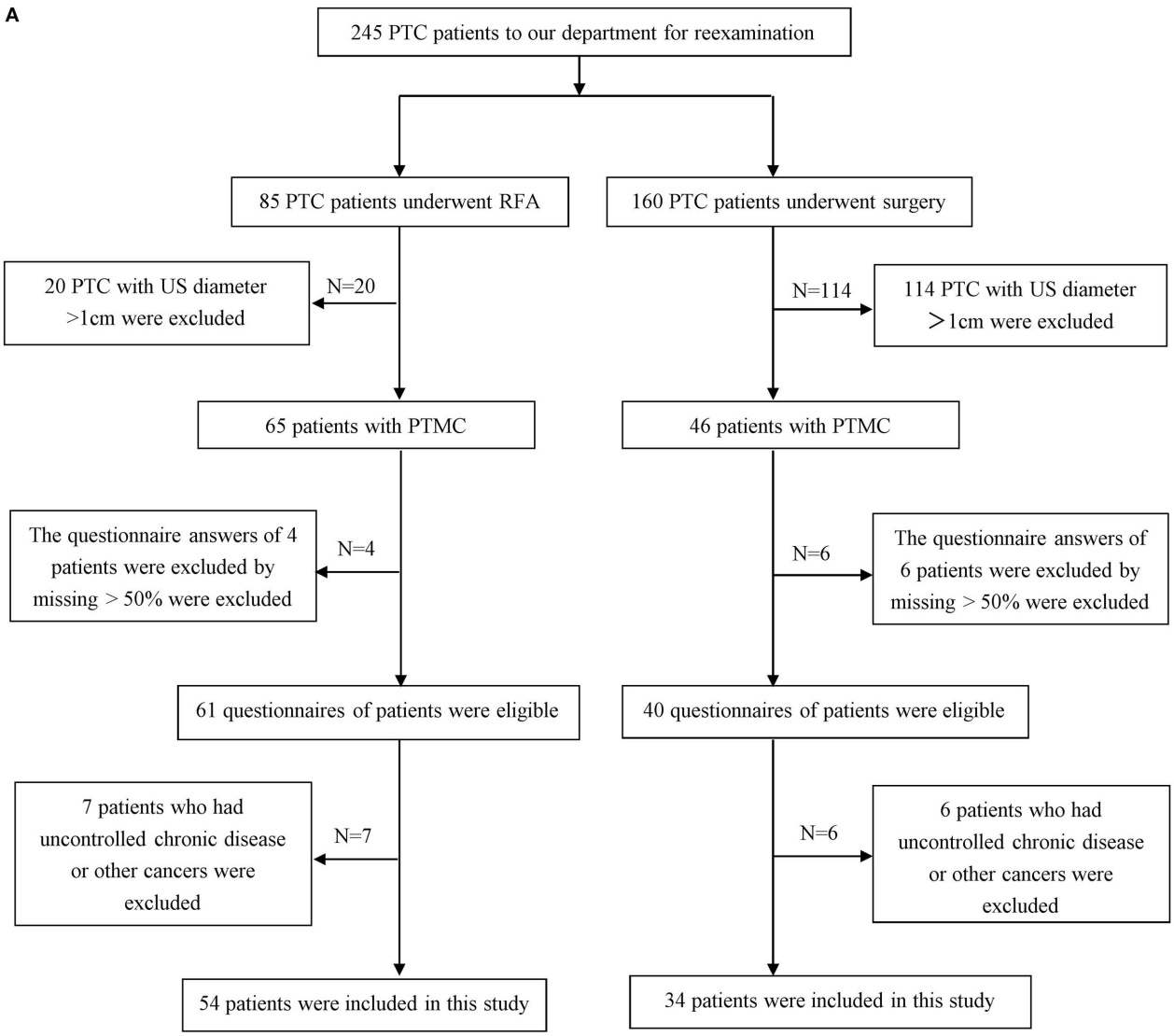

FIGURE 1A | The flow chart of inclusion and exclusion of the RFA and surgery group. PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; US, ultrasound.

protecting the surrounding vital structures to prevent serious complications such as hematoma formation or nerve injury. After RFA, all patients were observed for 1 to 2 h and were evaluated for any complications during or immediately after RFA operation.

Surgery Procedure

Patients in the surgery group were operated on by surgeons (W.T. or Z.Q.) with more than 20 years of experience in thyroid surgery. They complete more than 1,000 surgical procedures each year. Surgical procedures are performed according to the ATA guidelines (2), including unilateral lobectomy or total thyroidectomy with or without cervical lymph node dissection and iodine therapy.

Demographic and Clinical Characteristics

Demographic characteristics, such as age, sex, height, weight, marital status, education level, employment status, source of medical expenses, and place to live, were collected. Clinical characteristics such as data regarding levothyroxine (LT4) supplementation, comorbidity, and family history of thyroid cancer were collected.

HRQoL Questionnaires

Short-Form Survey

The SF-36 (Chinese version) is a multi-purpose short form survey, a well-validated and standardized questionnaire measuring HRQoL that is used in many publications (31–35). It consists of 36 questions measuring eight domains: physical functioning (PF), role-physical (RP), bodily pain (BP),

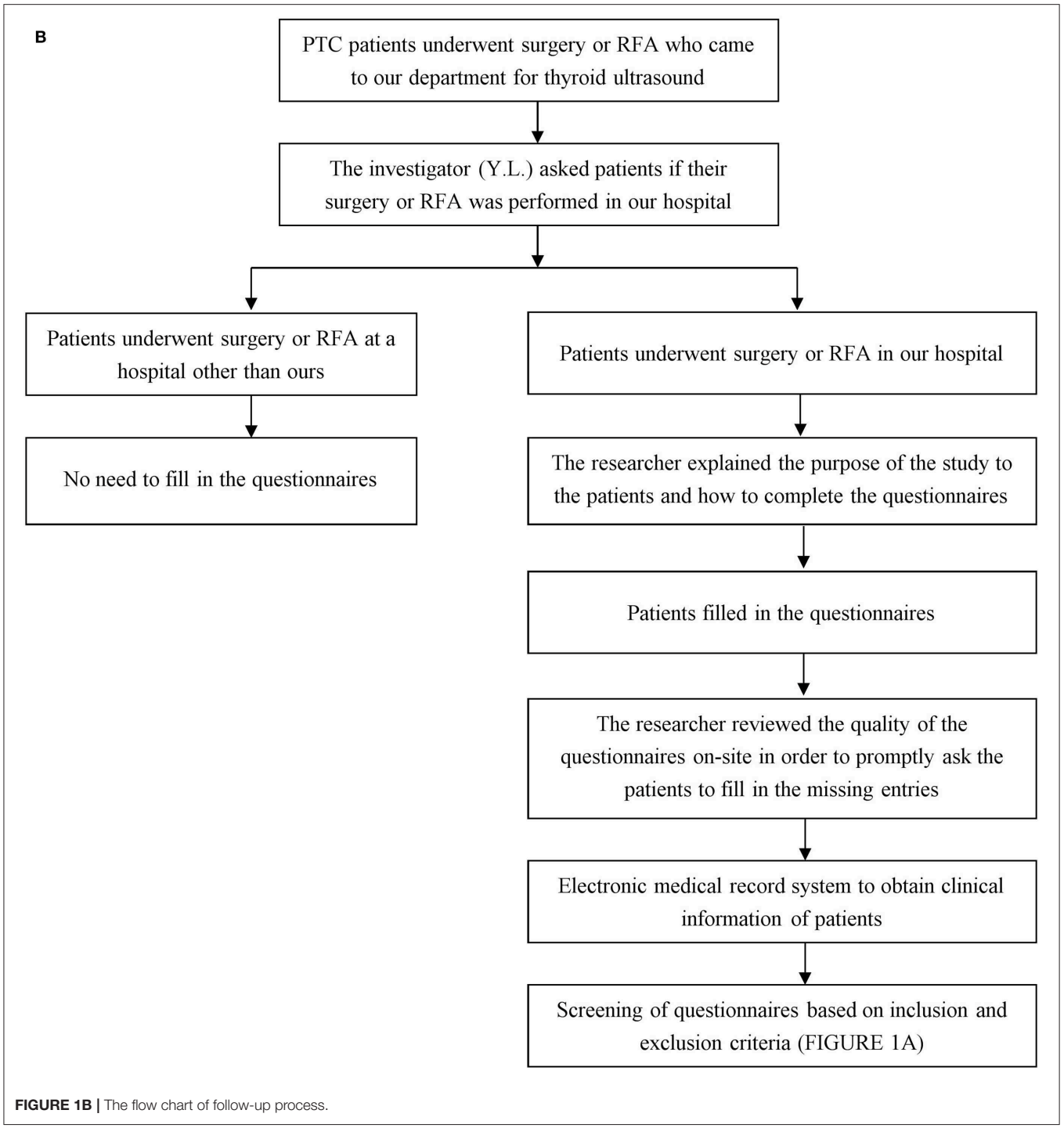

FIGURE 1B | The flow chart of follow-up process.

general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Two total scores can be calculated: physical component summary (PCS) and mental component summary (MCS) representing the physical wellbeing and emotional wellbeing, respectively. All scores of domains are transformed to scales of 0 to 100. The higher scores on the domains indicate lower disability and better HRQoL.

Thyroid Cancer-Specific Quality of Life Questionnaire (THYCA-QOL)

The Chinese version of THYCA-QOL was used to assess the thyroid-specific symptoms resulting from the thyroid cancer itself or its treatment (36). It includes 24 questions measuring seven symptom domains (neuromuscular, voice, attention, sympathetic, throat/mouth, psychological, and sensory

TABLE 1 | Tumor characteristics of RFA and surgery group.

Characteristics	Ablation group ($n = 54$)	Surgery group ($n = 34$)	p-value
Location			0.380
Left	32	15	
Right	21	18	
Isthmus	1	1	
Composition			/
Cystic or almost completely cystic	0	0	
Spongiform	0	0	
Mixed cystic and solid	0	0	
Solid or almost completely solid	54	34	
Echogenicity			0.154
Anechoic	0	0	
Hyperechoic or isoechoic	0	0	
Hypoechoic	41	30	
Very hypoechoic	13	4	
Shape			
Wider-than-tall	19	8	
Taller-than-wide	35	26	
Margin			0.094
Smooth	20	6	
Ill-defined	11	6	
Lobulated or irregular	23	22	
Extra-thyroidal extension	0	0	
Echogenic foci			0.231
None or large comet-tail artifacts	33	15	
Macrocalcifications	0	0	
Peripheral(rim)calcifications	1	2	
Punctate echogenic foci	20	17	

symptoms), as well as six single scales (scar, feeling cold, tingling sensation, weight gain, headache, and reduced sexual interest) (7, 37). The questionnaire has a strict time scale (4 weeks for the sexual interest item, 1 week for the other items). All items are classified into four levels (1 = "not at all," 2 = "a little," 3 = "quite a bit," and 4 = "very much") and are counted as 1 to 4 points. A higher score represents more complaints and worse HRQoL caused by that symptom (37).

Fear of Progression Questionnaire

This questionnaire was developed by Mehnert et al. (38) and has been applied to patients with systemic sclerosis (39) and cancer (40) with high reliability and validity. It consists of 12 items measuring two domains (physiological health dimension and social family dimension). The Likert 1 to 5 score method is adopted. Each item is scored from 1 to 5: "never" to "often." The scale is self-rated by patients with a total score of 12 to 60 points. A higher score indicates a greater level of anxiety about disease progression.

All questionnaires in this study were sent and received by the investigator (Y.L.), who explained the method of filling in the questionnaires. The three questionnaires mentioned above were completed after obtaining the patients' informed consent. The researcher checked whether the questionnaire was wrongly written or omitted and corrected in time.

Statistical Analysis

Categorical variables were expressed as numbers, and continuous variables were presented as the mean and standard deviation. Continuous variables were compared using t-test. By using univariate and multivariate regression analyses, we compared the differences in scores between RFA group and surgery group. The age, sex, medical expense, and interval time were adjusted in multivariate model. All p-values were two-sided, and $p < 0.05$ was considered as statistically significant difference. The SPSS statistical software (version 24.0; IBM, Inc., Chicago, IL) was used to perform all statistical analyses, and the figures were generated using Graph Pad Prism 8.0 (Graph Pad Software, Inc., San Diego, CA).

RESULTS

Baseline Characteristics of the Patients

Baseline characteristics had no difference between the RFA group and surgery group in age, sex, BMI, marital status, education level, employment status, comorbidity, family history of thyroid cancer, place to live, and LT4 supplementation. However, in comparison to the patients in the RFA group, patients who underwent surgery were more likely to be patients who can receive medical reimbursement. The time interval from operation to questionnaires completion was also significantly different (5.57 months vs. 20.29 months, $p < 0.001$; **Table 2**). Meanwhile, there was no significant difference in the baseline characteristics of patients in the unilateral lobectomy group and the total lobectomy group (all $p > 0.05$, **Table 2**).

Among the 34 patients who underwent open surgery, two experienced postoperative hoarse voice. One patient recovered 1 month after surgery and another one was still not recovered at the time of questionnaire completion (3 months after surgery). No complications occurred in the RFA group in this study.

In order to find out the factors related to the HRQoL of PTMC patients, univariate analysis was performed. Both sex and medical expense as categorical variables, as well as age and follow-up duration as continuous variables, are associated with many HRQoL parameters (**Table 3**). Thus, in order to control the interference of confounding factors, the variables for age, sex, medical expenses, and follow-up time were adjusted during the multivariate analysis.

SF-36 Questionnaire Scores

The RP, BP, SF, RE, and PCS scores of patients in the RFA group were clearly higher than that in the surgery group (**Figure 2**). In both univariate and multivariate analyses, the RP, RE, and PCS scores showed a significant negative linear association between

TABLE 2 | Baseline characteristics of papillary thyroid microcarcinoma patients in RFA group and surgery group.

	Ablation group ($n = 54$)	Surgery group ($n = 34$)	p-value	Subgroup of surgery		p-value
				Lateral lobectomy ($n = 18$)	Total thyroidectomy ($n = 16$)	
Age(years)	41.89 ± 10.21	42.41 ± 9.86	0.813	42.00 ± 10.30	42.88 ± 9.66	0.801
Sex			0.104			
Male	12	3		2	1	
Female	42	31		16	15	
BMI	23.65 ± 2.51	25.11 ± 3.98	0.061	26.29 ± 3.79	23.79 ± 3.87	0.067
Marital status			0.987			0.900
Married/partner	49	30		16	14	
Living alone	5	4		2	2	
Education level			0.381			0.464
College degree or higher	29	15		9	6	
Others	25	19		9	10	
Employment status			0.932			0.180
Employed	37	23		14	9	
Unemployed	17	11		4	7	
Comorbidity			0.755			0.683
None	50	30		15	15	
Yes	4	4		3	1	
Medical expenses			<0.001*			0.855
Public	19	25		13	12	
Self-paying	35	9		5	4	
Family history of thyroid cancer			0.633			0.932
No	52	32		17	15	
Yes	2	2		1	1	
Place to live			0.989			0.732
Urban	46	29		15	14	
Rural areas	8	5		3	2	
LT4 supplementation			0.427			/
No	3	0		0	0	
Yes	51	34		18	16	
Follow-up duration (months)	5.57 ± 5.46	20.29 ± 17.07	<0.001*	24.44 ± 20.02	15.63 ± 11.98	0.126

*$p < 0.05$.

RFA group and the surgery group: RP (coefficient [coef] −22.613 [confidence interval (CI) −33.504 to −11.723], $p < 0.001$, RE (coef: −21.901 [CI −36.737 to −7.064], $p = 0.004$), and PCS (coef: −8.312 [CI −13.694 to −2.930], $p = 0.003$). The results suggested that the physical wellbeing of patients in the RFA group was better than in the surgery group (**Table 4**). In addition, RP, SF, and PCS scores of patients in the unilateral lobectomy group were clearly higher than that in the total thyroidectomy (**Table 5**).

THYCA-QOL Questionnaire Scores

The "problems with scarring" and "less interest in sex" scale scores of patients in the RFA group were lower than in the surgery group, indicating a lower level of complaint relating to symptom in the RFA group (**Table 4**, **Figure 3**). In both univariate and multivariate analyses, the "problems with scarring" scale score showed a significant positive linear association between groups (coef: 10.246 [CI 1.330 to 19.162], $p = 0.025$ according to the multivariate analysis). The "less interest in sex" scale score showed a significant difference between the two groups in the univariate analysis but in the multivariate analysis there was no significant difference (**Table 4**). Psychological scores were clearly higher in the unilateral lobectomy group than in the total thyroidectomy (**Table 5**).

FoP-Q-SF Questionnaire Scores

Neither physical health nor social family domain had significant differences in FoP-Q-SF questionnaire scores between the two groups in all analyses ($p > 0.05$) (**Table 4**).

TABLE 3 | Factors related to the quality of life of papillary thyroid microcarcinoma patients.

	Age			Sex			Medical expense			Follow-up duration		
	Coef	**CI**	***p*-value**	**Coef**	**95% CI**	***p*-value**	**Coef**	**95% CI**	***p*-value**	**Coef**	**95% CI**	***p*-value**
SF-36												
PCS	−0.245	[−0.472 to−0.018]	0.035*	−6.989	[−12.973 to −1.005]	0.023*	5.139	[0.633 to 9.646]	0.026*	0.002	[−0.172 to 0.175]	0.986
PF	−0.047	[−0.172 to 0.079]	0.463	−3.393	[−6.647 to −0.138]	0.041*	1.023	[−1.476 to 3.521]	0.418	0.001	[−0.093 to 0.094]	0.989
RP	−0.237	[−0.717 to 0.244]	0.330	0.068	[−12.740 to 12.877]	0.992	13.068	[3.852 to 22.285]	0.006*	0.199	[−0.159 to 0.557]	0.272
BP	−0.396	[−0.691 to 0.01]	0.009*	−6.436	[−14.454 to 1.581]	0.114	6.216	[0.244 to 12.187]	0.042*	−0.112	[−0.339 to 0.116]	0.332
GH	−0.293	[−0.679 to 0.093]	0.135	−16.067	[−25.834 to −6.300]	0.002*	0.250	[−7.538 to 8.038]	0.949	−0.062	[−0.353 to 0.229]	0.674
MCS	−0.104	[−0.376 to 0.167]	0.448	0.989	[−6.230 to 8.209]	0.786	−1.594	[−7.015 to 3.827]	0.560	0.016	[−0.187 to 0.219]	0.875
VT	0.009	[−0.349 to 0.368]	0.958	−3.507	[−12.975 to 5.961]	0.464	−5.455	[−12.501 to 1.592]	0.128	−0.104	[−0.371 to 0.162]	0.439
SF	−0.117	[−0.380 to 0.147]	0.381	−4.769	[−11.709 to 2.171]	0.176	5.555	[0.415 to 10.695]	0.034*	−0.087	[−0.283 to 0.110]	0.384
RE	−0.136	[−0.734 to 0.462]	0.653	−0.822	[−16.699 to 15.056]	0.918	9.848	[−1.905 to 21.602]	0.099	0.065	[−0.381 to 0.511]	0.773
MH	−0.024	[−0.321 to 0.273]	0.873	−4.026	[−11.846 to 3.795]	0.309	−0.182	[−6.099 to 5.735]	0.951	−0.277	[−0.490 to −0.063]	0.012*
THYCA-QoL												
Neuromuscular	0.305	[0.087 to 0.523]	0.007*	−1.481	[−7.510 to 4.547]	0.626	0.000	[−4.540 to 4.54.]	1.000	0.104	[−0.064 to 0.273]	0.222
Voice	0.180	[−0.075 to 0.435]	0.164	−4.718	[−11.481 to 2.045]	0.169	1.515	[−3.618 to 6.648]	0.559	−0.099	[−0.290 to 0.093]	0.309
Concentration	0.154	[−0.094 to 0.402]	0.220	1.065	[−5.562 to 7.692]	0.750	−1.515	[−6.491 to 3.461]	0.547	0.043	[−0.144 to 0.229]	0.651
Sympathetic	0.028	[−0.284 to 0.341]	0.857	−0.944	[−9.223 to 7.335]	0.821	1.515	[−4.705 to 7.734]	0.630	0.052	[−0.181 to 0.284]	0.661
Throat/mouth	−0.008	[−0.247 to 0.232]	0.950	−0.223	[−6.574 to 6.128]	0.944	−1.010	[−5.782 to 3.762]	0.675	0.058	[−0.120 to 0.236]	0.519
Psychological	0.217	[−0.073 to 0.506]	0.141	9.064	[1.530 to 16.599]	0.019*	−3.598	[−9.398 to 2.203]	0.221	0.100	[−0.118 to 0.318]	0.364
Sensory	0.174	[−0.131 to 0.479]	0.259	5.556	[−2.504 to 13.615]	0.174	−7.197	[−13.126 to 1.267]	0.018*	0.048	[−0.181 to 0.277]	0.678
Problems with scar	0.099	[−0.251 to 0.448]	0.576	5.144	[−4.070 to 14.358]	0.270	−2.272	[−9.234 to 4.690]	0.518	0.047	[−0.214 to 0.307]	0.723
Felt chilly	−0.101	[−0.634 to 0.432]	0.707	9.102	[−4.901 to 23.105]	0.200	−2.273	[−12.895 to 8.349]	0.672	0.119	[−0.278 to 0.516]	0.553
Tingling hands/feet	0.175	[−0.077 to 0.426]	0.171	0.578	[−6.162 to 7.319]	0.865	−0.758	[−5.825 to 4.310]	0.767	0.099	[−0.090 to 0.287]	0.300
Gained weight	−0.075	[−0.447 to 0.298]	0.691	−0.487	[−10.372 to 9.398]	0.922	−3.030	[−10.436 to 4.376]	0.418	0.222	[−0.052 to 0.496]	0.112
Headache	−0.044	[−0.414 to 0.326]	0.812	5.205	[−4.538 to 14.949]	0.291	2.273	[−5.087 to 9.632]	0.541	0.005	[−0.271 to 0.281]	0.971
Less interest in sex	−0.436	[−0.921 to 0.049]	0.078	−5.662	[−18.698 to 7.374]	0.390	−12.121	[−21.618 to −2.623]	0.013*	0.220	[−0.145 to 0.585]	0.234
FoP-Q-SF												
Physical health	−0.004	[−0.019 to 0.011]	0.621	0.481	[0.096 to 0.866]	0.015*	−0.292	[−0.585 to 0.001]	0.051	−0.004	[−0.015 to 0.007]	0.466
Social family	0.003	[−0.010 to 0.016]	0.696	0.308	[−0.031 to 0.647]	0.074	−0.254	[−0.507 to 0.000]	0.050	0.001	[−0.009 to 0.010]	0.875

*$p < 0.05$.

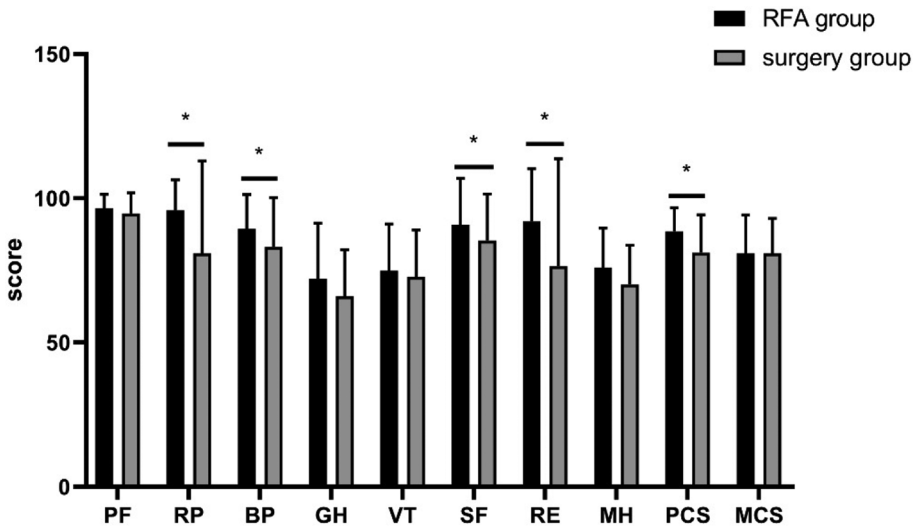

FIGURE 2 | SF-36 score comparison between patients with PTMC in the RFA group and in the surgery group: the patients in the RFA group showed significantly higher scores than the surgery group in 4 domains of HRQoL (*$p < 0.05$).

TABLE 4 | Comparison of quality of life in patients with papillary thyroid microcarcinoma who underwent ablation vs. those who underwent surgery.

	Ablation group	Surgery group	*p*-value	Univariate analysis			Multivariate analysis		
				Coef	CI	*p*-value	Coef	CI	*p*-value
SF-36 (THE HIGHER SCORE, THE BETTER QUALITY OF LIFE)									
PCS	88.48 ± 8.21	81.18 ± 13.06	0.005*	−7.295	[−11.795 to −2.795]	0.002*	−8.312	[−13.694 to −2.930]	0.003*
PF	96.57 ± 4.84	94.71 ± 7.17	0.186	−1.868	[−4.412 to 0.676]	0.148	−1.981	[−5.194 to 1.232]	0.224
RP	95.83 ± 10.58	80.88 ± 32.01	0.012*	−14.951	[−24.309 to −5.593]	0.002*	−22.613	[−33.504 to −11.723]	<0.001*
BP	89.42 ± 11.87	83.15 ± 17.09	0.045*	−6.270	[−12.407 to −0.132]	0.045*	−3.918	[−11.411 to 3.575]	0.301
GH	72.09 ± 19.24	66.00 ± 16.18	0.128	−6.093	[−13.983 to 1.798]	0.128	−5.524	[−15.087 to 4.038]	0.254
MCS	80.92 ± 13.25	80.92 ± 12.08	0.780	−0.787	[−6.363 to 4.788]	0.780	−2.429	[−9.601 to 4.743]	0.502
VT	74.91 ± 15.49	72.79 ± 18.76	0.568	−2.113	[−9.434 to 5.208]	0.568	−2.881	[−12.129 to 6.366]	0.537
SF	90.74 ± 10.29	85.30 ± 14.66	0.044*	−5.446	[−10.736 5 to −0.156]	0.044*	−3.730	[−10.435 to 2.976]	0.272
RE	92.00 ± 18.24	76.47 ± 37.18	0.029*	−15.505	[−27.308 to −3.701]	0.011*	−21.901	[−36.737 to −7.064]	0.004*
MH	76.00 ± 13.70	70.12 ± 13.58	0.053	−5.882	[−11.826 to 0.061]	0.053	−2.995	[−10.489 to 4.500]	0.429
THYCA-QoL (THE LOWER SCORE, THE BETTER QUALITY OF LIFE)									
Neuromuscular	10.70 ± 11.00	12.42 ± 10.15	0.464	1.719	[−2.929 to 6.366]	0.464	0.786	[−4.937 to 6.509]	0.785
Voice	8.02 ± 12.43	5.88 ± 11.52	0.420	−2.142	[−7.404 to 3.119]	0.420	0.070	[−6.577 to 6.716]	0.983
Concentration	5.86 ± 10.81	7.35 ± 13.10	0.564	1.448	[−3.623 to 6.599]	0.564	0.651	[−5.913 to 7.214]	0.844
Sympathetic	13.58 ± 13.76	16.67 ± 15.89	0.337	3.086	[−3.275 to 9.448]	0.337	4.660	[−3.542 to 12.861]	0.262
Throat/mouth	12.96 ± 11.37	15.36 ± 10.95	0.332	2.396	[−2.482 to 7.274]	0.332	2.235	[−4.089 to 8.558]	0.484
Psychological	15.43 ± 13.68	20.83 ± 13.33	0.072	5.401	[−0.495 to 11.297]	0.072	3.439	[−3.912 to 10.790]	0.355
Sensory	13.89 ± 14.01	18.63 ± 14.66	0.133	4.739	[−1.470 to 10.948]	0.133	2.571	[−5.189 to 10.332]	0.512
Problems with scar	5.56 ± 12.54	13.72 ± 20.30	0.022*	8.170	[1.220 to 15.119]	0.022*	10.246	[1.330 to 19.162]	0.025*
Felt chilly	21.60 ± 22.58	25.49 ± 28.50	0.480	3.885	[−7.002 to 14.772]	0.480	1.205	[−12.774 to 15.184]	0.864
Tingling hands/feet	4.32 ± 11.30	5.88 ± 12.90	0.552	1.561	[−3.635 to 6.757]	0.552	−0.012	[−6.651 to 6.626]	0.997
Gained weight	12.34 ± 16.25	19.61 ± 18.56	0.057	7.262	[−0.212 to 14.735]	0.057	5.803	[−3.842 to 15.449]	0.235
Headache	9.88 ± 15.36	12.74 ± 20.12	0.452	2.869	[−4.680 to 10.418]	0.452	4.543	[−5.131 to 14.217]	0.353
Less interest in sex	17.28 ± 21.22	29.41 ± 24.30	0.016*	12.128	[2.357 to 21.899]	0.016*	10.754	[−1.265 to 22.773]	0.079
FoP-Q-SF (THE LOWER SCORE, THE BETTER QUALITY OF LIFE)									
Physical health	1.82 ± 0.68	2.00 ± 0.74	0.285	0.165	[−0.140 to 0.471]	0.285	0.145	[−0.227 to 0.518]	0.440
Social family	1.54 ± 0.59	1.72 ± 0.64	0.185	0.177	[−0.086 to 0.441]	0.185	0.108	[−0.224 to 0.439]	0.520

*$p < 0.05$.

TABLE 5 | Comparison of quality of life in patients with papillary thyroid microcarcinoma who underwent unilateral lobectomy vs. those who underwent total thyroidectomy.

	Lateral lobectomy (n = 18)	Total thyroidectomy (n = 16)	p-value
SF-36			
PCS	86.15 ± 8.55	75.59 ± 15.14	0.022*
PF	95.83 ± 5.75	93.44 ± 8.51	0.339
RP	95.83 ± 12.86	64.06 ± 38.70	0.006*
BP	84.72 ± 18.89	81.38 ± 15.22	0.577
GH	68.22 ± 15.05	63.50 ± 17.52	0.404
MCS	79.68 ± 14.27	80.63 ± 9.46	0.822
VT	78.33 ± 17.06	66.56 ± 19.12	0.067
SF	90.12 ± 12.57	79.86 ± 15.30	0.040*
RE	87.04 ± 23.26	64.59 ± 46.30	0.094
MH	71.33 ± 14.34	68.75 ± 13.00	0.588
THYCA-QoL			
Neuromuscular	10.49 ± 11.09	14.58 ± 8.81	0.247
Voice	9.26 ± 14.26	2.08 ± 5.69	0.062
Concentration	4.63 ± 9.58	10.42 ± 15.96	0.219
Sympathetic	12.96 ± 12.20	20.83 ± 18.76	0.165
Throat/mouth	16.67 ± 12.78	13.89 ± 8.61	0.469
Psychological	14.81 ± 10.13	27.60 ± 13.51	0.004*
Sensory	16.67 ± 12.8	20.83 ± 16.67	0.416
Problems with scar	9.26 ± 19.15	18.75 ± 20.97	0.177
Felt chilly	25.93 ± 35.34	25.00 ± 19.24	0.924
Tingling hands/feet	3.70 ± 10.78	8.33 ± 14.91	0.314
Gained weight	16.67 ± 17.15	22.92 ± 20.07	0.335
Headache	11.11 ± 19.80	14.58 ± 20.97	0.623
Less interest in sex	31.48 ± 24.18	27.08 ± 25.00	0.606
FoP-Q-SF			
Physical health	1.86 ± 0.75	2.14 ± 0.72	0.287
Social family	1.60 ± 0.60	1.86 ± 0.68	0.255

*$p < 0.05$.

DISCUSSION

With the development of medicine, the definition of health has been changing (41), which is defined as a combination of physical, emotional, and social potential, not simply the absence of disease. Additionally, HRQoL reflects personal satisfaction or happiness with their life, and to some extent it may affect or be affected by a certain aspect of the "health" definition mentioned above. Thus, HRQoL has been introduced as an assessment of an individual's health status. The recent ATA Guidelines also emphasize the importance of long-term HRQoL outcomes when physicians make treatment decisions (2).

Our study evaluated the HRQoL of patients with PTMC under different treatment strategies. Several significant differences were found in parameters of the SF-36 questionnaires between the RFA group and the surgery group. After adjusting for age, sex, medical expense, and follow-up duration, the surgery group reported more problems associated with PCS, RP, and RE than the RFA group. RP and RE represent restrictions on daily activities or work due to physical and emotional effects, respectively. PCS represents the overall physical health of the patients. Therefore, patients in the surgery group suffered more adverse effects than those in the RFA group, especially for those who underwent total thyroidectomy. The result is consistent with the results of Lubitz CC et al., which reported that the domain of RE remained decreased years after surgery even without the recurrence of PTC (42).The cause may be due to surgical trauma or complications (43). In general, the greater the surgical trauma, the more likely it is to cause complications (44, 45). According to research reports, the probability of permanent recurrent laryngeal nerve injury after surgery is 0 to 12%, and the probability of permanent hypocalcemia is 0 to 7% (46–48). However, RFA seems to present fewer complications (48). In our study, no patients in the RFA group reported complications. Therefore, we believe that the smaller the trauma, the lower the possibility of complications and the higher the quality of life in patients with PTMC.

In addition, the THYCA-QoL questionnaire used in our study had an item about scarring problems. The problem of scarring was more common in patients who underwent surgery than those who underwent RFA. This was one of the major causes of quality of life decline in the surgery group. Previous studies had revealed that an obvious scar may negatively affect the HRQoL of PTC patients (49) because of the majority of women with thyroid cancer and a good prognosis, a significant number of patients are concerned about permanent and unsightly scars. Although surgery was recommended, the concerns about scarring may affect the HRQoL of survivors from seemly minor problems such as difficulties in choosing clothes to more significant problem such as avoiding communicating with others and developing an inferiority complex, even influencing their career development (50). Additionally, quite a lot of patients may think that the apparent scar may have caused damage to their body image, which is a definition of an individual's subjective view of their own body and has to do with self-esteem and self-perception, closely related with HRQoL.

Some studies had revealed that patients with post-treatment thyroid cancer are constantly concerned about recurrence and metastasis during long-term follow up (51). Hedman et al. reported that only 7% of patients actually experience disease recurrence, but up to 48% of thyroid cancer patients are under pressure to worry about recurrence, which has seriously affected their quality of life (52). The perceptions of the disease from thyroid cancer survivors are often subjective and emotional, and may be inconsistent with the actual severity of the disease. However, in our study, it had no significant difference between the RFA group and the surgery group in the analysis of anxieties and fears associated with disease progression using the FoP-Q-SF questionnaire. This reveals that the patients in the RFA group were not more concerned about the progression of the disease although ablative therapy was only localized to the lesion, which was one of the main concerns during the follow-up of patients who

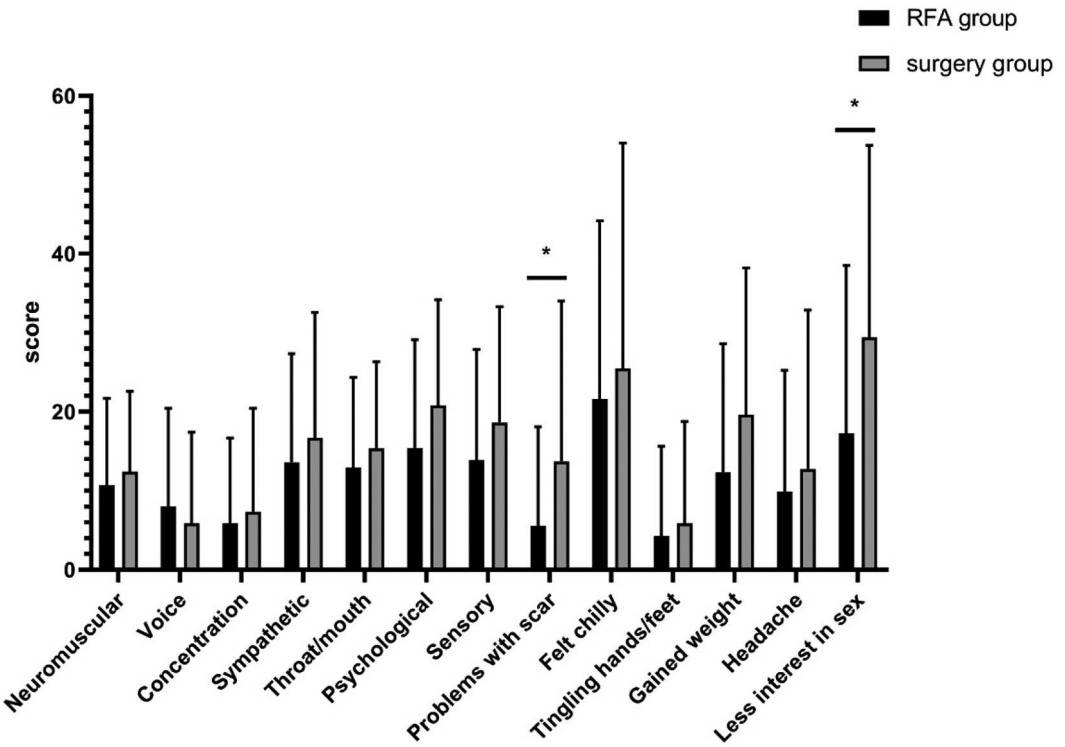

FIGURE 3 | THYCA-QoL score comparison between patients with PTMC in the RFA group and in the surgery group: the patients in the RFA group showed significantly lower scores than the surgery group in 2 domains of HRQoL (*$p < 0.05$).

underwent RFA. However, the patients in the RFA group reported less interest in sexual activity with no statistical significance after adjustment in the multivariate analysis, which may be associated with some anxiety resulting from cancer itself (53).

The three questionnaires used in this study have been demonstrated by previous studies to be validated in evaluating patients' HRQoL. Among them, SF-36 is considered to be a commonly used and sensitive instrument in measuring HRQoL in thyroid cancer in previous studies (54). Gou J et al. reported that RP, RE, and PCS of SF-36 were the factors associated with the HRQoL of patients with PTMC (43). These results are consistent with our study. It indicates that SF-36 is an appropriate tool to evaluate HRQoL of thyroid cancer survivors. However, the SF-36 cannot evaluate all aspects of HRQoL such as disease symptoms or treatment side effects. Thus, the THYCA-QoL questionnaire and FoP-Q-SF were included as a reasonable complement to evaluate important aspects regarding thyroid cancer-specific symptoms (7) and fear of disease progression, which may be the strong determinants of the quality of life after thyroid cancer.

Since the strategy of RFA was first introduced in patients with PTMCs, many studies reported its safety and efficacy for treating low-risk PTMCs (26, 55). Our study suggests that RFA may have advantages in improving the HRQoL of patients with no relationship to anxiety or fear associated with disease progression.

This study has several limitations. First, the baseline characteristics of patients between the two treatment groups were not all matched even though the multivariate analysis was adjusted for patients' follow-up duration, which was a key factor in the assessment of HRQoL (56) as well as medical expense (57). Thus, the results of this study can be biased. Second, the number of patients included in our study was limited. Third, the follow-up time is not long enough, which may overestimate the negative impact of surgery to HRQoL (58), since the HRQoL of cancer patients may improve over time after surgery (7). Last, preoperative quality of life was unknown in both groups. Thus, prospective studies with large samples and longer-term follow-up are proposed.

In conclusion, our study suggested that US-guided RFA offers advantage in terms of HRQoL and supports the role of ablation as an alternative strategy for patients with PTMC except for surgery.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by institutional review board of General Hospital

of Chinese PLA (S2019-211-01). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YLu: integrity of the whole study, analysis of data, and review of final manuscript. YLa and MZ: management of data and manuscript writing. LY and YZ: statistical analysis of data. ZJ and JX: literature review and input of scores in questionnaires. YLa: distribution and recovery of questionnaires, collection and analysis of data.

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MINI REVIEW
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Radiofrequency Ablation on Autonomously Functioning Thyroid Nodules: A Critical Appraisal and Review of the Literature

Roberto Cesareo[1†], Andrea Palermo[2†], Valerio Pasqualini[3], Silvia Manfrini[2], Pierpaolo Trimboli[4,5], Fulvio Stacul[6], Bruno Fabris[7,8] and Stella Bernardi[7,8]*

[1] Unit of Metabolic Diseases, S. M. Goretti Hospital, Latina, Italy, [2] Unit of Endocrinology and Diabetes, Campus Bio-Medico University, Rome, Italy, [3] Department of Radiology, S. F. Neri Hospital, Rome, Italy, [4] Clinic for Nuclear Medicine and Competence Centre for Thyroid Disease, Imaging Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland, [5] Faculty of Biomedical Sciences, Università di Lugano (USI), Lugano, Switzerland, [6] Unit of Radiology (Maggiore Hospital), ASUGI, Trieste, Italy, [7] Unit of Medicina Clinica (Cattinara Hospital), ASUGI, Trieste, Italy, [8] Department of Medical Sciences, University of Trieste, Trieste, Italy

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Edited by:
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***Correspondence:**
Stella Bernardi
stella.bernardi@asugi.sanita.fvg.it

[†]These authors have contributed equally to this work

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Background: Thyroid nodules are an extremely common occurrence, as their prevalence in the general population is estimated to range between 50 and 70%. Some of these nodules are autonomously functioning such that they can cause hyperthyroidism over time. In this case, surgery and radioiodine represent the standard of care. Nevertheless, patients might have contraindications or be unwilling to undergo these treatments. Minimally-invasive ultrasound-guided techniques, such as laser and radiofrequency ablation (RFA), have been recently introduced into clinical practice as an alternative treatment for symptomatic benign thyroid nodules. Due to their efficacy and tolerability, these techniques have become increasingly available and their usage has been extended also to autonomously functioning thyroid nodules (AFTN).

Methods: In this narrative review, we will describe the studies reporting the therapeutic effects of RFA on AFTN, the studies reporting how RFA compares to the other treatment modalities, as well as the current indications for the use of RFA in patients with AFTN. For this purpose, a comprehensive literature search was independently conducted by three investigators on PubMed, EMBASE, and the Cochrane Library from inception up to February 2020 to identify published articles concerning the effects of RFA on AFTN.

Results and Conclusions: Current consensus statements and guidelines support the notion that RFA should be regarded as a first-line therapy for non-functioning benign thyroid nodules, while it remains a valid second-line option for AFTN treatment in case of contraindications or patient unwillingness to undergo surgery or radioiodine.

Keywords: radiofrequency ablation, AFTN, benign thyroid adenoma, guideline, thyroid

INTRODUCTION

Thyroid nodules are an extremely common occurrence. Some of them are autonomously functioning thyroid nodules (AFTN), which are characterized by the production of a greater amount of thyroid hormones, causing hyperthyroidism over time. The prevalence of AFTN varies according to the geographical area and iodine intake. In the general population, it is estimated

that their prevalence ranges from 2.7 to 4.4% (1), but moving from iodine sufficient to iodine deficient areas such as South America and Europe, AFTN can account for as much as 30% of cases of hyperthyroidism (2). Iodine deficiency, which impairs thyroid hormone synthesis and stimulates cellular growth, is the major risk factor for thyroid nodule autonomy development (2). In addition, many AFTN exhibit a somatic point mutation in the *TSHR* gene leading to a constitutive activation of TSHR (3), with subsequent tissue enlargement and thyroid hormone overproduction. Although AFTN can produce greater amounts of thyroid hormones, causing hyperthyroidism over time, many do so slowly, as shown in a study on euthyroid patients with AFTN, who became hyperthyroid at a rate of 4% per year (4). Nevertheless, nodules with a maximum diameter >3 cm (or with a volume >5 ml) are more likely to cause hyperthyroidism over time (5).

Given that antithyroid drugs can reduce thyroid hormones but can not cure AFTN, surgery and radioactive iodine represent the standard of care for this condition (6), particularly when AFTN become symptomatic (7). Nevertheless, patients might have contraindications or be unwilling to undergo these procedures. Recently, minimally-invasive ultrasound-guided techniques, such as laser and radiofrequency ablation (RFA), have been introduced into clinical practice as an alternative treatment for symptomatic benign thyroid nodules (8), including AFTN (9–11).

Focusing on RFA, this is an outpatient procedure, which is generally performed under local anesthesia. It requires the ultrasound-guided insertion of an electrode needle generating an alternating electric field into the nodule. Then, the electrode tip is sequentially moved from the deepest to the superficial parts of the nodule, inducing rapid heating of the target zones. Treatment is accompanied by the formation of coagulative necrosis, and, over time, by fibrotic changes with progressive nodule shrinkage (12, 13). The use of RFA to treat symptomatic thyroid nodules is supported by robust evidence of efficacy and tolerability (14), with a risk of major complications lower than 1% (15).

Here, we will review the therapeutic effects of RFA on AFTN, how this technique compares to the other existing procedures (surgery and radioiodine) in terms of efficacy, complications, and cost, as well as the current indications to RFA in patients with AFTN. For this purpose, a comprehensive literature search was independently conducted by three investigators on PubMed, EMBASE, and the Cochrane Library from inception up to February 2020 to identify published articles concerning the effects of RFA on AFTN. The term radiofrequency was matched with the following terms: thyroid, hyperthyroidism, thyrotoxicosis, autonomous, or toxic or hyperfunctioning adenoma, or autonomously functioning thyroid nodules. We searched for articles published in English and those involving human participants. Additional exclusion criteria for full texts included pediatric populations and case reports. Three investigators independently searched papers, screened titles, and abstracts of the retrieved articles, reviewed the full-texts and selected articles for their inclusion.

Therapeutic Effects of Radiofrequency Ablation on AFTN

Since the first report on the efficacy of RFA in reducing benign thyroid nodules (16), several works have evaluated whether RFA could normalize thyroid function as well (**Table 1**) (17–24). Overall, in these works, despite the average volume reduction was always >50%, the rate of thyroid function normalization at last follow-up was extremely heterogeneous, ranging from 24 to 86%. This variability has been ascribed to technical reasons given that in the first studies (17, 19, 20) the procedure was carried out with the multiexpandable needle, while in the most recent ones it was carried out with the moving shot technique and the 18-G needle. In addition, in some of these studies, patients underwent more than one RFA session (18, 19, 22). Moreover, these studies had a retrospective design, a short follow-up period, a small sample size, and they included AFTN together with non-functioning thyroid nodules.

To overcome these limitations, our groups designed two separate prospective studies. The first study (21) aimed at evaluating the 12-month efficacy of a single session of RFA performed with the moving shot technique. In this work, RFA was performed on 30 AFTN, with an average volume of 17 mL. After 12 months, RFA reduced thyroid nodule volume by 75%, leading to thyroid function normalization in 50% of patients. Interestingly, in this study, patients went into remission when their nodules were reduced on average by 81% after 12 months from the procedure. Patients who improved, in comparison, had their nodules reduced by 68%. The second study aimed at comparing the response to RFA of small AFTN (<12 mL) to that of medium size AFTN (>12 mL) (23). Interestingly, in this work, the rate of thyroid function normalization significantly increased in small nodules (whose average volume was 5 mL) as compared to medium size nodules (whose average volume was 18 mL). Specifically, the rate of thyroid function normalization was 86% in small nodules vs. 45% in medium size nodules. This was consistent with the rate of nodules converting from hot to cold at the scintiscan, which was 86% in small nodules as compared to 16% in medium size nodules. In addition, small size nodules exhibited a greater volume reduction, as they were reduced by 82 and 84% after 12 and 24 months, as compared to medium size nodules, which were reduced by 67 and 68% after 12 and 24 months. These data indicate that small AFTN have a more favorable outcome. In addition, also in this study there was a higher probability of symptom resolution and thyroid function normalization when the volume ablation was >80%, which is in line with the concept that the greater the baseline volume the higher the likelihood to undertreat hyperfunctioning areas, leading to hyperthyroidism/symptom relapse.

Most of these studies (17–24) have been included in a recent metanalysis (25) evaluating the efficacy of RFA in AFTN in terms of TSH normalization, scintiscan changes, and volume reduction rate. Overall, this metanalysis included 8 articles and 205 AFTN treated with RFA. Five studies used a single session of RFA. Follow-up ranged from 6 to 24 months. This metanalysis showed that the pooled rate of TSH normalization was 57%, the pooled rate of scintiscan changes was 60%, and the pooled

TABLE 1 | Summary of studies evaluating RFA efficacy on AFTN.

Author (references)	Study design	Mean patient age (years)	No. AFTN (AFTN/total nodules)	Electrode type	No. of sessions	Previous treatments (no. of pts)	Therapy with ATD	Nodule type	Mean initial volume (mL)	Follow-up duration (months)	Mean volume reduction rate at last follow-up	Percentage of patients with thyroid function normalization at last follow-up
Deandrea et al. (17)	Prospective	67	23/31	14-G	1	–	All	Solid/mixed	27.7	6	50.7%	24%
Baek et al. (18)	Retrospective	47	9/9	17-G and 18-G	1–4	–	2/9	Solid/mixed/cystic	14.9	6	70.7%	56%
Spiezia et al. (19)	Prospective	72.5	28/94	14-G	1–3	Surgery (9) Radioiodine (12)	All	Solid	24.5	24	79.4%	79%
Faggiano et al. (20)	Prospective	58	10/20	14-G	1	Surgery (2) Radioiodine (2)	All	Solid	13.3	12	86%	40%
Sung et al. (22)	Retrospective	43	44/44	18-G	1–6	–	5/44	Solid/mixed	18.5	6	74.5%	82%
Bernardi et al. (21)	Prospective	69	30/30	18-G	1	–	All	Solid/mixed	17.1	12	75%	50%
Cesareo et al. (23)	Prospective	51	29/29	18-G	1	–	None	Solid	5 (A) 18 (B)	24	84% (A) 68% (B)	86% (A) 45% (B)
Dobnig and Amrein (24)	Prospective	52	32/277	18-G	1	–	17/32	Solid/mixed	Not specified for AFTN	3–12	N/A	84.3%

*Nodule volume (V) and Volume reduction (Vreduction) were calculated by the following formulas: $V = \pi abc/6$ (where V is the volume, a is the maximum diameter, and b and c are the other two perpendicular diameters) and Vreduction = (initial–finalV/initialV) * 100. Thyroid function normalization was defined as TSH normalization (within reference ranges) without anti-thyroid drugs.*
(A) is for small AFTN group; (B) is for medium size AFTN group; N/A is for not applicable.

volume reduction at 1 year was 79%. Interestingly, also in this metanalysis baseline nodule volume was associated with the rate of TSH normalization.

Comparison Between Radiofrequency Ablation and the Other Techniques for the Treatment of AFTN

Only a few studies comparing RFA to surgery or to radioiodine have been published so far. In addition, the studies comparing RFA to surgery either included AFTN together with non-functioning nodules (26–28), or did not specify the functional status of the nodules (29). In the first study comparing RFA to surgery (hemithyroidectomy) (26), there were no differences between the techniques in terms of improvement of nodule-related symptoms and cosmetic concerns, while RFA was significantly less effective than surgery in terms of thyroid function normalization in the subgroup of patients with AFTN. Surgery was not as well tolerated as RFA, and the cost of one session of RFA was €1,661.50 as compared to conventional hemithyroidectomy whose cost was €4,556.30 and short-stay hemithyroidectomy whose cost was €4,139.40, which is consistent with the costs reported by other Authors (30). In 2017, the same group conducted a telephone survey in 115 patients treated with RFA and 68 patients treated with hemithyroidectomy to enquire about their satisfaction after 12 months from either procedure. While in the subgroup of patients with non-functioning nodules these techniques did not differ, in the subgroup of patients with AFTN, RFA was not as fully satisfactory as surgery in terms of resolution of nodule-related symptoms (27).

As mentioned above, other groups have compared RFA to surgery. In particular, Che et al. (28) reported that RFA had lower postoperative medication use, lower hypothyroidism, and lower complication rate than surgery. Nevertheless, this is a study where both lobectomy and total thyroidectomy were included in the surgery group, which might not be the appropriate comparison group for RFA, given that the ideal candidate of RFA is a patient with a single benign thyroid nodule (31), who should be generally treated with lobectomy (and not thyroidectomy). In the study of Yue et al., where RFA was compared to lobectomy, the Authors found that RFA was associated with a significantly better health-related quality of life (HRQoL) scores in terms of mental general health, vitality, and mental health after 6 months from the treatment. Nevertheless, it has to be taken into account that surgery requires at least 1 year for a full recovery. On the other hand, RFA was found more expensive than surgery, possibly because all patients were hospitalized (29).

Traditionally, radioiodine is the main alternative to surgery for AFTN treatment, due to its efficacy and low cost (32). So far, only one study has compared RFA to radioiodine in AFTN (33). In this retrospective study, nodule volume was reduced by 76% after 12 months from RFA, and by 68% after 12 months from radioiodine. Interestingly, euthyroidism restoration was achieved in 90.9% of patients with RFA and 72% of patients with radioiodine. These percentages of thyroid function normalization are higher than those reported by other authors (21). This could be ascribed—at least in part—to the baseline volume of the nodules (23), which was 14 mL.

Besides RFA, the ultrasound-guided technique that has been recently used for AFTN is laser ablation (34). Although there are no studies comparing RFA to laser ablation in terms of AFTN management, the direct comparison of the two techniques has been the focus of recent studies reaching different conclusions (35–39). In this context, the only randomized clinical trial comparing RFA to laser ablation showed that technique efficacy was achieved in 86.7% of patients treated with RFA as compared to 66.7% of patients treated with laser ablation, and that RFA was associated with a significantly greater nodule volume reduction after 6 months from the procedure (38).

Consensus Statements and Guidelines on the Use of Radiofrequency Ablation for the Treatment of AFTN

The first recommendations on RFA for treating benign thyroid nodules were released by the Korean Society of Radiology in 2012. In these recommendations, the indications to RFA included symptoms, cosmetic concerns, and thyrotoxicosis due to a benign thyroid nodule (9). A few years later, in 2015, a panel of several Italian scientific societies advised the use of RFA in case of either large non-functioning benign thyroid nodules or AFTN, when surgery and radioiodine were contraindicated or declined (10). Interestingly, in this consensus statement, the Authors put forward the potential usefulness of combining RFA with radioiodine for the treatment of large toxic goiters, based on the promising results obtained combining laser therapy with radioiodine (40), as this would increase nodule volume shrinkage and allow for a reduction of the radioiodine dose.

Then, in 2016, the AACE updated its guidelines on thyroid nodule and it included RFA as a treatment option for solid or complex nodules that progressively enlarged, were symptomatic, or caused cosmetic concern (8). Likewise, also the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) produced a set of recommendations on the use of ultrasound-guided procedures, highlighting the concept that RFA should be considered as an alternative to surgery or radioiodine for symptomatic benign thyroid nodules (41).

It is only recently that consensus statements and guidelines have differentiated the indications to RFA between patients with non-functioning nodules and patients with AFTN, suggesting that RFA should be a first-line option for non-functioning nodules and a second-line option for AFTN. In particular, in the last revision of the Korean Society of Radiology recommendations (11), benign thyroid nodules causing local symptoms or cosmetic concerns were considered as a strong recommendation to the procedure, while AFTN only a weak recommendation. In addition, this guideline differentiated the number of cytology reports of benignity requested prior to the procedure, because in case of non-functioning nodules the panel recommended two benign cytology reports, while in case of AFTN only one report, due to the fact that AFTN are generally considered benign lesions (6). However, given that AFTN show a

wide morphologic spectrum of follicular neoplasms (42) and they may fall into the cytological category of indeterminate/follicular lesions, it remains to be clarified if, in such case, they can be equally treated with RFA. Recently, the Italian Minimally-Invasive Treatment of the Thyroid (MITT) group has produced a consensus statement, which is in line with the 2017 Korean guidelines. In particular, in case of AFTN, before the procedure it is required only one cytology report of benignity. In addition, RFA can be proposed as a first-line treatment for non-functioning thyroid nodules, while in case of AFTN it represents only a therapeutic option when conventional treatments are refused or contraindicated. Moreover, as compared to the Korean guidelines, the MITT group consensus statement has introduced the concept that, when advising patients, it is important to consider that the best responses have been observed in small size AFTN, and that the highest probability of symptom resolution and thyroid function normalization is when the nodule is reduced by 80% (43).

DISCUSSION/CONCLUSIONS

In conclusion, the literature shows that RFA normalizes thyroid function in 45–50% of medium size AFTN and in more than 80% of small size AFTN. This is associated with a significant nodule volume reduction after 24 months from the treatment, ranging from 68 to 84%. Only a few low quality studies have compared RFA to other techniques. However, if RFA does not seem to perform as well as surgery, at least in terms of symptom control in patients with AFTN, the comparison between RFA and radioiodine showed promising results.

Consistent with the available literature, current consensus statements, and guidelines support the notion that RFA effectively reduces thyroid nodule volume and improves local symptoms, while it does not always normalize thyroid function. In particular, while RFA is regarded as a first-line therapy for non-functioning benign thyroid nodules, it remains a valid second-line option for AFTN treatment in case of contraindications or unwillingness to undergo surgery or radioiodine. In addition, it has to be taken into account that AFTN are more likely to respond in terms of volume reduction and function normalization, when their baseline volume is <12 mL and when volume is reduced by at least 80% after 12 months from the treatment.

Prospective studies with larger sample sizes to evaluate RFA effects and randomized controlled trials comparing RFA to surgery and radioiodine are needed to confirm and improve our current understanding of RFA on AFTN.

AUTHOR CONTRIBUTIONS

RC, SB, AP contributed to conception and design of the review and carried out an independent comprehensive literature search. RC, AP, VP, SM, PT, FS, BF, and SB wrote the first draft of the manuscript, wrote sections of the manuscript, contributed to manuscript revision, and approved it for publication.

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A Novel Strategy for Single-Session Ultrasound-Guided Radiofrequency Ablation of Large Benign Thyroid Nodules: A Pilot Cohort Study

Zhicheng Yao[1†], Tao Wu[2†], Bowen Zheng[2], Lei Tan[2], Yufan Lian[2], Bo Liu[1] and Jie Ren[2*]*

[1] Department of General Surgery, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2] Department of Interventional Ultrasound, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

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Loredana Pagano,
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***Correspondence:**
Bo Liu
jakeliubo@qq.com
Jie Ren
renjieguangzhou@126.com

[†] These authors have contributed equally to this work

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Background: Ultrasound-guided radiofrequency ablation (RFA) of thyroid nodules (TNs) is a minimally invasive procedure that has been widely used to induce volume reduction in symptomatic solid benign TNs. The goal of this study was to investigate a novel therapeutic approach for single-session ablation of large thyroid nodules (LTNs, vol > 20 ml).

Methods: We performed a pilot cohort study of 21 patients with symptomatic solid benign LTNs (vol > 20 ml), who accepted ultrasound-guided RFA treatment between September 2018 and November 2019. RFA was performed using an 18-gauge internally cooled electrode with ultrasonographic guidance in a single session combined with intraoperative hydrodissection and immediate contrast-enhanced ultrasound (CEUS) to optimize safety and efficacy. Nodule volume was evaluated before ablation and at 1, 3, and 6 months after initial ablation, and all patients were asked to assess the cosmetic score (from 1 to 4) and symptom score (from 0 to 10) before ablation and at every follow-up after ablation.

Results: At the 6 month follow-up, there was significant nodule volume reduction, from 27.49 ml ± 7.9 (standard deviation) to 3.82 ml ± 5.02 ($p = 0.001$). Cosmetic signs ($p = 0.001$) and pressure symptoms ($p = 0.001$) were significantly improved. All patients underwent RFA without any major complications, and very few patients developed a change in voice (2/21). However, the changes subsided within 1 month. Almost half of the patients received an additional RFA (11/21) treatment to achieve complete ablation on the intraoperative immediate CEUS evaluation.

Conclusion: RFA is effective for treating LTNs (vol > 20 ml) and controlling clinical symptoms with a low complication rate. Patients were satisfied with cosmetic sign and pressure symptom improvement. The intraoperative hydrodissection and immediate CEUS represent a novel therapeutic approach for single-session ablation of LTNs.

Keywords: ultrasound-guided ablation, radiofrequency ablation, hydrodissection, benign thyroid nodule, CEUS (contrast-enhanced ultrasound)

INTRODUCTION

Recently, thyroid nodules (TNs) have become a more common clinical problem, with a high incidence resulting from increased use of thyroid ultrasonography (US) (1). Epidemiologic studies have shown that palpable prevalence of TNs is very high in the iodine-sufficient parts of the world, especially for women and the elderly (2, 3). Most TNs are benign, but the vast majority of palpable TNs require treatment for the compressive symptoms and for cosmetic reasons (4, 5).

Thyroid surgery is the main treatment for symptomatic TNs, but it has several drawbacks (6). Radiofrequency ablation (RFA) is a non-surgical, minimally invasive procedure that was introduced for TN treatment in 2006 and has been proven to be an effective and safe procedure for treating benign TNs by many recent studies (7, 8). Consequently, RFA has also been recommended by several mainstream guidelines, such as those of the American Association of Clinical Endocrinologists, the American College of Endocrinology, Associazione Medici Endocrinologi (AACE/ACE/AME), and the Korean Society of Thyroid Radiology (KSTR) (9, 10).

As TNs are a benign disease, the major goals of treatment are to effectively reduce TN volume, as well as to relieve the compressive symptoms, cosmetic problems, and related anxiety. According to the current literature, RFA for benign TNs can reach this goal effectively, with a volume reduction rate (VRR) from 33 to 58% after 1 month and 51 to 85% after 6 months, indicating its ability to resolve most nodule-related clinical symptoms (8, 11–14).

BTNs with a large initial volume (vol > 20 ml) rarely achieve complete ablation during only one RFA treatment session. The large nodule occupies vast space, and if situated close to vital structures, ablation difficulty is increased, even for skillful doctors. US-guided ablation for large nodules is most likely to leave some unablated residual, which can result in failure to resolve clinical symptoms (15). Then, additional ablation sessions must be performed, resulting in increased medical costs and pain to subjects. A prospective randomized controlled study has proven that single-session RFA could achieve a satisfactory clinical response in most patients, but not for those patients with a large nodule (vol > 20 ml) (16). A 4-year follow-up study showed that the complete ablation of BTNs is important for preventing regrowth after RFA (17). All recurrent nodules come from the untreated residual left by the previous RFA (18).

Therefore, a new strategy of single-session treatment for large benign TNs is needed to ensure maximal ablation without impacting safety. Two key technologies of this strategy include hydrodissection and intra-procedural contrast-enhanced ultrasound (CEUS), which not only can protect critical structures from conducted heating but also can identify the unablated portion in the same treatment session. Therefore, we combined standard RFA procedure with this strategy to treat large TNs and summarized its clinical outcomes and safety. This study aimed to provide a feasible and effective strategy to resolve the shortcomings of single-session RFA for large TNs.

METHODS

Patients

All patients were selected with the following inclusion criteria: (a) volume of the TN > 20 ml; (b) confirmation of benignancy (Bethesda Class II) with fine-needle aspiration (FNA) cytology; (c) reports of pressure symptoms or cosmetic problems; (d) anxiety about malignancy; (e) serum levels of thyroid hormone thyrotropin, platelets, blood counts, and blood coagulation tests within normal limits; and (f) patient underwent one single-session RFA treatment.

The exclusion criteria were as follows: (a) substernal nodules or nodules that were difficult to monitor during the RFA procedure; (b) nodules showing malignant features (i.e., taller than wide, speculated margin, marked hypoechoic, or microcalcifications) during US; (c) the patient underwent other treatments for the TN within 6 months before the procedure; and (d) pregnancy.

There were 21 patients with 21 nodules meeting the inclusion criteria from September 2018 to November 2019. This study population consisted of 18 females and 3 males, aged 27–68-years (mean age, 46.1-years).

Pre-treatment Assessment

Before the procedure, conventional US, US-guided FNA, CEUS, and the laboratory and clinical results were evaluated. Two radiologists (T.W. and J.R. with thyroid US experience of 10 and 18-years, respectively) performed US, US-guided FNA, and CEUS using a Logiq E9 US machine (GE Medical Systems, Milwaukee, WI, USA) equipped with a ML6-15 liner transducer with a center frequency of 7 MHz (frequency range: 2–8 MHz). The US examination included characterization of the position, size, volume, solid/cystic proportions, echogenicity, localization, internal vascularity, and peripheral flow of each nodule. The nodule volume was calculated using the equation: $V = \pi \times (a \times b \times c/6)$ (V: volume; a, b, c: three diameters of the nodule).

The machine was equipped with CEUS imaging technology. The installed contrast-specific imaging (CSI) mode was coded phase inversion (CPI) at a low mechanical index (<0.2). The contrast agent used in this study was SonoVue (Bracco, Milan, Italy), which contains sulfur hexa?uoride microbubbles. The agent was injected as an intravenous bolus of 2.4 ml into the antecubital vein, followed by a 5-ml 0.9% saline solution flush. The TNs were observed continuously for 2 min to examine the enhanced status and coagulation zone of the nodule with the hybrid contrast visualization mode.

Laboratory tests included the levels of thyroid-stimulating hormone (TSH), thyrotrophin, free triiodothyronine (FT3), and free thyroxin (FT4); a complete blood count; and a coagulation test (prothrombin time, activated partial thromboplastin time). Additionally, all patients underwent vocal cord function assessment performed by an experienced laryngologist before the ablation procedure.

We categorized symptom and cosmetic scores as defined in a previous consensus statement (10). All patients were asked to grade their neck compression discomfort on a scale ranging from 0 to 10 as a symptom score. A cosmetic score was obtained using

the following scale: (1) no palpable mass; (2) a palpable mass with no cosmetic problem; (3) a cosmetic problem on swallowing only; (4) readily visible TN.

Ablation Procedure

All RFA procedures were performed by one radiologist (J.R.) with 3-years of experience in an RFA outpatient clinic. We used an RF generator (Viva RF System®, Starmed, Gyeonggi-si, South Korea) and an internally cooled 18-gauge, 70-mm length, 7- or 10-mm active tip electrode (Star RF Electrode®, Starmed, Gyeonggi-si, South Korea). Local anesthesia with 2% lidocaine was applied to the puncture site. Under US guidance, hydrodissection technique was applied: 5% glucose and norepinephrine were mixed and injected into the surrounding thyroid capsule, which provide a safe distance (>3 mm) between needle tip and adjacent critical structures (**Figure 1**).

During the procedure, we paid special attention to the preservation of surrounding important structures to prevent significant complications. Therefore, two essential techniques, trans-isthmic or lateral cervical approach and moving-shot technique, were applied. The RFA was performed in transverse US view. Ablation was suspended when the index nodule was covered by hyperechoic zones. After that, initial treatment efficacy was evaluated by CEUS 5–10 min after RFA, until the hyperechoic zones disappeared.

When the nodule showed persistence of enhancement after treatment and viable residual tissue on CEUS, CEUS-guided additional ablation was carried out to ablate the enhanced areas, aiming to destroy as much viable residual tissue as possible, while at the same time, treatment safety was the foremost consideration. CEUS was performed again to assess unablated residual tissue after additional RFA (**Figure 2**).

During treatment, patients' vital signs were continuously monitored (19). The procedure was ended when the nodule presented prevalent devascularization with an unenhanced pattern, the patient exhibited discomfort, or the patient had a high risk of complications that not only interfered with continuation of the procedure but also endangered the patient's life.

Post-Procedural Follow-Up

Post-procedural follow-up was carried out at 1, 3, and 6 months after treatment. In each follow-up, US examination, CEUS, and thyroid serum tests were performed, symptom score and cosmetic score were evaluated, and VRR of the treated nodule was calculated based on the formula: VRR = [(initial volume − final volume) × 100%]/initial volume. During the follow-up period, any specific complaints or concerns were also recorded.

Complications and Side Effects

The major complications, minor complications, and side effects are defined by the Society of Interventional Radiology (20). Major complications are defined as events that lead to substantial morbidity and disability, increase the level of care, result in

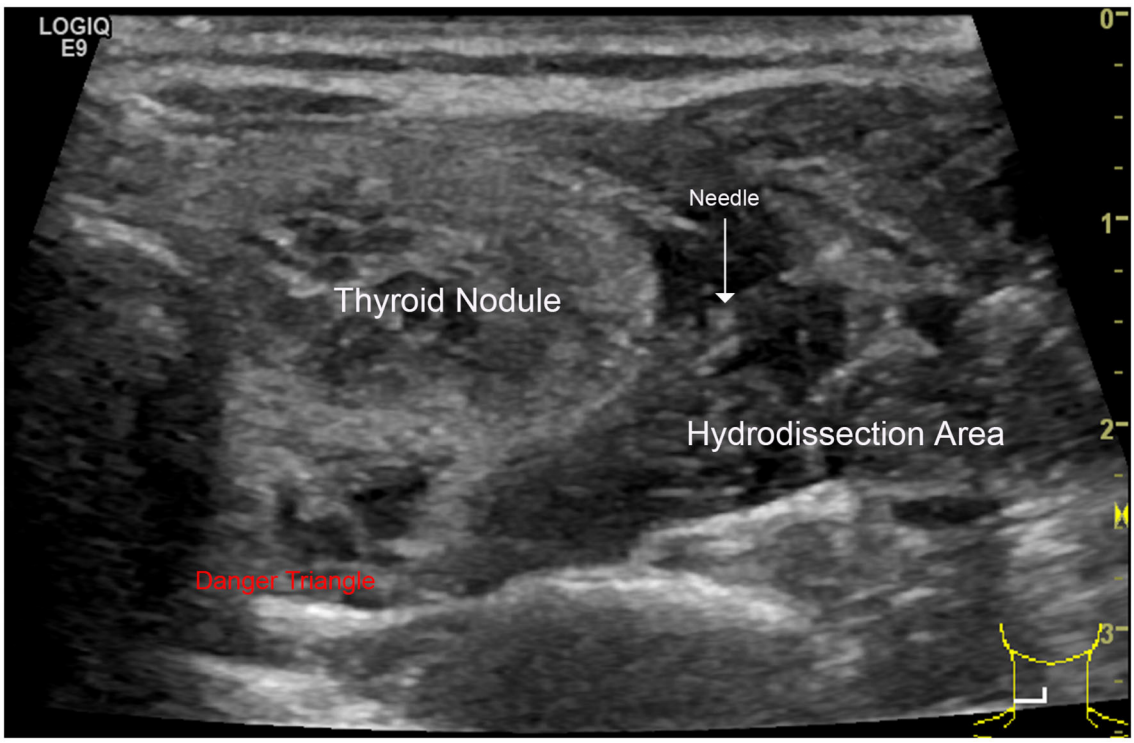

FIGURE 1 | Hydrodissection technique: this technique consists of a pressurized injection of 5% glucose between the danger triangle and the thyroid to reduce possible nerve injury caused by RFA hyperthermia.

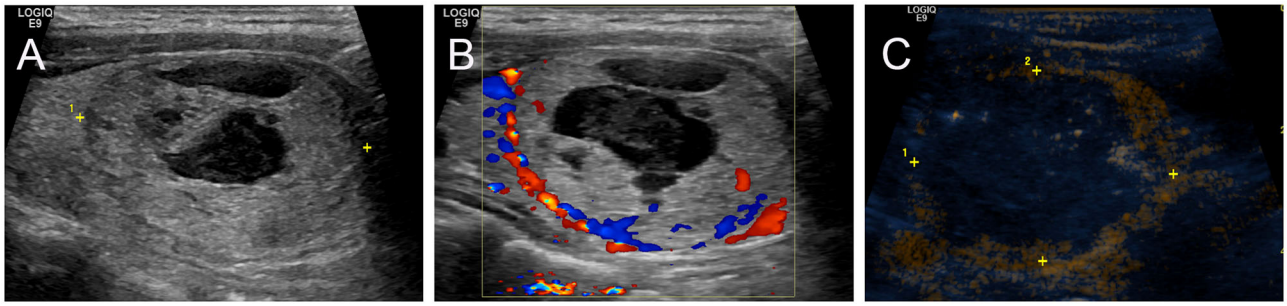

FIGURE 2 | Intraoperative CEUS evaluation: A 38-year-old female had a predominantly solid nodule in the left lobe of the thyroid. The nodule was close to the trachea, carotid artery, and danger triangle area. **(A)** US examination showed that the baseline volume of the nodule was 26.48 ml, and the largest nodule diameter was 4.3 cm. **(B)** CDU showed nodule vascularity was defined as type 1. **(C)** CEUS after initial RFA: the nodule showed non-enhancement during the phase.

TABLE 1 | Baseline characteristics of the patients and nodules.

Variable	
Number of patients	21
Number of nodules	21
Age (years)	46.05 ± 13.69
Range	27–68
Sex (male/female)	3/18
BMI (kg/m^2)	22.41 ± 3.65
Nodule position	
Left/isthmus/right	12/0/9
Mean nodule volume (ml)	27.49 ± 7.90
Range	20.36–45.72
Mean largest nodule diameter (cm)	4.88 ± 0.77
Range	4–6.9
Internal nodule component	
Predominantly solid/predominantly cyst	11/10
Echogenicity	
Hypoechoic/isoechoic/hyperechoic	1/20/0
Nodules close to dangerous structures	
Trachea (yes/no)	14/7
Carotid artery (yes/no)	13/8
Danger triangle area (yes/no)	12/9
Esophagus (yes/no)	8/13
Vagus nerve (yes/no)	5/16
Vascularity	
0/1/2/3	4/14/3/0
Peripheral flow (yes/no)	11/10
FT3 (pmol/L)	4.37 ± 0.54
FT4 (pmol/L)	13.07 ± 1.95
TSH (mIU/ml)	0.97 ± 0.60
Cosmetic score (=4/<4)	21/0
Symptom score (≥4/<4)	4/17

BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxin; TSH, thyroid-stimulating hormone.

hospital admission, or substantially lengthen the hospital stay. All other complications were considered minor complications. Side effects are defined as untoward consequences that do not require therapy or prescription medications and undesired consequences of the procedure.

TABLE 2 | Nodule treatment characteristics.

Variable	
Mean total energy deposition (kcal)	6.28 ± 3.39
Mean generator time (min)	13.88 ± 7.04
Mean ablation time (min)	61.48 ± 20.31
Additional ablation during the procedure (yes/no)	11/10

Statistical Analysis

Continuous variables were expressed as means ± standard deviations, and chi-squared tests were used to compare categorical variables. Groups were compared using the Mann–Whitney *U*-test. All statistical analyses were performed using IBM SPSS Statistics 20.0 (Armonk, NY, USA). A *p*-value of 0.05 or less was considered statistically significant.

RESULTS

Baseline Characteristics of the Patients and Nodules

The baseline characteristics of the patients and nodules are summarized in **Table 1**. The mean nodule volume of 27.49 ml corresponds to the mean largest nodule diameter of 4.88 cm. As expected, due to the large nodule volume, TNs were adjacent to at least two important structures, such as the trachea, carotid artery, danger triangle area, thyroid capsule, esophagus, and vagus nerve (**Table 1**).

Nodule Treatment Characteristics

The treatment characteristics of the nodules are presented in **Table 2**. During the procedure, initial treatment efficacy was evaluated by CEUS. Eleven of the 21 TNs underwent additional ablation in the same session.

VRR

The changes in TN volume at each follow-up are summarized in **Figure 3**. The mean VRRs of all nodules were 60.86 ± 23.25%, 74.71 ± 16.57%, and 83.41 ± 13.96% at the 1, 3, and 6 month follow-ups, respectively ($p < 0.05$) (**Figure 3**).

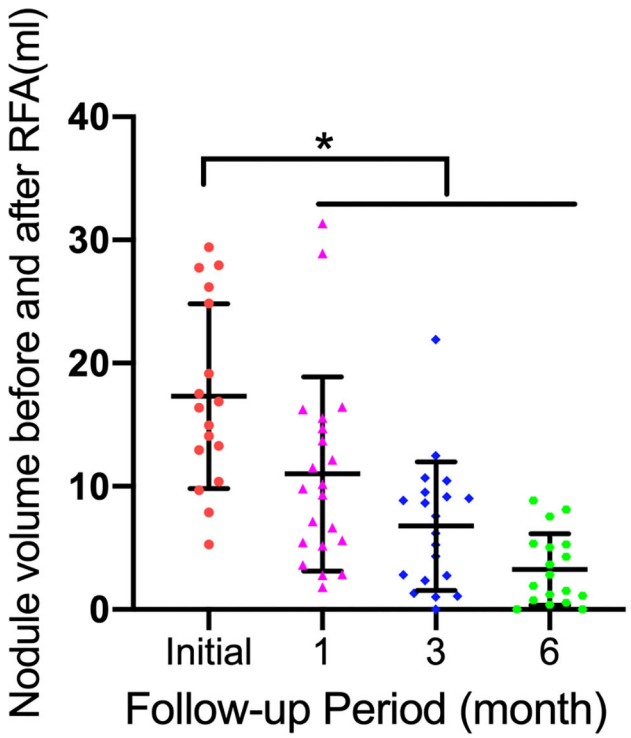

FIGURE 3 | Graphs show mean thyroid nodule volume change during follow-up (FU) and individual nodule volumes. Error bars = standard deviation; *$p < 0.05$.

Cosmetic Score and Symptom Score

Before RFA, all patients had a readily visible TN. At the 6 month follow-up, this percentage decreased to 5% ($p < 0.01$). Patients with a symptom score of ≥1 (47.6%) at baseline also decreased to 0% at the 6 month follow-up ($p < 0.01$). Patient percentages for cosmetic and symptom scores are provided in **Figure 4**.

Complications and Side Effects

Complications and side effects are summarized in **Table 3**. The overall complication rate was 9.5% (2/21). No patient experienced a life-threatening or delayed complication during follow-up.

Representative Typical Cases

A 38-year-old woman who had a 43-mm-sized predominantly solid nodule (75% solid component) complained of a foreign body sensation and neck appearance. The nodule in the left lobe of the thyroid was in contact with the lateral wall of the trachea. This patient underwent the procedure with a maximum output of 55 W. After the initial procedure, intra-operative CEUS indicated the presence of residual nodule components. We then performed

TABLE 3 | Complications and side effects after RFA.

List of complications	Number of complications
Major complication ($n = 0$)	
None	0
Minor complication ($n = 2$)	
Voice change (<1 month)	2
Side effects ($n = 5$)	
Vomiting/nausea	1
Pain	4

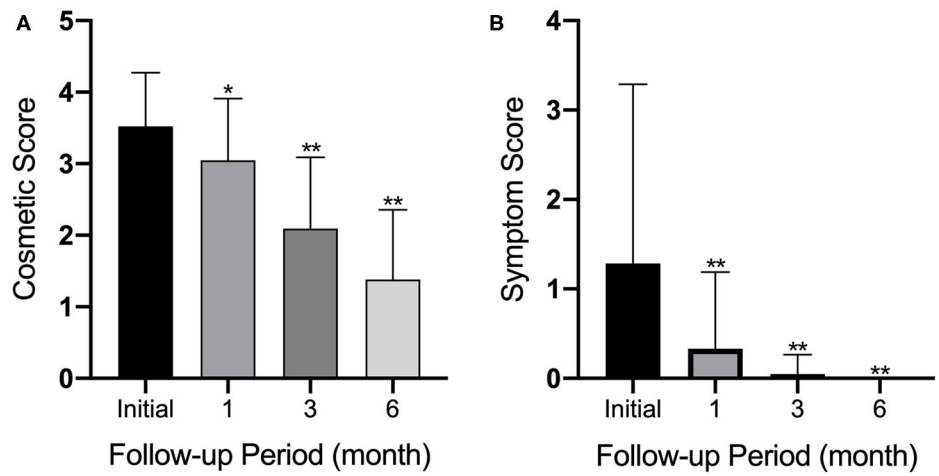

FIGURE 4 | Graphs show **(A)** cosmetic and **(B)** symptom scores at enrollment and at 1, 3, and 6 months after initial RF ablation. Error bars = standard deviation; *$p < 0.05$; **$p < 0.01$.

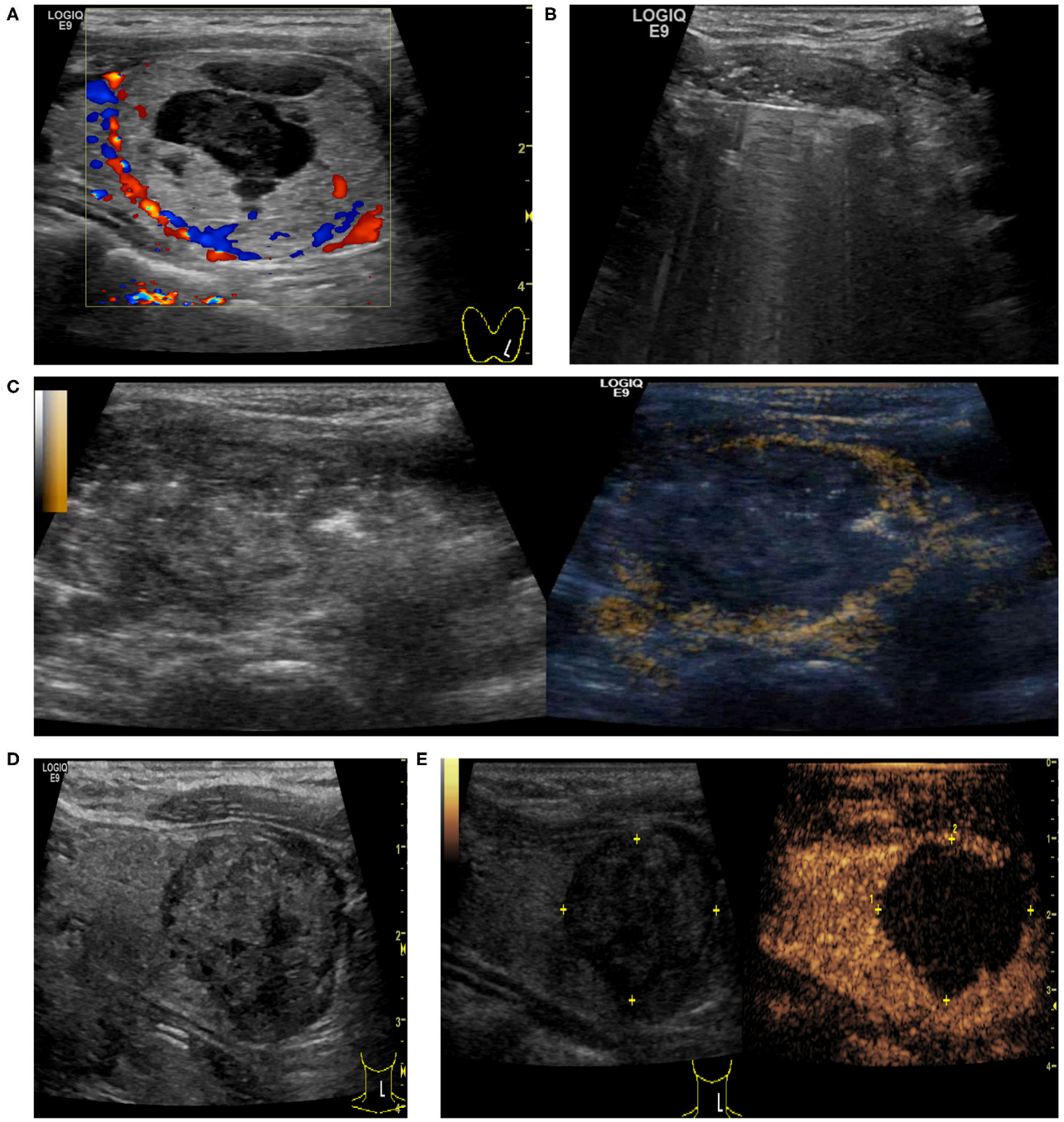

FIGURE 5 | A 38-year-old female had a predominantly solid nodule in the left lobe of the thyroid with a cosmetic score of 4. **(A)** US examination showed that the baseline volume of the nodule was 26.48 ml with the largest nodule diameter of 4.3 cm, and CDU showed nodule vascularity was defined as type 1. **(B)** Ultrasonically guided RFA of thyroid nodule was performed. **(C)** CEUS after initial RFA: some tissue showed enhancement within the nodule, indicating residual tissue. CEUS-guided additional ablation was carried out to ablate the enhanced areas. **(D,E)** At 6 months after ablation, US examination showed that the volume of the nodule decreased to 8.84 ml (the volume reduction rate was 66.6%) and there was no enhancement within the nodule on CEUS.

an additional ablation treatment to achieve complete ablation in a single session (**Figure 5**).

Finally, the initial foreign body sensation dissolved completely after 6 months of follow-up (**Figure 6**).

DISCUSSION

Recently, lots of minimally invasive treatment modalities, such as ethanol ablation (EA), percutaneous laser ablation (PLA),

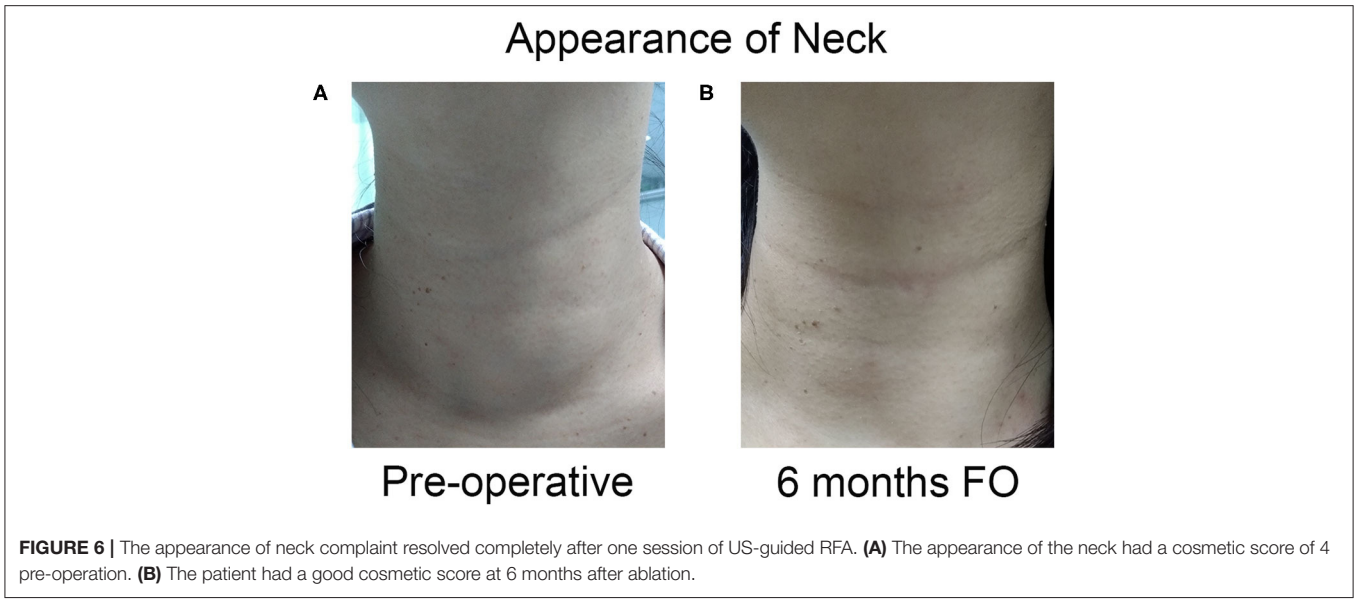

FIGURE 6 | The appearance of neck complaint resolved completely after one session of US-guided RFA. **(A)** The appearance of the neck had a cosmetic score of 4 pre-operation. **(B)** The patient had a good cosmetic score at 6 months after ablation.

microwave ablation, and RFA have proven their efficacy and safety as viable TN treatment alternatives to thyroidectomy (21–23). EA is the first-line choice for treating benign cystic nodules (4) but is less effective for solid ones (18). Compared with laser ablation, RFA has shown a superior effect in reducing benign solid TN volume (24) and has a low rate of side effects (25). Since most of the 21 nodules enrolled in this study were solid nodules, RFA was the better option according to some research and guidelines (9, 10).

Despite the fact that these minimally invasive procedures are effective and safe methods of nodule treatment, large TNs (initial volume $>$ 20 ml) consistently influence treatment efficacy and require additional ablation. Del Prete et al. (26) found that EA can be a very effective treatment for thyroid cystic nodules with a 10-year follow-up. However, for TNs with a volume $>$40 ml, a limited number of sessions (2.7 $\pm$ 0.75 sessions) should be performed in order to treat large TNs completely. Cesareo et al. (27) reported that the large nodule subgroup accepting PLA treatment can reach a 60% volume reduction that could be satisfactory, but they still cannot exclude that a second procedure may be necessary considering the large size of these nodules. Huh et al. (16) showed that single-session RFA is effective on most TNs, but for the subgroup with a mean initial volume $>$ 20 ml, additional ablation cannot be avoided if clinical symptoms are to be resolved. Frequently, this subgroup required more than one additional ablation session; in fact, some retrospective studies with long-term follow-up have found that most larger TNs underwent repeated RFA sessions, with some cases requiring as many as seven sessions (17).

Repeat ablation can cause many clinical problems and also has non-medical influence. First, the primary ablation can induce adhesions around the residual tissue, which may cause failure of local anesthesia to prevent pain as well as critical nerve injury caused by conducted heating. Second, the tissue around the residual can become so hard that it inhibits the smooth insertion of the electrode and increases the difficulty of the procedure. Third, the tissue next to the residual can become fibrotic and calcified, a sign of malignancy. These signs may confuse the decision-maker and give rise to some unsatisfactory and unwanted medical disputes, especially in China.

For large TNs, there are two factors associated with the single-session ablation strategy to avoid re-ablation. Safety is the premise of this strategy. The thyroid is a superficial and small organ located in the central neck that is adjacent to several critical structures, such as the common carotid artery, recurrent laryngeal nerve, and vagus nerve. Therefore, despite the nodule location, a large TN will inevitably be close to these vital vessel or nerves (28), and more importantly, a large TN could alter the vagus nerve location, making it closer to the nodule (29). Hereby, we introduce US-guided large volume hydrodissection as a means of protecting the critical structures during our procedure. Hydrodissection has been applied widely in various procedures and surgeries to protect the peripheral nerve (30, 31), and a study has proven the effectiveness of large volume hydrodissection strategy for orthopedics surgery (32). Our research applied continuous D5W (5% dextrose in water) injection to surround the large nodule during the procedure. We found that there were no major complications from injecting as much as 200 ml in the space of the neck, which indicates that large volume hydrodissection can be a feasible approach to protect vital nerves during RFA of large TNs.

Furthermore, incomplete ablation is a common problem for large TNs. The "moving shot" principle is recommended by KSTR guidelines (10) and is more feasible and powerful than fixed electrode techniques (33). Consequently, when multiple ablation units overlap the whole nodule, a complete ablation has occurred. However, it is difficult to avoid leaving a small margin of residual in large TNs monitored only by conventional US surveillance, because the anterior ablation unit with tiny bubble would interfere with the residual definitely. Undoubtedly, the

residual will cause regrowth. Lim et al. (17) reported that the overall regrowth rate was 5.6% (7/126) with regrowth defined as a >50% increase in nodule volume compared with the previous follow-up volume. That often means some extent of treatment failure and unsolved clinical problems.

Complete ablation of the periphery of the nodule is the most important factor to prevent marginal regrowth and avoid re-ablation. Therefore, we used intra-procedural CEUS to evaluate the initial treatment response, which facilitated quick decision-making for whether to perform additional ablation in the same session or to finish the procedure and proceed to follow-up. Recently, Zhao et al. (34) reported that some TN factors, including proximity to danger triangle area, proximity to carotid artery, and peripheral blood flow on color-Doppler US, can cause an incomplete ablation; intra-procedural CEUS can be used to avoid this incomplete ablation. Another similar study showed that CEUS could increase the single-session complete ablation rate of US-guided PLA on benign TNs (35). In our research, we found that intra-procedural CEUS can increase the detecting rate of marginal residual after the initial RFA (11/21, 52.4%); consequently, the VRR in this study of large TNs was 60.86 ± 23.25%, 74.71 ± 16.57%, and 83.41 ± 13.96% at 1, 6, and 12 month follow-ups, respectively. To our knowledge, this is a higher VRR for large TN ablation, and more importantly, no major complications occurred in this study. Recently, both Xiaoyin et al. (36) and Cui et al. (19) proved that the strategy of hydrodissection combined with intra-procedural CEUS is safe and effective for relatively large BTNs (diameter > 2 cm). Though the nodules are smaller than our research, it still supports our perspective in some extent.

There were several limitations to the current study. First, this is a retrospective study that may cause some selection bias. Additional prospective studies should be performed in the near future. Next, the case numbers enrolled in this study are relatively small, indicating a need for further research with large case series. In addition, the operator's experience can be a very important factor for the success of this strategy on large TNs, and thus, the operator's level of experience should also be evaluated carefully. Finally, this study's relatively short follow-up period may not be sufficient to assess the real efficacy of this strategy.

CONCLUSION

The strategy for single-session complete ablation of large TNs combining RFA with large volume hydrodissection and intra-procedure CEUS, as well as an additional RFA, should be performed in one session. Therefore, large TNs treated with this strategy could achieve a better outcome in terms of VRR compared with the regular method.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZY, TW, BL, and JR conceived and designed the project. BZ, LT, and YL acquired the data. TW, BZ, LT, and YL analyzed and interpreted the data. ZY and TW wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Novel Approaches for Treating Autonomously Functioning Thyroid Nodules

Pia Pace-Asciak, Jon O. Russell, Mohammad Shaear and Ralph P. Tufano *

Division of Otolaryngology-Head and Neck Surgery, Johns Hopkins University, Baltimore, MD, United States

Benign thyroid nodules are exceedingly common in the adult population. Only a small percentage of nodules are toxic or autonomously functioning thyroid nodules (AFTNs). The options clinicians have for treating the symptoms of hyperthyroidism include anti-thyroidal medications, radioactive iodine, or surgery. Depending on the patient population treated, these options may not be suitable or have inherent risks that are undesirable to the patient. On the other hand, untreated hyperthyroidism can lead to osteoporosis, atrial fibrillation, emotional lability, and neurological consequences. Thus, we present a review of two novel safe and effective approaches for treating AFTN; one surgical (transoral endoscopic thyroid surgery) and one non-surgical (radiofrequency ablation), as a means for expanding our treatment armamentarium.

Keywords: benign thyroid nodules, toxic nodules, transoral endoscopic thyroidectomy, radiofrequency ablation, hyperthyroidism

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Bernadette Biondi,
University of Naples Federico II, Italy

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Trevor Edmund Angell,
University of Southern California, United States
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Local Health Authority Naples 1 Center, Italy

****Correspondence:***
Ralph P. Tufano
rtufano@jhmi.edu

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INTRODUCTION

Benign thyroid nodules (BTNs) are generally asymptomatic but can cause symptoms due to size or autonomous function. The frequency of incidental nodules is common in the adult population and can be found on high resolution ultrasound anywhere from 19 to 68%, with a higher proportion in females and the elderly (1). Over time, about 5–10% thyroid nodules can undergo progressive development to become autonomously functioning thyroid nodules (AFTNs) and secrete an abnormally higher amount of thyroid hormone. This may be more common in iodine deficient parts of the world (2, 3). AFTN is the second most common cause of hyperthyroidism, which occur more commonly in older women as these nodules degenerate with age (2).

Accompanying symptoms of hyperthyroidism can be overt or mild depending on the severity and include anxiety, emotional lability, weakness, tremor, palpitations, heat intolerance, increased perspiration, and weight loss despite a normal or increased appetite (4). Untreated hyperthyroidism can have deleterious effects on the cardiovascular and neurologic system, while also increasing the risk of osteoporosis and fractures (3, 4).

For decades, clinicians have treated the symptoms of hyperthyroidism with anti-thyroid drugs (ATDs) such as Methimazole or Propylthioruacil, Radioactive iodine ablation (RAI), or Surgery (4). Each treatment has unique risks, and the treatment therefore should be tailored to meet the needs of the patient population being treated. ATDs are commonly used to decrease thyroid hormone production and are useful in the short term, but they are not as definitive as surgery or radioactive iodine ablation (RAI) (3). Moreover, RAI may not be suitable in young women of child-bearing age,

or patients who may not wish to endure the possibility of hypothyroidism (3). Surgery is a definitive intervention, but not all patients with AFTN are eligible for thyroid surgery or want surgery. While each of these strategies is appropriate for some patients, the inherent risks and limitations of each leave some patients seeking a more definitive option with more limited risks. In an age where there is a push towards 'personalized medicine', we review two recent advancements for the treatment of AFTN which may potentially broaden the surgical and non-surgical options for patients.

TRANSORAL ENDOSCOPIC THYROID SURGERY VESTIBULAR APPROACH

For decades, surgical resection of the affected lobe or the whole thyroid using a mid-transcervical incision has been the primary surgical approach for AFTNs. Surgery is rarely the first option offered to patients in the Western Hemisphere (3). However, surgery is recognized as a safe and definitive option for the treatment of AFTN (3). Surgical removal of an AFTN is effective in alleviating the pressure from the trachea while also normalizing thyroid function. However, surgery is not without risk, and may be elevated in older patients (5). Potential surgical complications include the presence of a life-long visible scar despite having benign disease, recurrent laryngeal nerve injury, and temporary or permanent hypocalcemia (6, 7). Additionally, thyroid lobectomy has the 5–49% chance of leading to postoperative hypothyroidism (8–11).

Novel minimally invasive techniques have emerged over the years to avoid the need for a traditional mid-cervical scar. Transoral endoscopic thyroidectomy vestibular approach (TOETVA) has gained favor because it allows remote access to the thyroid through an incision in the mucosa of the lower lip, avoiding the need for any kind of visible scar in the neck (12). Other remote access techniques include the retroauricular approach, trans-axillary technique, and bilateral axillo-breast approach (13–16). To date, none of these other approaches have become common in the West, while TOETVA is becoming relatively popular due to broad operative indications, wide eligibility and applicability for patients with benign or malignant disease, and even with a BMI greater than 30 (17–19). Although TOETVA has longer operative time when compared to the conventional open technique, patient satisfaction and cosmesis are superior with TOETVA (20, 21).

TOETVA evolved from a sublingual incision to a small incision in the oral vestibule (12, 18). In the initial series of TOETVA, Anuwong et al. found TOETVA to be safe, efficacious, with quick recovery and a superior cosmetic outcome (12). The momentum for this novel approach gained favor among international circles, and several trials have reproduced the safety and efficacy of TOETVA in Asia, Europe, and the United States (18, 22–29). When compared to open surgical approaches, TOETVA has reliably demonstrated similar rates of postoperative infection, reduced pain, safety, and a similar complication profile to open techniques (recurrent laryngeal nerve injury and hypoparathyroidism) (17, 22, 25, 26, 30)

Surgical removal of AFTN is a recognized indication for TOETVA (31). Due to the novelty of this approach and low incidence of AFTN, the data regarding resection for AFTN is limited. There are no published studies specifically looking at the outcome of TOETVA in AFTN alone; rather toxic nodules are likely grouped into 'benign thyroid disease' in the literature (23, 25, 32, 33) or TOETVA is compared to the open approach in patients with Graves disease (34). Given that one of the largest published series demonstrated a similar safety and complication rate for TOETVA compared to the traditional open approach, one can assume that the rate of success for treatment in AFTN would be similar to the open surgical open (22, 34). Luo et al. describe their case series of 204 patients; however, only one patient in their series demonstrated hyperthyroidism secondary to a secreting nodule as part of the 'benign nodule' category (35). Future studies would need to address this aspect directly.

TOETVA has been shown to be a safe approach with minimal complications. Russell et al.'s analysis of literature yielded 689 cases whereby TOETVA outcomes were evaluated, and articles using robotic or floor of mouth techniques were excluded. Of the 689 cases that underwent TOETVA, there were no published cases of RLN injury or permanent hypoparathyroidism, and only one report of a hematoma (0.1%) (32, 36). Technique-specific complications, such as mental nerve injury and related hypoesthesia, CO2 embolism, and neck infection were extremely limited, with no cases of permanent mental nerve injury or CO2 embolism and only one case of neck infection (0.1%). Given that access is through an intraoral incision, perioperative antibiotic treatment is recommended to avoid potential infection. Furthermore, surgeons should be aware of the rare but potential complication of CO2 insufflation. CO2 embolism has been reported in four other cases where other transoral techniques were employed as well (two *via* a floor of mouth technique and two *via* the transoral vestibular approach) (37–39). Finally, 683/689 (99%) cases were completed *via* TOETVA without conversion to another technique. Five cases reported excessive bleeding that could not be controlled *via* TOETVA, and one case reported excessive tumor size with evidence of pretracheal nodal metastasis (32, 36).

Other smaller technique-specific complications are related to thinning of the skin or perforation of the skin flap in three cases (0.4%) resulting in a skin burn. In terms of postoperative pain control, some reports show TOETVA to be superior compared with the open thyroidectomy, but in our experience, pain control is relatively equal (22, 32, 34, 36).

For benign thyroid disease, the benefits of TOETVA may not be limited to cosmesis alone. From a surgical point of view, the birds-eye view magnifies the operative view and gives excellent visualization of the RLN and its insertion site. This allows for access to a favorable dissection plane centrally and bilaterally, providing a view that is familiar to most endocrine surgeons (25). The magnified view also enhances visualization of the parathyroid glands, allowing for their preservation and may reduce the risk of temporary postoperative hypocalcemia that

can occur 14–40% of patients when accessing the central neck (40). Furthermore, even though the endoscopic approach affords a narrow working space, TOETVA provides a birds-eye view that enables the surgeon to have meticulous control of bleeding (12). While these theoretical benefits remain unproven, early evidence suggests that TOETVA is not inferior to the traditional surgical approach while offering improved cosmesis.

As with any new technique, there is a learning curve associated with implementing and refining the endoscopic approach which leads to longer operative times. Various authors have noted similar learning curves (22, 35, 41). As this technique becomes readily available at institutions, and surgeons become facile with this approach, it will likely become more available. There are very few barriers to adopting this technique since laparoscopic equipment is readily available at most institutions. Utilizing this novel approach adds very little extra cost making this approach accessible to motivated surgeons that wish to add TOETVA to their surgical armamentarium (42).

NON-SURGICAL APPROACH: RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is a novel minimally invasive approach that is a potential alternative to surgery for treating symptomatic benign nodules (43) as well as AFTN (44). This approach eliminates the need for a general anesthetic, an incision, radioactive iodine, or prolonged ATD treatment, making it an attractive non-surgical option. With the use of local anesthesia, the RFA probe is introduced into the midline of the anterior neck at the level of the isthmus, and the nodule is approached using the moving shot technique under ultrasound guidance (45). This causes tissue necrosis and fibrosis by introducing a high frequency alternating current, which raises tissue temperatures to 60 to 100 C (46). Over time, there is progressive shrinkage of the ablated nodule. In benign nodules, the volume of the nodule is thought to decrease between 50 and 80% for most patients, although this is operator and tumor dependent (47, 48).

RFA has been offered to patients internationally since 2000 and has been used to treat primary and metastatic tumors of the liver, lung, bone, and kidney and to ablate aberrant conduction pathways in the heart (49–53). More recently, RFA has been applied to the head and neck, particularly for thyroid nodules. While the early results have been promising internationally, there is little North American data (47, 48, 54–61). The current international recommendations for treating benign thyroid nodules include patients who are symptomatic or those who have a disfiguring goiter or a nodule that exceeds 2 cm, or if an AFTN is present (43, 44, 57). Prior to RFA treatment of AFTN, confirmation that the nodule is benign on at least one US-guided FNA or core biopsy is recommended, unless there are concerning features on ultrasound in which case two biopsies should be obtained (43, 44). Nodules that are benign on FNA but that have suspicious US features (EU-TIRADS 5), the latest European Thyroid Association Guidelines strongly recommend (moderate quality evidence) against thyroid ablation to avoid potential delay in treatment of a malignant lesion (62).

RFA has shown excellent efficacy and safety in the management of cosmesis related concerns and pressure symptoms (47, 48, 54–61, 63, 64). In a systematic review and meta-analysis of RFA in benign nodules, a pooled proportion of 2.38% for overall RFA complications was noted (95% CI: 1.42–3.34%), with 1.35% for major complications (95% CI: 0.89–1.81%) and no evidence of any life-threatening complications. The most common complaint post treatment was transient or rarely permanent voice changes (35/2,421). Nodule rupture, permanent hypothyroidism 6 months after treatment, and transient brachial plexus injury was only found in one patient out of 2,421 patients (65). Minor complications included pain during or after the procedure (16/2421), hematoma which disappeared after 1–2 weeks (25/2,421), vomiting (9/2,421), skin burns (six patients had first degree burns and 1 patient had second degree burn which recovered after a month) and transient thyroiditis (one patient three months after the treatment) (65). Furthermore, various studies have shown that the volume of a benign symptomatic thyroid nodule can be reduced by more than 50%, and up to 75–97% in long-term follow-ups (60, 66, 67).

The American Thyroid Association Guidelines outline that surgery or radioactive iodine (RAI) are effective for the treatment of AFTN (1, 3). These two options are not always acceptable for patients since RAI involves receiving radiation which is controversial in women of childbearing age, or for patients reluctant to endure the long-term risks associated with radiation (3). Additionally, both treatments have potential complications such as hypothyroidism. Even with lobectomy, surgery confers roughly a 30% chance of hypothyroidism, which is generally avoided in RFA-treated patients (10, 11, 68). RFA may gain favor with patients wishing to avoid developing hypothyroidism (55, 57, 58, 69–71).

Many trials have demonstrated the efficacy and safety of treating AFTN with RFA (55, 57, 58, 69–71). In a large multicenter trial, Sung JY et al. demonstrated improved symptoms of hyperthyroidism along with normalized TSH levels in 81.8% of study patients without the development of hypothyroidism post RFA (35, 69). In a systematic review, more than 50% of patients after RFA could discontinue their anti-hyperthyroid medications after RFA (44, 46). Additionally, patients that received RFA found significant improvement in their compressive symptoms due to the reduced nodule volume (mean volume reduction ratio, 81.7% during the mean follow-up period of 19.9 months). No major complications were reported in this trial; however, in previous trials, the most common complication reported was temporary pain (55, 57, 58, 63). Progression of hypothyroidism, if any, after treatment may be better explained by the progression of autoimmune thyroiditis associated with preexisting thyroid antibodies.

In a recent systematic review and meta-analysis, Cesareo et al. demonstrated moderate efficacy of RFA in AFTN (72). The overall rate of patients with TSH normalization or scintigraphically proven

efficacy was about 60%, with a volume reduction of 79% found 1 year later in RFA treated AFTN (72). Bernardi et al. demonstrated that 50% of patients with AFTN treated with RFA withdrew their ATD after 12 months (70), which is similar to Deandrea (55) and Faggiano (73) who reported normalized thyroid function in 40% of patients after 12 months. However, Cervelli et al. demonstrated a greater volume reduction rate of 76% with a 91% TSH normalization at 12-month follow-up in AFTN treated with RFA (74). Even though there is heterogeneity between studies, and patients were only followed for 12 months, longer follow-up is warranted as well as how to achieve a predictable response rate with discontinuation of ATD after one session of RFA. It is also possible that these findings represent technical differences in the procedure, as it may be assumed that there is a learning curve with this procedure. Nevertheless, it is apparent that, while many patients benefit in the short term, a sizeable component may need additional treatment.

The success rate of RFA is greater when the volume of the AFTN is relatively small in size. Cesareo et al. compared the reduction between medium sized nodules (18 ml) and smaller sized nodules (5 ml), euthyroidism was achieved 86% in small nodules *vs.* 45% in medium size nodules (75). Similarly, Cappelli et al. report a volume reduction rate of 73% with TSH normalization in 94% of patients treated with RFA with nodules an average of 7 ml (76). An earlier study by Lim et al. confirmed that larger nodules (>20 ml) required repeat RFA treatment compared with smaller nodules to achieve a similar volume reduction in during 4 year follow-up (77). This work has improved our understanding of how to counsel patients with AFTN.

Since the Korean Guidelines in 2012, the consensus for RFA of AFTN has evolved. In line with the Korean Guidelines, the Italian Minimally Invasive Treatment of the Thyroid (MITT) group have advised clinicians to offer RFA as first line treatment in non-functioning nodules. However for AFTN, RFA is best reserved as second line treatment in patients who refuse conventional therapy or when it is contraindicated (75, 78). RFA can be considered as primary treatment for small sized AFTN (average 5 ml) since an optimal response (symptom improvement and TSH normalization) is noted when the nodule is reduced in size by more than 80% (72, 75).

Key factors that affect the therapeutic response of RFA on AFTN have been debated. Baek et al., demonstrated the importance of nodule vascularity on ultrasound for normalization in TSH and volume reduction (67), while Bernardi et al. found the percentage of volume reduction at 12 months correlated with the therapeutic response (70). Whereas, Cesareo et al.'s work demonstrates the importance of the size of nodule prior to RFA and the volume reduction after 12 months (75).

Localization of the nodule with ultrasound is also key in determining whether partial or complete ablation can be achieved, particularly if the nodule is adjacent to the trachea or recurrent laryngeal nerve. Ideally, complete ablation is preferred to avoid nodule regrowth. The moving shot technique is the standard approach that is used in conjunction with ultrasound for real time surveillance of nearby structures (43, 45). As with any awake technique, patient comfort is key in order to avoid patient movement which could result in injury to one of the neighboring structures. Light sedation can overcome this potential risk and ease patient comfort along with local anesthetic. Finally, the proficiency of the operator is important since there is a learning curve associated with complete removal of tissue to avoid recurrence of an untreated remnant. Tracing the residual viable area of the nodule by ultrasound (usually isoechoic and on the periphery of the ablation zone) can be helpful to predict regrowth and the area to target for reablation (79).

Single-session RFA has shown significant volume and symptom reduction (43, 45, 47, 48, 55–57, 66, 70, 72, 73, 76). Progressive reduction in the volume of treated nodules occurs incrementally over time, with reports ranging from 50 to 80% after 6 months and 79 to 90% after 2 years follow-up (55, 57, 70, 72). Previous studies report a mean number of RFA treatment sessions to be 1.8–2.2 (one to six sessions) for AFTN (58, 66). Previous reports show that single session RFA allowed withdrawal of ATD in 22–57% of patients (55, 70, 72), with one report showing 100% in pre-toxic nodules and 53% in toxic nodules (57). Other reports show a reduced dose of Methimazole after RFA in 78% of patients (55). The improvement in thyroid function is seen over time after RFA treatment, with up to 57% remission 12 months after the procedure (70, 72). However, other studies have demonstrated a tendency for regrowth after 2 to 3 years follow-up in non-functioning nodules (77, 79). The number of required treatments or how often nodules require RFA treatments still needs to be determined, especially when treating AFTNs. However, the pre-treatment nodule volume seems to play a key role in volume reduction and discontinuation of ATD. Currently, the Korean Guidelines suggest that follow-up should be based on TSH post RFA treatment of the AFTN. This will determine whether the patient's antithyroidal medications can be stopped or if they require another treatment with RFA.

Imaging such as ultrasound examination and a thyroid scan with scintigraphy can also be helpful to know whether RFA was successful. Previous studies show post-treatment, scintigraphy demonstrated the majority of hot nodules (45–80%) became cold or normal, while 20.4–56% nodules had decreased uptake but still remained as hot nodules (58, 66). After treatment, evaluation *via* ultrasound should be done to ensure the absence of potential early complications from the procedure, such as an evolving hematoma, burns or damage to the thyroid capsule (62). On ultrasound, changes in the size, volume, intranodular vascularity and echogenicity are assessed (43). On ultrasound, the ablated area appears as a mildly hypoechoic and inhomogenous zone, with scattered hyperechoic spots due to tissue vaporization compared with the non-treated tissue (43, 62, 80). Color Doppler mapping of the treated areas are devoid of vascular signals (62, 80). If a patient is still symptomatic, the nodule can be assessed for persistent vascularity as a potential source for regrowth (81). The wide range of therapeutic effects of RFA may be attributed to remaining thyroid tissue left at the margin of the nodule. The best modality for detecting intranodular vascularity is

contrast-enhanced ultrasound since color-Doppler is not as sensitive to detect small vessels and slow blood flow (43). Repeat RFA can be considered after 3 months from the first treatment because the most change is seen within the first 3 months (43, 69).

Given the potential for long-term cardiovascular mortality in the setting of untreated hyperthyroidism, the need for multiple treatments for patients treated with RFA does pose a theoretical risk that must be discussed appropriately (3, 57, 58, 70, 82). As newer evidence emerges, hopefully RFA will become standard of care. However, currently the Korean guidelines as well as the Italian MITT group discussed above take a more cautious tone when discussing the role of RFA in managing AFTN (43).

CONCLUSION

AFTN are benign nodules with multiple treatment options. TOETVA and RFA are two novel treatments that may be safe and effective in the treatment of symptomatic benign thyroid nodules and could be applied to AFTN. TOETVA offers a surgical approach with the removal of the thyroid gland which avoids a cervical scar and is definitive, whereas RFA offers a non-surgical approach for patients who wish to avoid surgery altogether or are poor surgical candidates. Because there is risk associated with multiple rounds of treatment, it may not be appropriate for all patients and international guidelines suggest exercising caution (43). Each of these approaches may be appropriate in the right clinical setting.

AUTHOR CONTRIBUTIONS

PP-A reviewed the literature and wrote the paper. JR was involved with the writing and editing as well as the key concepts behind the paper. MS was involved with reviewing/editing the paper. RT was involved with editing as well as the key concepts behind the paper. All authors contributed to the article and approved the submitted version.

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Image-Guided Thermal Ablation as an Alternative to Surgery for Papillary Thyroid Microcarcinoma: Preliminary Results of an Italian Experience

Giovanni Mauri[1,2], Franco Orsi[2], Serena Carriero[3], Paolo Della Vigna[2], Elvio De Fiori[4], Dario Monzani[1,5], Gabriella Pravettoni[1,5], Enrica Grosso[6], Marco F. Manzoni[6], Mohssen Ansarin[6] and Gioacchino Giugliano[6]*

[1] Dipartimento di Oncologia ed Emato-Oncologia, Università degli Studi di Milano, Milan, Italy, [2] Divisione di Radiologia interventistica, Istituto Europeo di Oncologia, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Milan, Italy, [3] Scuola di Specializzazione in Radiodiagnostica, Università degli Studi di Milano, Milan, Italy, [4] Unità di Radiologia Clinico Diagnostica, Istituto Europeo di Oncologia, IRCCS, Milan, Italy, [5] Divisione di Psiconcologia, Istituto Europeo di Oncologia, IRCCS, Milan, Italy, [6] Divisione di Otorinolaringoiatria e Chirurgia Cervico Facciale, Istituto Europeo di Oncologia, IRCCS, Milan, Italy

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***Correspondence:**
Serena Carriero
serena.carriero@gmail.com

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Purpose: To report the results of our preliminary experience in treating patients with papillary thyroid microcarcinoma (PTMC) with image-guided thermal ablation, in particular estimating the feasibility, safety and short-term efficacy.

Materials and Methods: From 2018 patients with cytologically proven PTMC < 10 mm were discussed in a multidisciplinary team and evaluated for feasibility of image-guided thermal ablation. In case of technical feasibility, the three possible alternatives (i.e., image-guided thermal ablation, surgery, and active surveillance) were discussed with patients. Patients who agreed to be treated with image guided thermal ablation underwent radiofrequency (RFA) or laser ablation under local anesthesia and conscious sedation. Treatment feasibility, technical success, technique efficacy, change in thyroid function tests, side effects, minor and major complications, patients satisfaction and pain/discomfort perception during and after treatment, and disease recurrence during follow-up were recorded.

Results: A total of 13 patients were evaluated, and 11/13 (84.6%) patients (9 female, 2 male, mean age 49.3 ± 8.7 years) resulted suitable for image-guided thermal ablation. All 11 patients agreed to be treated with image-guided thermal ablation. In addition, 3/11 (27.3%) were treated with laser ablation and 8/11 (72.7%) with RFA. All procedures were completed as preoperatively planned (technical success 100%). Technique efficacy was achieved in all 11/11 (100%) cases. Ablated volume significantly reduced from 0.87 ± 0.67 ml at first follow-up to 0.17 ± 0.36 at last follow-up ($p = 0.003$). No change in thyroid function tests occurred. No minor or major complications occurred. All patients graded 10 the satisfaction for the treatment, and mean pain after the procedure was reported as

1.4 ± 1.7, and mean pain after the procedure as 1.2 ± 1.1 At a median follow-up of 10.2 months (range 1.5–12 months), no local recurrence or distant metastases were found.

Conclusions: Image guided thermal ablations appear to be feasible and safe in the treatment of PTMC. These techniques hold the potential to offer patients a minimally invasive curative alternative to surgical resection or active surveillance. These techniques appear to be largely preferred by patients.

Keywords: papillary thyroid microcarcinoma, radiofrequency ablation, laser ablation, thermal ablation, complications, recurrence, thyroidectomy

INTRODUCTION

Thyroid cancer is the most common malignant neoplasm of the endocrine system, representing the 3.1% of all cancers (1). In the last three decades, its incidence has increased worldwide due to the real increase onset and mostly to the increased detection (2). The most common malignancies arising in the thyroid gland are differentiated thyroid cancers, deriving from follicular cells. They include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) (3). PTC is the most common subtype of thyroid malignancy accounting for 85% of thyroid cancer (4). The 50% of PTC is papillary thyroid microcarcinoma (PTMC), defined, according to the World Health Organization Classification of Thyroid Tumors, as a PTC less than 10 mm in maximum diameter (5). Most of these tumors remain clinically silent, have a bright prognosis, and a disease-specific mortality under 1% (2, 6).

Surgery is recommended as the first line-treatment for PTMC by current guidelines, the standard treatment modality being lobectomy (3, 7). However, surgery has some drawbacks, such as potential recurrent laryngeal nerve paralysis, hypothyroidism, hypoparathyroidism, need for lifelong medication, scarring, and risks connected with general anesthesia (6, 8). Moreover, it is not suitable for all patients because there are some ineligible patient due to systemic diseases, or others that refuse surgery (9, 10). Another therapeutic option, recommended by the American Thyroid Association, is active surveillance. Nevertheless, there is a low-risk of disease progression with this strategy (2%–6%) and this option is sometimes not well accepted by some patients (6, 9). Ito et al. analyzing data of 1,253 patients with PTMC under active surveillance, found that no one died or had distant metastasis during the observation period which ranged from 1.5 to 19 year (11). However, 58 (4.6%) had size enlargement, 19 (1.5%) had appearance of lymph-node metastasis, and 43 (3.5%) showed progression to clinical disease. Thus, patients with disease progression under active surveillance might require a much more aggressive surgical management than at the moment of the initial diagnosis.

Image-guided thermal ablations have been successfully applied in the treatment of several type of tumors, and have been recently proposed as a potential alternative to surgery also in patients with thyroid diseases (4, 12–14). These minimally invasive treatments, compared to surgical treatment have similar efficacy, fewer complications, better quality of life, and better cosmetic outcomes (15–17). These procedures allow precise delivery of the heat locally to the lesion, sparing the surrounding thyroid tissue, and thus minimizing the invasiveness of the treatment and the impact on thyroid function. However, even if first application of image-guided thermal ablations to treat a patient with PTMC has been reported in Italy in 2011 (18), experiences in literature are still limited, the majority of series having been reported by Chinese groups. At our center, we started to propose image-guided thermal ablation as a potential therapeutic option to patients with PTMC from 2018. Thus, this study aimed to report the results of our preliminary experience in treating patients with PTMC with image-guided thermal ablation, in particular estimating the feasibility, safety and short-term efficacy.

MATERIALS AND METHODS

Our Institutional Review Board approved this retrospective study. Patients included in this study provided written consent for anonymized data usage for research purpose. Institutional Review Board accepts this consent as informed consent for the present study.

Data of patients treated with image-guided thermal ablation for PTMC was retrieved from our prospectively collected database. All cases were discussed in our internal multidisciplinary tumor board. Image-guided thermal ablation was considered as a therapeutic option in patient with a single cytologically confirmed PTMC measuring <10 mm, with no contact with the thyroid capsule, and no ultrasound evidence of metastatic disease in the neck. All possible options, including image-guided thermal ablation, surgery or active surveillance were carefully discussed with the patient before treatment choice. Before treatment, a careful analysis by the interventional radiologist performing ablation was performed, evaluating the feasibility of the treatment, and the best path and technique for treating the patient. Exclusion criteria for image-guided thermal ablation were patients with clinically apparent multicentricity confirmed by ultrasound, with other type of thyroid malignancies, with cervical or distant metastasis revealed by ultrasound or other image techniques, with family history of thyroid cancer and/or history of radiation therapy, with contralateral vocal cord dysfunction, or with blood coagulation disorders.

Ablation Technique

All procedures were performed with ultrasound (US) guidance under local anesthesia and conscious sedation. In all cases, a

preoperative US evaluation was performed, to assess the nodule size and shape, proximity with critical structures, and to establish the best path to the target nodule. In case the nodule is located close to the periphery of the gland, or in a critical area, hydrodissection with the injection of sterile water was performed through a 21G needle. Contrast-enhanced US (CEUS) was always performed before ablation to assess nodule vascularization. At the end of the ablation CEUS was performed in order to immediately evaluate the result of the ablation. At our center, both radiofrequency ablation (RFA) and laser ablation are available for thyroid interventions. Decision of the best technique to be used is taken on a case by case basis by the interventional radiologist performing the procedure. For laser ablation one or two 21G introducer needles (depending from nodule size and shape) were inserted into the target nodule. Subsequently, a 300 micron quartz bare optic fiber was introduced into each introducer needle that was subsequently slightly withdrawn to expose the distal portion of the fiber. The optic fibers were connected to a multi-source laser system operating at 1.064 nm (EchoLaser X4, Elesta srl, Calenzano, Italy). A support planning tool device (ESI, Echolaser Smart Interface, Elesta srl, Calenzano, Italy), can be connected to a general US scanner and used for treatment planning. A fix power protocol (3 watts) was used, changing application time case by case, in order to maintain the power of each single application between 1,200 and 1,800 Joules.

For RFA an internally cooled, 18G electrode available with and 0.5 to 1.5-cm active tip (RFT-RFTS, RF Medical, Seoul, South Korea) was used. The free-hand technique was applied in all cases. Short ablations were performed with 30–50 watts power and eventually the electrode was repositioned in a different area in order to cover with subsequent ablations the entire volume of the target.

Two cases of patients treated with RFA and laser ablation for a PTMC are shown in **Figures 1** and **2**.

Study Endpoints

Treatment feasibility, technical success, technique efficacy, change in thyroid function tests, change in ablated area volume, side effects, minor and major complications, disease recurrence during follow-up and patients' satisfaction and pain/discomfort during and after procedure were recorded. Standard definitions and reporting criteria were followed (19, 20).

Particularly, technical success was defined as the ability to complete the treatment that was preoperatively planned.

Technique efficacy was evaluated with US and CEUS at 6 weeks from the treatment.

Patients are followed with serum test evaluation of thyroid function, US and CEUS at 6 weeks, 6 months, and 12 months after treatment.

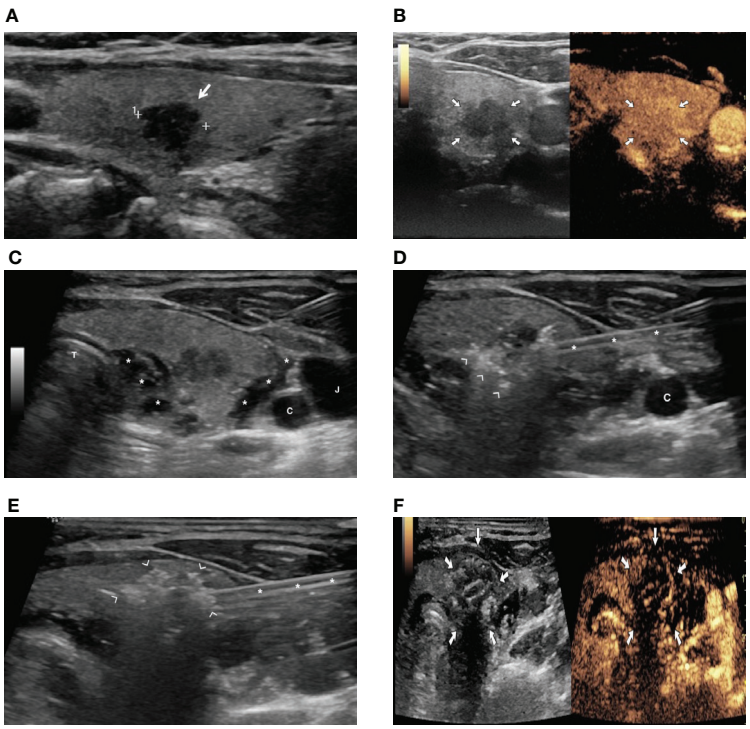

FIGURE 1 | A patient with a PTMC treated with image-guided radiofrequency (RFA) ablation. **(A)** US image showing an 8-mm hypoechoic nodule in the right thyroid lobe (arrow). **(B)** Preoperative contrast-enhanced US demonstrating vascularization of thyroid lesion (arrows). **(C)** Hydrodissection with injection of 5% glucose solution (asterisks) to achieve separation of thyroid from vessels (C, carotid artery; J, jugular vein) and trachea (T). **(D)** Hyperechoic foci (arrowhead) due to gas formation during ablation around the thyroid nodule (asterisks = radiofrequency electrode). **(E)** Hyperechoic area (arrowhead) due to gas formation encompassing the whole thyroid nodule at the end of the ablation (asterisks = radiofrequency electrode). **(F)** Contrast-enhanced US image at the end of ablation, demonstrating lack of enhancement in the ablated area (arrows).

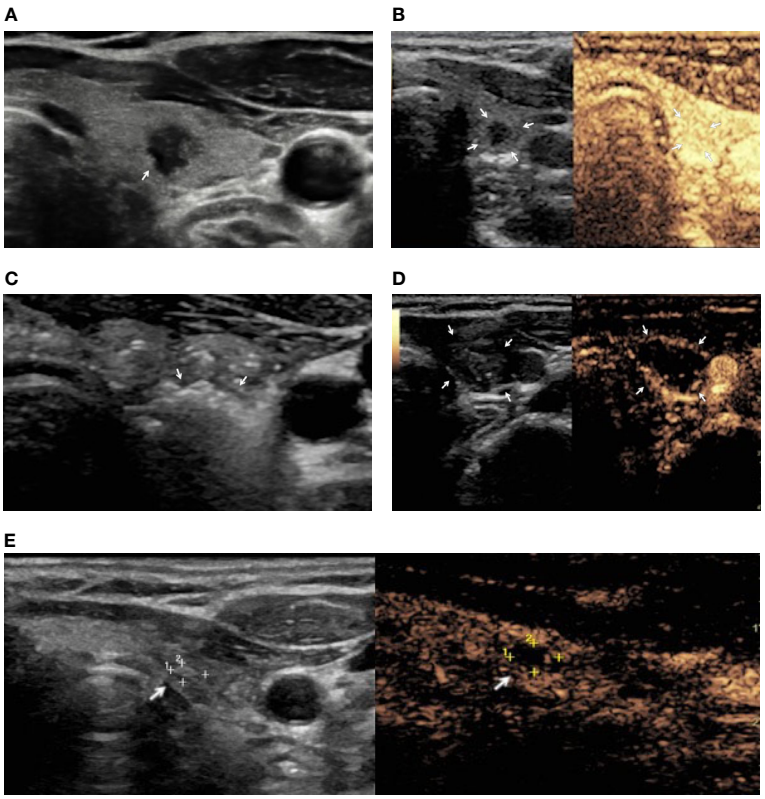

FIGURE 2 | A female patient with PTMC treated with image-guided laser ablation. **(A)** US image demonstrating a 6 mm hypoechoic nodule with irregular margins (arrow). **(B)** Preoperative contrast US image demonstrating vascularization of thyroid lesion (arrows). **(C)** Hyperechoic areas (arrows) resulting from tissue heating and vaporization observed during laser ablation. **(D)** Contrast-enhanced US after ablation showing lack of enhancement in the treated area (arrows). **(E)** Nine-month follow-up: US image showing the residual ablated area decreased in size (arrow) and contrast-enhanced US demonstrating lack of enhancement in the ablation area (arrow).

Patients were contacted by phone and were asked to grade on a scale from zero to ten the overall satisfaction regarding the procedure, the pain/discomfort perceived during the procedure and the pain/discomfort after the procedure.

RESULTS

A total of 13 patients were discussed for potential image-guided thermal ablation from 2018 and send to the interventional radiologist for evaluation of feasibility of the procedure. At the US examination, 2 cases demonstrated contact or invasion of the thyroid capsule, and so finally 11/13 (84.6%) patients (9 female, 2 male, mean age 49.3 ± 8.7 years) resulted suitable for image-guided thermal ablation. Patients' characteristics are shown in **Table 1**. After discussion of all the three possible alternatives (i.e., image-guided thermal ablation, surgery, and active surveillance), all 11 patients agreed to be treated with image-guided thermal ablation. All patients had normal thyroid function before treatment.

Of the 11 tumors treated, 3 (27.3%) were treated with laser ablation and 8 (72.7%) with RFA. All procedures were completed as preoperatively planned (technical success 100%). Technique efficacy was achieved in all 11/11 (100%) cases at 6 weeks control. 2/11 (18.1%) patients experienced a transient dysphonia beginning immediately after the local anesthetic injection around the thyroid capsule, before the ablation, that resolved few hours after treatment. 3/11 (27.3%) patients experienced mild discomfort and pain immediately after the procedure, which resolved in few days with only use of painkillers, and were regarded as side effects (19). No minor or major complications occurred. At a median follow-up of 10.2 months (range 1.5–12 months), no local recurrence or distant metastases were found. No change in thyroid function tests occurred. Ablated volume significantly reduced from 0.87 ± 0.67 ml at first follow-up to 0.17 ± 0.36 at last follow-up ($p = 0.003$). All patients graded 10 the satisfaction for the treatment, and mean pain after the procedure was reported as 1.4 ± 1.7, and mean pain after the procedure as 1.2 ± 1.1 (mean ± standard deviation).

DISCUSSION

The results of our preliminary experience show that image-guided thermal ablation can be safely applied in the treatment of PTMC, offering a potentially curative, minimally invasive treatment to patients in alternative to surgical resection or active surveillance.

Image-guided thermal ablations have been introduced in the treatment of cancer as an alternative to surgery in patients not

TABLE 1 | Characteristics of 11 patients with papillary thyroid microcarcinoma treated with image-guided thermal ablation.

Sex (Male/Female)	2/9
Age (years)	49.3 ± 8.7*
RCP cytology class (n)	
Thy 4	5
Thy 5	6
Nodule max diameter (mm)	7.9 ± 1.3*
Nodule volume (ml)	0.34 ± 0.51*
Power (Joules)	7,560 ± 3,786*
Ablation time (min)	5 ± 3.1*
Ablation volume at 1st FU	0.87 ± 0.67*
Ablation volume at last FU	0.17 ± 0.36*
Mean patient satisfaction (n)#	10 ± 0*
Mean pain during ablation (n)#	1.4 ± 1.7*
Mean pain after ablation (n)#	1.2 ± 1.1*

**mean ± standard deviation; #on a scale from 0 to 10; RCP, Royal College of Patologists; FU, follow-up.*

suitable for surgical treatment several years ago (21, 22). Nowadays, indications have expanded, and image guided thermal ablations are applied in the treatment of a large variety of cancers (23–28), and in some cases represent the first suggested therapeutic option instead of surgery, as for the treatment of small hepatocellular carcinoma (29). Deriving from experience in other organs, and thanks to technological advancements with the creation of small dedicated ablative devices, image-guided thermal ablations have been applied also to the treatment of thyroid disease (30–35). Initially, image-guided thermal ablations have been used in the treatment of benign thyroid nodules, and then their use have been expanded to thyroid cancers not suitable for surgery and even metastatic disease (34, 36–40). Thus, in the large debate regarding the best management of indolent PTMC, were imaging derived overdiagnosis can drive a not negligible overtreatment, image-guided thermal ablations have been introduced with the rationale of providing a curative treatment to patients minimizing the invasiveness of treatment itself (41–44). Some series have been reported, mainly from Chinese and Korean authors, on the application of image guided thermal ablations in the treatment of PTMC with favorable results (45–47).

In our center, we included image-guided thermal ablation among the possible treatment option for PTMC starting from 2018. In our experience, 84.6% of patients sent for feasibility evaluation resulted finally suitable for treatment. This highlight the critical relevance of an accurate US evaluation before treatment, as selection of proper patient is of paramount importance for a successful procedure. Furthermore, of the suitable 11 patients, all agreed to be treated with image-guided thermal ablation over surgery or active surveillance. This highlights the potential impact of this technique for patients, which seems to prefer a treatment over active surveillance and is favorable to a minimally invasive approach. By taking into account results of a previous study assessing patient satisfaction for RFA or surgery for benign thyroid nodules (17), we might speculate that image-guided thermal would be preferred over surgery because of its lower invasiveness and higher cosmetic results. Simultaneously, ablation could be preferred over active surveillance because of anxiety and negative emotion likely related with receiving a cancer diagnosis without receiving active treatment and thus living with untreated cancer (48, 49). However, future research is essential to further assess patient preferences for image-guided thermal ablation, surgery, and active surveillance and identify main treatment attributes (e.g., clinical outcomes, aesthetic aspects, expected QoL, invasiveness, etc.) that might explain patient preferences for ablation over other therapeutic options for PTMC. Assessing patient's perceptions and preferences for available treatments is becoming every day more important in decision making in oncology. Specifically, in recent years, there has been a shift toward a more patient-centered care and a growing emphasis on the relevance of involving patients in the clinical decision-making (50–53), as well in the evaluation of competing treatment options or health interventions (54, 55). For example, as highlighted by the P5 medicine approach (56, 57), each patient has a peculiar set of psychological and cognitive factors, such as preferences and needs and, as well as hopes, fear, beliefs and cognitive dispositions. The effective consideration of this psychological uniqueness and its integration with biological and clinical information is crucial to empower cancer patients and support their involvement in the clinical decision-making process as active decision-makers instead of merely passive recipients. Finally, the P5 medicine approach underlines the relevance of informing patients about all the available treatments in order to foster their participation in the treatment decision-making process. Thus, future efforts might be required to develop supportive and reliable tools that, such as patient decision aids (58, 59), provide patients with evidence-based health information about main therapies for PTMC.

From a clinical perspective, image-guided thermal ablation resulted feasible in all the selected cases, with a technical success of 100%. Also, no major or minor complications occurred in our experiences, while only a small percentage of patients referred side effects, which were mainly mild discomfort or pain after the procedure. This could be explained also with the large application of adjunctive procedures such as hydrodissection in our experience, which are crucial to preserve the surrounding structures, minimize the potential complications, and allow for an adequate safety margin for ablation (60–62). Immediate dysphonia after injection of local anesthesia around the thyroid capsule, can be due to the transient anesthesia of the recurrent laryngeal nerve, and is not regarded as a complication of the thermal ablation. Notably, no patients had change in their thyroid function after image-guided thermal ablation. Finally, during follow-up, no evidence of recurrence or disease progression was found in our patients. In a recent meta-analysis, thermal ablation techniques have shown efficacy in the treatment of PTMC, as noted by the pooled proportion of disappearance, the recurrence, and the volume reduction rate of PTMC which have been respectively of 57.6%, 0.4%, and 98.1% (9). Moreover, the pooled proportion of major complications was extremely low (0.7%), being represented by non-life-threatening voice change (9). In a recent series of 74 patients treated with RFA for 84 PTMC and followed for at least 5 years Cho et al., showed a disappearance rate of 100% at 60 months, no

local tumor progression, no lymph node or distant metastasis, and no need for delayed surgery (47). Additional ablations were performed in 13 of 84 tumors. The major complication rate was 1.4% (1/74), and no procedure related death occurred.

Some limitations of our paper should be taken into account. First, this is a single center retrospective study, thus the number of patients is limited. However, this is the first experience in Europe on clinical application of image-guided thermal ablation in the multidisciplinary management of PTMC and highlights the potential of a larger application of these techniques in our countries. Second, the follow-up of patients is limited, in a disease with known slow progression. Thus, results on long-term clinical effectiveness cannot be derived from our results, which should be regarded as preliminary. Multicentric studies, evaluating larger samples and with longer follow-up are needed to better evaluate the potential role of image-guided thermal ablations in the treatment of patients with PTMC. Finally, we did not make comparisons with patients treated with surgery or who underwent active surveillance. As with thermal ablation, as with active surveillance, small foci of microcarcinoma or small central lymph node can be missed, it is of paramount importance to evaluate in the future long term follow-up in comparison with surgery.

In conclusion, image guided thermal ablations appear to be feasible and safe in the treatment of PTMC. These techniques hold the potential to offer patients a minimally-invasive curative alternative to surgical resection or active surveillance. Also, image-guided thermal ablations appear to be largely preferred by patients. Further studies on larger patient's cohort are necessary to further address this issue.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by European Institute of Oncology review board. The patients included in this study provided their written informed consent to participate in this study and for anonymized data usage for research purpose.

AUTHOR CONTRIBUTIONS

GM, FO, SC, PD, EF, DM, GP, EG, MM, MA, and GG contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Initial Ablation Ratio Predicts Volume Reduction and Retreatment After 5 Years From Radiofrequency Ablation of Benign Thyroid Nodules

Stella Bernardi[1,2], Marco Cavallaro[3], Giacomo Colombin[1], Fabiola Giudici[1,4], Giulia Zuolo[1,2], Adrian Zdjelar[1,5], Chiara Dobrinja[6], Nicolò De Manzini[1,6], Fabrizio Zanconati[1,7], Maria Assunta Cova[1,5], Fulvio Stacul[3] and Bruno Fabris[1,2]*

[1] Department of Medical Sciences, University of Trieste, Trieste, Italy, [2] Institute of Medicina Clinica, Ospedale di Cattinara, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy, [3] Unit of Radiology, Ospedale Maggiore, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy, [4] Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padova, Italy, [5] Department of Radiology, Ospedale di Cattinara, Azienda Sanitaria Giuliano-Isontina, Trieste, Trieste, Italy, [6] Department of General Surgery, Ospedale di Cattinara, Azienda Sanitaria Giuliano-Isontina, Trieste, Trieste, Italy, [7] Department of Anatomical and Histo-pathology—Ospedale di Cattinara, Azienda Sanitaria Giuliano-Isontina, Trieste, Trieste, Italy

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***Correspondence:**
Stella Bernardi
stella.bernardi@asugi.sanita.fvg.it

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Background: Radiofrequency ablation (RFA) has gained ground as an effective and well-tolerated technique to treat benign thyroid nodules. Most of the available studies have described the short-term outcomes of RFA, whereas there is a limited number of studies evaluating long-term issues, such as regrowth and the likelihood of retreatments. In addition, risk markers of regrowth and retreatment remain to be defined. The initial ablation ratio (IAR) is an index that measures the amount of ablation after RFA, which has been associated with technique efficacy (i.e. volume reduction >50% after 1 year from the procedure). This study aimed at evaluating i) IAR reproducibility and ii) IAR predictive value for RFA 5-year outcomes.

Materials and Methods: This is a retrospective single center study on patients with benign thyroid nodules treated with RFA and followed for 5 years after initial treatment. IAR interobserver reproducibility was evaluated with Bland-Altman method and Lin's concordance correlation coefficient (ρc). IAR predictive value for RFA 5-year outcomes was evaluated with linear and logistic regression models, as well as with Cox models, while receiver operating characteristic (ROC) analyses were used for cut-offs.

Results: We selected 78 patients with 82 benign thyroid nodules. The procedure significantly reduced nodule volume and this reduction was generally maintained over time. Technique efficacy was achieved in 92% of patients, while 23% of nodules regrew and 12% of nodules were retreated. Median IAR was 83%. Lin's concordance and Pearson's correlation coefficients suggested a good interobserver reproducibility of this index, consistent with the limits of agreement of the Bland-Altman plot. IAR was significantly associated with technique efficacy, 1- and 5-year volume reduction ratio,

and with the likelihood of a retreatment, but not with nodule regrowth. ROC analyses showed that IAR cut-off was 49% for technique efficacy and 73% for retreatment.

Conclusions: Our results show for the first time that IAR is reproducible and that it predicts the volume reduction and the likelihood of a retreatment after 5 years from RFA.

Keywords: radiofrequency ablation (RFA), initial ablation ratio (IAR), efficacy, regrowth, retreatment, 5 years, thyroid

INTRODUCTION

In the last decade, thermal ablation has gained ground as an effective treatment for symptomatic thyroid nodules (1, 2), particularly in patients refusing or having contraindications to standard treatment modalities, as well as in patients with recurrences of differentiated thyroid cancer (3). Thermal ablation refers to a group of techniques, whose operating principle is to induce nodule shrinkage by rapid heating and destruction of the target zone. These techniques include laser, radiofrequency, and microwave ablation, as well as high-intensity focused ultrasound (4). Among them, laser and radiofrequency ablation (RFA) are the most thoroughly assessed techniques.

Focusing on the use of RFA to treat benign thyroid nodules, this technique has been proven effective and well-tolerated. Several studies have demonstrated that RFA significantly reduces nodule volume, with improvement of local symptoms (5, 6). In addition, large retrospective series have demonstrated that RFA carries an extremely low risk (<1%) of major complications (recurrent laryngeal nerve injury or damage to cervical structures) (7), and that it does not impair thyroid function (8, 9), or subsequent thyroid surgery (10).

Most of the available studies have described the short-term outcomes of RFA, whereas there is a limited number of studies evaluating long-term issues, such as nodule regrowth and the likelihood of retreatments (11–13). We have recently shown that even though RFA induces a clinically significant and long-lasting volume reduction of benign thyroid nodules, 20% of patients experience nodule regrowth and 12% of patients are retreated over time (14). Nevertheless, risk markers of regrowth and retreatment are still limited and remain to be fully defined.

Recently, the ratio between the ablated volume and the total volume of a nodule, i.e. the initial ablation ratio (IAR), has been proposed as a semi-quantitative index that predicts technique efficacy and might predict long-term outcomes, such as regrowth and retreatment (15). In particular, the IAR was correlated with nodule reduction, and when the IAR exceeded 70%, nodules were reduced by more than 50% (15).

Thus, this retrospective study aimed at evaluating *i*) IAR reproducibility and *ii*) IAR predictive value for RFA 5-year outcomes, including regrowth and retreatment.

MATERIALS AND METHODS

Study Design

This is a retrospective single center study, whose aims were to evaluate IAR reproducibility and IAR predictive value for 5-year outcomes of thyroid RFA, such as efficacy, volume reduction, regrowth and retreatment. For this purpose, we screened all the patients treated with thyroid RFA in the Hospitals of ASUGI (Azienda Sanitaria Universitaria Giuliano Isontina) in Trieste (Italy). Patient inclusion criteria were as follows: *i*) benign cytology before RFA (diagnostic category Thy2/Tir2 or Bethesda II, as assessed by FNAB and cytologic examination); *ii*) no prior thyroid treatment (radioiodine, ethanol injection); *iii*) follow-up of 5 years after the first ablation; and *iv*) availability of B-mode US scan images to calculate IAR. All patients were asked to give their written informed consent before inclusion. This study is part of the project 268_2019FYTNAB, whose protocol was approved by the local Ethics Committee (CEUR-2020-Os-039), and which was conducted in accordance with the declaration of Helsinki.

The following parameters were collected: age, sex, year of treatment, baseline nodule volume (ml), nodule structure, nodule function (non-functioning/autonomously functioning nodules), nodule volume (ml) after 1, 2, 3, 4, 5 years from the treatment. Technique efficacy, regrowth and retreatment were recorded as binary variables (yes/no). *Nodule volume* was measured by US examination, which was generally performed with linear transducers except for very large nodules, whose volume was quantified with convex transducers. *Volume reduction ratio* (VRR) was defined as the percentage reduction in volume and it was calculated as follows: VRR = [(initial volume – final volume)/initial volume] x 100. *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%. *Nodule function* was assessed with laboratory examination as well as thyroid scintigraphy, which was performed in case TSH was <0.4 microU/ml. *Technique efficacy* was defined as a volume reduction ≥ 50% after 1 year from the treatment. *Regrowth* was defined as a ≥50% increase compared to the previous smallest volume at US examination (14, 16).

Initial Ablation Ratio Measurement

The initial ablation ratio (IAR) is a semi-quantitative index that measures the amount of ablation, which has been associated with technique efficacy (15). IAR measurement is based on the concept that the total volume (Vt) of a nodule can be divided into an ablated (Va) and a vital portion (Vv), i.e. Vt=Va+Vv, as shown in **Figure 1**. The IAR is the ratio between the ablated volume (Va) and the total volume (Vt), and it is calculated as follows: IAR=(Va/Vt) x 100. Of note, the Vt that should be taken into account is the one measured prior to RFA. In this study, in order to evaluate the interobserver variability of IAR

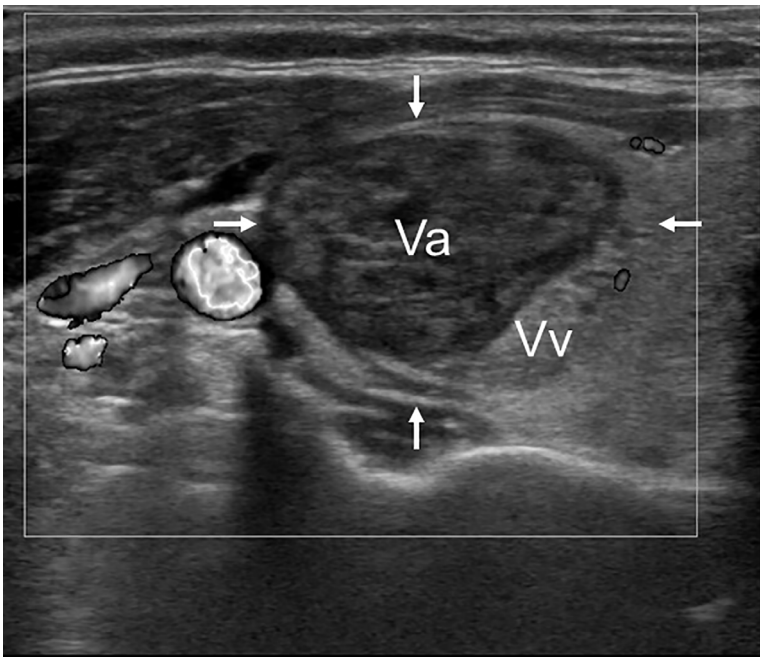

FIGURE 1 | Representative B-mode US image of a thyroid nodule 1 month after RFA, showing that total volume (arrows) can be divided into an ablated volume (Va) and a vital volume (Vv). In particular, the ablated volume (which corresponds to the treated area) appears hypoechoic and avascular.

measurement, IAR was assessed by two Radiologists (GC and AZ) on B-mode US scan images that had been recorded at baseline and 1-month after RFA. All the B-mode US scans were performed in the same Institute by two Radiologists (MC and FS). All RFA procedures were performed by one Radiologist (FS).

Statistical Analyses

All statistical analyses were carried out in R system for statistical computing (Ver. 3.5.0; R Development Core Team, 2018). Statistical significance was set at $p<0.05$.

Shapiro-Wilk test was applied to quantitative (continuous) variables to check for distribution normality. Continuous variables were reported as median with range (minimum-maximum). Qualitative (categorical) variables were reported as absolute frequencies and/or percentages (rates of technique efficacy, regrowth and retreatment). Continuous variables were compared by student's t test (and ANOVA) or by Mann–Whitney test (and Kruskall Wallis test), depending on data distribution and number of groups. Categorical variables were compared by Chi-square test or Fischer's exact test whenever appropriate. Variations over time of nodules' volume were evaluated with non-linear mixed-effects models (NLME) for repeated measures. Multiple comparisons of nodules' volume with respect to different follow-up periods (baseline vs 1, 2, 3, 4, and 5 years) were performed with Friedman test for repeated measures and p-values adjusted with Bonferroni post-hoc test.

The interobserver variability of IAR was evaluated by assessing the agreement and reliability of IAR measurements performed by two operators. The Bland-Altman plot was used for analyzing the IAR interobserver agreement: the mean difference and the limits of agreement were calculated. In addition, IAR interobserver reliability was assessed with Lin's concordance correlation coefficient (ρc) (17). This coefficient evaluates the reproducibility in measuring a continuous variable. In particular, ρc contains a measurement of precision (how close the data are about the line of best fit) and a measure of accuracy (how far the best-fit line deviates from the 45° line through the origin, this 45° line representing perfect agreement). This coefficient is used as a complementary approach to the Bland-Altman analysis. Like a correlation, ρc ranges from -1 to 1, with perfect agreement at 1 while values near to 0 indicates no agreement. The value of ρc can be interpreted with the Landis and Koch scale (0.2–0.4: fair; 0.4–0.6: moderate; 0.6–0.8: substantial; 0.8–1.0: almost perfect).

To evaluate if IAR was associated with nodule volume reduction, we conducted a univariate linear regression analysis. Statistically significant variables with a p value <0.10 on univariate analysis were then selected for multivariate linear regression analysis. To evaluate if IAR could be a risk marker of technique inefficacy, regrowth, and retreatment we conducted a univariate logistic regression analysis and calculated the odds ratio of IAR as well as of age, sex, baseline volume, nodule structure and function. Given the small numbers of technique inefficacy (n=7), regrowth (n=19), and retreatment (n=10), the multivariate logistic regression analysis could not be performed. Moreover, given that retreatment is a time-dependent occurrence, a univariate Cox proportional hazards regression model was performed to verify if IAR was associated to retreatments (results reported as Hazards Ratios (HR) with 95% confidence interval (95%CI).

Receiver operating characteristic (ROC) analyses were used to calculate the accuracy of IAR as predictor of technique efficacy and retreatment. Area under the (ROC) curves with 95% confidence interval, were interpreted according to Sweets criteria, and were used to identify a cut-off value of IAR that best predicted technique efficacy and retreatment. Specificity and sensitivity were also calculated (95% confidence interval, CI). The best possible cut-off point was defined as the highest Youden Index [(specificity + sensitivity) – 1 (R package "OptimalCutPoints")]. DeLong method was used to test the statistical significance of the difference between the areas under the curve.

RESULTS

Study Population

Inclusion criteria were met by 78 patients (82 benign thyroid nodules), who were selected for this study. All patients were treated between 2012 and 2015 with RFA, which was performed with the moving shot technique and a monopolar 18-G needle (18). **Table 1** shows the clinical and US characteristics of the study population. Median age was 60 years (18–86); there were 59 females (76%) and 19 males (24%). Median baseline thyroid nodule volume was 11.3 ml (0.44–54.6). Nodule structure was solid in 44% of cases, predominantly solid in 35% and predominantly cystic in 21% of cases. The majority of nodules were non-functioning (66%), while the remaining were autonomously functioning thyroid nodules (34%).

Nodule Volume Reduction

Nodule volume was significantly reduced by RFA ($p<0.001$ for repeated measures). In particular, the nodules' volume was 11.3 ml (0.5–54.6) at baseline, 2.8 ml (0.02–52.6) after 1 year from the procedure, 2.6 ml (0.008–59.9) after 2 years, 2.07 ml (0.001–70.23) after 3 years, 2.26 ml (0.001–25.02) after 4 years, and 2.29 ml (0.001–23.44) after 5 years. In other words, the volume decreased by 76%, 76%, 77%, 79%, and 79% at 1, 2, 3, 4, and 5 years after RFA. Predominantly cystic nodules were associated with greater volume reduction after 1 year, while volume reduction did not differ between predominantly cystic and predominantly solid or solid nodules after 5 years from the treatment (**Table 2**).

TABLE 1 | Characteristics of study population.

Number of patients		78
Age (years)		59.5 (18–86)
Sex	**M**	19 (24.4%)
	F	59 (75.6%)
Number of nodules		82
Baseline nodule volume (ml)		11.3 (0.44-54.6)
Nodule structure	**Solid**	36 (43.9%)
	Predominantly solid	29 (35.4%)
	Predominantly cystic/cystic	17 (20.7%)
Nodule function	**Non-functioning nodules**	54 (65.9%)
	Autonomously functioning thyroid nodules	28 (34.1%)
IAR (%)		83.8 (-48.2; 100)
Technique efficacy	**Yes**	75 (91.5%)
	No	7 (8.5%)
Regrowth	**Yes**	19 (23.2%)
	No	63 (76.8%)
Retreatment	**Yes**	10 (12.2%)
	No	72 (87.8%)

Continuous variables are reported as median (min-max).

Interobserver Reproducibility of Initial Ablation Ratio

Median IAR was 83% (-48%; 100%), as shown in **Table 1**. To measure IAR interobserver reproducibility and reliability, we compared the IAR values measured by two operators on the same nodules. The Bland-Altman analysis (**Figure 2A**) showed that the average discrepancy between the two operators was small, being 8.4 with 95% limits of agreement ranging between -23.4 and 40.1. Lin's concordance correlation coefficient provided additional information, confirming a good interobserver reproducibility (**Figure 2B**). In particular, Pearson's correlation (ρ) and Lin's concordance (ρc) coefficients were respectively $\rho=0.80$ (95%CI; 0.68–0.86) and $\rho c=0.74$ (95%CI: 0.62–0.82), indicating good reproducibility, with a bias corrector factor Cb of 0.94 (no systematic bias). It has been suggested that IAR reproducibility could further increase on contrast-enhanced US scans (19).

Initial Ablation Ratio and Volume Reduction Ratio

There was a good correlation between IAR and VRR after 1 and 5 years from the procedure (**Figures 3B–C**), whereas there was an inverse correlation between IAR and baseline volume (**Figure 3A**). On linear regression model analyses, IAR was independently associated with 1- and 5-year volume reduction (**Table 2**).

Initial Ablation Ratio and Technique Efficacy, Regrowth, and Retreatment

Technique efficacy was achieved in 92% of nodules. Regrowth was observed in 23% of nodules. Retreatment was performed in 12% of nodules, as shown in **Table 1**. Causes of retreatment were: not reaching technique efficacy (40%), regrowth (40%), and symptom persistence (20%).

Figure 3 shows that the amount of ablation (i.e. IAR) was significantly higher in the nodules that shrunk by more than 50% (**Figure 3D**) and that did not require any retreatment (**Figure 3E**), while IAR did not change between the nodules that regrew or not (**Figure 3F**). On logistic regression model analyses (**Table 3**), IAR was significantly associated with technique efficacy and the likelihood of not being retreated, but not with regrowth. Likewise, IAR was significantly associated with the likelihood of not being retreated over time as assessed by Cox regression model analysis (**Table 4**).

Initial Ablation Ratio Cut-Offs

On ROC curve analysis, when looking at technique efficacy, we found that IAR had an AUC of 0.87 (95%CI:0.71–1.00) and the cut-off best predicting technique efficacy was 49% (sensitivity =

TABLE 2 | Linear regression models for 1- and 5-year VRR.

		1-year volume reduction ratio					
		Univariate linear regression			Multivariate linear regression		
		Beta	SE	*p*-value	Beta	SE	*p*-value
Age (years)		-0.002	0.002	0.15	//		
Sex	Male	-0.07	0.05	0.21	//		
Baseline volume (ml)		-0.003	0.002	0.06	-0.001	0.001	0.27
Nodule structure	PC	0.14	0.06	0.01	0.11	0.04	0.007
	PS	0.01	0.05	0.82	0.04	0.03	0.29
Nodule function	Non-AFTN	0.06	0.05	0.21	//		
IAR		0.005	0.006	<0.001	0.004	0.0007	<0.001
		5-year volume reduction ratio					
		Univariate linear regression			Multivariate linear regression		
		Beta	SE	*p*-value	Beta	SE	*p*-value
Age (years)		-0.002	0.002	0.38	//		
Sex	Male	0.02	0.07	0.72	//		
Baseline volume (ml)		0.0001	0.002	0.95	//		
Nodule structure	PC	0.09	0.07	0.18			
	PS	0.02	0.06	0.80	//		
Nodule function	Non-AFTN	0.03	0.06	0.64			
IAR		0.005	0.001	<0.001	0.005	0.001	<0.001
Therapeutic efficacy	Yes	0.36	0.13	0.006	0.25	0.11	0.02

AFTN is for autonomously functioning thyroid nodules, PC is for predominantly cystic, and PS is for predominantly solid.

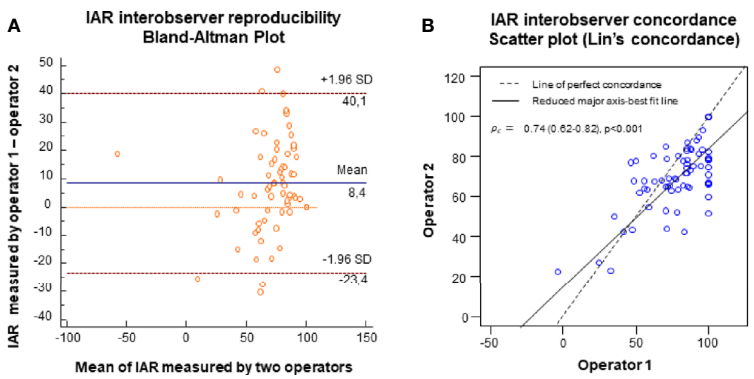

FIGURE 2 | **(A)** Bland-Altman plot showing interobserver agreement of IAR measurements on B-mode US images. The x-axe shows the mean of IAR measurements, the y-axe shows the difference between the measurements. Orange line = 0; blue line = mean difference between operators, red lines = ± 95% (± 1.96 SD) limits of agreement. **(B)** Scatter plot of the Lin's concordance (interobserver concordance) coefficient, showing how far the fitted relationship between x and y deviates from the 45° concordance line through the origin. The graph shows good precision (ρ=0.80), almost no systematic bias (C_b), and a substantial interobserver concordance (ρ_c=0.74).

0.71; specificity =0.92). When looking at retreatments, IAR had an AUC of 0.84 (95%CI: 0.73–0.94) and the cut-off best predicting no retreatment over time was 73% (sensitivity = 0.80; specificity =0.72). ROC curves are shown in **Figure 4**.

DISCUSSION

It has been largely demonstrated that RFA is an effective treatment for benign thyroid nodules. In randomized controlled trials, the volume reduction induced by RFA ranged from 69% to 78% after 1 year from the procedure (5, 6). Smaller baseline volume (20), spongiform US appearance (20), and higher amount of energy delivered (21) have been associated with this outcome. Consistent with these data, in this study, we found that volume reduction was 76% after 1 year from thyroid RFA and that it was significantly associated with nodule structure, as predominantly cystic nodules were reduced more than predominantly solid or solid nodules in the short term.

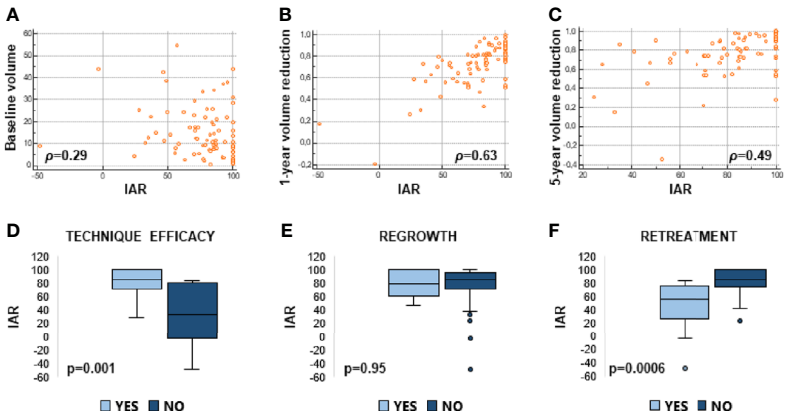

FIGURE 3 | Linear correlations between IAR and baseline volume **(A)**, IAR and 1-year volume reduction ratio **(B)**, IAR and 5-year volume reduction ratio **(C)**. Box plots representing median IAR (min -max) in cases of technical efficacy vs inefficacy **(D)**; presence or absence of regrowth **(E)**; retreatment vs no retreatment **(F)**.

The IAR is a semi-quantitative index that measures the amount of ablation induced by radiofrequency. This index has been associated with technique efficacy (15). This study confirms that the amount of ablation, which was 83% was significantly associated with technique efficacy (i.e. 1-year VRR >50%), regardless of baseline volume and nodule structure. In particular, the IAR cut-off best-predicting technique efficacy was 49%. In other words, when more than 49% of the nodule is ablated, it is likely that the nodule will shrink by at least 50% after 1 year from the procedure. In addition, this study shows for the first time that IAR was significantly associated not only with 1-year but also with 5-year volume reduction.

As compared to the works by Sim (15) and Schiaffino (19), here we decided to ascertain if IAR measurement was reproducible. Our data show that IAR measurement, as assessed on B-mode US scans, was reproducible. In particular, despite the fact that the Bland-Altman plot showed that the 95% limits of agreement were wide for interobserver variability, the mean difference among observers was only 8.4%, suggesting that it is more likely that observers' readings were closer to the reference measurement than to the extremes of the 95% limits of agreement. In addition, Lin's concordance correlation coefficient was 0.74, indicating that there was substantial agreement.

It has been shown that thyroid RFA is effective in reducing nodule volume, and that the reduction achieved may remain stable for years. Nevertheless, in a minority of patients, regrowth may occur and patients may need a second treatment. To date, only a few papers have reported the 5-year outcomes of RFA. Most of them are limited by incomplete patient follow-up and variable number of treatment sessions (11–13, 22). In these studies, 5-year VRR ranged from 67% to 93.5%, whereas regrowth rate ranged from 4 to 24%, depending on the definition that was used. By contrast, in a study that followed a group of 216 patients for 5 consecutive years after thyroid RFA,

TABLE 3 | Univariate logistic regression models for technique inefficacy, regrowth, and retreatment.

	Technique inefficacy (number of events = 7)		Regrowth (number of events = 19)		Retreatment (number of events = 10)	
	OR (95%CI)	***p*-value**	**OR (95%CI)**	***p*-value**	**OR (95%CI)**	***p*-value**
Age (years)	1.03 (0.97–1.09)	0.29	0.96 (0.92–0.99)	0.03	0.97 (0.92–1.01)	0.14
Sex						
Female	1.00 (ref)	0.05	1.00 (ref)	0.32	1.00 (ref)	0.05
Male	4.98 (1.00–24.7)		0.50 (0.13–1.96)		3.86 (0.98–15.2)	
Baseline volume (ml)	1.02 (0.96–1.08)	0.54	0.97 (0.93–1.02)	0.30	0.97 (0.93–1.10)	0.10
Nodule structure						
S	1.00 (ref)	0.95	1.00 (ref)	0.47	1.00 (ref)	0.48
PS	0.92 (0.19–4.50)	0.99	1.59 (0.48–5.40)	0.14	1.67 (0.40–6.88)	0.55
PC	0.0002 (0.00–INF)		2.73 (0.72–10.30)		0.50 (0.05–4.85)	
Nodule function						
AFTN	1.00 (ref)	0.20	1.00 (ref)	0.18	1.00 (ref)	0.32
Non-AFTN	0.35 (0.07–1.70)		2.31 (0.69–7.77)		2.26 (0.45–11.50)	
IAR	0.94 (0.90–0.98)	0.002	1.01 (0.98–1.03)	0.60	0.96 (0.93–0.98)	0.002

AFTN is for autonomously functioning thyroid nodules, PC is for predominantly cystic, PS is for predominantly solid, and S is for solid nodules.

TABLE 4 | Cox proportional hazard regression model.

	Retreatment (n=10)	
	HR (95%CI)	***p*-value**
Age (years)	0.97 (0.92–1.01)	0.13
Sex		
Female	1.00 (ref)	0.05
Male	3.39 (0.99–11.73)	
Baseline volume (ml)	1.04 (0.99–1.08)	0.09
Nodule structure		
S	1.00 (ref)	0.50
PS	1.57 (0.42–5.85)	0.54
PC	0.51 (0.06–4.54)	
Nodule function		
AFTN	1.00 (ref)	0.34
Non-AFTN	2.14 (0.45–10.1)	
VRR	0.02 (0.004–0.13)	<0.001
IAR	0.97 (0.96–0.98)	<0.001

AFTN is for autonomously functioning thyroid nodules, PC is for predominantly cystic, PS is for predominantly solid, and S is for solid nodules, VRR is for volume reduction ratio.

nodule volume reduction was 77% at last follow-up, 20% of patients had nodule regrowth and 12% of patients underwent further treatments (14). In line with these figures, in this study, we found that after 5 years from RFA, nodule volume was reduced by 79%, 23% of nodules regrew, and 12% were retreated.

Unfortunately, the parameters that could help predict the risk of regrowth and/or retreatment over time remain to be fully identified (14). In a study evaluating the response of 206 nodules to RFA during a mean follow-up time of 22 months (range: 6–68 months), Yan showed that regrowth rate was 13% and that residual vital ratio, initial volume, location, and vascularity were all independent factors associated with regrowth (22). By contrast, in the study following 216 patients for 5 consecutive years after thyroid RFA, the only variable significantly associated with regrowth was the quantity of energy delivered, which turned out to be a poor predictor of regrowth, but a good predictor of retreatment (14). Consistent with these data, in this study, IAR was significantly associated with the likelihood of being retreated after 5 years from RFA but not with nodule regrowth. In particular, IAR cut-off best predicting no need of retreatments was 73%. In other words, when more than 73% of the nodule is ablated further treatments are unlikely. To translate it into clinical practice, an IAR value <73% might identify those patients who will benefit from a closer follow-up, as they are more likely to be retreated.

Our data suggest that predictors of technique efficacy and retreatment, such as IAR, are not necessarily predicting regrowth. The underlying reasons might include the fact that the current definition of regrowth is quite broad, and—for instance—it might fail to differentiate subclinical from clinical regrowths. Most importantly, it has to be taken into account that retreatments are due not only to regrowths but also to unsatisfactory volume reduction or symptom persistence, indicating that regrowth and retreatment are not exactly the two sides of the same coin.

Strengths and limitations of the study. The strengths of this study include the fact that it addresses for the first time the issue of IAR reproducibility and its predictive value for regrowth and retreatment over 5 years of follow-up. In addition, there was no patient loss during the follow-up, and being a single-center study we limited biases due to too many operators performing RFA and US scans. On the other hand, the limitations of this study include its retrospective design, and the low number of events (technique inefficacy, regrowths, and retreatments), such that we could not perform any logistic multivariate analysis.

In conclusion, this study shows that IAR is an index that is reproducible, and that it correlates not only with 1-year volume reduction and technique efficacy, but also with 5-year outcomes of RFA, such as 5-year volume reduction and the likelihood of being retreated over time. For this reason, the IAR is an index that might help clinicians in patient management. In particular, when more than 73% of the nodule is ablated, the need of further treatments is unlikely for—at least—5 years after thyroid RFA. Further studies with larger cohorts of patients are needed to confirm and extend our data, in order to identify markers of regrowth.

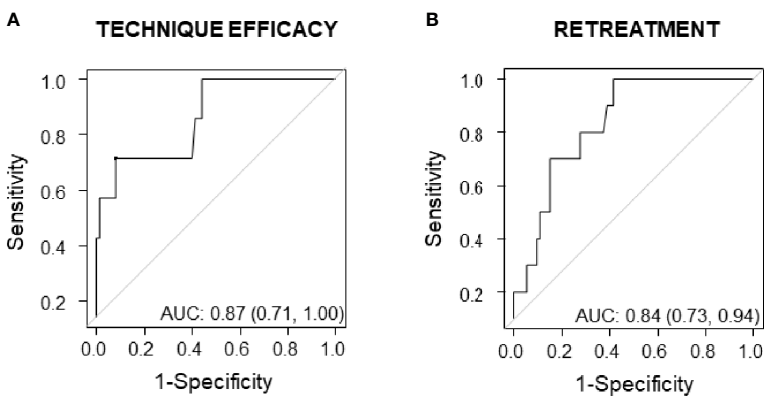

FIGURE 4 | ROC curves showing predictive accuracy of IAR for technique efficacy **(A)** and for retreatment **(B)**.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Unico Regionale—FVG. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SB, MC, and BF contributed to the conception and design of the study. MC and FS contributed to the data collection (they performed US scans) and FS performed all RFA procedures. GC and AZ contributed to the data collection (performed IAR measurements). FG performed the statistical analysis. SB, GC, and GZ organized the database. SB wrote the first draft of the manuscript. CD, NDM, FZ, and MAC contributed to patient recruitment. All authors contributed to the article and approved the submitted version.

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The Ablation of Thyroid Nodule's Afferent Arteries Before Radiofrequency Ablation: Preliminary Data

*Chiara Offi[1], Sara Garberoglio[2], Giovanni Antonelli[1], Maria Grazia Esposito[1], Umberto Brancaccio[1], Claudia Misso[1], Edoardo D'Ambrosio[1], Daniela Pace[3] and Stefano Spiezia[1]**

[1] Department of Endocrine and Ultrasound-guided Surgery, "Ospedale del Mare", Naples, Italy, [2] Division of Endocrinology, Diabetology and Metabolism, Department of Medical Sciences, University of Turin, Turin, Italy, [3] Department of Endocrinology, Valmontone Hospital, Valmontone, Italy

Induced radiofrequency thermal ablation is the cytoreductive treatment of symptomatic benign thyroid nodules, metastatic and recurrent thyroid tumors and papillary thyroid microcarcinomas. It is a safe and effective alternative to surgery and it allows to obtain satisfactory results in terms of volumetric reduction of the nodule with significant improvement in the quality of life. The trans-isthmic approach and the moving shot technique are the two basic techniques; however, an advanced technique, artery-first feeding radiofrequency ablation, has been developed and validated. We have prospectively included 29 consecutive patients who have undergone radiofrequency ablation (Group A) or artery- first vRFA (Group B). All included patients had a diagnosis of benign nodular goiter and they underwent a single session of radiofrequency ablation. All patients followed a follow-up program at 1 month, 3 months, and 6 months. Continuous variables (age, TSH value, basal volume of nodule, used Joule, time in second of the procedure, nodules' volume at 1-, 3-, and 6- months of follow-up and percentage of volume reduction at 1-, 3-, and 6- months of follow-up) were described as mean, standard deviation and range, while categorical variables (gender, nodule structure and nodule vascularization) were described as number of cases and percentage. Independent samples t-test were performed to compare the continuous variables. A Test of Proportions was applied to the categorical variables. The Fisher's exact test was used to analyze the gender. Statistical significance was considered in case of p-value <0.05. Solid structure and spongiform structure showed statistic differences with p-values of 0.022 and 0.023 respectively between two groups. The percentage of reduction at 1 month did not show a significant difference between two groups; instead, the percentage of volume reduction was decreased mostly in the Group B at 3 months and 6 months of follow-up with a p-value of 0.003 and 0.013, respectively. The Joules/energy used showed a statistically significant difference (p-value=0.05), more energy must be used in vascular radiofrequency ablation. These data allow us to hypothesize that vRFA may improve the effectiveness of the procedure, allowing for a reduction in volume more quickly. They were preliminary but promising results, clearly a larger series of cases and prolonged follow-up are needed to clarify and confirm our observations.

Keywords: radiofrequency ablation, thyroid nodules, technique, ultrasound, thermal ablation

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Francesco Frasca, University of Catania, Italy

****Correspondence:***
Stefano Spiezia
stefanospiezia@tiroide.org

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INTRODUCTION

Induced radiofrequency thermal ablation (RFA) is a minimally invasive technique developed to treat the symptoms and aesthetic outcomes of benign thyroid nodules. Thyroid nodules are the most common pathology of the thyroid gland, in most cases they are asymptomatic, stable over time and incidental; in a low percentage of cases, however, they have rapid growth associated with compression symptoms and unsightly outcomes (1). Until the last decade, these pathologies, when symptomatic, could only be treated with surgery. Recently, with the progress of minimally invasive techniques, thyroid nodules can be treated with various minimally invasive techniques including RFA (2).

RFA, performed by expert hands can be considered a safe and effective alternative to surgery for the treatment of selected pathologies. The RFA technique allows to obtain satisfactory results in terms of volumetric reduction of the nodule with a significant improvement in the quality of life. Patients treated with RFA ablation refer reduction of compression symptoms and discomfort, previously related to the presence of a mass in the neck. The trans-isthmic approach and the moving shot technique are the two basic techniques validated in many studies; however, an advanced technique, vascular radiofrequency ablation (vRFA), has been developed and validated (3).

Various International guidelines, indeed, consider RFA treatment a valid alternative to surgery in the case of symptomatic benign thyroid nodularities. Moreover, RFA may be an indication in the treatment of microcarcinoma, in recurrent thyroid cancers, in lymph node metastases and in cases where surgery is contraindicated or rejected by the patient (2–9). Especially in the treatment of papillary thyroid carcinoma recent data suggest the use of RFA as an alternative treatment to surgery (3, 4, 10–12).

The aim of this study is to evaluate the percentage of nodular volume reduction at 1 month, 3 months, and 6 months in patients treated with RFA and in patients treated with vRFA. The goal is to evaluate the difference between the two techniques in the time of reduction of the nodular volume and to identify the superiority of one technique compared to the other.

MATERIALS AND METHODS

We have prospectively collected data of 29 consecutive patients who underwent RFA or artery- first vRFA at Department of Endocrine and Ultrasound-guided Surgery of "Ospedale del Mare", Naples, Italy. All patients had a diagnosis of nodular goiter and underwent radiofrequency ablation of thyroid nodule between January 2018 and August 2019.

We included patients aged over 18 years and not pregnant with: single thyroid nodule of the thyroid lobe with benign cytological diagnosis (Thy2/TIR2 or Bethesda II) to two consecutive fine needle cytology (FNC) (13, 14); complete medical history, complete preoperative blood tests and complete follow-up. We excluded patients with: presence of multiple thyroid nodule in a thyroid lobe; cystic nodules or predominantly cystic nodules on ultrasound (cystic portion >50% of the nodule); cytological diagnosis of TIR1c, TIR3a, TIR3b, TIR4 and TIR5; non diagnostic cytological report (TIR1) to one FNC; autoimmune thyroid disease; TSH <0.15 mU/L or TSH >3.5 mU/L; previous thyroid radiofrequency ablation or ethanol injection; neck surgery within 5 years; previous radiation therapy; previous cancers. The flow chart (**Figure 1**) shows the patients enrolled according to the inclusion and exclusion criteria.

We divided the population in two groups based on RFA technique used. Group A included RFA patients. Group B included, on the other hand, patients subjected to vRFA. All patients underwent coagulation index and blood cells count sample, thyroid function samples, thyroid antibody samples, twice FNC, thyroid and later cervical lymph nodes B-mode US examination and fiberoptic-laryngoscopy tests in the 30 days prior to ultrasonographic ablation techniques. Clinical and demographic data (age, gender, baseline nodule volume, nodule structure, nodule vascularization, nodule function and a complete anamnesis) were obtained at first examination and were collected in an electronic database.

The US examination was conducted with a 7.5–12 MHz linear probe or with a convex probe in very large nodules equipped with CD and PD nodules (MyLab^{TM}ClassC and MyLab^{TM}9 Platform, Esaote Biomedica, Genova Italy) and assessing the volume of the nodule, the structure and the vascularization. The

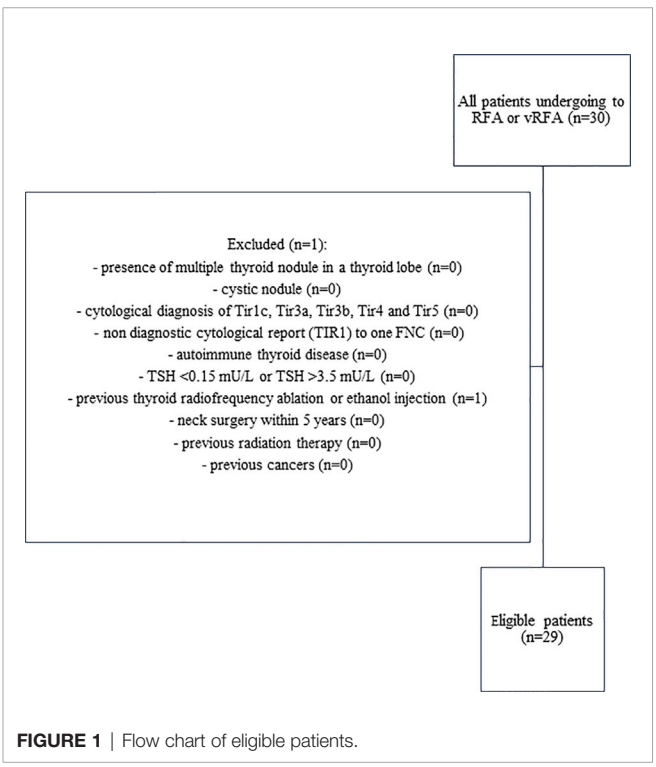

FIGURE 1 | Flow chart of eligible patients.

Abbreviations: CD, Color Doppler; FNC, fine needle cytology; PD, Power Doppler; RFA, radiofrequency ablation; SD, standard deviation; TgAb, thyroglobulin antibody; TPOAb, Thyroperossidase antibody; TSH, thyro-stimulating hormone; US, ultrasound; vRFA, vascular radiofrequency ablation.

basal volume of the nodule was automatically calculated with ellipsoid equation by the software with the measurements of depth, width and length in longitudinal and transverse scans. The structure was defined as solid (fluid component was less than 10% of volume), spongiform (cystic areas occupied less than 50% of the nodule's volume) and predominantly solid (solid component was more than 50% of the volume). The vascularity was studied by CD examination and classified as peri-nodular, intra-nodular and both peri- and intra- nodular. Cytology findings, according to SIAPEC-IAP classification, were collected and we included patients with twice TIR2 at two consecutive FNCs.

The examined variables, relating to the technique, were the Joules (energy used to deliver the power of one watt for one second) used and the time expressed in seconds. Radiofrequency ablation was performed with the M-3004 generator and the RFT-TIP 0710N, 7 cm length, 1cm exposed tip (RF Medical Co., South Korea) inserted with US guidance.

The patients were submitted to a single RFA session, in supine position, in neck hyperextension and with a skin and pericapsular anesthesia. The skin local anesthesia was done in the needle insertion site in the midline. During the treatment, all patients had a feeling of compression at the neck's level, which did not require the interruption of the procedure. All patients were discharged 3 h after the procedure, after ultrasound examination. No cases of major or minor complications were observed.

The trans-isthmic approach and the moving shot technique are performed under ultrasound (US) guidance. The trans-isthmic approach allows the treatment of the left and right thyroid nodules by inserting the RFA electrode in the neck midline to lateral direction. It shows advantages over other approaches. Before reaching the target, the electrode crosses much of the thyroid parenchyma limiting involuntary excursions of the needle-electrode due to patients' involuntary movements (speaking, swallowing or coughing). It prevents the leakage of hot material from the thyroid parenchyma during the procedure. This approach also allows continuous ultrasound monitoring to minimize the risk of complications or side effects due to thermal injuries in surrounding structures (recurrent laryngeal nerve, carotid artery, internal jugular vein, trachea and esophagus) (5–7, 15–17). Moreover, the use of Color Doppler (CD) and/or Power Doppler (PD) prevents serious bleeding, identifying the blood vessels along the path of the electrode.

A radiofrequency generator (M-3004, RF Medical Co., Ltd., South Korea), connected to the needle-electrode, produces an alternating electric current (between 200 and 1,200 kHz) which causes ions movement in adjacent tissues of the tip. The ions vibrate rapidly producing energy that is transformed in heat, raising local temperature between 60°C and 100°C. The high temperature induces a protein denaturation of cell membrane and the irreversible death of the cells of the tissues around the tip. The energy decreases exponentially in the length of the needle and the remote tissues are heated due to thermal conduction. This needle protection mechanism prevents tissues away from the target from undergoing coagulation necrosis due to the heat generated (18). At the beginning of the procedure, the temperature necroses all around the tip. US transient hyperechoic area is displayed and to the touch a vibration is perceived, described as a "shot".

The RFA has benefited from the moving shot technique as the thyroid nodules mainly have an ellipsoidal appearance and it is difficult to treat them with the fixed technique. The periphery of the thyroid nodules is undertreated or overtreated with the fixed technique. Using the moving shot technique, instead, the nodule is ideally divided into multiple smaller units, each to be ablated separately. The subunits are smaller on the periphery and larger in the central area and in regions far from critical structures. The procedure begins with the treatment of the deeper and more peripheral areas, as the heat generated causes the appearance of transient hyperechoic air bubbles that reduce the acoustic window for ultrasound monitoring, moreover, saving the "dangerous triangle" (the nodular periphery area close to trachea) to avoid thermal injury to the recurrent laryngeal nerve. It continues with the treatment of superficial areas of the nodule. The moving shot technique allows to obtain an ellipsoidal ablation area, similar to the morphology of the frequent thyroid nodules. The treatment ends when the entire nodule appears completely replaced by transient hyperechoic areas (3, 5, 10, 19–22).

The anesthetic infiltration of skin and pericapsular tissue is performed before the RFA: the needle is inserted at the midline of the anterior neck to anesthetize the skin. Once the skin has infiltrated, the needle is pushed in lateral direction, depending on the right or left position of the nodule, up to the virtual space between the strap muscles and the thyroid capsule. A solution with lidocaine 2% is injected and appears as an anechoic band, which gradually disappears deeply into antero-superior mediastinum, and laterally tools the main vessels of the neck. The risk of major complications decreases with local anesthesia, because the operator can monitor the pain, an early indicator of heat propagation, while a moderate sedation or a general anesthesia prevent the patients' active collaboration and the early manifestation of complications such as changes in tone of voice, cough or pain (10, 15, 23).

The thyroid upper polar nodules are usually vascularized by arterial branches of the upper thyroid artery that derives from the external carotid artery and mainly supplies the upper and anterior part of the thyroid gland. The nodules of the lower pole of the thyroid are vascularized by the lower thyroid artery, which derives from the thyrocervical trunk and provides the postero-inferior parts of the gland.

The vRFA is a technique used to treat the hypervascular thyroid nodule. The artery-first vRFA is used in hypervascularized nodules that show an evident feeding artery. Authors propose this technique to reduce the dispersion of the generated heat, in the nodules with important vascularization (24). The feeding artery is detected with a CD and PD study (**Figure 2**) and the use of artery-first vRFA decreases the complications and increases the techniques efficiency. Intranodular linear echogenicities appear in the target nodule when the feeding artery is ablated due to air microbubbles in the arterioles

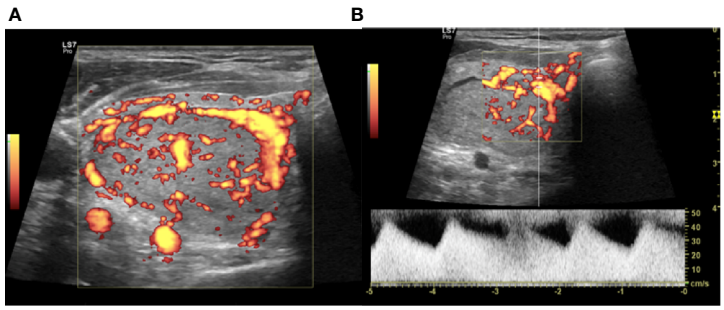

FIGURE 2 | Right lobe nodule, intraoperative transverse ultrasound (US) scan. **(A)** Power Doppler (PD) evaluation of the nodule to be treated with vascular radiofrequency ablation (vRFA). **(B)** Identification at PD and PWD of the main afferent artery.

(**Figure 3**). In a few cases, it's possible to have wedge-shaped hypoechoic area after the ablation due to the infarction of the area vascularized by the ablated feeding artery (25).

We carried out the thermo-ablative treatment of an afferent arterial branch of nodule as a first step of RFA treatment, improving the moving shot technique, in order to obtain a better ablation of nodular tissue, amplifying the volume of the induced necrosis (**Figure 4**) (3, 22, 25).

In the follow-up program we assessed the nodule volume and its percentage of reduction at 1 month, 3 months and 6 months. We assessed the volume with the ultrasound examination, evaluating the 3 diameters studied in the two projections. The reduction percentage was calculated comparing the follow-up volume with the basal volume.

Statistical analysis was performed with SPSS version 23 (SPSS©, Chicago, IL, USA). Continuous variables were described as mean, standard deviation (SD) and range, while categorical variables were described as number of cases and percentage. The population was divided in patients who underwent RFA and patients who underwent vRFA. Independent samples t-test were performed to compare the continuous variables (Joule, procedure's time in second, basal volume, volume at 1 month, % of volume reduction at 1 month, volume at 3 months, % of volume reduction at 3 months, volume at 6 months and % of volume reduction at 6 months). A Test of Proportions was applied to the categorical variables (number of patients, nodule structure and vascularization). The Fisher's exact test was used to analyze the gender. Statistical significance was considered in case of p-value <0.05.

Written informed consent was obtained from all participants. All procedures were performed in accordance with the Helsinki Declaration.

RESULTS

Twenty-nine patients (10 males and 19 females) with a single benign thyroid nodule were enrolled in the study for the treatment with radiofrequency ablation. Patients were divided into two groups based on the treatment they were subjected to, Group A treated with RFA (12 cases) and Group B treated with vRFA (17 cases). Population's mean age was 55.03 years (± 10.9 SD) without a statistical difference between two groups. Patients included were euthyroid and they had normal values of Thyroglobulin Antibody (TgAb), Thyroperossidase Antibody (TPOAb) and calcitonin (**Table 1**). In a case of subclinical hyperthyroidism (TSH 0.12 mU/L) thyroid scintigraphy was performed prior to treatment and it identified a non-

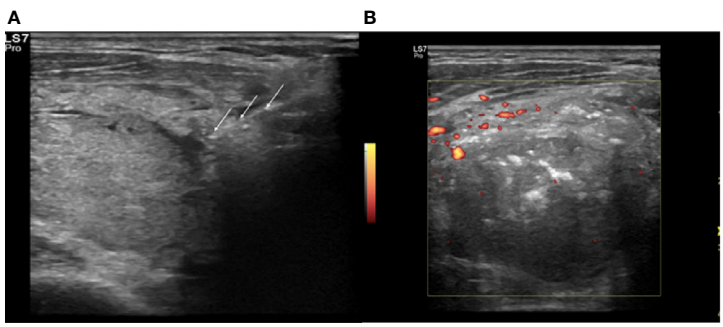

FIGURE 3 | Right lobe nodule, intraoperative transverse ultrasound (US) scan. **(A)** Insertion of the electrode (white arrows) in the identified arterial afferent pole. **(B)** Power Doppler (PD) evaluation at the end of the procedure, absence of peri- and intranodular vascularization.

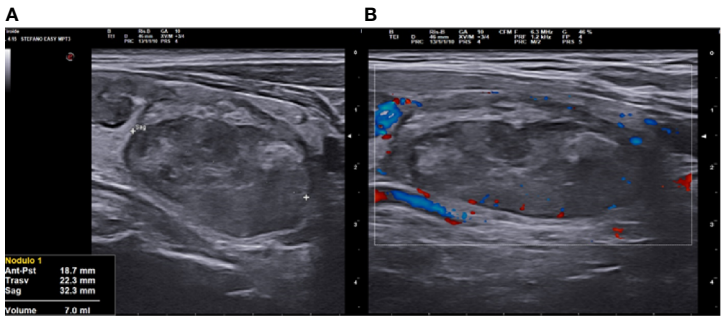

FIGURE 4 | Right lobe nodule, longitudinal ultrasound (US) scan at 3 months follow up after vascular radiofrequency ablation (vRFA). **(A)** The nodule shrunk from 18.5 to 7 ml in 3 months, strongly hypoechoic, solid. **(B)** at Color Doppler (CD) evaluation, absence of peri- and intranodular vascular signal.

TABLE 1 | Baseline demographic and clinical data of the study population.

Characteristics	Population	Group A	Group B	p-value
Patients (%)	29 (100)	12 (41.4)	17 (58.6)	0.14
Mean age in years ± SD (range)	55.03 ± 10.90 (28–80)	57.50 ± 7.28 (46–69)	53.29 ± 12.80 (28–80)	0.315
Gender (%)				
Male	10 (34.5)	4 (13.8)	6 (20.7)	0.99
Female	19 (65.5)	8 (86.2)	11 (79.3)	
Mean TSH in mU/L ± SD (range)	1.03 ± 0.49 (0.12–2.21)	0.93 ± 0.42 (0.54–1.78)	1.11 ± 0.54 (0.12–2.21)	0.337
Mean basal volumes ± SD (range)	26.90 ± 19.09 (1.60–74)	21.15 ± 20.34 (1.60–74)	30.96 ± 17.65 (10.40–70.10)	0.178
Nodule structure (%)				
Solid	9 (31)	7 (58)	2 (11.8)	0.023
Spongiform	18 (62)	4 (33.5)	14 (82.4)	0.022
Predominantly solid	2 (7)	1 (8.5)	1 (5.8)	0.99
Nodule vascularization (%)				
Peri-nodular	8 (27.6)	5 (41.7)	3 (17.7)	0.315
Intra-nodular	1 (3.5)	1 (8.5)	0 (0)	0.858
Intra-peri-nodular	20 (68.9)	6 (49.8)	14 (82.3)	0.14

SD, standard deviation; TSH, thyro-stimulating hormone.

functioning nodule. The mean Thyroid-stimulating hormone (TSH) value was 1.03 mU/L (± 0.49 mU/L SD) and showed no significant differences between the two populations (**Table 1**).

Ultrasound nodule structure was summarized in **Table 1**. Nodules with solid, spongiform and predominantly solid structure were selected. Solid structure and spongiform structure showed statistically significant differences with p-values of 0.022 and 0.023 respectively. The solid structure nodules were treated more with RFA (seven cases with RFA versus two cases with vRFA), while the spongiform nodules were treated more with vRFA (four cases with RFA versus 14 cases with vRFA).

Baseline nodule vascularization characteristics are summarized in **Table 1** and do not show significant difference.

At baseline, the nodule volume ranged 1.60 to 74 ml with a mean of 26.90 ± 19.09 ml (**Table 1**). Considering the two groups separately, the Group A' mean volume was 21.15 ± 20.34 ml, in the other hand, Group B' mean volume was 30.96 ± 17.65 ml with a p-value=0.178. The variables of the ablative techniques are illustrated in **Table 2**. The Joules/energy used showed a statistically significant difference between the two techniques, with a mean of 29663.83 ± 21040.14 J/s in Group A and a mean of 48275.47 ± 26029.28 J/s (p-value=0.05), showing that more energy must be used in vRFA. The execution time expressed in seconds showed no significant difference. Both techniques were conducted by two skilled operators of a tertiary thyroid center.

After radiofrequency ablation treatment the mean volume of nodule decreased progressively (**Table 3**, **Figure 5**): it was 14.15 ± 11.37 ml 1 month after treatment; 9.26 ± 8.48 ml 3 months after treatment and 6.41 ± 6.53 ml 6 months after treatment (p-value of 0.279, 0.784 and 0.451, respectively). The nodule volume decreased gradually during 1 month of follow-up with a mean of 14.15 ml versus 26.9 ml at baseline. The percentage of reduction at 1 month was 47.26% in study population without a significant difference between Group A and Group B (p-value= 0.369). Subsequently, percentage of volume reduction was decreased mostly in the Group B at 3 months and 6 months of follow-up with a p-value of 0.003 and 0.013, respectively. At 3 months of follow-up, Group B showed a mean percentage reduction of 72.71 ± 8.99% compared to the Group A's mean percentage reduction of 56.28 ± 14.55%. Moreover, at 6 months follow-up, Group B showed a mean percentage reduction of 83.01 ± 5.04%

TABLE 2 | Radiofrequency ablation characteristics (SD, standard deviation).

Characteristics	Population	Group A	Group B	p-value
Mean used Joule ± SD (range)	40,574.10 ± 25,457.69 (4,560–98,000)	29,663.83 ± 21,040.14 (4,560–71,180)	48,275.47 ± 26,029.28 (9,800–98,000)	0.05
Mean time in seconds ± SD (range)	638.55 ± 299.33 (192–1,320)	537.58 ± 244.47 (192–985)	709.82 ± 320.42 (204–1,320)	0.129

TABLE 3 | Thyroid nodule volume in follow-up (SD, standard deviation).

Characteristics	*Population*	*Group A*	*Group B*	*p-value*
1 month volume ± SD (range)	14.15 ± 11.37 (1.60–45)	11.38 ± 12.36 (1.60–45)	16.09 ± 10.55 (4.12–38.40)	0.279
1 month % volume variation ± SD (range)	47.26 ± 16.5(0–74.26)	43.45 ± 22.67 (0–69.54)	49.95 ± 10.23 (35.58–74.26)	0.369
3 months volume ± SD (range)	9.26 ± 8.48 (0.95–38)	9.78 ± 10.8 (0.95–38)	8.88 ± 6.73 (1.60–25)	0.784
3 months % volume variation ± SD (range)	65.91 ± 14.04 (36.64–85.88)	56.28 ± 14.55 (36.64–76.93)	72.71 ± 8.99 (57.14–85.88)	0.003
6 months volume ± SD (range)	6.41 ± 6.53 (0.21–31)	7.68 ± 9.11 (0.21–31)	5.51 ± 3.92 (0.90–14.40)	0.451
6 months % volume variation ± SD (range)	77.64 ± 12.07 (48.07–91.34)	70.04 ± 15.04 (48.07–89.72)	83.01 ± 5.04 (75.89–91.34)	0.013

compared to Group A's mean percentage reduction of 70.04 ± 15.04%. Data showed that the percentage of nodule reduction was not dissimilar between the two groups after one month from the ablative treatment. At 3 months, instead, there was a significant percentage of major reduction in patients treated with vRFA. This statistical significance remained unchanged at 6 months, registering a greater volume reduction percentage in patients treated with vRFA than in patients treated with RFA.

DISCUSSION

Numerous studies have shown that radiofrequency ablative treatment is an effective and safe treatment in symptomatic benign nodules of the thyroid (1, 12, 16, 19, 21, 26). International guidelines show that radiofrequency is effective in the treatment of microcarcinomas and recurrent carcinomas of less than 2 cm in diameter, not only in the treatment of symptomatic benign nodules (2, 10). Any study has shown the difference in the efficacy of RFA versus vRFA with artery-first step ablation techniques. The aim of our study was to evaluate the difference in the effectiveness of RFA and vRFA with a 6-month follow-up in symptomatic benign thyroid nodule.

Effective cytoreduction occurs when large volumes of necrosis are rapidly obtained with ablative treatments (22). In our population study, the percentage of volume reduction was similar between the two groups at 1-month follow-up, but it's statistically different in Group B at 3- and 6-months follow-up. The percentage of reduction at 1-month is not different in the two groups due to infarction of the nodule treated with vRFA. The infarction is due to a reduction in the vascularization of the nodule and to a reduction in venous drainage (3). This scenario changes at 3 and 6 months of follow-up, in which there is a reduction in inflammation due to necrosis and a resumption of venous drainage with the removal of the necrotic cells from the treated nodule. Some Authors suggest that a volumetric reduction of treated nodule is from 50 to 80% after 6 months and from 70 to 90% after two years. In our cases we had a volume reduction of 43.45%, 56.28%, and 70.04% at 1-, 3-, and 6- months in Group A and a volume reduction of 49.95%, 72.71%, and 83.01% at 1-, 3-, and 6-months in Group B. The percentage of volume reduction is in line with the Literature data with a

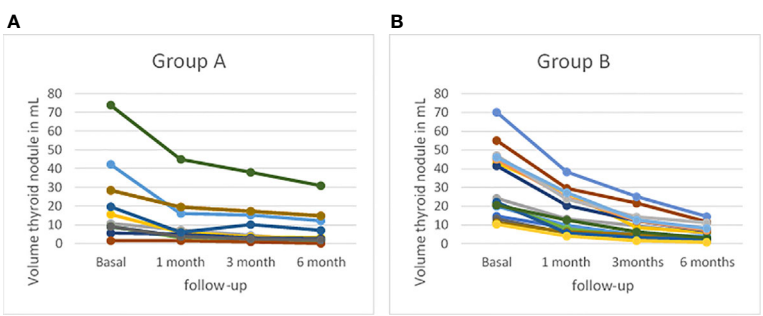

FIGURE 5 | Profiles of thyroid volume assessed by B-mode ultrasound (US) at baseline and at 1-, 3-, and 6-month follow-up **(A)** in patients treated with radiofrequency thermal ablation (RFA) (Group A) and **(B)** in patients treated with vRFA (Group B).

reduction of more than 50% of the volume already after 3 months of treatment in both techniques (21). In the future we will publish a study with a wider case history and a longer follow-up, to evaluate the percentage of reduction over the years and a possible regrowth of the nodule, comparing the two methods. The long-term efficacy of the treatment is assessed by observing the absence of nodular vital tissue regrowth, which can be demonstrated during ultrasound examinations carried out in the period following the treatment. Nodular regrowth, in the other hand, has been associated with the presence of inadequately treated nodular margins (21, 26–28).

In our population study, the nodules' feeding artery is ablated with RFA before starting the ablative treatment. The rational of RFA is to increase the local temperature in order to induce tissue necrosis. Many benign thyroid nodules are hyper-vascularized. The adjacent vascular structures can dissipate the heat generated during the procedure reducing the treatment's effectiveness. The early ablation of afferent artery reduces the vascularization of the nodule and the heat dissipation. Moreover, the afferent artery ablation reduces the risk of bleeding and of hematomas. The hemorrhage, during the RFA, leads to increase of volume and to obstacle the thermal conduction (3, 22). Our population shows a difference compared to the structure of the nodule. In Group A we have 58% of the population with a solid echostructure of the nodule, while in the Group B we have 82.4% with a spongiform echostructure of the nodule. The significant difference is affected by the choice of technique. vRFA can be used in the treatment of nodules with a feeding artery visible and nodules with a spongiform echostructure are nodules of greater size and intensely vascularized. Deandrea et al. suggest that spongiform nodule and cystic nodule have a greater reduction volume compared to solid nodules (21). Deandrea et al. hypothesize that in the nodules with a greater fluid component and in the more vascularized ones, the heat induced by the electrode produces more steam and the steam improves the thermocoagulation process (21). These data are in line with the ones observed in our study population. The energy utilized (J/s) shows significant difference. In vRFA group we have utilized increased energy (29663.83 vs 48275.47 J/s) as the method foresees two treatment steps: a first phase in which the nutritious artery is ablated and a second phase in which the nodule is ablated.

Park et al. describe an US hyperechoic linear streak at the nodule periphery after the afferent artery ablation. The US image is due to overheating which induces the appearance of microbubbles inside the arterioles. In some cases, on the other hand, it's possible to view a wedge-shaped hypoechoic area due to ischemia. The ischemic area is a rare finding especially in hypervascularized nodules due to the presence of several collateral circles (3).

Our preliminary experience, conducted on symptomatic thyroid nodules, shows that the radiofrequency treatment is a safe and an effective treatment. The method allows to reduce the compression symptoms, to obtain high percentages of reduction of the volume of the nodule even with just one treatment, to treat the nodule with the most effective technique based on the anatomical conditions and is squeezed to a risk of complications absent when performed by expert hands.

We achieved a significant percentage of greater volume reduction in the vRFA group compared to patients treated only with RFA. At follow-up, peripheral vascularization appears less evident on CD, in patients undergoing vRFA than in those treated only with RFA. These considerations allow us to hypothesize that vRFA may improve the effectiveness of the procedure, allowing for an improvement in symptoms and a reduction in volume more quickly. They were preliminary but promising results, clearly a larger series of cases and prolonged follow-up are needed to clarify and confirm our observations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee Campania Center Prot. no 375/C.E 18-2020 oss of 09/15/2020. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the present research and reviewed the entire manuscript. CO participated substantially in conception, design and execution of the study and in the analysis and interpretation of the data; also participated substantially in the drafting and editing of the manuscript. SG participated substantially in conception, design and execution of the study and in the analysis and interpretation of the data; also participated substantially in the drafting and editing of the manuscript. GA participated substantially in conception and design of the manuscript and in the analysis and interpretation of the data. ME participated substantially in conception and design of the manuscript and in the analysis and interpretation of the data. UB participated substantially in conception and design of the manuscript and in the analysis and interpretation of the data. CM participated substantially in conception and design of the manuscript and in the analysis and interpretation of the data. ED'A participated substantially in conception and design of the manuscript and in the analysis and interpretation of the data. DP participated substantially in conception and design of the manuscript and in the analysis and interpretation of the data. SS participated substantially in conception, design and execution of the study and in the analysis and interpretation of the data; also participated substantially in the drafting and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Radiofrequency Thermal Ablation for a Small Papillary Thyroid Carcinoma in a Patient Unfit for Surgery: A Case Report

Francesca Maletta[1], Sara Garberoglio[2], Alessandro Bisceglia[2], Alberto Ragni[3], Francesca Retta[3], Marco Gallo[3,4], Roberto Garberoglio[2] and Mauro Papotti[5]*

[1] Pathology Unit, Department of Laboratory Medicine, Città della Salute e della Scienza Hospital, Turin, Italy, [2] Division of Endocrinology, Diabetology and Metabolism, Department of Medical Sciences, Città della Salute e della Scienza Hospital, University of Turin, Turin, Italy, [3] Oncological Endocrinology Unit, Department of Medical Sciences, Città della Salute e della Scienza Hospital, University of Turin, Turin, Italy, [4] Endocrinology and Metabolic Diseases Unit, AO S.S. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, [5] Pathology Unit, Department of Oncology, University of Turin, Turin, Italy

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***Correspondence:**
Francesca Maletta
francesca.maletta@libero.it

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Ultrasound-guided radiofrequency thermal ablation has been proposed as an effective and safe procedure for treating patients who have low-risk papillary thyroid microcarcinomas and/or are unfit for surgery. We present the case of a 72-year old male patient with a small thyroid nodule diagnosed as papillary carcinoma after fine needle aspiration. Since the patient had other serious comorbidities, priority was given to other therapies and the malignant thyroid nodule was submitted to active surveillance. After detecting at a follow-up examination a slight dimensional increase of the nodule, the possibility of a radiofrequency thermal ablation was proposed to our patient, who accepted. The procedure was safely and effectively carried out. Follow-up examinations with ultrasonography (or contrast enhanced ultrasound), conducted after 1, 3, 6, and 12 months, demonstrated a progressive reduction of size and loss of vascularization in the treated area. The fine needle aspiration was repeated after 6 months: the sample revealed a very poor cellularity composed of inflammatory cells and thick colloid; no residual neoplastic cells were observed. Our experience confirmed what already demonstrated by previous reports: radiofrequency ablation can effectively eliminate small papillary carcinomas, with a very low complication rate. It may be an alternative strategy for the treatment of low-risk, indolent papillary thyroid microcarcinomas, thus avoiding the potential side-effects of surgery in patients at risk for relevant comorbidities.

Keywords: radiofrequency, ablation, papillary carcinoma, thyroid, fine needle aspiration, minimally invasive procedure, case report

INTRODUCTION

Surgery represents the first approach for the treatment of papillary thyroid carcinoma (PTC). However, considering the overall good prognosis of this neoplasm, extensive radical resection may not be indicated for some patients due to the risk of surgical complications and impaired quality of life in the postoperative period (1, 2). For years, radiofrequency ablation (RFA) has been considered a safe and effective method for the treatment of benign thyroid nodules and recurrent thyroid tumors. Currently, several guidelines recommend RFA treatment for symptomatic benign thyroid nodules, while indications for the treatment of malignant nodules are limited to palliative treatment in recurrent thyroid tumors or metastatic lymph nodes, when surgery is contraindicated or refused by the patient (1–5). RFA has also been recently suggested as an alternative treatment modality for primary thyroid microcarcinomas (1–3, 6) and in 2017, the RFA guidelines of the Korean society of thyroid radiology proposed the use of RFA for patients with primary thyroid cancer who refuse or are unfit for surgery (7).

CASE DESCRIPTION

A 72-year old male patient was referred to our clinic after the diagnosis of a left axillary lymph node metastasis from Merkel cell carcinoma (MCC) with high mitotic activity and proliferation index. A dermatologic evaluation showed no sign of a primary skin lesion. A ^{18}F-fluoro-2-deoxy-d-*glucose Positron Emission Tomography* (^{18}FDG-PET)/Computed Tomography (CT) scan was performed for initial tumor staging and revealed an uptake in the left axilla (site of the known lymph node lesion) and a focal uptake in the left thyroid lobe. The subsequent thyroid ultrasound (US) showed, in the medial third of the left thyroid lobe, an 8x8x7 mm markedly hypoechoic, solid, subcapsular nodule with irregular margins and microcalcifications (high-risk category according to the 2016 AACE/ACE/AME US classification system) (8). No suspicious cervical lymph-nodes were detected. TSH and calcitonin levels were normal. Given the suspicious US features and the ^{18}FDG-PET uptake, a US-guided fine needle aspiration cytology (FNAC) was performed, being consistent with PTC (Tir 5 according to SIAPEC/IAP classification of thyroid cytology or category VI according to the Bethesda System) (9, 10) (**Figure 1**).

In consideration of the clinical aggressiveness of MCC and its staging, priority was given to the treatment of MCC and a strategy of active surveillance for the small malignant thyroid nodule was chosen.

Subsequently, patient underwent external beam radiotherapy treatment to the axillary lesion (50 Gy/25 fractions), and, after detection of metastatic liver lesions and peri-pancreatic lymph node metastases, multiple cycles of systemic Carboplatin/Etoposide chemotherapy were administered. After a further disease progression, the patient was switched to an immunotherapy-based, second-line systemic treatment regimen with avelumab. The following restaging CT scans showed progressive reduction in the size of known liver metastases, confirming a partial response to the immunotherapy regimen, which was then discontinued after 18 months due to stable disease.

During the US follow-up exams, the malignant thyroid nodule showed a slight dimensional increase, reaching the size

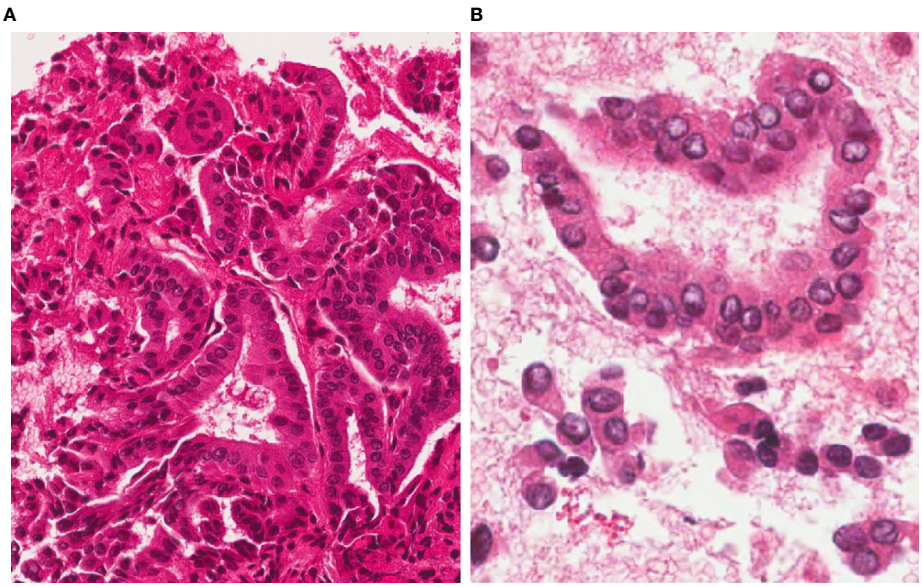

FIGURE 1 | FNAC before RFA. 4 µm-thick H&E stained sections from the cell-block show a highly cellular sample, with a typical papillary architecture; thyrocytes show irregular, large and clear nuclei. A diagnosis of Papillary Thyroid Carcinoma (TIR5 according to the Italian SIAPEC-IAP classification of thyroid cytology) was formulated (**A**, magnification x200; **B**, x400).

of 11x9x8 mm of maximum diameter. Taking into consideration patient's age, performance status, the overall clinical situation and surgical risk, a less invasive treatment approach was preferred, and after obtaining patient's informed consent, a procedure of RFA of the malignant thyroid nodule was performed.

DESCRIPTION OF THE PROCEDURE

The treatment of RFA was carried out in day hospital regimen. A peripheral vein was cannulated in the forearm with a venous catheter. During the procedure, 500 ml saline and 50 mg of Ranitidine were administered. The patient was connected to a monitor which allowed to check peripheral oxygen saturation, electrocardiogram, respiratory rate and blood pressure during the whole duration of the procedure. He was placed supine with his neck extended, in order to allow a better exposure of the jugular region.

The nodule was assessed by ultrasound: it was sub-capsular and localized in the left thyroid lobe, in the para-isthmic region; its diameters were 11x9x8mm. The echostructure was solid, irregular, hypoechoic, with slightly spiculated margins and with microcalcifications (**Figure 2**). At the Echo Color Doppler (ECD) investigation, vascularization was mainly endonodal; on strain elastosonography it appeared mainly rigid. The investigation was completed with the contrast-enhanced US (CEUS) (SonoVue Bracco, Milan) which allowed the complete visualization of the nodule vascular micro-network: it appeared mainly endonodal but irregular, with a scarcely vascularized central nucleus.

The procedure was carried out by RG, a collaborator of our group with at least 30 years of diagnostic and interventional ultrasound experience, especially of the neck region. After disinfecting the skin and setting up the sterile field, the suitable point was identified by US to proceed with local anesthesia with 2% lidocaine: the anesthetic was injected at the site of the skin puncture and in the space between the thyroid capsule and the fascia of the peri-thyroid muscles (strap muscles), where the algogenic endings of the sensory nerves are located.

The needle for RFA (needle used RFT-0710N RF, Medical Co.Ltd) was then inserted, under US guidance, with a trans-isthmic approach, always displaying the needle along its major axis. This type of approach allows to constantly monitor the needle in the context of the nodule, keeping it away from the recurrent laryngeal nerve, in order to reduce the risk of thermal injury (1–3). For the RFA procedure, a maximum power of 50 Watts was used.

As a rule, the technique of ablation consists in ideally dividing the nodule into smaller units that are independently treated using the "moving shot" technique: the tip of the electrode is initially positioned in the deeper portion with subsequent retractions towards the more superficial portions.

Given the small size of the nodule, the procedure was carried out quickly, with a duration of 5'11".

At the end of the procedure, before removing the needle, another CEUS examination was performed to assess the extension of the ablated area and compare it to the pre-treatment situation: the ablation proved complete and the ablated area was clearly wider than the edge of the previously assessed neoplasm.

After the procedure, the observation period lasted about 6 hours, with infusion of Methylprednisolone (125 mg), Acetaminophen (1 g) and Ranitidine (50 mg) in 500 ml saline solution. A last US exam of the anterior cervical region was performed to assess the absence of complications and then the patient was discharged home.

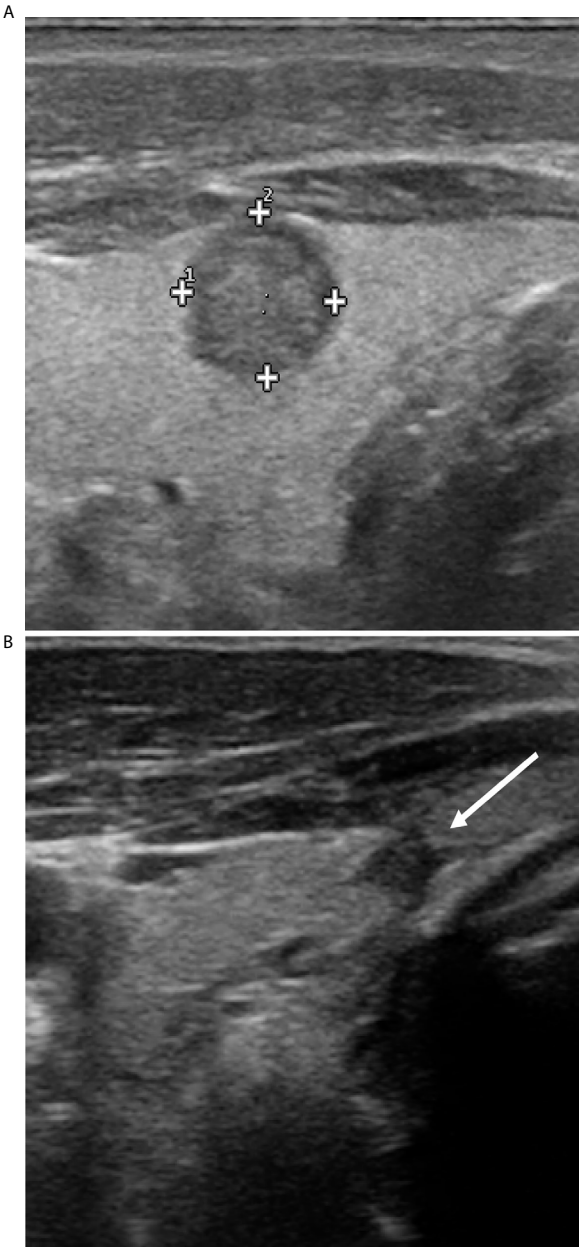

FIGURE 2 | Ultrasound features of the nodule before and after RFA. Before RFA **(A)**, the nodulation has a solid, irregular, hypoechoic structure, with slightly spiculated margins and microcalcifications. At control 12 months after RFA only a small nodular, hypoechoic and homogeneous area is appreciable **(B)**; it is in contact with the thyroid capsule that appears slightly retracted but with no signs of extra-thyroidal extension.

FOLLOW-UP

The patient was reassessed with the US at 1, 3, 6, and 12 months after the procedure, making a multiparametric US evaluation and adding the CEUS in the 3rd and 6th month controls.

At the examination performed after 1 month, the nodule had an oblong shape, measured approximately 13 x 22 x 9 mm (respectively, transverse, lateral and antero-posterior diameters) (T x L x AP) and had a solid, hypoechoic, slightly inhomogeneous echostructure, with regular margins. In the control performed after 3 months, the nodule had a slightly oblong shape, with a substantially unchanged volume from the previous exam, with measurements of approximately 12 x 18 x 8 mm (T x L x AP). The nodule had a solid, slightly irregular and hypoechoic structure. CEUS assessed, the described area appeared clearly avascular.

In the control performed after 6 months, the nodule had clearly reduced dimensions, always oblong in shape with dimensions of approximately 8 x 12 x 6 mm (T x L x AP), with a hypoechoic, uneven echostructure, with a small anterior marginal hyperechoic area.

When investigated by CEUS, the nodular area appeared to be totally avascular with less clear vascular margins compared to the previous examination. During this evaluation, FNAC with thin needle (22 Gauge) was performed. The sample was partly smeared on two slides, of which one was immediately alcohol-fixed and stained with Hamatoxylin and Eosin (H&E) for rapid on site evaluation while the other was air-dried and stained with Giemsa afterwards; the remaining sample in the syringe was collected and alcohol-fixed in a test tube. From this material, a paraffin-embedded cell-block was obtained, from which 5-µm thick sections were cut and stained with H&E.

The FNAC (both smears and cell-block) yielded a poorly cellular sample containing inflammatory cells (histiocytes and multinucleated cells), necrotic debris, fibrotic tissue, thick colloid and scattered thyrocytes, the latter showing no significant nuclear atypia (regular nuclear margins without groovings or pseudoinclusions) (**Figure 3**). If compared with the pre-RFA procedure FNAC, cellularity was considerably reduced and the typical signs of papillary carcinoma were totally absent.

After 12 months, only a small nodular area in the site of the previous treatment was appreciable, with a maximum size of about 4 mm, hypoechoic, homogeneous, without significant vascularization under ECD investigation (**Figure 2**). The nodule was in contact with the thyroid capsule that appeared slightly retracted, but seemed confined within the thyroid parenchyma, with no sign of extra-thyroidal extension. No pathological cervical lymph-nodes were found.

Nowadays, two years after the diagnoses of MCC and thyroid cancer, the patient is alive and well, substantially free of disease.

DISCUSSION

Since the first reported series in 2006 (11, 12), a number of studies showed the efficacy and safety in treating benign 'cold' and 'hot' thyroid nodules with RFA. Currently, several guidelines recommend RFA for generally benign thyroid nodules for symptomatic or cosmetic reasons and until recent years, recommendations for malignant diseases were restricted to palliative treatment for recurrent thyroid cancers or metastatic lymph nodes when surgery was contraindicated or declined by the patient (13–15).

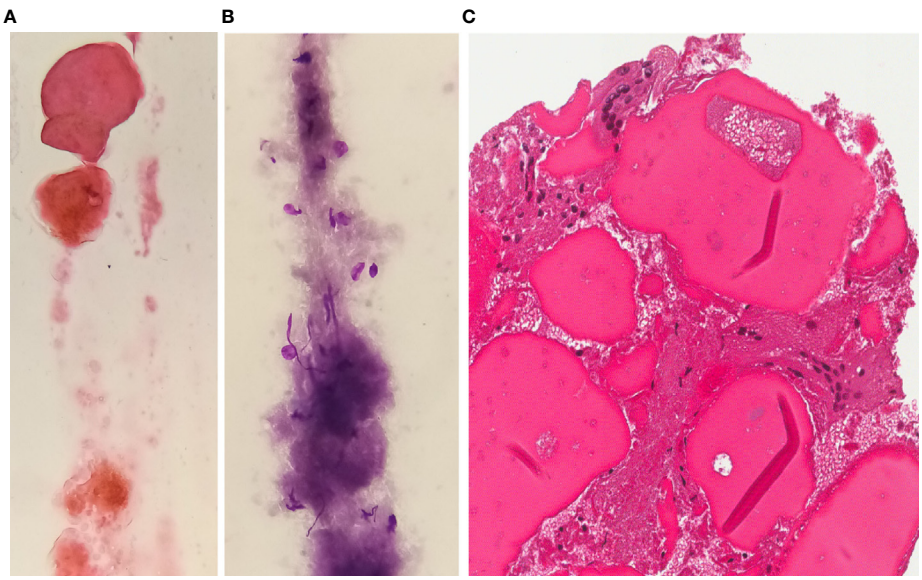

FIGURE 3 | FNAC after RFA H&E **(A)** or Giemsa **(B)** stained smears and H&E stained section from cell-block **(C)** exhibit a poorly cellular sample with sparse inflammatory elements or multinucleated giant cells in a background of thick colloid and fibrosis (magnification x400).

However, several previous studies also showed that image-guided RFA is safe and effective in the treatment of primary thyroid microcarcinoma (PTMC) (16, 17) and this procedure was included in the 2017 RFA Guidelines of the Korean Society of Thyroid Radiology as an alternative to surgery for patients who refuse it or who cannot undergo an operation (7). Satisfactory results of image-guided thermal ablation for primary thyroid cancer were also reported using means other than radiofrequency, like laser and microwave (18, 19) but whether there is a difference among the efficacy of different techniques remains unclear and should be investigated with further studies.

As previously reported, after about two years of follow up, no sign of PTC recurrence was seen in our patient. This, together with the anatomo-pathological findings 6 months after the procedure, with no evidence of typical PTC cells, testifies the effectiveness of RFA in the treatment of malignant thyroid nodules. However, it should be considered that the patient was concomitantly taking avelumab; even if nowadays there are no data about the use of this drug in PTC treatment, there is a growing evidence regarding the efficacy of immunotherapy, and in particular of pembrolizumab, in the field of advanced thyroid cancer treatment (20). Therefore, we cannot exclude that this factor may also have contributed to the successful control of PTC in this patient)

The present case report recaps on some topics about RFA. As described elsewhere (1), the procedure starts by positioning the electrode into the deepest conceptual ablation unit of the nodule and under continuous US guidance and using the "moving shot" technique, the output RF power is administered until all conceptual units of the nodule have been covered. Our experience highlights an important concept about the technique of RFA: when treating a malignant nodule, thermoablation-induced necrosis must be extended beyond the borders of the nodule, even if it is in contact with the capsule, in order to be sure of the total ablation of the nodule. The US (morphological and contrast-enhanced) checks carried out in our case showed a tissue necrosis wider than the area of the tumor, thus testifying a positive result of the procedure. The tumor area was totally ablated and, at the end of the treatment, it appeared very small and avascular. However, attention must be paid not to damage the surrounding noble structures and in some cases it may be useful to interpose some liquid between the muscle band and the capsule. In the event that the nodules are in a position very close to the thyroid capsule or to the trachea, esophagus or arterial vessels, it is possible to perform a local infusion of liquid (saline solution, or 5% glucose), in order to create a liquid barrier between the nodule to be treated and the surrounding anatomical structures to protect the noble structures of the neck (the so-called "hydrodissection technique"). In our case, due to the position of the target nodule, it was not necessary to recur to this technique.

Contrary to the growing experience in using non-surgical procedures for thyroid nodule treatment (ethanol ablation, laser ablation, RFA, high-intensity focused ultrasound), morphological changes produced by ablation are rarely investigated apart from occasional descriptions of minimally-invasive techniques such as core needle biopsies (CNB) on residual nodule detected during follow-up after these procedures. In 2016, Branovan et al. (21) analyzed the gross and microscopic alterations in human thyroid tissue induced by RFA: the experiment was conducted on 37 thyroid glands surgically removed for follicular adenoma or adenomatous colloid goiter. After dividing the nodules into two parts, one was a subject for histological routine processing, the other one was used for the RFA procedure. On the half nodule treated with RFA, pathological examination revealed destructive and diffuse alterations in shape and size of parenchymal structures (follicles), stroma and vessels. Moreover, extensive necrotic areas, wrinkling of the tissue, swelling and blurring of cell details were observed. Also, larger vessels (venules) appeared spastic, while smaller ones (small lymphatics) were dilated.

Valcavi et al. (19) investigated the pathological effects of US-guided thermal laser ablation in three papillary microcarcinomas. The patients underwent percutaneous laser ablation and, subsequently, total thyroidectomy: conventional histology showed destructured and carbonized tissue, with no viable cells in the ablated area and in the rim of normal tissue surrounding the tumor. Similar results were obtained by Piana et al. (22) who evaluated the histopathological effects on 22 benign nodules treated with laser ablation and compared the cytological findings before and after the treatment with the histological features on surgical specimens.

Moreover, Zhang et al. (23) reported a case series of 98 patients treated with RFA on low-risk PTC. The follow-up CNB was performed in all patients after 3 months from the procedure, both in the ablation area and in the surrounding parenchyma and it showed degeneration of follicular epithelial cell, fibrosis with hyaline degeneration of interstitial collagen fibers and inflammatory lymphocytic infiltration at the center and at the edge of the ablation area. No residual or recurrent tumors were detected, which confirmed complete elimination of the PTMC lesions. These data were confirmed by a larger cohort of the same group (1), with CNBs showing degenerative changes such as edema, inflammation and sclerosis. Recently, Xiao et al. (24) evaluated the efficacy and safety of US-guided RFA for treating low-risk T1bN0M0 PTC. US-guided CNB was routinely performed at the center and edge of the ablation zone as well as in the surrounding thyroid parenchyma 3 or 6 months after ablation; among the ablation zones that did not disappear (28 cases on a total of 66 patients), CNB revealed no viable neoplastic cells in 26 cases, while two patients were found to have malignant cells on CNB at the edge of their ablation zones after 6 months of follow-up; these patients successfully underwent a second RFA session. A metastatic lymph-node was detected at ipsilateral level IV in one patient 3 months after ablation and this lymph-node was successfully treated with RFA. No distant metastases were detected during follow-up.

To our knowledge, our case is the first report on a FNAC (instead of a core biopsy) on a PTC nodule treated with RFA: results are similar to those shown in CNBs by Zhang et al. (23) and Wu et al. (1), namely a sample showing prevalent sclerosis, inflammation and absence of residual neoplastic cells. Thus, traditional FNAC may prove as effective as CNB in order to assess complete response to RFA or to detect a possible residual disease. Moreover, it has the advantage of being a less invasive procedure than CNB: CNB needles in fact are larger in caliber than FNAC needles and they should be used only by experienced operators; less-experienced operators may have difficulties in tracking the needle tip under US, thus increasing the possibility of complications (25).

In conclusion, image-guided thermal ablation of low risk PTC is becoming a widely accepted procedure: with the advantage of minimal invasiveness, it might be chosen as first line treatment for patients unfit for surgery or to avoid its complications. Some authors even suggest that image-guided thermal ablation might be a good option to compensate for image-derived cancer overdiagnosis (26), with PTCs being more and more often detected in their very initial stage due to improved imaging techniques.

However, so far, some limitations to the widespread use of RFA for treating PTMC still exist: first of all, available data are based on retrospective studies only, with inevitable sample bias (1). Moreover, considering the good prognosis of PTC, definitive conclusions about the efficacy of RFA might be drawn only after longer term follow-up, not yet available at the present moment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FM and SG conceived the idea of this essay. SG, AB, AR, FR, MG, and RG participated in the treatment and collected the case history. FM made the cytological diagnoses. FM, SG, and RG wrote the case report. RG and MP revised the manuscript.

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Predictor Analysis in Radiofrequency Ablation of Benign Thyroid Nodules: A Single Center Experience

Alessandro Bisceglia[1], Ruth Rossetto[1], Sara Garberoglio[1,2], Angelica Franzin[1], Alice Cerato[1], Francesca Maletta[3], Mauro Giulio Papotti[4], Ezio Ghigo[1], Loredana Pagano[1], Mauro Maccario[1] and Roberto Garberoglio[1,2]*

[1] Division of Endocrinology, Diabetology and Metabolism, Department of Medical Sciences, University of Turin, Turin, Italy, [2] Centro Multidisciplinare Della Tiroide (CMT), Humanitas Cellini, Turin, Italy, [3] Pathology Unit, Department of Laboratory Medicine, City of Health and Science Hospital, Turin, Italy, [4] Pathology Unit, Department of Oncology, University of Turin and City of Health and Science Hospital, Turin, Italy

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***Correspondence:**
Alessandro Bisceglia
bisce90@hotmail.it

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Purpose: To confirm the efficacy of ultrasound (US) guided radiofrequency ablation (RFA) in the treatment of benign thyroid nodules, we evaluated as primary outcome the technical efficacy and clinical success in a single center dataset. The secondary outcome was to find a correlation between nodules' pre-treatment features and volume reduction rate (VRR) ≥75% at 12 months after RFA and during follow-up period.

Methods: This retrospective study included 119 consecutive patients (99 females, 20 males, 51.5 ± 14.4 years) with benign thyroid nodules treated in our hospital between October 2014 and December 2018 with a mean follow-up of 26.8 months (range 3–48). Clinical and US features before and after RFA were evaluated by a US examination at 1, 3, 6, 12 months and annually thereafter up to 48 months.

Results: The median pre-treatment volume was 22.4 ml; after RFA we observed a statistically significant volume reduction from the first month (11.7 ml) to the last follow-up ($p < 0.001$ for all follow-up times). The median VRR was 47.1, 55.3, 61.2, 67.6, 72.8, 71.3, and 62.9% at 1, 3, 6, 12, 24, 36, and 48 months of follow-up respectively, showing a progressive significant improvement up to 24 months (VRRs 1 *vs* 3 months, 3 *vs* 6 months and 6 *vs* 12 months $p < 0.001$, 12 *vs* 24 months $p = 0.05$) while no differences at 24 *vs* 36 and 36 *vs* 48 months were observed. Symptoms improved significantly (complete resolution 64.35%, partial resolution 35.65%), and neck circumference was reduced as compared to pre-treatment ($p < 0.001$). Lower pre-treatment neck circumference (37.5 *vs* 36.0 cm, $p = 0.01$) was a positive predictor of VRR ≥75% at 12 months. Macrocystic echostructure (HR 2.48, p 0.046) and pre-treatment volume >22.4 ml (HR 0.54, p 0.036) were found to be independent positive and negative predictors of VRR ≥75% respectively. One-month post RFA VRR ≥50% represented the best positive predictor of technical success.

Conclusions: This study confirmed the efficacy of RFA in the treatment of benign thyroid nodules. In particular we show that by selecting macrocystic nodules smaller than 22.4 ml better long-term response can be achieved, which is predicted by an early shrinkage of the nodule.

Keywords: predictive factors, efficacy of radiofrequency ablation, radiofrequency ablation (RFA), benign thyroid nodules, volume reduction

INTRODUCTION

Thyroid nodules are a relatively common clinical condition that affects up to 65% of the general population with large variability mostly originating from geographical heterogeneity and sensitivity of diagnostic methods (1). The incidence seems to be related to gender, insufficient iodine intake (2), and particularly, age (3). In most cases, these lesions are not symptomatic and, therefore, are diagnosed incidentally during instrumental examinations performed for some other reasons (4–6). Less frequently, thyroid nodules are diagnosed due to the presence of a palpable nodule in the cervical region or related symptomatology (*i.e.* compression trouble linked to the position and/or size) or thyroid hyperfunction (7, 8).

Although most thyroid nodules are benign, treatment could be required in the case of excessive size enlargement, compressive and/or cosmetic symptoms (9), or anxiety for the possibility of turning malignant (10, 11).

In these cases, the surgical approach represents the treatment to be preferred for thyroid nodules with compressive symptoms, even if it is known that neck surgery could lead to serious complications, *i.e.* hypocalcemia and dysphonia (12, 13).

For these reasons, in the last two decades, image-guided ablation procedures have been proposed. These procedures are minimally invasive and are also applicable to patients with contraindications to major surgery, or in patients who refuse it. The most consolidated alternative are percutaneous ethanol injection (PEI) (5, 14–16), laser ablation (LA) (17–20) and radiofrequency ablation (RFA) (21–26); more recently, microwave ablation (MW) and then high-intensity focused ultrasound (HIFU) have been proposed (27, 28).

In particular, RFA has been recommended as a treatment to be preferred for benign thyroid nodule by several guidelines (15, 29–32).

RFA of benign thyroid nodules have shown good results in volume reduction rate (VRR), ranging from 33 to 58% one month after treatment, and 51–85% up to six months, improving most of nodule-related clinical symptoms (21, 23, 24, 33–37).

However, the way of predicting the outcome of RFA treatments is still not well understood (38).

This study aimed to confirm the efficacy of RFA in the treatment of benign thyroid nodules in a single center dataset and to detect a significant correlation between pre-treatment features, including clinical and ultrasonographic features, and volume reduction rate (VRR) ≥75% at 12 months after the procedure and then during all follow-ups.

MATERIALS AND METHODS

This retrospective observational study included 119 consecutive patients referred to our Centre (Città della Salute e della Scienza University Hospital in Turin) for RFA of thyroid benign nodules from October 2014 to December 2018.

The inclusion criteria were: (a) patients aged 18 years or older; (b) confirmation of benignity (Tir2, SIAPEC-IAP) (39) or indeterminate lesions at low risk of malignancy (Tir3A) (39, 40) at two fine-needle aspiration cytology without echographic features suspicious for malignancy and normal level of serum calcitonin; (c) compressive or cosmetic symptoms in patients with refusal or ineligibility for surgery; (d) patient underwent one single-session RFA.

The exclusion criteria were: (a) malignant (Tir5) or suspicious of malignancy (Tir3b-Tir4) thyroid nodules, (b) pregnancy.

The Institutional Review Boards of our hospital approved this study, and patient consent was obtained in all cases.

Pre-Treatment Assessment

Clinical Evaluation

We categorized symptom and cosmetic scores as defined in a previous consensus statement (41). Subjective compression symptoms were assessed by a visual analogue scale (grades 0–10) where 0 indicates the absence of compression-related disorders and 10 indicates the maximum tolerable discomfort; the cosmetic assessment was performed based on a four-point scale: 1 = absence of palpable mass; 2 = palpable but not visible mass; 3 = cosmetic problem during swallowing alone; 4 = easily identifiable visible mass.

Neck circumference, expressed in centimeters (cm) and measured by placing the tape measure in the middle of the neck of the patient, was evaluated.

Biochemical Evaluation

Laboratory tests included: thyroid stimulating hormone (TSH), serum free thyroxine (fT4), calcitonin, complete blood count, coagulation tests, dibucaine number and cholinesterase, hepatic and renal function. Additionally, all patients underwent baseline electrocardiogram and vocal cord function assessment performed by an otorhinolaryngologist before the ablation procedure.

Ultrasound Evaluation

Both transverse and longitudinal sonograms were obtained by real-time imaging of the thyroid nodules using an Esaote MyLab Twice real-time US system with a linear multifrequency (7–14 mHz) probe. Still and video clip sonographic images

were evaluated by two board-certified radiologists (RG and SG) and two endocrinologists (RR and LP) with >10 years of experience.

The sonographic findings were analyzed based on the current guidelines (5, 15, 42) and reported as defined in a previous consensus statement (41).

Diameters (anteroposterior, transverse, and longitudinal) of each thyroid nodule were measured in centimeters (cm); the nodular volume, expressed in milliliters (ml), was calculated by the ultrasound machine on the basis of the diameters using the ellipsoid volume formula (length × width × depth × 0.524).

The nodular echostructure was classified as solid (≤10% of fluid component), microcystic (predominantly solid, 11–50% of fluid component), macrocystic (predominantly cystic, 51–90% of fluid component), cystic (>90% of fluid component), and spongiform (nodules containing multiple small cysts smaller than 5 mm interspersed within the solid tissue component for nearly all the volume).

The nodules echogenicity was classified as hypoechoic, isoechoic, or hyperechoic compared to the adjacent strap muscles of the neck. Regarding nodular shape, nodules were divided into regular or taller than wide. Nodular margins were categorized as smooth or irregular. Calcifications were reported as present or absent. Perinodular or intranodular vascularization was assessed by color and power Doppler examination; stiffness was evaluated by qualitative elastography (strain Elastosonography): the pressure is exerted freehand through the ultrasound transducer. An elastographic image (elasto-gram) is then produced, represented as a color-coded image superimposed on the image in mode B (43, 44); in our study, we used the classification proposed by Rago et al. (45). We defined the nodules with patterns 1 and 2 as soft; the nodules corresponding to pattern 3 were classified as intermediate elasticity and finally the nodules with patterns 4 and 5 were considered hard.

RFA Procedure

Access to the procedures was carried out on a day hospital basis. RFA procedures were performed by an operator with an experience of >10 years (RG).

A single session of RFA was performed with the patient in a supine position with mild neck extension. Patients underwent treatment in a state of conscious sedation and were managed with 0.75% ropivacaine around the thyroid gland for puncture site anesthesia, always with ultrasound guidance.

We used an internally cooled electrode: 18 gauge, 7 or 10 cm length with a 10 mm active tip (*RFT(S) Tip/RFTP(S) RF Medical Co.Ltd.*) connected to a radiofrequency generator (Mygen M-3004).

A transisthmic approach method with the 'moving shot technique' (29, 46) was adopted; the insertion of the needle-electrode took place under freehand ultrasound guidance with a mid-lateral path, in such a way as to direct the flow of energy towards the lateral regions of the neck and away from areas at risk due to contiguity of thermal injury, such as the inferior laryngeal nerve and tracheoesophageal structures. The target nodule is ideally divided into several ablation units prior to the procedure. Starting from the deepest portion, the treatment is carried out unit after unit by moving the needle towards the most superficial portions. Due to the heat, necrosis is obtained and a hyperechoic area is formed on the tip of the needle-electrode; the generator shuts down power and impedance increases (47). The needle is then gradually brought back along the electrode axis in order to reach another tissue unit still to be treated. The procedure ends when all the ideal units of the nodule have been treated, which therefore appears completely hyperechoic.

The applied power and the actual time of treatment were recorded at the end of each session; the mean power used during the treatment was 55 Watt (W) and the treatment time about 15 min (49,500 J).

The procedures were monitored under the control of the B-mode ultrasound method in real time to assess the correct positioning of the needle-electrode within the lesion to be treated. A transient and complete hyperecogenicity of the target nodule, linked to heat-induced changes, represents the parameter that identifies the end of the procedure (48). Before removing the electrode, we performed an examination with Contrast Enhanced Ultrasound (CEUS), SonoVue (Bracco, Milan, Italy) to evaluate the extent of the necrosis area: ablation was considered complete when the total volume of the nodule appears not-vascularized. Once the needle-electrode was extracted, a new ultrasound evaluation was performed to exclude intra or extranodular complications.

The patients were observed for at least 3 h and were finally discharged, in some selected cases with the prescription of oral analgesic therapy.

Follow-Up

Post-RFA, patients were followed up by US and clinical evaluations at 1, 3, 6 and 12 months after treatment and annually thereafter up to 48 months. In each follow-up, US examination, symptom and cosmetic score were evaluated while thyroid hormonal function was assessed every year. Thyroid nodule volume was assessed, and the volume reduction rate (VRR) of the treated nodule was calculated based on the formula: VRR = [(initial volume − final volume) × 100]/initial volume (26).

Study Outcome

The primary outcome was the therapeutic efficacy in terms of volume reduction, VRR, and clinical success (41), defined as the ability of the treatment to resolve the condition itself (compression symptoms or cosmetic concerns); it was classified as complete (*i.e.*, complete resolution of presenting symptoms), partial (*i.e.*, symptom improvement but still present), or absent (*i.e.*, no symptom improvement) and by modification of cosmetic score.

The secondary outcome was to find a significant correlation between pre-treatment features of the nodules and technique efficacy, defined as a volume reduction ≥75% at 12 months after RFA and then during all follow-up period.

Statistical Analyses

According to the descriptive statistics, continuous variables with normal distribution are expressed as mean ± standard deviation, while non-parametric data as median with interquartile range.

Statistical differences between continuous variables were evaluated with the Wilcoxon test for paired data or paired sample T-test.

To investigate the existence of an association between the technique efficacy of RFA (VRR ≥ 75%) and the clinical and pre-treatment ultrasound variables, a univariate analysis was conducted: Fisher's $\chi 2$ test was used for binary and categorical variables, while, for the continuous variables, in consideration of the non-normal distribution of the data despite the good number of the sample under study, the Mann–Whitney U test was assessed.

Secondly, for the comparison between multiple groups, the Kruskal–Wallis H test was performed.

Finally, a multivariate logistic regression model was constructed to confirm the existence of independent variables.

A dynamic analysis was then carried out, considering for each subject the time, expressed in months, between the RFA treatment and a volume reduction rate ≥75%, considered as the technical success, or the time between treatment and the last follow-up, in case of a volumetric reduction <75%. It was possible to evaluate the cumulative incidence of success (VRR ≥ 75%) by constructing the Kaplan–Meier curves, for a maximum follow-up period of 48 months; by using the Log Rank test, the Kaplan–Meier curves were then compared to evaluate the existence of possible predictors. For continuous variables, this test was performed by dividing the subjects into two categories based on the median of distribution of the variable itself.

Finally, a multivariate Cox regression model was constructed to confirm the presence of independent predictors.

The results were considered statistically significant if the p-value was less than 0.05.

All statistical analyses were performed with STATA IC 10 (STATACORP, LP, Texas, USA) analytic software.

RESULTS

Demographic and Sonographic Characteristics of Thyroid Nodules

In this study, 99 out of 119 patients were females (83.20%); the mean age at treatment was 51.5 ± 14.4 years with a mean follow-up of 26.8 months (range 3– 48) after RFA. All patients had normal TSH value. As regards the echostructural ultrasound pattern, out of a total of 119 nodules, 29 (19.33%) were solid, 62 (52.1%) microcystic, nine (7.56%) macrocystic, and finally 11 (9.24%) spongiform. No cases of pure cystic nodules were treated. Regarding the nodules with the first cytological result of TIR3A, they were TIR2 at the second fine-needle aspiration cytology in four out of five cases; only one case was confirmed as TIR3A, GALECTIN 3 negative for immnocytochemistry. In this case, the intermediate ultrasound risk nodule (15) with a size >3 cm created tracheal compression. The patient refused surgery. The baseline clinical and ultrasound characteristics of the patient and nodules are summarized in **Tables 1** and **2** respectively.

TABLE 1 | Pre-treatment clinical features of 119 thyroid RFA-treated nodules.

Clinical Features		**Total n = 119 (%)**
Thyroid function	Euthyroidism	100 (83.00)
	Hypothyroidism	16 (13.50)
	Hyperthyroidism	3 (2.50)
Citology	Tir2	114 (95.80)
	Tir3A	5 (4.20)
Compressive symptoms	0	3 (2.52)
(0–10)	1	2 (1.68)
	2	14 (11.76)
	3	13 (10.92)
	4	14 (11.76)
	5	35 (29.41)
	6	19 (15.97)
	7	7 (5.88)
	8	9 (7.56)
	9	2 (1.68)
	10	1 (0.84)
Cosmetic score	1	1 (0.84)
(1–4)	2	2 (1.68)
	3	2 (1.68)
	4	114 (95.80)
Clinical Features	**Mean ± DS**	**Median (interquartile range)**
Neck circumference (cm)	37.59 ± 3.57	37 (5.00)
Volume (ml)	25.25 ± 16.81	22.4 (20.70)

TABLE 2 | Ultrasonographic features of 119 thyroid RFA-treated nodules.

Ultrasound Features		**Total n = 119 (%)**
Structure	Solid	29 (19.33)
	Microcystic	62 (52.10)
	Macrocystic	9 (7.56)
	Spongiform	11 (9.24)
Echogenicity	Anechoic	0 (0.00)
	Isoechoic	72 (60.50)
	Hypoechoic	47 (39.50)
	Markedly Hypoechoic	0 (0.00)
Margins	Regular	116 (97.48)
	Irregular	3 (2.52)
Calcifications	Absent	80 (67.23)
	Present	29 (32.77)
Shape	Regular	119 (100)
	Taller than wide	0 (0.00)
Vascularization	Perinodular	29 (24.37)
	Endonodular	0 (0.00)
	Peri-Endonodular	88 (73.95)
	Unknown	2 (1.68)
Elastosonography	Soft	42 (35.29)
	Intermediate	52 (43.70)
	Hard	3 (2.52)
	Unknown	22 (18.49)
Volume (mL)	≤ 10	21 (17.65)
	11-30	60 (50.42)
	>30	38 (31.93)

Volume and VRR

The median pre-treatment volume was 22.4 ml; after RFA we observed a statistically significant volume reduction from the first month (11.7 ml) to the last follow-up ($p < 0.001$ for all follow-up times). The median VRR was 47.10% (range 31.30–56.50), 55.30% (range 46.70–68.80), 61.20% (range 52.0–73.60), 67.60% (range 53.90–79.20), 72.80% (range 56.60–83.20), 71.30% (range 56.10–84.40), 62.90% (range 50.50–87.90), at 1, 3, 6, 12, 24, 36, and 48 months of follow-up respectively, showing a progressive significant improvement up to 24 months of follow-up (VRRs 1 *vs* 3 months, 3 *vs* 6 months and 6 *vs* 12 months $p < 0.001$, 12 *vs* 24 months $p = 0.05$), while no significant differences between VVRs at 24 *vs* 36 months and 36 *vs* 48 months were observed (**Figure 1**).

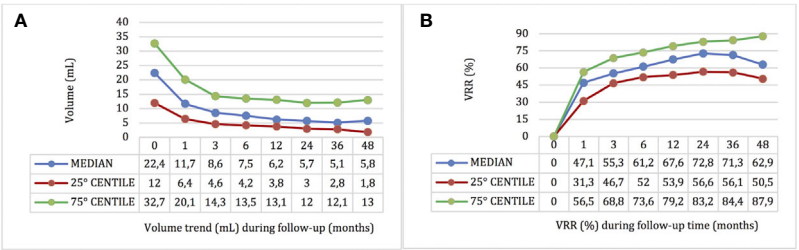

FIGURE 1 | Nodules' volume **(A)** and VRR **(B)** by time after RFA.

Stratifying the study sample into three categories based on the pre-treatment volume (41) (nodules ≤ 10, 10–30, and >30 ml), a significant volume reduction was confirmed for each category ($p < 0.001$) (**Figure 2**). Furthermore, a significant improvement in VRR was confirmed for each category ($p < 0.001$), and in the comparison between the three groups, nodules with volume ≤10 ml had a higher VRR although in a non-statistically significant way (**Figure 3**).

These results were also observed dividing the study sample into four categories by pre-treatment echostructure (41); a significant and progressive reduction in volume ($p < 0.001$) and improvement in VRR ($p < 0.001$) were confirmed for each echo pattern (**Figure 2**) and the nodules with macrocystic and spongiform echostructure showed a higher VRR compared to the other groups, but not statistically significance (**Figure 3**).

Clinical Success

Compressive symptoms (complete resolution 64.35%, partial resolution 35.65%) and cosmetic score improved significantly ($p < 0.001$); a statistically significant reduction in neck circumference was obtained at 6, 12, and 24 months post-treatment ($p < 0.001$). The mean pre-treatment neck circumference was 37.59 ± 3.57 cm and decreased to 36.02 ± 3.43, 35.94 ± 3.02, and 35.79 ± 2.92 cm respectively at 6, 12, and 24 months post-treatment.

Technical Success (VRR ≥75% at 12 Months) of Predictors' Analysis

At the end of the global follow-up, 108 out of 119 patients reached a VRR ≥50%.

The patients were divided into two groups in relation to the percentage of volumetric reduction obtained 12 months after treatment: BR (Best Responders) group in case of VRR ≥75% (36 cases) and MR (Mild Responders) group in case of VRR <75% (75 cases); subsequently, variables associated with VRR (predictors) were analyzed.

The two groups did not show gender ($p = 0.645$) or age ($p = 0.731$) differences regardless of the cytological result.

Regarding neck circumference before treatment, the BR group showed significantly lower values ($p = 0.012$) than the MR group.

In terms of volume, the BR group had lower nodular volumes than the MR group, with a difference close to statistical significance ($p = 0.063$).

Analyzing nodular echostructure, the microcystic ($p = 0.037$) and macrocystic ($p = 0.022$) nodules were associated with a VRR ≥75% at 12 months.

Finally, we analyzed as a possible positive predictor of response a VRR ≥50% at 1 month (VRR1m), considered the minimum percentage of RFA success by recent literature (41); this binary parameter was able to differentiate the two groups ($p < 0.001$), and specifically, the BR group presented a greater VRR1m than the MR group (56.30 *vs* 40.30%).

At multivariate logistic regression analysis, only VRR1m ≥50% was confirmed as an independent predictor of a VRR ≥75% at 12 months after treatment ($p = 0.001$; OR: 6.91; CI: 2.23–21.45).

Time-Dependent Predictors' Dynamic Analysis

The cumulative incidence of the technical success curve showed that most of the RFA technical success was achieved within 12

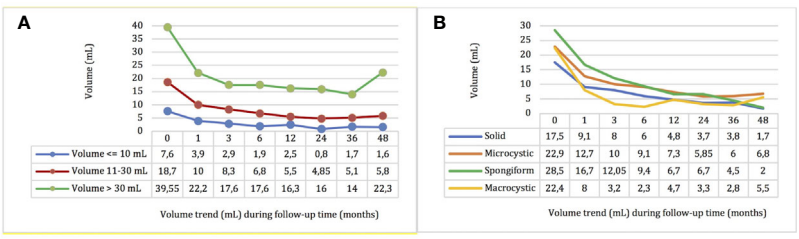

FIGURE 2 | Nodules' volume by time after RFA stratified by pre-treatment volume **(A)** and echostructure **(B)**.

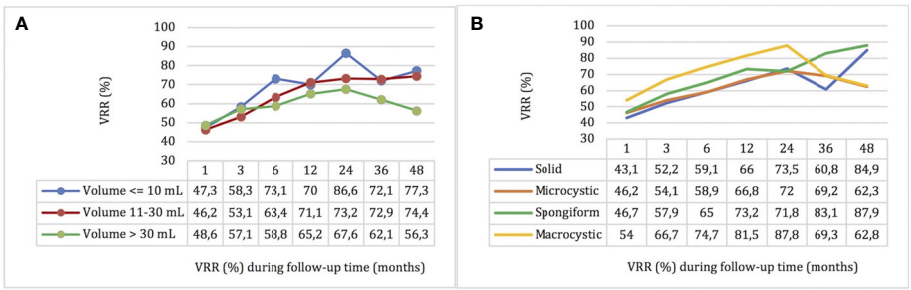

FIGURE 3 | Nodules' VRR by time after RFA stratified by pre-treatment volume **(A)** and echostructure **(B)**.

months (36%) with a progressive and clear improvement up to 24 months (48%). After 24 months, although there was a slight effectiveness improvement, it was significantly lower than the effectiveness obtained within 24 months.

By comparing the Kaplan–Meier curves, we observe that gender, older age (over the median value, 50 year), and larger neck circumference (over the median value, 37.5 mm) do not significantly affect the final outcome.

The pre-treatment volume is found to be a good predictor of treatment efficacy (p = 0.01). The group of patients with a nodular volume ≤22.4 ml (median) responded to the treatment better than the others; on the contrary, a pre-treatment volume >22.4 ml represented a negative predictor of success with an overall efficacy that never exceeds 40%, **Figure 4**.

The pre-treatment volume was confirmed as a good predictor of technical success even when stratified into three categories, as proposed by the recent literature (p = 0.037), **Figure 4**.

In fact, a clear divergence of the three curves is observed; in particular, the effectiveness of the treatment is found very low (≤30%) in nodules >30 ml, while the technical success of RFA is rapidly increasing in nodes <30 ml, especially if ≤10 ml (52% at 12 months, 60% at 24 months).

The comparison of the Kaplan–Meier curves shows that pre-treatment echostructural patterns are able to separate the curves with good reliability (p = 0.015). In particular, it shows how the macrocystic echostructure positively modifies the outcome of the treatment with an efficacy of over 75% at 12 months and almost total at 24 months, **Figure 5**.

Finally, taking into consideration the post-treatment variables, Kaplan–Meier curves highlight that an early volumetric reduction, as evidenced by a VRR ≥50% at 1 month after treatment, was an excellent predictor of the achievement of a VRR ≥75% during the whole follow-up (p = 0.0000), **Figure 5**.

At multivariate Cox regression model (p = 0.037, χ^2: 13.41), macrocystic echostructure (HR 2.48, IC: 1.02–6.07 p 0.046) and pre-treatment volume >22.4 ml (HR 0.54, IC: 0.31–0.96, p 0.036) were found independent positive and negative predictors of VRR ≥75% respectively.

One-month post RFA VRR>50% represented the best positive predictor of technical success (HR: 2.48; CI: 1.40–4.39, p = 0.002).

DISCUSSION

RFA treatment of benign thyroid nodules aims at obtaining a sufficient reduction of nodule volume for the regression of the compressive symptoms and cosmetic disorder, keeping it as stable as possible over time (15, 29, 30).

Our retrospective study confirmed the efficacy and safety of RF ablation in a single large cohort of patients. Particularly, the nodular volume showed a notable reduction as early as 1 month

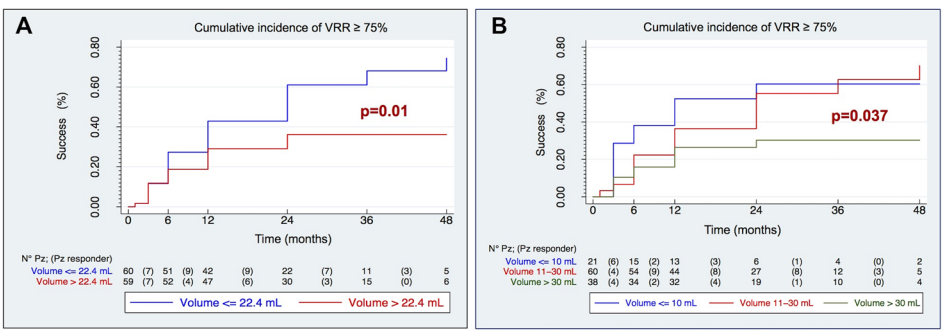

FIGURE 4 | Kaplan–Meier curves of cumulative incidence of technical success (VRR ≥ 75%) by median volume **(A)** and three volume categories **(B)**.

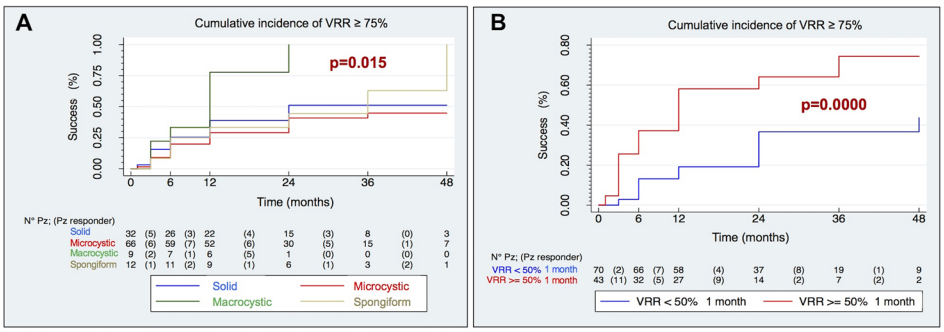

FIGURE 5 | Kaplan–Meier curves of cumulative incidence of technical success (VRR ≥ 75%) by echostructure **(A)** and VRR at 1 month **(B)**.

post-RFA, with a median VRR of 47.10% at 1 month of follow-up and 72.80% at 24 months, according to the literature (49–52).

RFA treatment of benign nodules has been introduced into clinical practice for a few years, so it still has a time-limited follow-up (51, 53, 54). To this purpose, this study is expected to provide additional information on the long-term result (up to 48 months) in terms of volume reduction (VRR) and the possible correlation between pre-treatment features and volume reduction rate.

First of all, our results (VRR at 3 months: 55.30%; VRR at 6 months: 61.20%) agree with some studies reporting that the achievement of a VRR ≥50% is detectable already at 6 months follow-up (52, 55). Then, in the literature, the technical success is usually identified in a VRR ≥50% at 12 months (41) which, at best, was achieved by 97.8% of patients (50). In our study, the achievement of RFA technical success, defined as a VRR ≥75%, was found in 36% of cases, with progressive improvement up to 24 months follow-up (48%) and beyond, although less significant, achieving a VRR ≥75% overall in the majority of treated nodules (57%).

Furthermore, according to our results, clinical success of the treatment was complete in most cases within 12 months post-RFA (64.35%); in the other cases the reduction was partial (35.65%), indicating that none of the patients undergoing RFA had an unsuccessful treatment, as highlighted by other authors (51, 52, 55). However, evaluation of symptoms and clinical success deriving from the volumetric reduction is subjectively expressed, and the results are not completely reliable as indicators of the success of the technique.

To date in the literature, some characteristics (47, 54), such as a spongiform echostructure, a liquid component, a smaller initial pre-treatment volume, an intense peripheral and intranodal pattern vascularity of the nodule, have been found positively correlated with a better result in terms of volumetric reduction, but no predictive pre-treatment factors of RFA success have been identified definitely. For this reason, we conducted a specific analysis to identify the differences between clinical and ultrasound parameters in best responder and mild responder patients.

Between the two groups, the indicative factors of a better technical success proved to be:

- the echostructural pattern: in our series, the best technical success was observed in macrocystic nodules ($p = 0.015$), in agreement with the literature (47, 56). The possible explanation for this is that, as is known, the heating of a tissue with a large fluid component, (be it colloid or blood) produces a greater amount of vapor and a higher temperature which favors the thermocoagulation process in the treated nodule;
- the pre-treatment neck circumference, lower in the best responder group, indicates that a larger neck is associated with a worse response to the treatment. This data, never considered in the literature, would deserve further prospective studies in our view. Since there are no other systems beyond the ultrasound to assess the goodness of the result, we have tried to insert a linear dimensional parameter such as the circumference of the neck in its maximum diameter. This parameter, never considered in the literature, could offer further important prospective studies. Certainly, this parameter is associated with some confounding factors, as weight changes; however, the measurement of the neck circumference pre-treatment and during the follow-up allows us to hypothesize that the volumetric reduction of a nodule in the thyroid induces a remodeling of the anatomical structures contained in the neck.
- the pre-treatment nodular volume: in best responding patients, the nodules with volume ≤22.4 ml had a substantially better response ($p = 0.01$). This result reinforces the hypothesis that the greater volume reduction in nodules with lower basal volume is probably due to reduced energy deposition during RFA within large ones, which therefore results in a lower response (32, 51).

In addition, in our cohort, we have pointed out that VRR1m is a good predictor of technical success (reaching 50% in 56.30% of responding patients; $p = 0.0000$); however, it should be emphasized that this parameter, not mentioned in the literature, although reliable, can only be evaluated after treatment and, therefore, does not fall within the definition of predictor of technical success.

Our study also highlights a progressive improvement in technical success up to 24 months (48%) which remains stable in the following months without however showing further significant volume reductions. This data allows us to

hypothesize therefore a stability of the effectiveness of the technique over a long period.

In clinical practice of management of symptomatic thyroid nodules, these data could strengthen the indication of using RFA on nodules with small volumes, without waiting for a volumetric increase that could make this treatment less effective.

In addition, we observe that the measurement of the neck circumference, despite possible confounding, combined with the ultrasound evaluation, could provide important information on the outcome of the procedure.

Finally, the strong correlation detected between VRR1m and technical success shows the importance of monitoring the nodular volumetric reduction during the first month post-RFA. This parameter could be considered as an important indicator of a successful outcome of the procedure (VRR1m >50%), or, on the contrary, it can hypothesize a poor success of the procedure, suggesting for example, to plan a second RFA or surgery treatment in accordance with the patient's opinion.

The major limitation is the retrospective nature of the study, which however, has the strength of having been conducted in a single center by the same personnel, thus lowering the risk of interobserver bias.

With the limit of a retrospective study, regarding the neck circumference as a factor to control in the follow-up, we have reported only data on cases of changes in body weight, but we have not adjusted the neck circumference for this parameter. However, looking at these cases, we can state that in this study the reduction in neck circumference occurred regardless of the change in body weight.

Unfortunately, in this retrospective study we did not collect data on thyroid autoantibodies. Further prospective studies should consider the role of thyroiditis in structural changes of the nodule after RFA.

An interesting future development could be the evaluation of the energy delivered during RFA procedures in order to identify energy values to be used for improving the final outcome.

CONCLUSION

Based on current findings, the selection of nodules for pre-treatment allows for better long-term responses, especially for nodules with a lower pre-treatment volume (≤22.4 ml) and/or a macrocystic echostructure; early shrinkage of the nodule, as observed by a VRR1m ≥50% at one-month follow-up, is shown to be a good predictor of positive RFA responses. Therefore, these factors represent the best positive predictors of the radiofrequency thermal ablation technique on benign thyroid nodules.

In conclusion, these parameters should always be evaluated before considering any treatment with RFA to estimate the probability of success or failure of the therapeutic method that is targeted for each case. This result has important implications from a clinical point of view: (i) patients can be made more confident on the resolution of reported symptoms, and (ii) it provides a valid alternative to the surgical approach while permitting to gain relevant information on the need of repeated treatment sessions, if these factors are absent.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection were performed by AB, RR, LP, SG, AF, and AC. Data analysis and table designing were performed by AB and MM. The first draft of the manuscript was written by AB and all authors commented on previous versions of the manuscript. EG, MP, MM, and RG verified the analytical methods and supervised the manuscript drafting. All authors contributed to the article and approved the submitted version.

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Radiofrequency Ablation for Cervical Metastatic Lymph Nodes in Children and Adolescents With Papillary Thyroid Carcinoma: A Preliminary Study

*Lin Yan, Ying Zhang, Bo Jiang and Yukun Luo**

Department of Ultrasound, First Medical Center, Chinese People's Liberation Army (PLA) General Hospital, Beijing, China

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***Correspondence:**
Yukun Luo
lyk301@163.com

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Objective: To evaluate the safety and efficacy of radiofrequency ablation (RFA) for metastatic lymph nodes (LNs) in children and adolescents with papillary Thyroid Carcinoma (PTC).

Materials and Methods: From December 2014 to March 2018, 10 metastatic LNs (mean volume 0.30 ± 0.38 ml, range 0.06-1.23ml) in 5 children and adolescents (3 females, 2 males; mean age 15.60 ± 2.97 years, range 12-19 years) with PTC treated by RFA were evaluated in this study. The mean number of surgical procedures performed before RFA was 1.2 (range 1-2) and the mean number of treated metastatic LNs per patient was 2 (rang 1-3). RFA was performed with an 18–gauge bipolar RF applicator under local anesthesia. Follow-up consisted of US and serum thyroglobulin (Tg) level at 1, 3, 6, 12 months and every 12 months thereafter.

Results: All the patients were well tolerant to RFA procedure and no procedure-related complications occurred. During a mean follow-up time of 52.00 ± 21.44 months, the initial volume of LNs was 0.30 ± 0.38 ml, which significantly decreased to 0.01 ± 0.03 ml (P = 0.005) with a mean VRR of 99.28 ± 2.27%. A total of 9 metastatic LNs (90.00%) completely disappeared. After RFA, 2 patients developed newly metastases. One patient had additional RFA. The other one with multiple LN metastases underwent total thyroidectomy with central neck dissection.

Conclusion: As a less invasive and effective technique, RFA may provide another alternative to the existing therapeutic modalities for cervical metastatic LNs in children and adolescents with PTC.

Keywords: papillary thyroid carcinoma, radiofrequency ablation, children, adolescents, metastatic lymph node

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common pediatric endocrine malignancy, accounting for 1% of all cancers in prepubertal children and up to 7% in adolescents, with a rising incidence in the pediatric population over the last decade (1). The most common subtype of DTC in pediatric patients is papillary thyroid carcinoma (PTC). It is generally agreed that the clinical presentation of PTC in pediatric patients is different from that in adults (2). The prognosis is excellent, but pediatric patients usually present in the advanced stage with a large size at diagnosis and the incidence of local or distant recurrence is much higher than their adult counterparts (2–5). The majority of recurrence is identified in cervical lymph node (LN) (2). The American Thyroid Association (ATA) guideline for children with thyroid nodules and DTC recommended three treatments for cervical metastatic LNs, which were repeat surgery, thyroid-stimulating hormone (TSH) suppression and ^{131} I therapy (2). Although repeat surgery was preferable to other treatments for the macroscopic cervical disease, finding a lesion in the neck intraoperatively could be difficult (6). For patients with small-volume cervical tumor, observation with TSH suppression could be considered, but there were no data to weigh the potential benefits against the potential risks of long-term suppression therapy for children and adolescents (2). ^{131} I therapy was another option for small-volume cervical tumor. Unfortunately, it could increase the risks of complications and secondary malignancies (6). Accordingly, in children and adolescents, it may be reasonable or appropriate to consider less invasive alternatives than repeated surgery and ^{131} I therapy.

Radiofrequency ablation (RFA), as a minimally invasive treatment, has been used as an alternative to surgery for various solid tumors in adults (7–9). It has been recommended as a safe and effective treatment for benign thyroid nodules and recurrent thyroid cancers (10). However, for children and adolescents, RFA was only considered as a treatment of choice for osteoid osteoma (11–13). There were limited experiences of thermal ablation in other organs or tissues (11, 14–18). Nevertheless, as less invasive and feasible treatments, thermal ablation techniques were promising alternatives for pediatric tumors (19). To date, there have been no studies on the clinical application of RFA for metastatic LNs in children and adolescents with PTC.

Therefore, the aim of this study was to evaluate the safety and efficacy of RFA for metastatic LNs in children and adolescents with PTC.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Chinese PLA General Hospital. Written information consent was obtained from all the patients' parents prior to RFA procedure.

Patients

Between December 2014 to March 2018, 5 patients (3 females, 2 males, mean age 15.60 ± 2.97 years, range 12-19 years) with 10 metastatic LNs from PTC were treated by RFA in our institution. Inclusion criteria were: (1) age ≤ 20 years; (2) prior resection of primary tumor with pathological PTC confirmation; (3) patients with metastatic LNs confirmed by ≥ 2 separate fine-needle aspiration (FNA) or core needle biopsy (CNB); (4) the number of metastatic LNs was ≤ 3; (5) LNs deemed technically treatable based on US imaging and patient's condition.

Pre-Ablation Assessment

US examinations before and after RFA, as well as during follow-up were performed using a Siemens Acuson Sequoia 512 Ultrasound System (Siemens, Mountain View) with a 15L8W linear array transducer or a Philips iU22 Ultrasound System (Philips Healthcare) with a L12-5 linear array transducer or a Mindray M9 Ultrasound System (Mindray) with a L12-4 linear array transducer.

Before RFA, all the metastatic LNs were evaluated by US including the location, size, echogenicity, component and vascularity. For each metastatic LN, the diameters in three dimensions (the largest diameter and two perpendicular diameters) were recorded. The volume was calculated with the equations (10):

$$V = \pi abc/6$$

V is the volume, while a is the largest diameter, b and c are the other two perpendicular diameters.

Ablation Procedures

All RFA procedures were performed by an experienced US physician with more than 20-year experience in thyroid US and interventional US. A bipolar RFA generator (CelonLabPOWER, Olympus Surgical Technologies Europe) and an 18–gauge bipolar RF applicator with 0.9 cm active tip was used (CelonProSurge micro 100-T09, Olympus Surgical Technologies Europe) in this study. During the application of RF energy, the generator continuously measured the electric impedance of the tissue between the two electrodes at the tip of the RF applicator. The power was automatically adjusted based on the change of tissue impedance.

RFA was performed in outpatient department. Patients were supine with the neck extended during the procedure. An IV line was introduced *via* the antecubital vein. Before RFA, in order to design the best insertion way, US and CDFI were performed by the operator to evaluate the relationship between metastatic LNs and cervical critical structures such as trachea, vessels, esophagus and recurrent laryngeal nerves. Local anesthesia with 1% lidocaine was injected at the subcutaneous puncture site and the periphery of metastatic LNs. RFA was performed using hydrodissection technique. Normal saline was injected using another needle (23 gauge) to separate the metastatic LN from critical structures in order to prevent thermal injury. The RFA power was 3 W, if a transient hyperechoic zone did not form at the electrode tip within 5–10 s, the radiofrequency power was increased to 5-8 W. The ablation was terminated when all portions of the target ablation area had changed to transient hyperechoic zones.

During the procedure, we gave special attention to the preservation of critical cervical structures in order to prevent significant complications such as hematoma or nerve injury. After ablation, each patient was observed for 1–2 hours in the hospital while any complication occurring during and immediately after ablation was carefully evaluated according to the clinical signs and symptoms.

Post-Ablation Assessment

Clinical follow-up consisted of US and serum thyroglobulin (Tg) levels at 1, 3, 6 and 12 months and every12 months thereafter. The ablated volume, the largest diameter, vascularity and the development of new metastatic tumors were evaluated during the follow-up. The percentage volume reduction ratio (VRR) was calculated as follows:

$$VRR = \frac{(\text{initial volume} - \text{final volume})}{\text{initial volume}} \times 100\,\%$$

Complications during follow-up were assessed using the reporting standards of the Society of Interventional Radiology (20, 21). The development of cervical metastatic LNs was evaluated by using criteria from ATA guideline for children with thyroid nodules and DTC (2), and suspicious lesions were submitted to biopsy.

Statistical Analysis

Statistical analysis was performed using the SPSS statistical software (Version 25.0). Continuous data was expressed as mean± SD (range). Changes of the mean volume and diameter were compared using Wilcoxon signed rank tests before RFA and at the last follow-up visit. A difference with $P < 0.05$ was considered as statistically significant.

RESULTS

Clinical Characteristics

Clinical characteristics of the 5 patients (3 females and 2 males) before RFA are summarized in **Table 1**. The mean age was 15.60 ± 2.97 years (range 12-19 years). All the patients had prior surgical history for PTC. Patient 1 had right lobectomy with isthmectomy. Patient 2 had subtotal thyroidectomy. Patient 3 had left lobectomy with isthmectomy initially and then central neck dissection because of cervical metastatic LNs. Patient 4 and Patient 5 had total thyroidectomy with central neck dissection and subsequent ^{131} I therapy. The mean number of surgical procedures performed before RFA was 1.2. The mean interval time between initial surgery and RFA was 3.20 ± 1.64 years (range 2-6 years). The mean number of treated metastatic LNs per patient was 2. The locations of metastatic LNs were as followed: 2 at right level IV, 5 at left level III, 2 at left level IV and 1 at right level VI. The mean of largest diameter of metastatic LNs was 1.16 ± 0.52 cm. The mean initial volume was 0.30 ± 0.38 ml.

RFA Procedure and Complications

A power of 3W was used in 4 patients and 6W was used in 1 patient. The mean ablation time was 158.80 ± 65.13s (range 98-263s), and the mean energy was 522.00 ± 211.59 J (range 290-760J). All the patients were well tolerable the RFA procedure. None of the patients experienced any life-threatening or delayed complications related to RFA during the follow-up.

Follow-Up

The outcomes of RFA for metastatic LNs in patients with PTC are summarized in **Table 2**. The mean follow-up time was 52.00 ± 21.44 months (range 15-70 months). The mean largest diameter of the metastatic LNs decreased significantly from 1.16 ± 0.52 cm to 0.07 ± 0.22 cm(P=0.005). The mean volume of the metastatic LNs decreased significantly from 0.30 ± 0.38 ml (range 0.06-1.23 ml) to 0.01 ± 0.03 ml (range 0-0.09ml) (P=0.005) with a mean VRR of 99.28 ± 2.27% (range 92.82-100%) (**Figures 1** and **2**). A total of 9 metastatic LNs (90.00%) completely disappeared at the last follow-up. The Tg level was decreased from 25.10 ± 15.20 ng/mL (range 11.40-43.40 ng/mL) to 12.27 ± 11.96 ng/mL (range 0.03-30.20 ng/mL) (P=0.042).

After RFA, there was no evidence of recurrence at the initial treatment location. A total of 2 patients developed newly metastases. Patient 3 had multiple LN metastases at 2 years after RFA. This patient underwent total thyroidectomy with

TABLE 1 | The clinical characteristics of the pediatric patients before RFA.

No. of patient	Sex/ Age	Type of initial surgery/interval time (years)	^{131} I therapy	Recurrence beyond neck	No. of LN	Location/ level	Largest diameter (cm)	Initial Volume (ml)
1	F/13	Right lobectomy with isthmectomy/2	No	No	1	Right/IV	0.7	0.06
					2	Right/IV	0.6	0.06
2	M/12	Subtotal thyroidectomy/2	No	No	3	Left/III	1.5	0.35
					4	Left/III	0.9	0.08
3	F/17	Left lobectomy with isthmectomy/6; Central neck dissection/2	No	No	5	Left/III	1.6	0.68
					6	Left/III	0.6	0.06
4	M/17	Total thyroidectomy with central neck dissection/3	Yes	Lung	7	Left/IV	2.0	1.23
					8	Left/IV	1.8	0.28
					9	Left/III	0.9	0.07
5	F/19	Total thyroidectomy with central neck dissection/3	Yes	No	10	Right/VI	1.0	0.16

TABLE 2 | Outcomes of RFA for metastatic LNs in pediatric patients with PTC.

No. of patient	No. of LN	Initial Volume (ml)	Follow-up time/Complete disappearance (months)	Volume at last follow-up (ml)	Recurrence after RFA/interval time (months)	Treatment for recurrence after RFA
1	1	0.06	62/6	0	–	–
	2	0.06	62/6	0		
2	3	0.35	56/3	0	–	–
	4	0.08	56/3	0		
3	5	0.68	70/8	0	Multiple LN metastases/24	Total thyroidectomy with central neck dissection
	6	0.06	70/8	0		
4	7	1.23	15/-	0.09	One metastatic LN in the right cervical level IV/15	RFA
	8	0.28	15/15	0		
	9	0.07	15/15	0		
5	10	0.16	58/6	0	–	–

central neck dissection. During the surgery, no adhesion with strap muscle by RFA was found. After histopathological examination, metastases were detected in 8 out of 10 resected LNs. Patient 4 had one newly metastatic LN (largest diameter 1.3cm, volume 0.44ml) at right level IV at 15 months after RFA and underwent additional RFA. A power of 6W was used. The ablation time was 77s, and the energy was 390J. This newly metastatic LN was ablated successfully with no complications.

DISCUSSION

This study is the first to demonstrate the efficacy and safety of RFA for cervical metastatic LNs in children and adolescents with PTC. Our study showed that after a mean follow-up time of 52.00 ± 21.44 months, the VRR of metastatic LNs was 99.28 ± 2.27% and 90.00% of the ablated LNs completely disappeared. After RFA, a total of two patients developed LN metastases. One patient underwent total thyroidectomy with central neck dissection and the other one chose additional RFA. All the patients were well tolerable the RFA procedure. No complications were encountered. These results showed that RFA might be effectively applied in children and adolescents without increasing technical difficulties by former surgery.

The incidence of pediatric DTC has been rising in recent years and PTC accounts for over 90% (2). The overall survival remains excellent with a low rate of mortality even in advanced stage, however, pediatric patients have a high rate of recurrence (2, 22). Perry et al. (23) reported that with a median follow-up time of 11 years, 34% of the children and adolescents experienced a recurrence and the mean time to first recurrence of disease was 5.3 years. Among them, 50% were LN metastases and 29% were

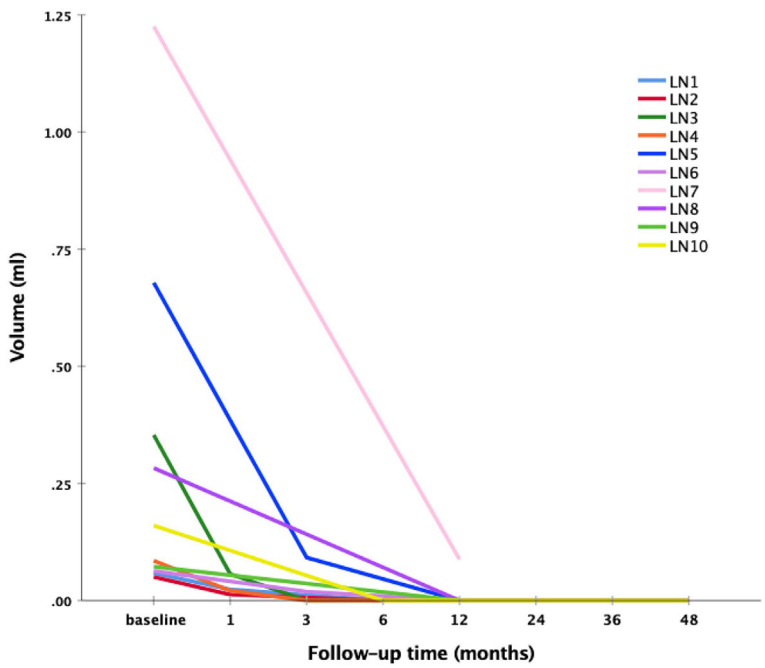

FIGURE 1 | The volume changes of ablated LN after RFA at follow-up.

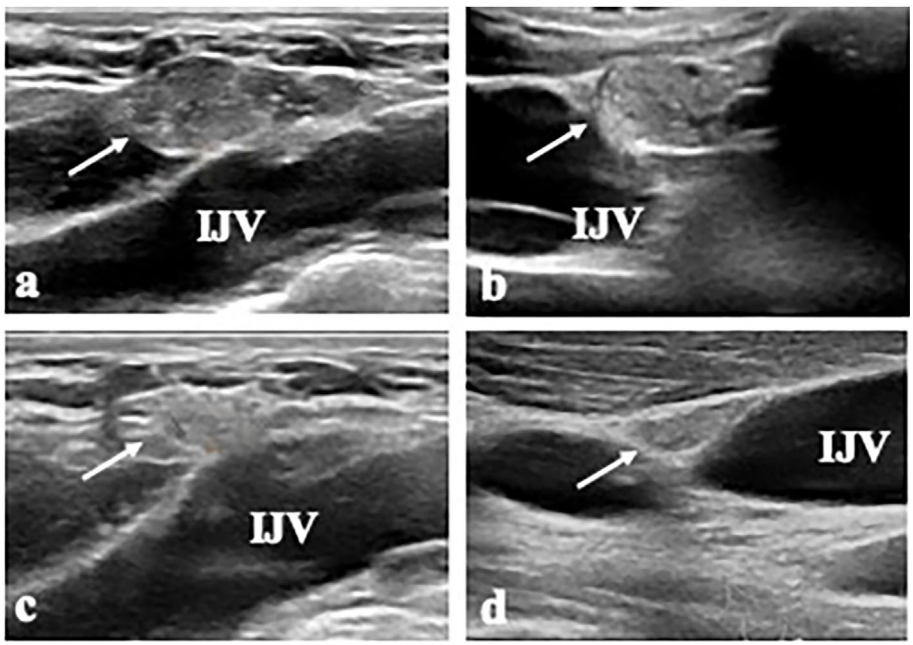

FIGURE 2 | A 17-year-old male patient (Patient 4) with metastatic LN (LN 7) at left level IV. **(A, B)** The transverse and longitudinal US shows a 2.0-cm-sized hypoechoic mass (arrow) near the internal jugular vein (IJV) at left level IV. **(C, D)** At 15 months after RFA, the transverse and longitudinal US shows the ablated LN is decreased in size (arrow).

lung metastases. Hay et al. (3) showed that by 40-year follow-up for 215 children and adolescents with PTC, 32% of patients had experienced a recurrence within the neck or at distant sites. Moreover, 73% of the first postoperative recurrences had been localized to the regional neck nodes. Spinelli et al. (22) found that multifocality, vascular invasion, infiltration of the thyroid capsule, minimal extrathyroidal extension, diffuse sclerosing variant of PTC and present of LN metastases in the lateral compartment were significantly associated with LN metastases in central compartment in children and adolescents. The predictive factors for LN metastases in lateral compartment were infiltration of the thyroid capsule, massive extrathyroidal extension, distant metastases, PTC, and the presence of LN metastases in the central compartment. Pediatric patients with those predictors might need a stricter follow up after PTC diagnosis and treatment. According to the ATA guideline, the decision to treat or to observe structurally identifiable cervical recurrent disease should be individualized (2). Repeat surgery was recommended for cervical disease > 1cm in size (2). However, the scar formation and normal tissue plane distortion by former surgery could bring technical challenges for repeat surgery (1, 24). It could also cause psychological trauma and serious complications, including hypoparathyroidism, recurrent laryngeal nerve damage and Horner syndrome (1, 2, 25). For patients with small-volume cervical disease, there were two options. One was observation with TSH suppression. However, there were no data in pediatric patients with which to compare the potential benefits with the potential risks of various TSH suppression strategies (2). The other one was ^{131}I therapy, which might reduce future recurrence risk but was unlikely to improve mortality (2). Given the increased risks of secondary malignancies and complications including short-term side effects and delayed toxicities, the use and dosage of ^{131}I therapy should be chosen in a thoughtful manner to avoid potential disease far worse than the one being treated (26–28). In addition, some patients were not suitable for ^{131}I therapy, because they only underwent thyroid lobectomy, not total thyroidectomy. Therefore, finding an alternative less invasive than repeat surgery and ^{131}I therapy might be helpful.

RFA, as a minimally invasive technique, can induce irreversible cell injury and ultimately tumor apoptosis and coagulative necrosis (29). It has been recommended as a safe and effective treatment for benign thyroid nodules and recurrent thyroid cancers in adults (10). However, its application in children and adolescents with thyroid disease was uncertain. Recently, Hong et al. (30) reported the application of RFA for nonfunctioning benign thyroid nodules in 14 children and adolescents. During a mean follow-up time of 36.9 ± 21.7 months, the volume was decreased from 14.6 ± 13.1 ml to 1.7 ± 4.4 ml with a mean VRR of 92.1 ± 11.4%. Both cosmetic and compressive symptoms improved significantly. It suggested that RFA had potential application in cervical thyroid-related disease of children and adolescents. This study showed that after a mean follow-up time of 52.00 ± 21.44 months, the VRR of metastatic LNs was 99.28 ± 2.27% and 90.00% of the ablated LNs completely disappeared. Although the object of this study was children and adolescents, similar results were observed in adults. Guang et al. (31) demonstrated that with a mean follow-up time

of 21 ± 4 months after RFA, the VRR was 94.9 ± 5.3% and 61.1% of the metastatic LNs completely disappeared. Chung et al. (32) reported after a long-term follow-up time of 80 ± 17.3 months, the volume of metastatic LNs decreased from 0.25 ± 0.42ml to 0.01 ± 0.08ml with a VRR of 99.5 ± 2.9% and the complete disappearance rate was 91.3%. These results indicated that the efficacy of RFA could not be affected by the age of patients.

The complications of RFA was various, but none of them was life-threatening. Some patients only had various degrees of pain or a sensation of heat during RFA for treating benign thyroid nodules (30). In this study, all the patients were tolerant to RFA procedure and no procedure-related complications occurred. We used three treatment strategies to reduce the rate of complications. First, the RFA procedure was performed by an experienced US physician. It was very important because the anatomical structures of pediatric patients were not developed completely and were distorted by former surgery. Second, in order to prevent thermal injury, hydrodissection technique was used to separate the target LN from critical structures. Meanwhile, real-time US imaging could also allow the physician to monitor the RFA electrode tip and adjacent critical structures (10). Third, careful lidocaine injection around the target LN could reduce the patient's pain and allow sufficient ablation. Furthermore, as a minimally invasive technique, RFA only needed local anesthesia in the outpatient department without scars and hospitalization, which could avoid operative-related risks and relieve long-term distress and psychological trauma in children and adolescents.

The recurrence rate after RFA for adults with metastatic LNs was from 1.9% to 12.5% (24, 31, 33, 34), however, the result in this study was relatively high. Similarly, previous studies reported the recurrence rate was 33-60% after RFA for solid tumors in pediatric patients (11, 14, 15, 19). There were two possible explanations. First, the incidence of PTC recurrence was much lower in adults than in pediatric patients (2). Bilimoria et al. (35) published a series of 52,174 adult patients with PTC from the National Cancer Database and found that the overall recurrence rates were 5.7% at 5 years and 9.4% at 10 years. In another study of 1088 adult patients with PTC, the recurrence rate was 4.8% at a median follow-up period of 17.6 years (36). However, the recurrence rates of pediatric PTC at 5, 10, 20 and 30 years were 20%, 22%, 27%, and 30%, respectively (3). Second, the risk of recurrence disease from pediatric PTC was associated with the initial surgical approach. Hay et al. (3) reported that during 40-year follow-up, the recurrence rates after bilateral lobar resection and lobectomy were 25% and 65%, respectively (3). The local and regional recurrence rates after lobectomy (35%, 60%) were significantly higher than after bilateral lobar resection (6%, 13%) (3). In this study, most patients (3/5) did not have total thyroidectomy and they may have a higher underlying burden of disease and an increased risk for recurrence. During the follow-up of RFA, a total of two patients developed newly metastases. One patient chose additional RFA. The other one underwent total thyroidectomy with central neck dissection and multiple microscopic metastases were found after histopathological examination. Because the sensitivity of US to detect central metastatic LN and microscopic metastases was low, malignancy could only be confirmed after surgical dissection. Therefore, repeat surgery was undoubtedly a definitive curative treatment for children and adolescence. However, RFA could be used as a safe and effective local control of cervical metastatic LNs and may provide another alternative to the existing therapeutic modalities for children and adolescents with multiple surgery or surgical ineligibility.

This study has some limitations. First, it was a single-center retrospective study. Further prospective multicenter studies are needed. Second, the number of cases included was small and the follow-up period was relatively short. Considering the rarity of pediatric PTC, it was difficult to accumulate more cases. According to a systematic review of ablation techniques for children, only 28 patients were identified to be treated by ablation (19). Based on the available data, this study seemed to have an acceptable sample size to summarize and evaluate our experience.

CONCLUSION

As a less invasive and effective technique, RFA may provide another alternative to the existing therapeutic modalities for cervical metastatic LNs in children and adolescents with PTC.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of patients' privacy. Requests to access the datasets should be directed to gemma-y@163.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Chinese PLA General Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LY interpreted the patient data and drafted the manuscript. YKL performed RFA procedure, conceived of the study and coordination. YZ and JB collected and analyzed the patient data. All authors contributed to the article and approved the submitted version.

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Long-Term Results of Ultrasound-Guided Radiofrequency Ablation of Benign Thyroid Nodules: State of the Art and Future Perspectives—A Systematic Review

Hervé Monpeyssen[1], *Ahmad Alamri*[2] *and Adrien Ben Hamou*[1,3]*

[1] American Hospital of Paris, Thyroid Unit, Neuilly-sur-Seine, France, [2] Department of Endocrinology, Diabetology and Nutrition, Paris Saint-Joseph Hospital, Paris, France, [3] Thyroid and Endocrine Tumors Department, Institute of Endocrinology, Pitié-Salpêtrière Hospital, Paris, France

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***Correspondence:**
Adrien Ben Hamou
adrien.benhamou@hotmail.fr
orcid.org/0000-0002-4986-8658

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Background: Nearly 20 years after the first feasibility study, minimally invasive ultrasound (US)-guided therapeutic techniques are now considered as a safe and effective alternative to surgery for symptomatic benign thyroid nodules. Radiofrequency ablation (RFA) is one of the most widely used treatment in specialized thyroid centers but, due to the relatively recent introduction into clinical practice, there are limited long-term follow-up studies. Aim of our work was to review the outcomes of RFA on solid nonfunctioning and on autonomous thyroid nodules (AFTN) on a long-time period for assessing the results in term of efficacy, complications, and costs and to compare them to the current indications of RFA.

Methods: A systematic review was performed using EMBASE and Medline library data between 2008 and 2021. Seventeen studies evaluated RFA for the treatment of benign solid (nonfunctioning or autonomous) thyroid nodules, with an at least 18 months of follow-up. Data extraction and quality assessment were performed by two endocrinologist according to PRISMA guidelines. Anthropometric data, safety and efficacy parameters were collected.

Results: The majority of the studies was retrospective study and reported 933 nodules, mostly solid. Baseline volume ranged between 6.1 ± 9.6 and 36.3 ± 59.8 ml. Local analgesia was used and the time duration of the treatment was between 5 ± 2 and 22.1 ± 10.9 min. The volume reduction rate at 12 months ranged from 67% to 75% for the nodule treated with a single procedure and reached to 93.6 ± 9.7% for nodules treated with repeat ablations. The regrowth rate at 12 months ranged from 0% to 34%.

Conclusion: All the studies under examination consistently validated the long-term clinical efficacy and the substantial safety of RFA for the treatment of benign thyroid nodules. Thermal ablation, however, is an operator-dependent technique and should be performed in centers with specific expertise. The selection of the patients should be

rigorous because the nodule size and the structural and functional characteristics influence the appropriateness and the outcomes of the treatment. Future perspectives as the treatment of micro-papillary thyroid cancer or cervical recurrence need further investigations.

Keywords: benign thyroid nodule, non-functioning thyroid nodule, minimally invasive treatment, thermal ablation, ultrasound-guided radiofrequency ablation

INTRODUCTION

Thyroid nodules (TN) are palpable in 4% to 7% of the general population and are identifiable by ultrasound (US) in 67% of cases (1, 2). If thyroid fine-needle aspiration (FNA) provides the cytological diagnosis of a benign thyroid nodule (Bethesda Category II), various therapeutic options are now available for symptomatic patients. The American Thyroid Association suggests surgical lobectomy if the long-axis of the nodule is >4 cm while European Guideline recommendations (3) consider as an alternative therapeutic option the treatment of symptomatic nodules with US-guided thermal ablation (TA) techniques (4). During the last years, a mounting evidence demonstrated the efficacy of radiofrequency ablation (RFA) (5), laser ablation (LTA) (6), high-intensity focused ultrasound [(HIFU) (7), and microwave (MWA) (8)]. This increasing interest in nonsurgical procedures is due to the present excess of thyroid surgery for benign lesions. Surgical management, indeed, is expensive, may be complicated by dysphonia and hypocalcemia (9, 10), and is followed in the majority of cases by need of lifelong replacement therapy (11, 12).

Nearly 20 years after the first publications, mini invasive ultrasound (US)-guided techniques are now considered as a safe and effective alternative treatment to surgery for symptomatic benign nodules. RFA is one of the most widely used procedures in specialized centers (13–16) as may be applied to all types of nodules (solid or partially fluid, autonomous or "cold"). The results in term of volume reduction rate (VRR) are satisfactory (>50% of nodule volume reduction) and are paralleled by the improvement of pressure symptoms and cosmetic concerns. In most of the available prospective and retrospective studies follow-up (FU) is up to 12 months, a time period insufficient to prove the real effectiveness of the technique in preventing late nodule regrowth. On the basis of a robust evidence (17–19), TA is now proposed as a possible first-line treatment option for selected patients by the Korean Health Authorities (20), the American Association of Clinical Endocrinologists, the American College of Endocrinology, the Italian Association of Clinical Endocrinologists (AME) (21), and, more recently, by the European Thyroid Association (ETA) (3).

The aim of our work was to review the therapeutic effects of RFA on solid nonfunctioning or autonomously functioning (AFTN) thyroid nodules on a long-time period setting the minimum FU at 18 months. A comprehensive literature search was conducted by consulting the PubMed, EMBASE, and the Cochrane Library data bases on original articles published in English concerning the effects of RFA on nonfunctioning thyroid nodules and AFTN between 2008 and 2021. Full texts were reviewed to exclude articles concerning systematic review and case reports. A dedicated systematic review of the literature assessed the frequency of nodule regrowth after RFA in the long term.

METHODS

Literature Search

By consulting the PubMed, EMBASE, and the Cochrane databases, we selected articles in the period between 2008 and 2021. We searched by the following algorithm "thyroid nodule'/exp AND ('radiofrequency thermal ablation'/exp OR 'radiofrequency thermal ablation' OR rfa OR ('radiofrequency'/exp AND ('thermal ablation'/exp OR (thermal AND ablation)))) NOT ('thyroid nodule'/exp AND ('radiofrequency thermal ablation'/exp OR 'radiofrequency thermal ablation' OR rfa OR ('radiofrequency'/exp AND ('thermal ablation'/exp OR (thermal AND ablation)))) AND ('case report'/de OR 'meta-analysis'/de)) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)" (**Figure 1**). Two endocrinologists, ABH and HM, with 5 and 31 years of experience in thyroid imaging, respectively, independently performed the literature search and selection.

Inclusion Criteria

Articles fulfilling the following criteria were included: (1) patients with a benign thyroid nodule that has not been treated with a different method TA, surgery, RIA, or PEI and, (2) FU data for more than 18 months after RFA.

Exclusion Criteria

The following criteria were excluded (**Table 1**): (1) age <15 years or >80 years; (2) women who were pregnant or lactating; (3) patients who were incapable to maintain a stable position while the neck is in hyperextension; (4) history of irradiation on the neck; (5) preexisting vocal cord palsy; (6) tattoos, skin moles, or scars on the neck area; (7) suspicion of malignancy (US or cytological); (8) if macro calcification or fluid collection are present; (9) if the lesion is in contact with the trachea, the esophagus or the carotid artery; (10) case reports or case series including fewer than 20 patients; (11) articles written in a language other than English; (12) articles lacking reference standards based on cytological test; (13) articles with overlapping populations; (14) letters, editorials, conference abstracts, systematic reviews or meta-analyses, consensus statements, guidelines, and review articles.

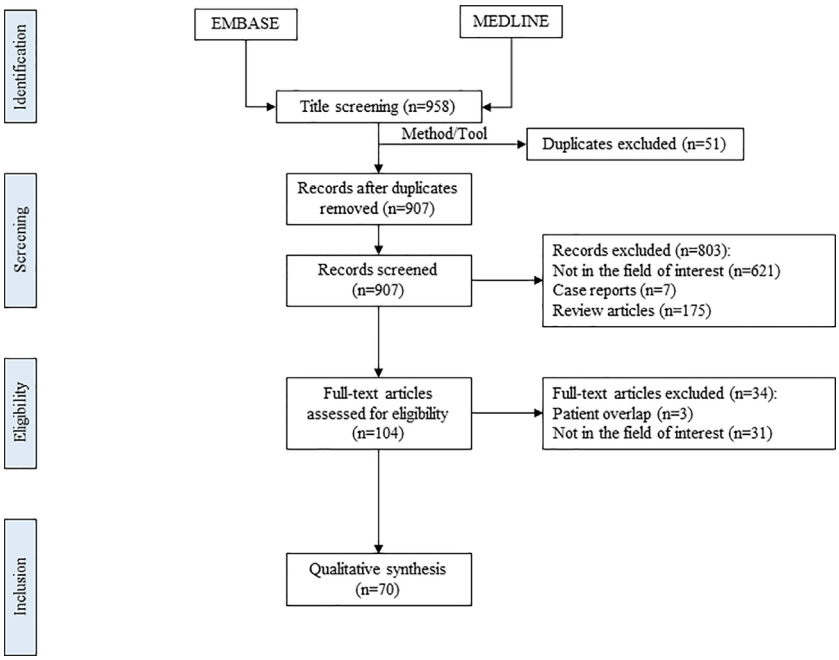

FIGURE 1 | Flowchart of the study selection process.

TABLE 1 | Inclusion and exclusion criteria in patients with thyroid nodules before RFA procedure.

Inclusion	Exclusion
≥18 years old	<18 years old
Written inform consent	Pregnancy
Functional and/or compressive complaints:	Nodule classified as Bethesda I, III, IV, V, VI
Anterior cervical discomfort	
Dyspnea	
Dysphagia	
Dysphonia	
Cosmetic complaint	Ultrasound (US) aspect compatible with medullary thyroid cancer and positive calcitonin
Two benign cytology or biopsy (Bethesda II)	Nodule too close to the "danger zone"
Autonomous thyroid nodule	Not available for thermal ablation after US evaluation
Refusal/contraindication for surgery	Multinodular thyroid
Not available for radioiodine treatment	
Not available for percutaneous ethanol injection (PEI)	
History of neck surgery or radiotherapy	

Patient Assessment Before RFA Procedure

Nodules were classified according to the Thyroid Image Reporting and Data System (TI-RADS) classification, and the vascularization of the nodules were assessed by color flow Doppler, with the vascularization classified using a four-grade scale (grade 0: no vascularity; grade 1: perinodular vascularity only; grade 2: intranodular vascularity <50%; and grade 3: intranodular vascularity >50%). Two fine needle aspiration cytology (FNA) guided by US were performed with a minimum interval of 90 days, according to the described technique. Before the procedure, US imaging was performed by high frequency linear US transducer. All of the nodules treated were predominantly or even completely solid (≤10% of fluid component) (22). Five series included autonomous or even toxic nodules (4.1% to 100% of the treated nodules). Some series report several nodules treated in the same session. The mean volume of the nodules was between 6 and 37 ml. The biological tests performed before the procedure were: complete blood count, blood calcium level (mg/L), calcitonin (pg/ml), TSH (μIU/ml), fT3 (pg/ml), fT4 (ng/dl), anti-TPO antibodies (IU/L). Patients that had a TSH level in the low normal range were tested by I^{123} nuclear imaging to eliminate the presence of hyper functioning nodules. A clinical examination was performed to assess pressure symptoms or cosmetic damage (on visual analogic scale); pressure symptoms were defined as a

persisting dysphagia or cervical constriction, while cosmetic damage was defined as the by physicians using a four-grade score (1. no palpable nodule; 2. palpable nodule without cosmetic damage; 3. the presence of a cosmetic problem on swallowing; 4. easily detected cosmetic problem).

We proposed an algorithm for the treatment of solid benign symptomatic thyroid nodules, based on the 2020 ETA guidelines (**Figure 2**).

The Procedure

All procedures were outpatient, with the use of US guidance. Patients were placed in supine position, while the extension of the neck was determined by the nodule localization. The electrodes used were monopolar, except in the study by Guang et al. (22) (bipolar) and in one of the older publications, Spieza used a HOOK (umbrella-like) electrodes (23). For TA, we used different generator and an electrode cooled by a 0.9% sodium chloride solution bag at 4°. The electrode was inserted using a trans-isthmic approach starting from the deepest part of the nodule, and a moving-shot TA technique was performed (successive treatment of small parts of the nodule). In two-thirds of the studies, only local anesthesia was used. Four series reported using conscious sedation, while some studies specified the use of Midazolam. The number of procedures was very variable, Sim (24), Dobrinja (25) and Valcavi (26) performed a single procedure. Lim et al. (16) has treated some of his patients seven times. In Ben Hamou's publication (27), one nodule received two treatments. The same is observe for Valcavi: the first procedure was stopped prematurely due to a vasovagal syncope. The power delivered during the procedure varies between 20 and 120 Watts. In the series treated as bipolar, the power used is much lower. The processing time is reported by nine teams. The duration varies between 8 and 22 minutes. In almost half of the studies, the energy delivered per milliliters of tissue treated is not available. The others use the energy delivered by nodule. Complications were evaluated during and immediately after the procedure (symptoms or clinical signs). Patients were observed for 2 to 6 h after the procedure.

RESULTS

Eligibility

The initial systematic search showed 958 articles. Fifty-seven duplicates were then removed, and following that the remaining 907 articles were screened (by looking through titles and abstracts), and 104 potentially eligible articles were found. The 19 publications were then assessed for eligibility: 17 publications in which the post-treatment FU was equal to or more than 18 months. Out of the seventeen publications, four of them were prospective studies. We ruled out studies where another therapy method (surgery, RIA, percutaneous ethanol injection (PEI) or other TA techniques) had been used or had preceded RFA. At the end of the assessment 7 out of the 19 articles were excluded (1 case report/series, 2 articles with overlapping data and 4 articles with no data more than 3-year follow up). Almost half of the studies come from the same team (Asan Medical Center, Seoul). The data extracted from the selected articles are shown in **Table 2**.

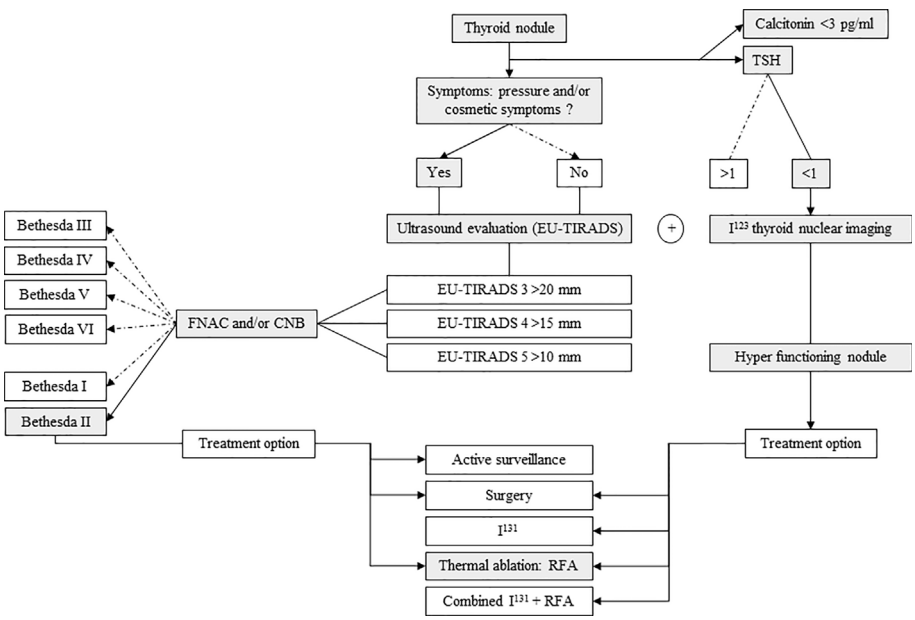

FIGURE 2 | Algorithm for the treatment of symptomatic benign thyroid nodules, based on the 2020 European Thyroid Association (ETA) guidelines. FNAC, fine-needle aspiration cytology; CNB, core needle biopsy; RFA, radiofrequency ablation. TSH expressed as μUI/ml.

TABLE 2 | Characteristics of the included studies.

Authors (year)	Patients (nodules)	Mean age (years)	M/F	Type	Structure	AFTN	Mean nodule volume (mL)	E-Type	Sedation	Power (watts)	Delivered energy (kJ)	Number of procedures	Time (minutes)	VRR	FU period (months)	Percentage of Regrowth	Re-treatment
Jeong et al. Eur Radiol (2008) 18:1244–1250 (28).	236 (302)	40.9	25/211	2	S: 54.3% C: 16.2% M: 29.5%	0	6.13 ±9.59	1	No	20 to 70	N/A	1 to 6	5 to 30	84.1 ±14.93	1 to 41	N/A	x2: 20.8% x3: 6.6% >3: 2.3%
Spiezia et al. Thyroid (2009) 19:219–225 (23).	94	72.5 ±0.5	39/55	1	S>70%	100%	24.5±2.1	1 (Hook)	No	N/A	N/A	1 to 3	5±2	79.4 ±2.5	24	34%	24%
Lim et al. Eur Radiol (2013) 23:1044–1049 (16).	111 (126)	37.9 ±10.6	10/101	1	S>65%	N/A	9.8±8.5	1	No	30 to 120	2.9±1.99	2.2 (1 to 7)	N/A	93.6 ±9.7	49.4 ±13.6	5.6%	x2: 23.8% x3: 19% >3: 13.5%
Sung et al. Thyroid (2015) 25:112–117 (29).	44 (44)	43 ±14.7	2/42	2	S: 59.1% C: 36.4%	100%	18.5 ±30.1	1	No	15 to 70	6.41±4.31	1.8±0.9	12±5.9	81.7 ±13.6	19.9	N/A	x2: 27% x3: 7% >3: 1%
Dobrinja et al. Int J Endocrinol (2015) 2015:576576 (25).	64	60.47 ±1.89	17/47	2	S: 85.9%	0	13.81 ±1.86	1	Yes	60 to 80	N/A	1	98.5±6.5	67±?	24	1.5%	0
Hong et al. J Vasc Interv Radiol (2015) 26:55–61 (30).	18(36)	49.9	2/16	2	N/A	0	24.4 ±32.2	1	N/A	N/A	N/A	>1	N/A	70.3 ±16.2	18.1 ±12.8	N/A	N/A
Valcavi et al. Endocr Pract (2015) 21 (8):887-96 (26).	40 (40)	54.9 ±14.3	5/35	2	S>80%	0	30±18.2	1	Yes	37.4 ±8.8	37.15 ±18.1/ nodule	1 or 2	22.1 ±10.9	80.1 ±16.1	24	0	0
Sim et al. Int J Hyperthermia (2017) 33:905–910 (24).	52 (54)	44.1 ±13.2	5/49	2	S: 70.4% M: 20.4% C: 9.3%	0	14±12.7	1	No	N/A	N/A	1	N/A	69.6	39.4	24.1%	0
Cervelli et al. J Vasc Interv Radiol (2017) 28:1400–1408 (5).	46 (51)	56.4 ±11.3	15/31	1	S>75%	0	9.1±42	1	Yes	30 to 50	35.2±14.5	1 to 2	N/A	84.3 to 86.4	18	N/A	x2: 13%
Jung et al. Korean J Radiol (2018) 19:167–174 (13).	345 (345)	46 ±12.7	43/302	1	S: 89.9% C: 10.1%	0	14.2 ±13.2	1	No	78.8± 41.6	4.16±2.9	1.3±0.4	9.52 ±5.50	80.3 ±13.7	12	5.6%	x2: 20.3%
Guang et al. BMC Cancer (2019) 19:147 (22).	103 (194)	47.6 ±11.3	36/67	2	S	0	21.2 ±19.7	2	No	3 to 8	N/A	1 to 3	N/A	72.3 to 98.7	16.3±5.6	0	x2: 44.9% x3: 4.6%
Ben Hamou et al. Int J Hyperthermia (2019) 36:666–676 (27).	99 (108)	49.7 ±12.2	19/80	2	S: 64.8% C: 13.9% M: 21.3%	13.8%	20.4 ±18.6	1	Yes	35 to 55	7.8±5.8	1 to 2	18.7 ±10.6	75 (64.6 – 83.3)	18	4.6%	x2: 1/108 3 surgeries
Ha et al. Endocrinol Metab (Seoul) (2019) 34:169–178 (31).	16 (16)	43.8 ±12.3	1/15	2	S: 81.3%	0	34.6 ±28.5	1	No	76	3.23±4.91	1.6±0.9	8.2±17.7	y2 71.5 ±5.8 y5 71.8 ±6.9	69.6 (38 to 98)	N/A	x2: 43% x3: 12.5% >3: 6%
Hong MJ et al. J Vasc Interv Radiol (2019) 30:900–906 (32).	14	15.7 ±2.3	4/10	2	N/A	0	14.6 ±13.3	1	No	47.1 ±22.9	3.15±2.06	2.1±1.2	7.3±2.75	92.1 ±11.4	36.9 ±21.7	N/A	x2: 28.5% x3: 28.5% x5: 7.1%

(Continued)

TABLE 2 | Continued

Authors (year)	Patients (nodules)	Mean age (years)	M/F	Type	Structure	AFTN	Mean nodule volume (mL)	E-Type	Sedation	Power (watts)	Delivered energy (kJ)	Number of procedures	Time (minutes)	VRR	FU period (months)	Percentage of Regrowth	Re-treatment
Deandrea et al. J Clin Endocrinol Metab (2019) 104:3751–3756 (33).	215 (215)	66	33/182	2	S>70%	0	20.9 (15–33)	1	N/A	55	55 (50 – 65)	1-2	14 (12–19)	69.8	35 (24 – 60)	4.1%	9 RFA N° 2 or surgery
Aldéa Martinez et al. J Vasc Interv Radiol (2019) 30:1567–1573 (34).	24	50.17 ±13.6	4/20	1	S: 54.2% M: 37.5% C: 8.3%	4.1%	36.3 ±59.8	1	Yes	45.8 ±8.3	N/A	3.5±0.93	15.6±6.5	76.84 ±15.92	36	N/A	N/A
Bernardi et al. Thyroid (2020) 30(12):1759-1770 (17).	216	57 (17-87)	102/304	2	S : 75% M:24% C: 1%	17.1%	17.2 (.4-179)	1	N/A	N/A	1.397j/ml 0.75-24	1.12	N/A	77.1	60	20%	26 (12%) 15 surgery 15 MITT

M/F, ratio male and female; Type, 1 prospective, 2 retrospective; Structure: C, cystic nodule; S, solid nodule; M, mixed; AFTN, autonomous functioning thyroid nodule; Type of electrode: 1, monopolar; 2, bipolar; volume, initial volume of the treated nodule (mean ± SD, or median (IQR), ml); VVR, volume reduction rate in percentage (mean ± SD or median (IQR), %); FU, follow-up (months); MITT, minimally invasive treatment of thyroid; N/A, not applicable.

The following data were extracted using standardized forms according to the PRISMA guidelines (35).

The primary outcome of the current systematic review was the serial VRRs of ablated nodules over 18 months or more. A secondary outcome was a description of the adverse effects of ablation, including the rates of complications and surgery during FU after ablation.

The Patients

The total number of patients in the cohorts included between 16 and 345 patients. One thousand seven-hundred and thirty-seven patients had a FU for more than 18 months for certain studies, some of which were multi-centric (6 studies) for a total of 1943 nodules treated. The majority of the population in all cohorts were females, the mean age ranged between 41 and 72.5 years, with two studies with patients in the seventh decade, and another in the eighth decade (72.5 years) (23) and one in children/adolescent (32).

All of the nodules treated were predominantly or even completely solid (≤10% of fluid component) (22). Five series included autonomous or even toxic nodules (4.1% to 100% of the treated nodules). Some series report several nodules treated in the same session. The mean volume of the nodules was between 6 and 37 ml.

Endpoints of Efficacy

The Volume Reduction Ratio (VRR) is used in all series. It is calculated with the formula: initial volume (ml) - Final volume (ml) x 100/initial volume (ml). Technical efficacy (TE) (4) was defined as a VRR ≥50% at 6 months (intermediate follow-up). In the early days of TA of TN, we considered a therapeutic success in case of a reduction in volume ≥50% at one year. With the multiplication of experiments and publications, the target has clearly increased and in our review, the VRR in all of the studies (mainly from Asian and European population) is between 67% and 93.6%. If we position the cutoff at 75%, 11 studies are above and 6 are below. In the main series (≥100 patients), we observed a VVR of 84.1 ± 14.93% (1 to 41 months of FU) (28), 79.4 ± 2.5% (24 months of FU) (23), 93.6 ± 9.7% (49.4 ± 13.6 months of FU) (16), 80.3 ± 13.7% (12 months of FU) (13), 72.3 to 98.7% (16.3 ± 5.6 months of FU) (22), 75% (64.6 – 83.3) (18 months of FU) (27), 69.8% (35 (24–60) months of FU) (33) and 77.1% (60 months of FU) (17). Notice that Bernardi et al. (17) proposes to perform another FNAC for the nodules that failed the treatment. However, TE was achieved in 85% of patients and regrowth occurred in 20% of patients in their study.

The second endpoint of effectiveness is the percentage of volume regrowth after treatment. The terms used are "regrowth", "marginal regrowth", "partial regrowth", "recurrence" (4). A nodule is considered to be recurrent if there is a volume recovery of 50% from the observed nadir. Other authors speak of regrowth when the volume exceeds the procedural volume. This relatively recent data was very little developed in the previous studies. A recent review by Sim (24) have summarized the data and have shown that for 54 patients who underwent RFA treatment, the mean FU period was 39.4 ± 21.7 months, the vital volume increases occurred in 31 nodules (57.4%) and there was regrowth in 13 nodules (24.1%).

Cervelli (5) introduces the notion of "residual vital tissue" which, when it is too large, will establish the indication of a second early treatment. Future studies should integrate these data. In our review, the proportion of regrowth ranges from 0 to 34%.

The third endpoint of assessment is the re-treatment of the nodule. In most of the studies, it is not possible to know whether these retreatments are due to a failure of the first treatment or to tissue regrowth, nor the objective criteria which prompted the proposal of a new therapeutic sequence. In Hong's study (30) given the bilateral nature of the lesions, two procedures were required. He reports that some large nodules were treated in several stages. Deandrea's study shows a re-treatment rate of 13.6% (RFA or surgery) with a re-growth rate of only 4.1% (33). Bernardi et al. in his recent publication (17) reported a re-treatment rate of 12% with surgery (3.9% non-benign lesion).

The fourth endpoint relates to the quality of life (QOL) indices. Data from the literature indicate that at 12 months, a very significant improvement in QOL and cosmetic score is noted in all studies. Beyond 12 months, a few publications report the maintenance of this improvement or even an improvement in the QOL.

The last endpoint is the evolution of thyroid function in patients treated for a pretoxic or toxic nodule. In the Spieza study (23), 28 patients presented with hyperthyroidism treated with anti-thyroid drugs. Twenty-two recovered their thyroid function without treatment, the other six required a lower dose of anti-thyroid drugs compared to the pre-TAT period. In the Sung study (29), all the patients became euthyroid after treatment, but 8/44 had a relapse of hyperthyroidism despite multiple treatments (up to six for one of them). In Ben Hamou study (27), 10/13 patients treated with RFA for hyperthyroidism became euthyroid. Finally, the toxic nodule in Aldea's study (34) reacted well initially but fell again and had to be treated with RAI. In a recent series, Dobnig (36) proposed RFA for the treatment of autonomous and toxic nodules under certain conditions (volume in particular). The treatment of pretoxic or toxic nodule has finally be validated by the European Thyroid Association (3), and notably for pregnant women.

Safety

In all the previous studies, early adverse events are mainly well-described. In Ben Hamou (27), five (3%) major adverse events (two transient recurrent laryngeal nerve palsy, one compressive hematoma and one sub-cutaneous abscess), 25 (15.1%) minor adverse events (seven transient dysphonia, two nodule ruptures with conservative treatment and sixteen benign hematomas), and 101 side effects (60.8%) occurred during the early FU (1 month). Cervelli (5) have shown two transient minor injury of the laryngeal nerve complete recovery after 2 weeks of corticosteroid therapy). In a recent retrospective study (37), one transient vocal cord palsy, one nodular rupture (which was detected one month after RFA as a red cervical lump with a fluid collection), and one vaso-vagal reaction forcing to interrupt the procedure, were observed. In the majority of the studies, early major adverse events occurred in less than 1% to 3% of cases.

The occurrence of hypothyroidism or hyperthyroidism during FU (>18 months of FU) has never been reported in any previous studies.

None of the publications has reported any complications occurring after 12 months of FU. In the article of Aldea Martinez (34), one patient retained the recurrent paralysis that was noticed earlier after the intervention (direct approach, not trans-isthmic).

Predictive Factors

Valcavi (26) shows that the predictive factor of success is the total energy deposited correlated with the initial volume (negative correlation). On the other hand, no relationship was found with age, sex and volume. In the very recent Italian multicenter study (17), a correlation was found between insufficient results and regrowth, and the low amount of energy deposited [low-energy delivery (optimal cutoff was 918 J/ml for RFA)], young age, large volumes, low VRR at one year. Jung et al. (13) have found that the solidity of the nodule and the energy delivered were independent predictive factors of the final volume reduction. However, many studies lack the information regarding the energy delivered. Very few data concerning the learning curve were mentioned. However, some studies report a higher success rate when the RFA procedure is performed by an experienced physician, with a suggested cutoff of 50 cases. Two recent studies (37, 38) have demonstrated that only baseline volume, total energy, and energy per volume were independently associated to a VRR >50% ($p = 0.001$, $p = 0.0178$, $p<0.001$, respectively) and that delivering 756 and 2670 J/ml gave a probability of VRR >50% in 50% and 99% of patients, respectively. Besides, Russ et al. evokes possible explicative factors: energy applied per volume was positively correlated to VRR and ablation ratio (AR) but not to TE. Ablation duration was associated with a greater reduction of AR but there was no significant correlation with TE and VRR. Lastly, time trend correlation showed a significant increase in delivered energy per volume and ablation duration with experience.

The Follow-Up

The lower limit was set in this review of the literature at 18 months. Intermediate data are most often taken at 3, 6, and 12 months. In most of the studies, 5% to 15% of the patients are lost to FU. The most important FU was 8 years (Ha) (31): the authors have decided to FU their patients annually [FU period of more than 5 years (mean, 5.8 years; range, 38–98 months)] and have shown a volume reduction rate of 81.3% ± 5.8% ($p<0.0001$).

US was performed, as long as the clinical examination (clinical signs and symptoms) to evaluate late complications (*i.e.*, complications appearing after one month following the treatment). The 2020 ETA guidelines have recommended in recommendation 8: "early-term (*e.g.*, 3 months) and intermediate-term (*e.g.*, 6 and 12 months) clinical, biochemical, and US evaluations; long-term FU monitoring is suggested, in the absence of symptoms every 1 to 2 years, in order to reveal regrowth," but finally, physicians do not know clearly how long the patients should be followed up (probably more than 2 years).

DISCUSSION

Efficacy and Safety

Radiofrequency ablation is now considered as an effective technique, safe, reproducible from one team to another, as an alternative to surgery as part of the management of benign TN, whether solid, mixed (solid/cystic), functional or non-functional (**Figure 3**). Large prospective and retrospective series carried out by Asian (20), European (3) and American (39) teams have demonstrated a significant volumetric reduction of treated thyroid nodules of 60 to 85% or even beyond 85% depending on the series, associated with a significant reduction in the symptomatology attributable to the thyroid nodule (compressive symptoms, cosmetics). RFA is widely used (more than LTA, microwaves and HIFU) probably because of its greater simplicity and reproducibility. However, treatment by thermal-ablation must be carried out within an expert center and requires indisputable ultrasound and anatomical expertise. This minimally invasive technique justifies an expert clinical, biological and ultrasound evaluation before its realization. In fact, several series have highlighted numerous factors predicting success such as the initial size of the nodule, its vascularization, the percentage of residual viable zone (40, 41). It should not be put in competition with surgery but should be presented as an additional therapeutic option which could be positioned as a first-line option depending on *(i)* the nodular characteristics and its clinical application, *(ii)* the patient's decision. In the current economic context, and to the extent that surgical treatment appears more expensive, it appears justified to propose an alternative which will make it possible to limit the economic impact of the treatment of nodules (which represents the most frequent endocrinopathy). The cost of the HIFU device is around 250,000 euros (€) *vs.* 30,000 € for LTA, 17,000 to 25,000 € for RFA and 20,000 to 25,000 € for MWA; and the cost of disposables is about 500 € *vs.* one fiber 300 to 500 € for LTA, one electrode 700 to 900 € for RFA and one antenna 900 to 1,000 € for MWA. But, also to limit the impact of surgery on the patient with all the risks that this implies (hemorrhage, recurrent paralysis, secondary hypocalcaemia, compressive hematoma) (11, 42) and to preserve thyroid function (20% of patients benefiting from lobectomy require hormone replacement therapy and the vast majority of patients undergoing thyroidectomy require lifelong hormone replacement therapy (43). In the majority of studies, a serious adverse event rate of <3% is reported (this prevalence tends to decrease with the experience of the operators). Treatment with TA involves regular

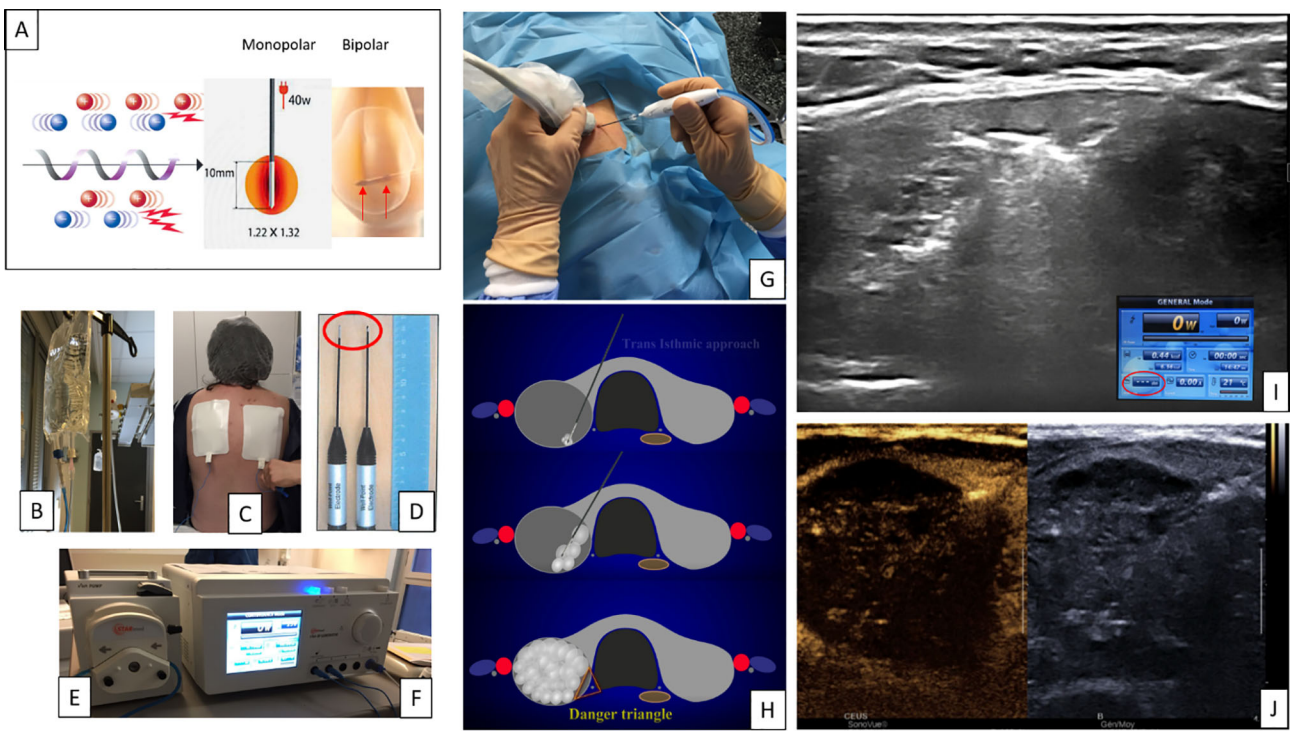

FIGURE 3 | Radiofrequency ablation (RFA): physiology, equipment and ablation. Ionic agitation **(A)** and formation of frictional heat. Monopolar: Using a 40W RF power, and an active-tip of 10 mm, the diameter of the action zone is 13 mm. Bipolar RFA electrode with two tips **(D)**. Internally cooled electrode (active-tip 5 and 10 mm) receives cold fluid **(B)** perfusing by a peristaltic pump **(E)**. The generator **(F)** supplies RF power through the active-tip of the electrode. Grounding pads **(C)** act to disperse electricity in the RF circuit. Using ultrasound guidance **(G)**, the electrode is inserted into the nodule. A trans-isthmic approach **(H)** and a moving shot technique are recommended. A cloudy effect **(I)** and an increase of the impedance (red circle) indicate the moment to change ablation zone. CEUS confirms **(J)** the complete treatment of the nodule ("vascular desert").

clinical and ultrasound monitoring in order to assess the long-term nodular development (VVR) and whether or not it requires a new session. Finally, there are very few series in the literature for which long-term FU (beyond 18 months) is available. It is accepted in its series the need to reprocess the nodules, sometimes twice, three times or even more than three times (**Table 1**). It is therefore advisable, before the procedure, to inform the patient of the possibility of nodular regrowth with the possibility of new TA sessions.

Optimization of Treatment Methods

Since the first rat trials for the treatment of hyperthyroidism (44) and the first representative series by Jeong et al. (28), techniques and technology have not stopped to improve in order to optimize the management of thyroid nodules. If we go back to the genesis, it is true that in Asia the preservation of the axis of fertility "head-genitals" motivated the development of alternative techniques such as TA but also surgical techniques with alternative approach (in particular axillary) robot assisted (45). From now on, TA is widespread throughout the world and carried out in reference centers which benefit from an accreditation by the Korean learned societies, pioneers in TA techniques. The suppliers and generator developer are constantly improving, with the help of the physicians, the technical methods. There are currently retractable radiofrequency electrodes making it possible to optimize the treatment of the treated zone; in particular in posterior zones and zones that are very close to the capsule. Lee et al. (46) have shown that an adjustable electrode for RFA of benign TN was effective and safe. This will most likely limit the viable residual area after treatment; therefore limiting nodular regrowth (47). Moreover, recent Chinese series have shown a reduction in procedural time when radiofrequency was coupled with prior ethanol injection, with a mean treatment time of 441.30 ± 243.31 seconds *vs.* 790.70 ± 349.82 seconds; t=4.403, *p=0.000*; that prior ethanol injection is effective in reducing nodule volume, relieving compressive symptoms, and cosmetic discomfort (48). Randomized trials will be needed to validate this new combined procedure. Procedures combined with the administration of iodine 131 (in particular in the context of solid AFTN) have already demonstrated their effectiveness (49), extend to develop in particular for large AFTN. Moreover, the achievement of about fifty RFA is necessary to obtain good clinical and ultrasound results (significant reduction of the initial symptomatology and significant reduction of the nodular volume) corresponding to the learning curve (27). It is notably correlated to the power used and to the energy deposited on the nodule which are associated with the appraisal of the operator training.

Comparison With Other Techniques

Regarding the procedure itself, whether for RFA or LTA, it takes place in a mini-intervention room or in the operating room in the presence or not of an anesthesiologist, more or less with sedation, the patient placed in dorsal decubitus, neck in hyper extension, under ultrasound guidance in aseptic conditions. The approach is trans-isthmic with the radiofrequency electrode with the possibility of using the 'moving-shot' technique, for the laser, the laser fiber (s) is (are) positioned using a fixator/trocar. Several studies have focused on the long-term FU of patients treated with laser. The efficiency of the laser in terms of volume reduction is comparable to that of the RFA (50–52). Several comparative studies have been carried out between LTA and RFA over a period of less than 2 years. Other series with a longer FU [18 months for Ben Hamou et al. (27) and 60 months for Bernardi et al. (17)] did not show a difference between the two techniques (VVR between 60 and 85%). However, the risk of nodular regrowth is lower in patients treated with RFA than in those treated with laser. Few studies have focused on percutaneous microwave ablation (PMWA), in the treatment of benign TN. Liu et al. (53) has shown that PMWA is an effective and safe technique in 474 benign solid TN with a mean 90% decrease in volume at 12 months after the treatment. Yue et al. (54) have also concluded the efficacy of PMWA with a signification volume reduction at 12 months after treatment (12.6 ± 15.1 to 3.2 ± 5.7 ml). A single-center retrospective study comparing the efficacy and safety of RFA (40 patients), PMWA (40 patients) and HIFU (14 patients), has shown a slight superiority of RFA, with a mean volume reduction of nodules of 50% *vs.* 44% for MWA and 48% for HIFU at three months after treatment (short period of time). Finally, in a recent series, the authors compared RFA and MWA (53). The RFA group achieved higher VRR than MWA group at 6 and 12 months (77.9 ± 21.0% *vs.* 68.7 ± 19.1% (*p=0.038*), and 85.4 ± 18.9% *vs.* 75.8 ± 19.4% (*p=0.029*), respectively).

Future Perspectives

The optimization of care and technical innovation is a fundamental point in the management of these patients. Benign thyroid nodules do not represent *a priori* any particular threat for the patient but when they become compressive and/or they increase in size (15% of the nodules progress in volume during the FU), then it is necessary that the patient can benefit from the best therapeutic option. A recent survey (55) by the members of the European Thyroid Association suggested that TA was the preferred option only for a 4-cm benign nodule in old patients with comorbidities. The objective is therefore to improve the diffusion and the access to these new minimally invasive techniques. Recent studies concerning patient satisfaction (QOL questionnaire) after treatment have all mainly shown patient satisfaction (22) concerning the technique. It has also been recently shown that there is no risk of cancer after treatment of a benign thyroid nodule by TA. In fact, Ha et al. (31) showed that at five years after RFA, no atypical cells nor neoplastic transformation were detected in the undertreated peripheral portion of treated benign nodules on the CNB specimen, concerning 16 nodules. On histo-pathological examinations, 81.2% of acellular hyalinization was observed.

The indications for thyroid RFA are now broadening with the treatment of papillary thyroid micro-cancers (PTMC) and the treatment of cervical lymph node recurrence. Indeed, Cho et al. (56) have shown the efficacy and safety of RFA in the management of low-risk papillary cancers (84 PTMC from 74 patients) with complete disappearance rates of 98.8% and 100% achieved at 24 and 60 months respectively after the

treatment. No occurrence of local tumor progression, lymph node, or distant metastasis were reported, and no delayed complications, procedure-related death, or delayed surgery occurred over the 72-month mean FU period. In patients with PTMC (57), RFA appears to have an advantage over surgery in terms of QOL, supporting the role of RFA as an alternative strategy to surgery. Another study (58) showed the efficacy and safety of RFA in the treatment for low-risk PTMC after a long-term FU period (42.1 ± 11.8 months); with a mean VRR of 98.8 ± 6.4%. After RFA 366 tumors (88.4%) completely disappeared. One patient had a residual cancer, four have developed metastatic lymph nodes, and ten patients had recurrent PTMC. Thirteen of those patient were retreated by RFA, with a complete disappearance of 11 lesions during FU. Moreover, RFA is considered as an effective and safe minimally invasive therapy of locally recurrent papillary thyroid cancer since a mean volume reduction of 99.5% ± 2.9% was observed and that 46 treated tumors (91.3%) had completely disappeared by the final evaluation (59). Lim HK et al. have shown similar results suggesting the efficacy of RFA treating low-risk PTMC in patients who are of high surgical risk or refuse surgery. They finally observed a complete disappearance of ablated tumors found in 91.4% (139/152) (60).

CONCLUSION

Thermal ablation is a safe and effective method for the treatment of benign thyroid nodules and radiofrequency seems to be one of most efficient techniques. The volume reduction rate can reach 80% of the initial nodule volume in most studies but the patient should be informed that a re-treatment may be needed in case of huge nodules or incomplete ablation. Minor adverse events are frequent but usually reversible while major complications are rare (<3% of cases). So, these findings represent a clear advantage versus the incompressible rate of surgical complications and the duration of sick-leave (about 10 to 21 days for surgery).

All the studies under examination consistently validated the long-term clinical efficacy and the substantial safety of RFA for the treatment of benign thyroid nodules. Thermal ablation, however, is an operator-dependent technique and should be performed in centers with specific expertise. The selection of patients should be rigorous because the nodule size and the structural and functional characteristics influence the appropriateness and the outcomes of the treatment. Future perspectives as the treatment of micro-papillary thyroid cancer or cervical recurrence need further investigations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

HM and ABH wrote the first version of the manuscript. ABH, HM, and AA contributed to the review of the literature. All authors contributed to the article and approved the submitted version.

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Radiofrequency Thermoablation On *Ex Vivo* Animal Tissues: Changes on Isolated Swine Thyroids

Paola Pregel[1*], *Elisa Scala*[1,2], *Michela Bullone*[1], *Marina Martano*[1,3], *Linda Nozza*[1], *Sara Garberoglio*[4], *Roberto Garberoglio*[4], *Enrico Bollo*[1] *and Frine Eleonora Scaglione*[1]

[1] *Dipartimento di Scienze Veterinarie, Università degli Studi di Torino, Torino, Italy,* [2] *Evidensia Specialisthästsjukhuset, Strömsholm, Sweden,* [3] *Dipartimento di Scienze Medico-Veterinarie, Università di Parma, Parma, Italy,* [4] *Dipartimento di Scienze Mediche, Università degli Studi di Torino, Torino, Italy*

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***Correspondence:**
Paola Pregel
paola.pregel@unito.it

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The use of Radiofrequency thermoablation (RFA) for treating large thyroid nodules is limited by the modest efficiency of the available systems in terms of volume of the ablation zones (AZs). This increases the risk of incomplete ablation of the nodule. Systems employing perfused electrodes have been developed to increase the volume of the AZ. Aim of this study is to compare the size of the AZ induced by RFA systems using internally cooled perfused vs. non-perfused electrodes in swine thyroids. RFAs were performed on 40 freshly isolated swine thyroids using both systems. The perfused system was tested using 0.9% saline, 7% and 18% hypertonic saline solutions. Energy delivery to the tissue was stopped when tissue conductivity dropped (real life simulations) and after an established time of 20 seconds (controlled duration). Following RFA, thyroids were transversally and longitudinally cut. Photographs were taken for macroscopic morphometry of the ablated zones before and after formalin fixation, to evaluate tissue shrinkage. Microscopic morphometry was performed on PAS stained sections. In real life simulation experiments, gross morphometry revealed that AZs produced with electrodes perfused using 7.0% saline are larger compared to isotonic saline. Microscopically, all the conditions tested using the perfused system produced larger AZs compared to non-perfused system after 20 seconds of RFA. In conclusion, the perfusion with 7.0% NaCl solution increased the electrical conductivity of the tissue in real life simulations, resulting in larger ablated areas compared to the use of isotonic saline.

Keywords: RFA, thyroid, swine, perfused electrodes, hypertonic saline

Abbreviations: AZ, Ablation zone; CT, computed tomography; DTC, differentiated thyroid cancer; MR, Magnetic Resonance; RF, Radiofrequency; RFA, Radiofrequency ablation; US, Ultrasound; IC, Internally cooled and non-perfused electrodes; WT, Internally cooled and perfused (wet tip) electrodes; FF, Formalin fixed; VT, Variable Time treatment; FT, Fixed Time treatment.

INTRODUCTION

In the last thirty years, minimally invasive techniques have been consistently raising in importance in human medicine. Radiofrequency ablation (RFA) is the most extensively studied and widely applied technique in human clinical practice (1), largely used to treat malignant and benign tumors in several organs (1, 2). It consists on the direct placement of one or more radiofrequency (RF) electrodes into the tumor tissue under ultrasound (US), computed tomography (CT) or magnetic resonance (MR) guidance (2). RF electrodes apply thermal energy (hyperthermia) through the passage of high-frequency alternating current through the electrode, producing tissue necrosis of the tumor, without the need for surgical removal. Among other organs, the application of RFA has been extended in the last decade to the treatment of thyroid neoplasia and nodular thyroid disease, with a proven efficacy in terms of reduction of thyroid nodule mean volume and improvement of the patient symptoms (3–7). To date, RFA is considered a safe alternative to surgery for benign thyroid nodules, and it is proposed for treatment of primary thyroid carcinomas and recurrent thyroid cancer (8–16).

Nodular thyroid disease refers to the presence of abnormal masses in the thyroid gland. It is a very common finding in clinical practice, with a good prognosis (17–19). Thyroid nodules are most frequently asymptomatic, stable or slow-growing over time, and require no treatment. Clinicians' concerns in these cases are imputable mainly to the space-occupying effect of such lesions, as well as to the associated endocrine disorders, such as hyperthyroidism and hypothyroidism. Large thyroid nodules may cause compression to the surrounding structures, neck discomfort, cosmetic complaints, and decreased quality of life. To date, the possible treatments include surgery, radioiodine therapy, TSH-suppression therapy, ethanol injection, and hyperthermic methods (18). The main limit of the latter is the small size of the induced AZ, considered adequate for treating lesions up to 5 cm^2 (2).

Tissue perfusion with saline has been shown to improve the performances of RFA systems in terms of volume of the AZs (20). The aim of this study was to compare the performances of RFA systems employing internally cooled and perfused vs. internally cooled and non-perfused electrodes in terms of AZ size, using ex-vivo swine thyroids. Moreover, we sought to determine whether using solution with increased osmolarity produced any effect on the size of AZs. Anatomic and physiologic characteristics of swine make them useful models in certain areas of surgical research (21). In particular, swine thyroid glands have an adequate size and a fine tissue structure resembling those of humans.

MATERIALS AND METHODS

Thermal Ablation Procedures

Forty freshly isolated swine thyroids from a pig slaughterhouse were stored at refrigerated temperature until RFA exposure, and then ablated using the fixed-shot technique. The moving shot technique, usually applied in thyroid treatment, was not evaluated in this work, since results are dependent on the number of passages and the tilt angles of the electrode. The single passage allowed a better measurement of the parameters obtained by a single ablation treatment.

Radiofrequency ablation procedures were performed using either a perfused or non-perfused system, with internally cooled and perfused (RFTS 1010N, RF Medical Co. Ltd., Korea) or internally cooled and non-perfused electrodes (RFT 1010N, RF Medical Co. Ltd., Korea), respectively. A high frequency alternating current generator specific for radiofrequency thermal ablation (RF Generator M-3004, RF Medical Co. Ltd., Korea), equipped with a peristaltic pump, was used to power the system.

A starting power output of 80 Watt was used. Ground pads were placed under each organ to close the RT circuit, placing a swine liver between the ground pads and the thyroid, to ensure an adequate distance and obtain a correct electrical conduction. Procedures were stopped using an impedance-based system. All electrodes used were monopolar, 10 cm in length, and 18G in diameter, with an exposed electrode of 10 mm. Internally cooled and non-perfused (IC) electrodes are provided with an internal cooling system pumping cold (5°C) sterile saline solution. This prevents the electrodes to reach temperatures above 100°C, which could induce tissue carbonization. Internally cooled and perfused (wet tip, WT) electrodes have a second system for instillation of liquids into the tissues while RFA is performed by means of a peristaltic pump. Cold (5°C) sterile isotonic solution 0.9% NaCl, hypertonic 7.0% NaCl solution, and hypertonic 18.0% NaCl solution were used in our study to perfuse thyroid parenchyma.

Energy delivery to the tissue was stopped when tissue conductivity dropped (real life simulations) and after an established time of 20 seconds (controlled duration).

Morphometric Analysis

The criteria proposed by Mulier and colleagues (22) were adopted for standardized description of the AZ size. At the end of the ablation procedure, the RF electrode was left *in situ* in order to easily identify the treated area. The organ was cut along the shaft of the RF electrode (axial plane of the AZ) obtaining the two orthogonal planes of the lesion. Then both halves of the AZ were cut in the transverse plane, perpendicular to the electrode, at the site of the largest transverse diameter of the coagulation zone.

Morphometric analysis of the macroscopically visible AZs was performed with the software *ImageJ 1.51j8* (National Institutes of Health, USA) on pictures taken from both faces of each plane (axial and transversal), including a calibrator in each picture. Thyroids were then individually fixed in buffered formalin (10%) and pictures and measurements of the parameters to assess the degree of tissue shrinkage were taken a second time. Area and perimeter of the AZ were calculated for each image. Both faces of each plane were measured, and mean data used for analyses. The volume of the rotation solid (lesion volume, calculated as: $Volume = \frac{4}{3}\pi\, abc$, where a, b and c were halves of each axis, assuming that it is ascribable to the area of a

rotation (23) ellipsoid) and the equivalent diameter (diameter that a round section would have with the same proportion of Perimeter P and Area A) were estimated from the former parameters. The semiaxes of the lesion were also measured.

Microscopic morphometry of the AZs was performed using an Olympus BX40 microscope and the software NIS-Elements F 2.30 (Nikon Corporation, Japan) on Periodic Acid Schiff (PAS) stained sections (20x magnification), following paraffin-embedding and 4μm cut. The parameters measures were the same already described for macroscopic morphometry. A 20x magnification was selected, allowing a general view of the lesion area, taking multiple pictures of the same slide when necessary, to include the whole lesion. Pictures were assembled with the software Adobe Photoshop CC 2018 (Adobe Systems Incorporated, USA).

Statistical Analysis

The statistical analysis of the morphometric values was performed using the software GraphPad Prism (vers. 6; GraphPad Software, California, USA). The Kolmogorov and Smirnov test was used to analyze data distribution. For the morphometric measurements, when the effect of a single variable was assessed among multiple groups, one-way ANOVA test was used, followed by Dunnett's post-tests, if the distribution was parametric; otherwise the Kruskal-Wallis test and Dunn's post-tests were employed. When the effect/interaction of two variables was evaluated among multiple groups, the two-way ANOVA test was used, followed by Tukey post-tests, with the Sidak correction. Paired Student's T-test was used for the comparison between lesions on unfixed and formalin-fixed (FF), whereas the non-parametric Wilcoxon test was applied for the comparison between the two semi-axis of the rotation solid on unfixed thyroids. In order to compare differences in measurements between the same lesion parameters analyzed on gross unfixed thyroids images and on the corresponding microphotographs, Paired Student's T-test or the non-parametric homologous Wilcoxon test were used. The coefficient of variation was evaluated to highlight the difference between repeated measurements, such as Area and Equivalent Diameter, available only in gross morphometric analysis, for both longitudinal and transverse views. All the results with a p-value<0.05 were considered statistically significant.

RESULTS

Macroscopic Investigations on Unfixed Thyroids

The macroscopic investigation of the thyroids treated with RFA revealed an area clearly identifiable from the surrounding, normal tissue. The area could be roughly described as an ovoid, even though it was often irregular. In the unfixed thyroids, the ablated area was divided in a brown centre, in which the tissue was in direct contact with the electrode, surrounded by a pale pink area. Minimal or non-existent hemorrhagic transitional zone between ablation and normal tissue was noticed. This partition was evident in some samples more than in others, and the type of applicator seemed to slightly influence it. In fact, when the IC electrode was used, the partition was evident, and the ablation had a definite outline (**Figure 1A**). In the case of WT electrode, independently from the solution used, the outline of the lesion appeared vanishing (**Figure 1B**). The thyroid was entirely or almost interested by the coagulation area in case a WT was used, especially when 7.0% NaCl solution was injected (**Figure 1C**).

In thyroids treated with IC electrode, the treatment was fixed at 20 seconds. Regarding WT electrodes, when applying a variable time (real life simulations), RF electrode was left to work until the impedance was enough high to automatically turn the generator off.

As a result, some organs were totally thermally ablated before the generator turned off, so that it had to be manually interrupted. In these groups of organs, the potential of WT electrode was evident, but the size of the lesion was strongly influenced by the size and margins of the thyroid. In order to determine the effects of saline solution on ablation size, a procedure at fixed time was also implemented. In this case, the duration of treatment was fixed at 20 seconds, forcing the generator to stop, independently from the completion of

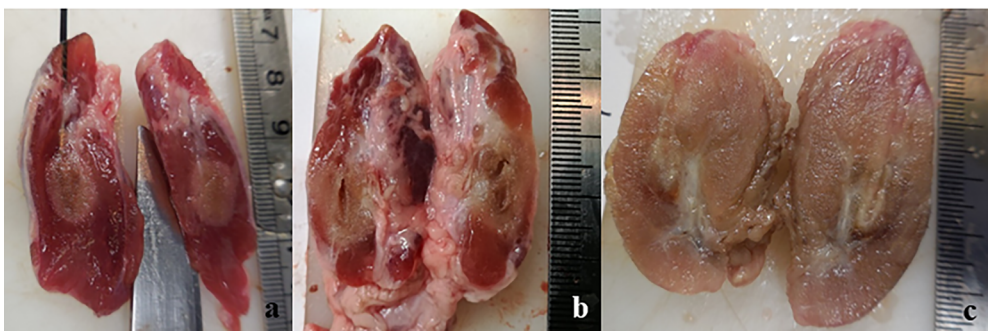

FIGURE 1 | Longitudinal section of unfixed thyroids: **(A)** treated with IC electrode, 20 seconds fixed time of treatment; **(B)** treated with WT electrode, 0.9% NaCl solution, 20 seconds fixed time of treatment; **(C)** treated with WT electrode, 7.0% NaCl solution, variable time of treatment (4 minutes and 30 seconds).

ablation. The latter procedure was implemented due to the small size of thyroids and following the finding that many of them were completely necrotized, thus interfering with a precise measurement of the ablation (being the size of the lesion strongly dependent from the margins and size of the thyroid). This procedure was not meant to be applied in clinic but to better understand the potential of saline use.

Macroscopic Morphometric Data From Unfixed Thyroid

The morphometric analysis data obtained from unfixed thyroids are stated in **Table 1**, reporting mean values and standard deviation for each group.

Effects of Time of Treatment and Solution on WT Electrode Performances

The performance of WT electrode on unfixed thyroids was analyzed through a comparison based on the used solution (0.9% or 7.0% NaCl) and the duration of treatment (variable or 20 seconds/fixed time).

The transverse area was influenced by both the solution used ($p<0.0004$) and the duration of treatment ($p<0.0001$) (**Figure 2A**). In the groups where the time of treatment was variable, a significant increase of ablation area was revealed when the 7% solution was used in comparison to 0.9% NaCl solution ($p<0.05$). No difference was observed in fixed time groups ($p=0.8694$). The groups treated for a fixed time both with 0.9%

TABLE 1 | Unfixed thyroids morphometric data.

Electrode	Solution	Time of treatment	Transverse section		Longitudinal section		a (mm)	b (mm)	c (mm)	Volume (mm³)
			Area (mm²)	Equivalent diameter (mm)	Area (mm²)	Equivalent diameter (mm)				
Internally cooled	–	20-sec fixed time	50.5 ± 8.9	7.4 ± 0.5	88.1 ± 19.7	8.6 ± 1.7	3.9 ± 0.6	7.2 ± 1.1	3.8 ± 0.3	448.6 ± 121.8
Wet tip	0.9% NaCl	Variable time	142.8 ± 76.4	11.6 ± 2.3	300.2 ± 169.6	15.3 ± 4.7	6.9 ± 2.4	13.2 ± 4.3	6.1 ± 1.4	2665.0 ± 1997.0
Wet tip	7.0% NaCl	Variable time	306.8 ± 41.7	17.3 ± 1.6	699.7 ± 112.6	23.7 ± 3.0	10.7 ± 1.0	20.8 ± 1.6	9.5 ± 0.7	8916.0 ± 1660.0
Wet tip	0.9% NaCl	20-sec fixed time	82.8 ± 22.6	9.0 ± 1.3	99.3 ± 38.6	9.7 ± 2.2	4.4 ± 1.2	7.1 ± 1.2	5.1 ± 0.9	704.4 ± 368.8
Wet tip	7.0% NaCl	20-sec fixed time	70.9 ± 28.7	8.1 ± 2.0	109.7 ± 35.7	9.7 ± 1.2	4.4 ± 0.7	7.9 ± 1.6	4.1 ± 1.1	620.5 ± 317.3
Wet tip	18.0% NaCl	20-sec fixed time	71.2 ± 12.3	7.7 ± 0.6	137.0 ± 65.4	11.3 ± 3.3	4.6 ± 1.5	9.1 ± 1.7	5.3 ± 0.8	1006 ± 551.7

Overview of the mean values of Area and Equivalent diameter for both transverse and longitudinal sections, a, b, and c semiaxes, and lesion volume.

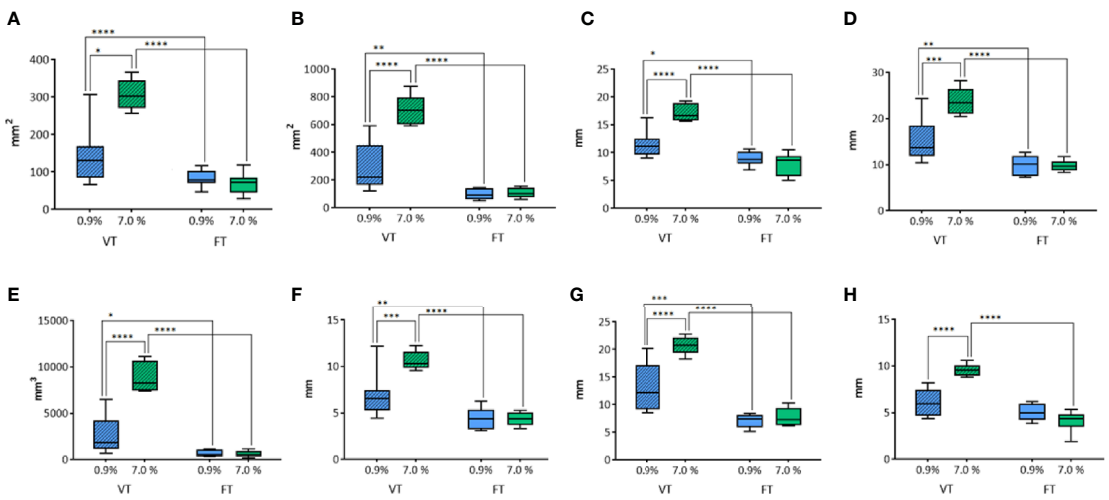

FIGURE 2 | Comparison of different parameters among the groups treated with WT, with variable and fixed time of treatment, and 0.9% and 7.0% NaCl solution on thyroids. In details, **(A)** transverse area; **(B)** longitudinal area; **(C)** transverse equivalent diameter; **(D)** longitudinal equivalent diameter; **(E)** volume; **(F)** semi-axis "a"; **(G)** semi-axis "b"; **(H)** semi-axis "c". VT, Variable Time treatment; FT, Fixed Time treatment; 0.9%= solution perfused into the tissue at 0.9% NaCl; 7.0%= solution perfused into the tissue at 7.0% NaCl; *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

and 7% NaCl solution showed a significant reduction of ablation area in comparison to the groups treated with the same solutions for a variable time (p<0.0001).

In addition, also the longitudinal area was influenced by the solution (p<0.0001) and the time of treatment (p<0.0001) (**Figure 2B**). As for the transverse area, the groups treated for a variable time enlightened a significantly greater area of ablation with 7.0% NaCl solution (p<0.0001). No significant difference was observed in fixed time groups (p=0.9782). In the groups treated for a fixed time the area of ablation was significantly smaller than the corresponding groups treated for a variable time (respectively, p<0.01 for 0.9% NaCl and p<0.0001 for 7.0% NaCl).

The same findings were obtained for the other parameters evaluated. The transverse equivalent diameter (**Figure 2C**) was influenced both by the solution (p=0.003) and the time of treatment (p<0.0001). Within Variable Time treatment (VT) groups, a significantly longer equivalent diameter was measured with 7.0% NaCl solution (p<0.0001). No significant difference was observed in fixed time groups (p=0.6008). In the groups treated with 0.9% NaCl solution, a significantly shorter equivalent diameter was detected for Fixed Time treatment (FT) in comparison to the corresponding VT group (respectively, p<0.05 for 0.9% NaCl, p<0.0001 for 7.0% NaCl treated groups).

The longitudinal equivalent diameter (**Figure 2D**) was influenced by the solution (p=0.0016) and the duration of treatment (p<0.0001), too. In the VT groups a significantly longer equivalent diameter was reported along with the use of 7.0% NaCl solution (p=0.0001). No difference was revealed in fixed time groups (p=0.9994). In the two VT groups a longer equivalent diameter was calculated when compared to the corresponding fixed time groups (respectively, p<0.01 for 0.9% NaCl and p<0.0001 for 7.0% NaCl).

The volume (**Figure 2E**) was influenced by the solution (p<0.0001) and the duration of treatment (p<0.0001). In the groups where the time of treatment was variable, a significant difference according to the use of 0.9% or 7.0% NaCl solutions (p<0.0001) was detected. No difference was observed in fixed time groups (p=0.9903). In the groups treated with 0.9% NaCl solution, a significant difference between variable and fixed time (p<0.05) was observed, as for the groups treated with 7.0% NaCl (p<0.0001).

The semiaxis "a" (**Figure 2F**) was influenced by the solution (p=0.0036) and the time of treatment (p<0.0001). In the groups where the time of treatment was variable, a significant increase of volume was detected according to the use of 7.0% NaCl solution when compared to 0.9%NaCl (p=0.0005). No difference was revealed in fixed time groups (p=0. 9995). In the groups treated with 0.9% NaCl solution, a significant difference between variable and fixed time (p<0.01) was detected, as for the groups treated with 7.0% NaCl (p<0.0001).

Similarly, the semiaxis "b" (**Figure 2G**) was influenced by the solution (p=0.0003) and the time of treatment (p<0.0001). Again, in VT groups a significant increase of semiaxis b length was detected when 7.0% NaCl solution was used instead of 0.9% (p<0.0001). No difference was observed in fixed time groups (p=0. 8206). In both the VT groups the semiaxis "b" was longer than in the corresponding FT groups (p<0.001 for 0.9% and p<0.0001 for the 7.0% NaCl, respectively).

The semiaxis "c" (**Figure 2H**) was influenced by the solution (p=0.0091) and the time of treatment (p<0.0001). In the groups where the time of treatment was variable, a significant difference related to the use of 0.9% or 7.0% NaCl solutions (p<0.0001) was detected. No difference was revealed in fixed time groups (p=0.1704). The time of treatment influenced the semiaxis "c" only in the groups treated with 7.0% NaCl solution (p<0.0001). No significant difference between variable and fixed time was found in the groups treated with 0.9% NaCl.

Comparison of IC and WT Electrodes Performances

The performance of WT electrodes (with 0.9%, 7.0% and 18.0% NaCl) was compared to IC electrode (control group) at fixed duration of treatment of 20 seconds.

For the transverse area (**Figure 3A**) a significant difference was shown among groups (p=0.0339) (in particular, between the control group IC and WT using 0.9% NaCl solution, p=0.014). No differences were found between the control group IC and other WT groups. For the longitudinal area no differences were observed using IC or WT electrodes (p=0.232) at 20 seconds fixed time treatment (**Figure 3B**). The transverse equivalent diameter (**Figure 3C**) and the longitudinal equivalent diameter (**Figure 3D**) were not affected by the use of either IC or WT electrodes at 20 seconds fixed time treatment (p=0.0991 and p=0.2239, respectively). The volume (**Figure 3E**) was not affected by the use of either IC or WT electrodes (p=0.2669) at 20 seconds fixed time treatment. The semiaxis "a" was not affected by the use of either IC or WT electrodes (p=0.6584) at 20 seconds fixed time treatment (**Figure 3F**). The semiaxis "b" was found not to be affected by the use of either IC or WT electrodes (p=0.0797) at 20 seconds fixed time treatment (**Figure 3G**). Regarding the semiaxis "c" (**Figure 3H**), a significant difference among groups was shown (p=0.0071). In particular, a significant longer measure was noticed in WT 0.9% NaCl solution (p=0.0215) and in WT 18.0% NaCl (p=0.0122) in comparison to IC control group. No differences were found between the control group IC and WT 7.0% (p=0.8493).

Comparison of the Semiaxes of the Rotation Solid

The two semi-axes of the rotation solid "a" and "c" are considered equivalent.

In the comparison between the two semi-axes of the rotation solid "a" and "c" of all the unfixed thyroids belonging to fixed time groups no significant difference was detected (p=0.4939) (**Figure 4**).

Macroscopic Investigations on Formalin-Fixed Thyroids

The ablated tissue was clearly detectable in FF thyroids as a pale, yellowish area, with no evident internal subdivision. Sometimes the lesion margins were more clearly evident compared to unfixed organs, even though the outline of the

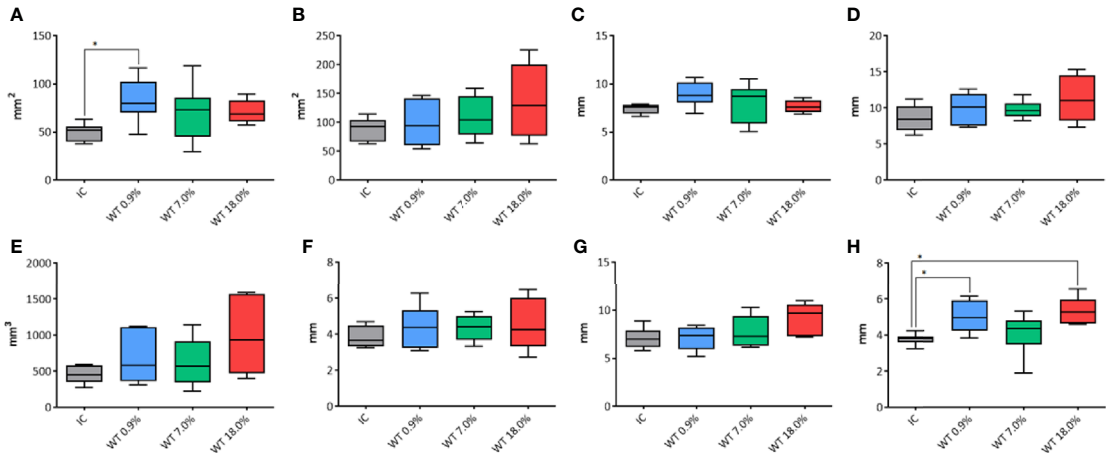

FIGURE 3 | Comparison of different parameters among the groups treated with IC electrode and WT electrode with different saline solutions on unfixed thyroids. In details, **(A)** transverse area; **(B)** longitudinal area; **(C)** transverse equivalent diameter; **(D)** longitudinal equivalent diameter; **(E)** volume; **(F)** semi-axis "a"; **(G)** semi-axis "b"; **(H)** semi-axis "c". IC, Internally cooled tip; WT, Internally cooled wet tip; WT 0.9%-7.0%-18.0%= solutions at 0.9%-7.0%-18.0% NaCl perfused into the tissue by the WT electrode; *P < 0.05.

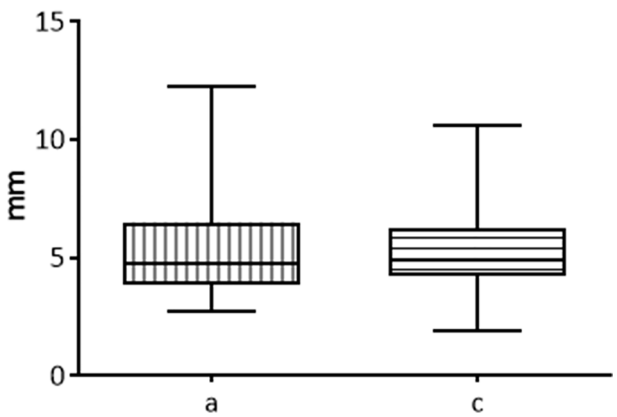

FIGURE 4 | Comparison between the two semi-axis "a" and "c" of ablated area in fresh thyroids, 20 seconds fixed time of treatment.

lesion in the thyroids treated with WT electrode was still vanishing (**Figure 5**).

Macroscopic Morphometric Data From Formalin-Fixed Thyroids

The morphometric analysis data reporting mean values and standard deviation for each group, obtained from FF thyroids are conveyed in **Table 2**.

Comparison Between Unfixed and Formalin-Fixed Thyroids

The pictures of unfixed thyroids were compared to the corresponding ones of formalin-fixed thyroids. Only fixed time groups were considered to lower the variability.

The compared measurements analyzed are reported in **Table 3**.

The transverse area (**Figure 6A**) and the longitudinal area (**Figure 6B**) were not significantly different between unfixed and FF thyroids (p=0.3392, p=0.3822, respectively). Similarly, the transverse equivalent diameter (**Figure 6C**) and the longitudinal equivalent diameter (**Figure 6D**) were not significantly different between unfixed and FF thyroids (p=0.0808, p=0.3446, respectively).

Similarly, the volume (**Figure 6E**) was not significantly different between unfixed and FF thyroids (p=0.3303). The semiaxis "b" was the only one to be significantly different between the two groups (p=0.0239) (**Figures 6F–H**).

During the morphometric analysis of gross thyroids, two halves of the lesion originated from transverse and longitudinal cuts, obtaining two values for the area and the equivalent diameter referred to the same view. The coefficients of variation of these measurements of gross unfixed thyroids were compared with the ones of FF thyroids. No statistically significant differences were detected in the distributions of the coefficients of variation for the transverse area (p=0.0587), for the longitudinal area (p=0.8615), for the transverse equivalent diameter (p=0.3038), and for the longitudinal equivalent diameter (p=0.6556). Generally, the ablated area showed shrunk and darker colloid in follicular tissue, creating an empty space between the follicular wall and the colloid.

Since the colloid is PAS-positive, the ablation area was easily recognizable in the sections stained with PAS, easily allowing the morphometric analysis (**Figure 7**). No difference was noticed between thyroids treated with IC or WT electrode, apart from larger ablated areas in the latter treatment group.

Microscopic Morphometric Data

The histological morphometric data are reported in **Table 4**.

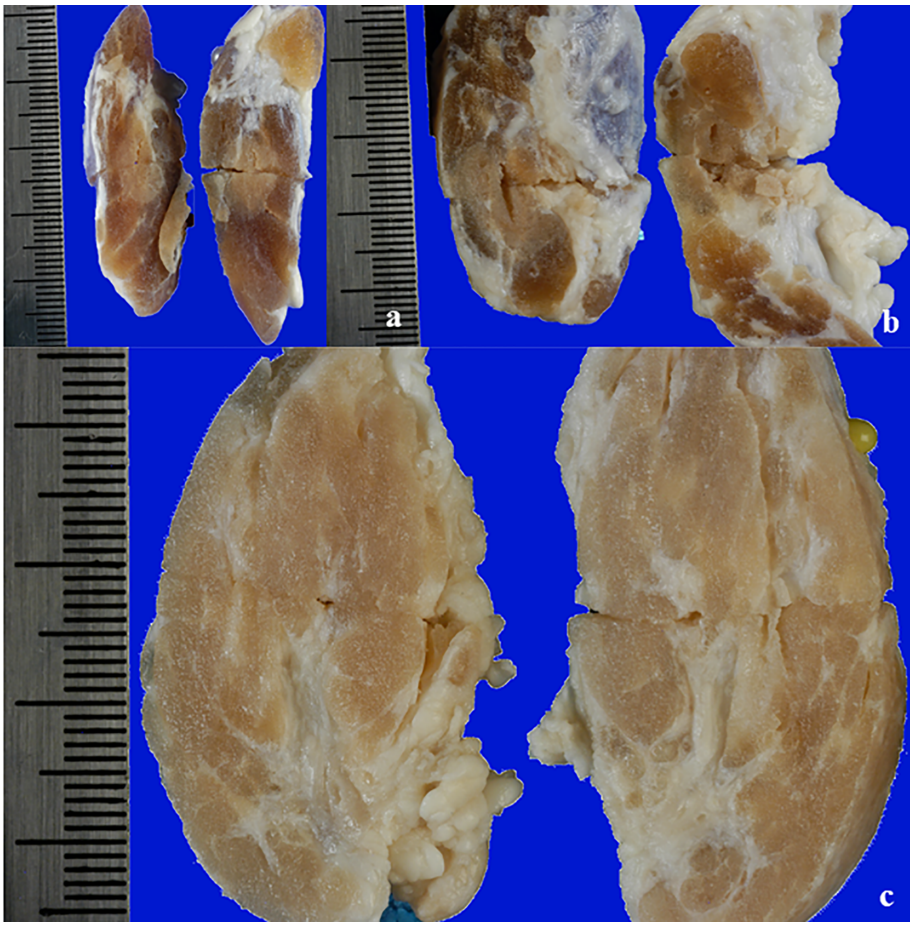

FIGURE 5 | View of a longitudinal section of a FF thyroid: **(A)** treated with IC electrode, 20 seconds fixed time of treatment; **(B)** treated with WT electrode, 0.9% NaCl solution, 20 seconds fixed time of treatment; **(C)** treated with WT electrode, 7.0% NaCl solution, variable time of treatment (4 minutes and 30 seconds).

TABLE 2 | FF thyroids morphometric data.

Electrode	Solution	Time of treatment	Transverse section		Longitudinal section		a (mm)	b (mm)	c (mm)	Volume (mm^3)
			Area (mm^2)	Equivalent diameter (mm)	Area (mm^2)	Equivalent diameter (mm)				
Internally cooled	–	20-sec fixed time	51.2 ± 8.3	7.8 ± 0.6	69.4 ± 21.6	7.5 ± 2.1	3.4 ± 0.8	6.2 ± 0.9	3.7 ± 0.6	351.6 ± 146.1
Wet tip	0.9% NaCl	Variable time	108.2 ± 50.7	10.4 ± 1.5	133.6 ± 29.5	10.3 ± 1.1	4.7 ± 0.6	9.0 ± 2.1	5.4 ± 1.7	1010.9 ± 536.8
Wet tip	7% NaCl	Variable time	295.6 ± 7.4	14.9 ± 0.6	540.4 ± 160.2	20.1 ± 4.5	9.7 ± 0.9	17.7± 3.5	9.3 ± 0.9	6777.0 ± 2585.5
Wet tip	0.9% NaCl	20-sec fixed time	89.6 ± 23.1	9.3 ± 1.8	108.1 ± 53.1	9.9 ± 3.0	4.5 ± 1.4	7.3 ± 1.4	4.9 ± 0.9	754.8 ± 525.4
Wet tip	7% NaCl	20-sec fixed time	82.2 ± 21.5	9.2 ± 1.2	133.3 ± 42.5	10.5 ± 0.4	4.9 ± 0.5	8.6 ± 1.8	4.4 ± 0.7	793.1 ± 365.9
Wet tip	18% NaCl	20-sec fixed time	96.9	9.0	135.1	13.7	4.5	9.6	5.4	969.0

Overview of the mean values of Area and Equivalent diameter for both transverse and longitudinal sections, a, b, and c semiaxes, and lesion volume.

TABLE 3 | Morphometric data of macroscopic images from unfixed thyroid and corresponding formalin-fixed ones.

Measurement	Unfixed thyroids		FF thyroids	
	VT+FT	FT	VT+FT	FT
Transverse area (mm^2)	100.0 ± 71.7	70.22 ± 25.5	102.0 ± 72.7	72.8 ± 24.2
Longitudinal area (mm^2)	178.4 ± 191.5	102.1 ± 36.3	145.5 ± 138.6	96.9 ± 43.2
Transverse equivalent diameter (mm)	9.7 ± 3.0	8.3 ± 1.1	9.6 ± 2.3	8.6 ± 1.3
Longitudinal equivalent diameter (mm)	11.48 ± 5.0	9.4 ± 2.0	10.3 ± 4.0	9.0 ± 2.5
Volume (mm^3)	1596.0 ± 2624.0	630.3 ± 359.3	1247 ± 1925	588.5 ± 377.8
a (mm)	–	4.1 ± 0.7	–	3.9 ± 0.8
b (mm)	–	7.6 ± 1.6	–	7.1 ± 1.5
c (mm)	–	4.4 ± 0.8	–	4.2 ± 0.6

Overview of the mean values of Area and Equivalent diameter for both transverse and longitudinal sections, a, b, and c semiaxes, and lesion volume. The values refer to both variable and fixed time of treatment (VT+FT), and only fixed time groups (FT).

Effects of Time of Treatment and Solution on WT Electrode Performances

The measurements of the transverse section were not considered, since the entire view of the lesion was not available due to the trimming procedure.

The longitudinal area (**Figure 8A**) was influenced by the solution (p=0.0001) and the duration of treatment (p<0.0001). In the VT groups, a significant larger area of ablation was detected when 7.0% NaCl solution was applied, in comparison to 0.9% (p<0.0001). No statistically significant difference was revealed in

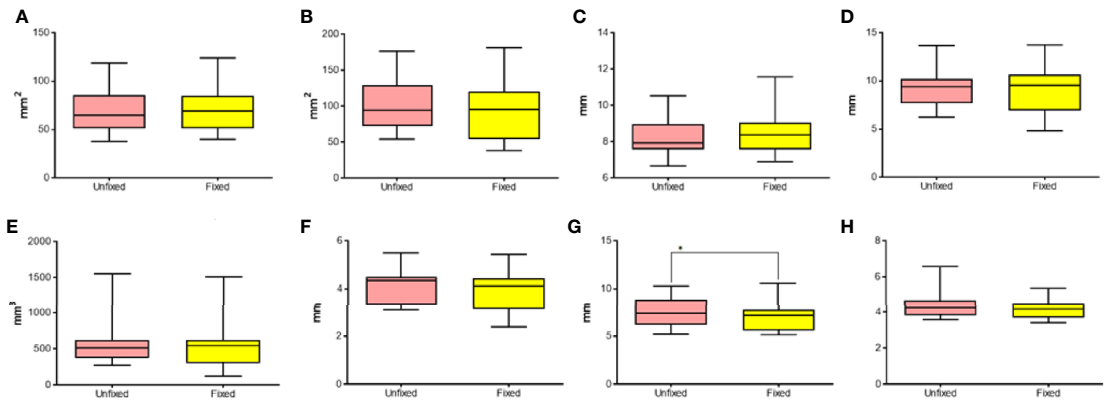

FIGURE 6 | Comparison of different parameters between unfixed and FF thyroids. In details, **(A)** transverse area; **(B)** longitudinal area; **(C)** transverse equivalent diameter; **(D)** longitudinal equivalent diameter; **(E)** volume; **(F)** semi-axis "a"; **(G)** semi-axis "b"; **(H)** semi-axis "c". *P < 0.05.

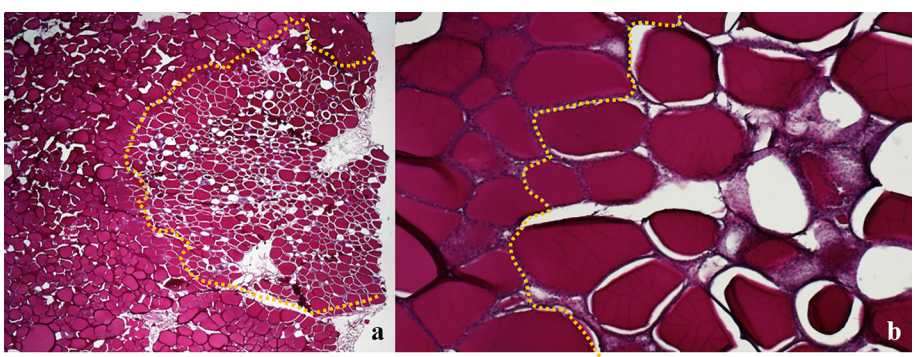

FIGURE 7 | Swine thyroid treated with Wet Tip electrode, 0.9% NaCl solution, variable time of treatment; longitudinal view PAS; the dotted line outlines the ablated areas, showing shrunk and darker colloid in follicular tissue, with empty spaces between the follicular wall and the colloid: **(A)** 20X; **(B)** 100X.

TABLE 4 | Morphometric data of histological sections of treated thyroids.

Electrode	Solution	Time of treatment	Transverse section	Longitudinal section		a (mm)	b (mm)	c (mm)	Volume (mm³)
			Area T/2 (mm²)	Area (mm²)	Equivalent diameter (mm)				
Internally cooled	–	20-sec fixed time	15.7 ± 5.7	33.1 ± 20.1	4.8 ± 2.0	2.3 ± 1.2	3.8 ± 1.3	3.2 ± 0.8	130.5 ± 97.8
Wet tip	0.9% NaCl	Variable time	99.5 ± 81.3	149.7 ± 119.9	7.9 ± 5.2	4.5 ± 2.3	9.5 ± 5.5	7.2 ± 4.7	1987.0 ± 2407.3
Wet tip	7% NaCl	Variable time	183.2 ± 38.8	543.8 ± 171.2	19.1 ± 4.5	9.3 ± 1.0	18.4 ± 4.8	12.1 ± 2.3	8465.5 ± 1999.4
Wet tip	0.9% NaCl	20-sec fixed time	43.0 ± 18.7	131.7 ± 28.3	8.5 ± 0.9	4.4 ± 0.9	7.9 ± 0.5	5.6 ± 2.0	846.2 ± 430.8
Wet tip	7% NaCl	20-sec fixed time	39.2 ± 16.0	87.2 ± 43.8	6.7 ± 1.7	3.9 ± 1.0	6.7 ± 2.7	4.7 ± 1.6	615.5 ± 530.8
Wet tip	18% NaCl	20-sec fixed time	19.3	74.5	6.9	3.6	8.0	3.4	406.3

Overview of the mean values of Area and Equivalent diameter for both transverse and longitudinal sections, a, b, and c semiaxis, and lesion volume. Only one sample was available for wet tip with 18% NaCl solution.

fixed time groups (p=0.6334). The longitudinal area in the groups treated with 7.0% NaCl solution was significantly larger in the group treated for a variable time in comparison to the fixed time's one (p<0.0001). No difference was observed between the groups treated with 0.9% NaCl. The longitudinal equivalent diameter (**Figure 8B**) was influenced by the solution (p=0.0018) and the duration of treatment (p=0.0002).

In the groups where the duration of treatment was variable, a significant difference according to the use of 0.9% or 7.0% NaCl solution (p<0.0001) was detected. No significant difference was revealed in fixed time groups (p=0.559). The time of treatment influenced the longitudinal equivalent diameter in the groups treated with 7.0% NaCl solution, where a significant difference between variable and fixed time (p<0.0001) was detected. No difference was found in the groups treated with 0.9% NaCl.

Also the volume (**Figure 8C**) was influenced by the solution (p<0.0001) and the duration of treatment (p<0.0001). In VT groups, a significant difference depending on the use of 0.9% or 7.0% NaCl solution (p<0.0001) was detected. No difference was observed in fixed time groups (p=0.9515). The time of treatment influenced the volume only in the groups treated with 7.0% NaCl solution, where a significant difference between variable and fixed time (p<0.0001) was detected. No difference was found in the groups treated with 0.9% NaCl.

The semi-axis "a" (**Figure 8D**) was influenced by the solution (p=0.0009) and the time of treatment (p<0.0001). In the group

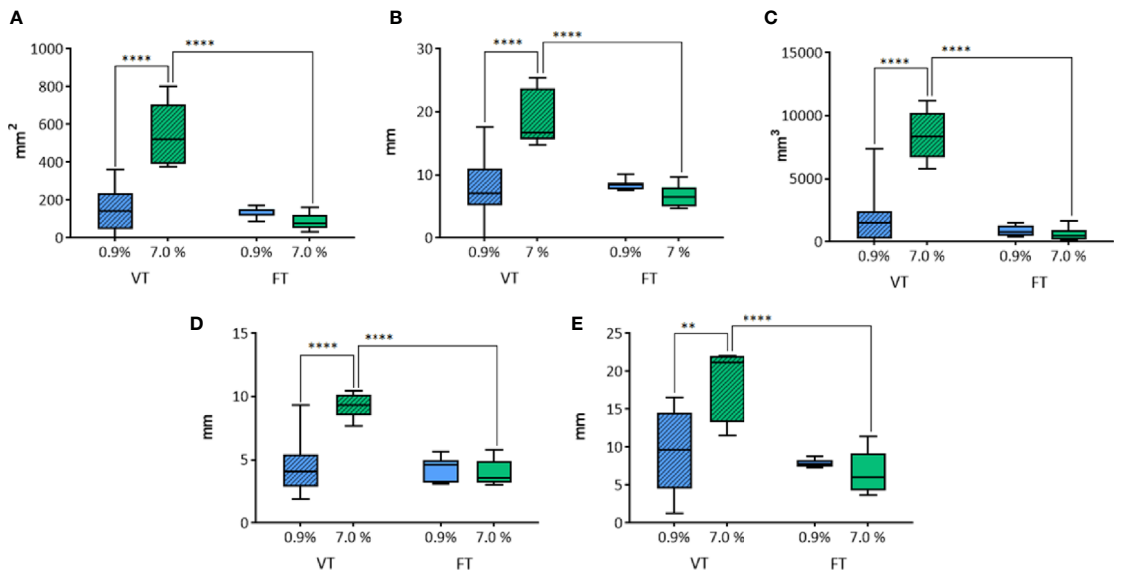

FIGURE 8 | Comparison of the different parameters among the groups treated with WT, with variable and fixed time of treatment, and 0.9% and 7.0% NaCl solutions in histological morphometric analysis. In details, **(A)** longitudinal area; **(B)** longitudinal equivalent diameter; **(C)** volume; **(D)** semi-axis "a"; **(E)** semi-axis "b". VT, Variable Time treatment; FT, Fixed Time treatment; 0.9%= solution perfused into the tissue at 0.9% NaCl; 7.0%= solution perfused into the tissue at 7.0% NaCl; *P < 0.05; ****P < 0.0001.

where the time of treatment was variable, a significant difference related to the use of 0.9% or 7.0% NaCl solution (p<0.0001) was detected. No significant difference was observed in fixed time groups (p=0.787). The variable time of treatment influenced the semi-axis "a" in the groups treated with 7.0% NaCl solution, revealing a significantly longer "a" semiaxis, in comparison to the homologous treatment at fixed time (p<0.0001). No difference was found in the groups treated with 0.9% NaCl.

The semi-axis "b" (**Figure 8E**) was influenced by the solution (p=0.0165) and the duration of treatment (p=0.0002). In the groups where the time of treatment was variable, a significant difference related to the use of 0.9% or 7.0% NaCl solution (p=0.001) was detected. No significant difference was revealed in fixed time groups (p=0.8144). The time of treatment influenced the semi-axis "b" only in the groups treated with 7.0% NaCl solution, where a significant difference between variable and fixed time (p<0.0001) was detected. No difference was found in the groups treated with 0.9% NaCl.

Comparison of IC and WT Electrodes Performances

The performances of IC (control group) and WT electrodes (0.9% and 7.0% NaCl) on unfixed thyroids were compared at 20 seconds fixed time of treatment, analyzing microscopic measurements. The transverse section was not considered, since the entire view of the lesion was not available due to the trimming procedure.

The longitudinal area was affected by the use of either IC or WT electrodes (p<0.0001) at 20 seconds fixed time treatment (**Figure 9A**). In particular, a significant increase of longitudinal area was revealed with WT, in comparison to the control group IC, both using 0.9% NaCl (p<0.0001), and 7.0% NaCl (p=0.0094) solution. The longitudinal equivalent diameter was affected by the use of either IC or WT electrodes (p=0.0014) at 20 seconds fixed time treatment (**Figure 9B**). A significant difference was detected between the control group IC and WT using 0.9% NaCl solution (p=0.0007), and between the control group IC and WT with 7.0% NaCl (p=0.0287). The volume was affected by the use of either IC or WT electrodes (p=0.0002) at 20 seconds fixed time treatment (**Figure 9C**). In particular, a significant increase of the lesion volume was detected in comparison with the control group IC using WT both with 0.9% NaCl solution (p=0.0009), and with 7.0% NaCl (p=0.0243). The semi-axis "a" was affected by the use of either IC or WT electrodes (p=0.0031) at 20 seconds fixed time treatment (**Figure 9D**). In particular, a significant difference was detected between the control group IC and WT using 0.9% NaCl solution (p=0.0025), and between the control group IC and WT with 7.0% NaCl (p=0.0069). Also the semi-axis "b" was affected by the use of either IC or WT electrodes (p=0.0007) at 20 second fixed time treatment (**Figure 9E**). A significant difference was detected between the control group IC and WT using 0.9% NaCl solution (p=0.0015), and between the control group IC and WT with 7.0% NaCl (p=0.0466).

Comparison Between Macroscopic and Microscopic Morphometric Analysis

The parameters calculated on macroscopic images from unfixed thyroids were compared to the corresponding data obtained from histological images (**Table 5**). The comparison was related to groups where the time of treatment was fixed at 20 seconds.

The longitudinal area (**Figure 10A**) was significantly larger in pictures from gross unfixed thyroids compared to the corresponding histological images (p=0.0466). The calculated longitudinal equivalent diameter (**Figure 10B**) was significantly longer in gross unfixed pictures compared to histological images (p<0.0001). The calculated volume (**Figure 10C**) was not

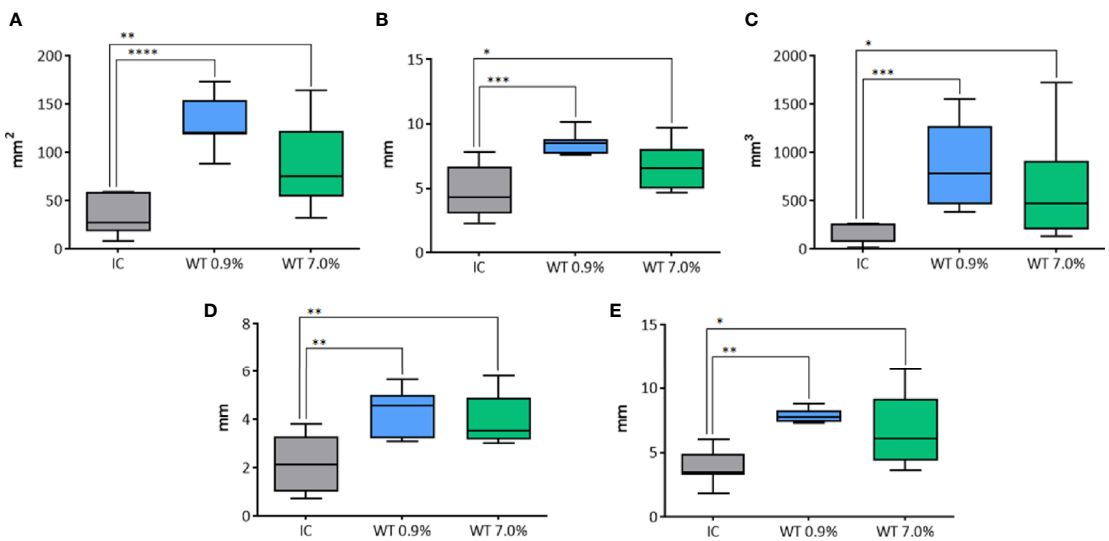

FIGURE 9 | Comparison of different parameters among the groups treated with IC and WT electrodes, and solutions in histological morphometric analysis. In details, **(A)** longitudinal area; **(B)** longitudinal equivalent diameter; **(C)** volume; **(D)** semi-axis "a"; **(E)** semi-axis "b". IC= Internally cooled tip; WT, Internally cooled wet tip; WT 0.9%-7.0%= solutions at 0.9%-7.0% NaCl perfused into the tissue by the WT electrode; *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

TABLE 5 | Morphometric data of macroscopic images from unfixed thyroid and corresponding histological sections.

Measurement	Gross morphometric analysis; unfixed thyroids	Histological morphometric analysis
Longitudinal area (mm^2)	102.9 ± 35.5	83.7 ± 50.0
Longitudinal equivalent diameter (mm)	9.6 ± 1.9	6.7 ± 2.1
Volume (mm^3)	634.1 ± 352.0	529.0 ± 478.4
a (mm)	4.3 ± 0.9	3.6 ± 1.3
b (mm)	9.6 ± 1.9	6.7 ± 2.1

Overview of the mean values of Longitudinal Area and Equivalent diameter, lesion volume, a and b semiaxes. The values refer to groups with 20 seconds fixed time of treatment.

significantly different between gross unfixed and histological lesions (p=0.1424). The semi-axis "a" (**Figure 10D**) and the semi-axis "b" (**Figure 10E**) were significantly longer in gross unfixed thyroids compared to their histological images (p=0.0046 and p=0.0113, respectively).

DISCUSSION

Minimally invasive image-guided thermal ablation has become common since the advent of modern imaging (2). Among all, RFA is becoming extremely popular in human medicine. It is the first commercially viable ablation device, it is currently widely available and it is relatively cost effective, compared to other newer devices (24). Moreover, RF is a versatile technique of thermal ablation, used in the treatment of small tumors of multiple organs, but also in cardiac diseases or denervation. The electrodes are usually of small size, and the safety profile is acceptable, especially in the treatment of thyroid nodules. RFA has also a hemostatic effect, helpful in periprocedural bleeding. In addition, the interactions with the immune system, together with its synergy with immunotherapy and conventional therapy, are interesting advantages in tumor treatment (24). Surgery is the primary strategy of therapy for patients with medullary thyroid cancer and differentiated thyroid cancer (DTC). In DTC patients, radioactive iodine is administered after thyroidectomy, but the iodide uptake ability of DTC cancer cells may be lost, with a negative impact on the prognosis (25). Recently, several drugs have been developed, and tyrosine kinase inhibitors play an important role in the molecular pathways of DTC, modulating several pathways involved in angiogenesis, lymphangiogenesis, cell proliferation, local and distant spread of cancer cells (26).

RFA main limitations are the lack of consistency when attempting to obtain larger homogenous tumor ablations, as well as the time needed to deliver sufficient energy with RF ablation (24). The main reasons of limited ablation are related to heat loss and inefficient thermal conduction.

The heat loss is mainly due to the hyperthermia dissipation effect caused by flowing blood or air. Many possible solutions have been developed in the last few years, such as vascular ablation techniques (3) and pharmacological agents (2). The inefficient thermal and electrical conduction is correlated with the intrinsic characteristics of the tissue (i.e. fibrous mass, bone), and by the development of desiccated and carbonized tissue around the electrode. The use of IC electrode may prevent temperatures above 100°C to develop, and the consequent tissue carbonization, leading to this insulating area. However, in this context, also WT electrodes have been developed, which combine the internal cooling system of IC electrodes with the injection of a solution in the tissue through side holes.

Studies on animal livers revealed that WT electrodes have the potential to generate larger, but less reproducible, AZs than IC.

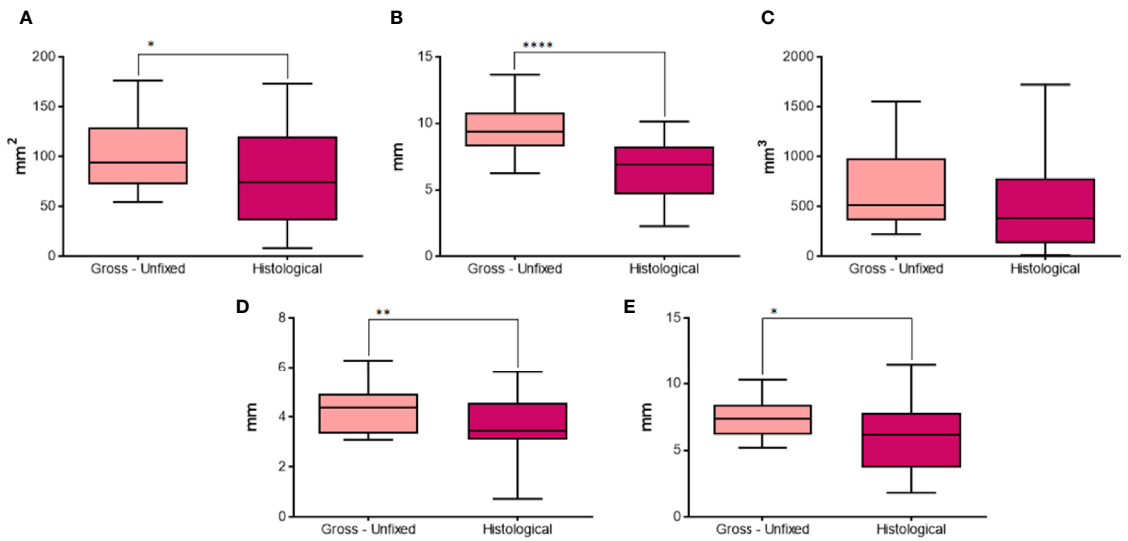

FIGURE 10 | Comparison of different parameters between gross unfixed and histological morphometric analysis in groups with 20 seconds fixed time treatment. In details, **(A)** longitudinal area; **(B)** longitudinal equivalent diameter; **(C)** volume; **(D)** semi-axis "a"; **(E)** semi-axis "b". *P < 0.05; **P < 0.01; ****P < 0.0001.

The larger size of the AZs may be attributed to the lower impedance resulting from a small amount of spilled saline (20). A study conducted on humans confirmed these results (27). However, no study was conducted on thyroids yet. Hence, the current study compared the performances of IC and WT electrodes on *ex-vivo* swine thyroids. Pigs were the selected species, like in other similar studies (23, 28), since swine thyroid glands have an adequate size and a fine tissue structure resembling that of humans.

In order to have an objective comparison, in this study morphometric analysis was conducted on thyroids, which were unfixed and formalin fixed, and on the corresponding histological sections. Particular attention was paid to the solution used with WT electrodes, and to the duration of treatment.

Thyroid radiofrequency ablation guidelines of the Korean Society of Thyroid Radiology recommended the moving-shot technique as the standard procedure for RFA of benign thyroid nodules (27, 28). However, the moving-shot approach was not considered suitable in this study, intended to perform morphometry and to obtain the more precise measurement and repeatability. In fact, moving-shot technique results are dependent on the number of passages and the tilt angles of the electrode, less replicable than a single passage. The latter allowed a more precise measurement of the parameters obtained by the ablation through the different electrodes and saline solutions.

To determine the effects of saline solution on ablation size, a fixed time procedure was also implemented, stopping energy deliver, independently from the completion of ablation, after 20 seconds, also for perfused electrodes. The procedure was implemented due to the small size of thyroids and following the finding that many of them were completely necrotized with the automatic procedure, thus interfering with a precise measurement of the ablation. The fixed time procedure was intended to better clarify the performances of WT electrodes in terms of ablation size and it is not to be considered for clinic purposes, since the benefit of WT electrodes is that they make larger ablations, but they require longer time. In fact, WT electrodes delay the impedance roll off and surely limiting time to 20 seconds annul the advantage of their use. However, in many cases measurements were not available on variable time treatments with WT electrodes, since the entire pig thyroid was ablated.

During the treatment, the ablation process was visible by sonography as an expanding hyperechoic area into the normal, surrounding tissue.

In unfixed thyroids, the coagulated areas were clearly distinguishable from the normal tissue, with a defined outline in IC treated thyroids, whereas the one obtained with WT electrode appeared to be vanishing. This may be ascribable to the increased thermal and electrical conduction of the tissue caused by the saline solution provided by WT electrode, which let the heat expand more easily and not to be focused in a restricted area, as in IC.

All the measurements, except the "c" semi-axis, carried out with the WT electrode were positively influenced by the use of 7.0% compared to 0.9% NaCl solution in the case of variable time treatments and positively influenced by the duration of treatment. In fact, the variable time treatment achieved significantly larger lesions than the fixed time technique, independently from the solution used (0.9% or 7.0% NaCl). The "c" semi-axis was also significantly longer with 7.0% than 0.9% NaCl solution at variable time of treatment. However, the variable time of treatment achieved higher values of "c" only when 7.0% NaCl was used.

At fixed time of treatment, the transverse area was significantly larger when the thyroid was treated with WT electrode and 0.9% NaCl solution compared to IC electrode and the "c" semi-axis was significantly longer if the WT electrode was used with 0.9% or 18% NaCl solution compared to IC electrode. Therefore, the type of electrode and solution used greatly influenced the measurements obtained on transverse sections. All the other measurements were not significantly different among the groups, even though it could be often noticed a gradual increase of each measurement from IC to WT 18% NaCl solution.

The "a" and "c" semi-axes are considered interchangeable in many studies (23, 29) and this study confirms the literature reports. This means that, even though the use of measurements from transverse section may guarantee more precise results, they are not strictly necessary for comparing performances of different electrodes.

In gross morphometric analysis on FF thyroids, the ablated area was usually better distinguishable than the one of corresponding unfixed thyroids. Usually, the formalin fixation causes a shrinkage effect on tissues. This would mean that the morphometric measurements should have evidently lower values in fixed than unfixed thyroids. When both variable and fixed time groups were included, longitudinal area, longitudinal equivalent diameter and volume were significantly lower in FF than unfixed thyroids. However, the measurements from variable time groups may affect the results, due to their wide variability. In fact, considering only groups with fixed duration of treatment, only the "b" semi-axis was significantly shorter in FF thyroids. Therefore, the effect of formalin fixation on the thermal lesion induced on thyroids seems to be inconstant. It may be influenced by the coagulation and the presence of water.

Moreover, results showed that connective tissue does not influence gross morphometric analysis.

The 18% NaCl solution caused some technical problems during the experiment, such as obstruction of the cooling system of the electrodes. These conflict with the clinical applications.

The coagulated area was clearly recognizable on histological sections, showing follicular tissue with colloid shrinkage and accumulation. However, it shall not be excluded that the parenchyma that is really ablated could be larger than the area histologically detected, due to a delayed damage induced by thermal stress in the following hours and days. In our study, the evaluation was performed on ex vivo tissues obtained soon after slaughtering, and samples were collected immediately after RFA, with no subsequent evaluation planned. The evaluation of a subsequent shrinkage, delayed in time, could require a time lapse collection of thermo ablated tissues, which could be the target of a future study, once established the best performances and conditions for RFA.

Moreover, our study on *ex vivo* tissues did not allow to investigate possible mechanisms of cell death, since vital processes are not active in explanted tissues. Evaluation of apoptosis could be worth of interest in future *in vivo* experiments.

The performances achieved by the WT electrode with the 7.0% NaCl were consistently higher than 0.9%, confirming results of gross morphometric analysis. Moreover, the variable duration of treatment allowed to achieve larger lesions only when the 7.0% NaCl solution was used, partially confirming the results of gross analysis. Further studies should be conducted to better clarify this finding.

WT electrode with 0.9% NaCl solution achieved larger lesions than IC at fixed time of treatment, moreover, WT electrode with 7.0% NaCl solution produced larger ablation than IC. Differently from results on gross morphometric data, even though each measurement appeared to gradually increase its values from IC to WT electrode and 0.9%, 7.0%, and 18% NaCl solutions, only the measurements taken on transverse section revealed a statistical relevance.

Comparing the longitudinal area and equivalent diameter, the volume, and "a" and "b" semi-axis in groups with fixed time duration of treatment, all the measurements on histological sections were significantly lower than on gross unfixed images, except for the volume. However, the thicker half of the lesion was usually selected for trimming the transverse face of the lesion, which makes the "c" semi-axis, and consequently the volume of the rotation solid, probably overestimated.

The reason of lower values in measurements taken on histological analysis may be the sectioning of the specimen. In fact, during the sectioning, the cut margin of the lesion could be broken, even partially, and lost. Another explanation could be the tissue shrinkage caused by the slide processing.

The present study showed that the duration of treatment definitely influences the performance of the WT electrode. Therefore, the perfusion with 7.0% NaCl solution does increase the electrical conductivity of the tissue, resulting in larger ablated areas, compared to the use of 0.9% NaCl solution, but the effect is evident only when the electrode works until the generator spontaneously turns off (as in the variable time) and not visible with short duration of 20 seconds. Moreover, the macroscopic analysis revealed that fixed time treatments usually generate smaller lesions compared to variable time treatments, as opposed to the histological analysis, underlining that this is relevant only when 7.0% NaCl solution is used. However, values of the measurements on thyroids treated with variable time and 0.9% NaCl solution are more different than expected and hence probably affected by some errors. More trials should be done to better clarify this finding.

The performances of WT electrode seem higher than the one obtained with IC at fixed time of 20 seconds. In fact, the histological analysis revealed a clear difference between IC and WT 0.9% NaCl, and a lower difference when 7.0% NaCl solution was used. This scenario is similar in gross thyroid analysis, since 0.9% NaCl seems to have a better performance than IC electrode and WT electrode with 7.0% NaCl at fixed time, although the difference is not statistically significant.

This fact may be attributable to two causes. The former is the lower statistical power of the analysis conducted on gross thyroids, where the comparison involved four groups (IC, WT 0.9% NaCl, WT 7.0% NaCl, and WT 18.0% NaCl), instead of the three groups of histology (where WT 18.0% NaCl was not included). The latter is the usually more precise outline of the ablated area boundary in the case of histology, which is less subjected to subjectivity, compared to gross analysis. The results indicate that the performances of different electrodes evaluated on gross unfixed lesions and on microphotographs agree.

In conclusion, the histological evaluation seems to be the best approach for morphometric analysis of RF ablated area on *ex-vivo* thyroids, showing a high potential. The WT electrode performances on thyroid are superior compared to IC. A similar finding was already reported for liver treatments (20, 22, 27).

Therefore, WT electrodes demonstrated to give larger AZs, if they are correctly used at their best, i.e. at a variable time. The advantage could be transposed in the clinical procedures, allowing treatments with a fewer number of shots in large thyroidal nodules. Moreover, WT electrode performances seem to depend on the solution used. In particular, the injection of 7.0% NaCl solution may be advantageous, because it achieves larger ablation in variable time procedures, such as the one usually adopted in clinical practice in the treatment of thyroid nodule as well as diseases in other organs in human medicine.

Percutaneous energy-based techniques have an expanding role, especially in the treatment of neoplasms (2). Hopefully, the current work will contribute to broaden the clinical indications of RFA in both human and veterinary medicine, where the ablation size has limited its use so far.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required in accordance with national guidelines and local legislation for the animal study because thyroids were collected from regularly slaughtered swine, during meat production procedures. The thyroids were collected at the slaughterhouse among discarded organs, not destined for human consumption. This type of sampling doesn't require any ethical approval.

AUTHOR CONTRIBUTIONS

PP: study design, statistical analysis, paper drafting. ES: experimental procedures. MB: statistical analysis, paper drafting MM: echographic procedures. LN: Morphometric analysis. SG: echographic procedures. RG: RFA procedures. EB: morhometric analysis, paper revision. FS: study design, paper drafting, coordination of the group. All authors contributed to the article and approved the submitted version.

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The Efficacy and Safety of Radiofrequency Ablation for Bilateral Papillary Thyroid Microcarcinoma

Lin Yan, Mingbo Zhang, Qing Song, Jing Xiao, Ying Zhang and Yukun Luo *

Department of Ultrasound, First Medical Center, Chinese PLA General Hospital, Beijing, China

Objective: To investigate the long-term clinical results of radiofrequency ablation (RFA) for bilateral papillary thyroid microcarcinoma (PTMC).

Materials and Methods: From October 2014 to February 2018, 47 patients (37 females, 10 males, mean age 43.39 ± 9.26 years) with 100 bilateral PTMC (mean volume 75.22 ± 73.87 mm^3) treated by RFA were included in this retrospective study. Bilateral PTMC was defined as at least one tumor located in the contralateral lobe. Patients were followed up at 1, 3, 6, 12 months and every 6–12 months thereafter. Volume, volume reduction ratio (VRR) and local tumor recurrence were evaluated during the follow-up period.

Results: After a mean follow-up period of 47.77 ± 11.54 months, the mean volume of bilateral PTMC decreased from 75.22 ± 73.87 mm^3 to 0.09 ± 0.44 mm^3. The mean VRR was 99.94 ± 0.28% and the complete disappearance rate was 92.00%. During the follow-up, one patient (2.13%) developed lymph node metastasis and two patients (4.26%) had recurrent PTMC. All the recurrent lesions underwent additional RFA and two of them disappeared completely. No life-threatening or delayed complications occurred.

Conclusions: With sufficient preoperative evaluation, RFA might be a promising alternative for bilateral PTMC patients who were unsuitable for surgery or refused surgery.

Keywords: radiofrequency ablation, papillary thyroid carcinoma, thyroid, ultrasound, clinical outcomes

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***Correspondence:**
Yukun Luo
lyk301@163.com

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INTRODUCTION

The incidence of thyroid cancer has increased worldwide, ranking in ninth among all cancers (1–4). Approximately 50% of the increase was attributed to the detection of papillary thyroid microcarcinoma (PTMC), which is a form of papillary thyroid cancer with a maximum diameter of 1 cm, with or without high-risk features (5). Bilateral lesions are very common in PTMC with an incidence of approximately 10–30% (6). It was previously correlated with a higher risk of locoregional recurrence. However, some studies have shown that tumor bilaterality was not associated with an increased risk of recurrence/persistence (7). According to the 8th AJCC/TNM risk of mortality system and American thyroid guideline (ATA) risk stratification, intrathyroidal bilateral PTMC was classified stage I with a low-risk of recurrence (8, 9). Surgery is the first-line treatment for bilateral PTMC. However, its drawbacks include invasiveness, cosmetic problems and life-long thyroid hormone replacement, which affect the quality of life (10). Moreover, the incidence of transient vocal fold paralysis and transient hypocalcemia after surgery were 5.5 and 4.3%,

respectively (11). Radiofrequency ablation (RFA) as a minimally invasive technique, might be a potentially alternative for bilateral PTMC who were unsuitable for surgery or are contraindicated for surgery.

RFA is a commonly used thermal technique, has been reported as an effective and safe treatment for low-risk PTMC patients who refuse surgery or active surveillance (12–19). After ablation, the pooled proportion of volume reduction rate (VRR) was 98.1% (20) and the pooled proportion of complete disappearance rate was 57.6–76.2% (20, 21). However, the results were based mainly on the clinical outcomes of RFA for unifocal PTMC. To the best of our knowledge, no study has reported the long-term clinical outcomes of ablation for bilateral PTMC.

Therefore, the purpose of this study was to evaluate the efficacy and safety of RFA for bilateral PTMC.

MATERIALS AND METHODS

The Institutional Review Board of our institution approved this retrospective study. All the patients were provided written information consent before RFA. The RFA informed consent emphasized that surgery was the routine treatment recommended by guidelines.

Patients

Bilateral PTMC was defined as at least one tumor located in the contralateral lobe (11). The inclusion criteria were: (1) PTMC lesions were confirmed by core-needle biopsy(CNB) or fine-needle aspiration(FNA); (2) no evidence of extrathyroidal extension(ETE) or lymph node(LN)/distant metastasis on US and chest CT; (3) patients who were unsuitable for surgery or refused surgery; (4) no neck irradiation history; (5) follow-up period was ≥24 months. The exclusion criteria of patients were: (1) no convincing evidence of aggressive disease by biopsy (9); (2) the maximum diameter of the tumor was ≥10 mm; (3) ETE was found; (4) LN metastasis or distant metastasis was detected; (5) patients with conscious disturbance or coagulation disorder or serious primary disease; (6) follow-up period was <24 months.

From October 2014 to February 2018, 468 patients with bilateral PTMC underwent treatment in this institution. Among them, 76 patients who were unsuitable for surgery or rejected surgery underwent RFA. Among them, patients with follow-up period less than 24 months (N = 29) were excluded. At last, a total of 47 patients with 100 low-risk PTMC were evaluated.

Pre-Ablation Evaluation

Before RFA, patients all underwent thorough examinations, including complete blood count, thyroid function tests, coagulation tests and imaging evaluation, including ultrasound and chest CT (12–14). The volume of PTMC was calculated with the equations:

$$V = \pi abc \quad / \quad 6$$

V is the volume, while a is the largest diameter, b and c are the other two perpendicular diameters.

US were performed using a Siemens Acuson Sequoia 512 Ultrasound System (Siemens) or a Philips iU22 Ultrasound System (Philips Healthcare) or a Mindray M9 Ultrasound System (Mindray). CNB and RFA were all performed using a Siemens Acuson Sequoia 512 Ultrasound System. Contrast-enhanced ultrasound (CEUS) was used to assess the tumor before and immediately after RFA procedure. The ultrasound contrast agent was sulfur hexafluoride (SonoVueR). After injection of 2.4 ml SonoVue followed by a 5 ml of normal saline flush, CEUS was applied to observe the real-time microbubble perfusions within the tumor and the surrounding thyroid tissues.

Ablation Procedures

All RFA procedures were performed by an experienced US physician. A bipolar RFA generator (CelonLabPOWER) and an 18-gauge bipolar RF applicator with 0.9 cm active tip (CelonProSurge micro 100-T09) were used.

Patients lay on an operating table in the supine position with the neck hyperextended. The targeted tumor was evaluated by multi-angle scanning to determine a practical and proper approach. Doppler ultrasound was used to access the detailed vascular anatomy along the approach route to prevent bleeding. Local anesthetic (1% lidocaine) was injected at the subcutaneous puncture site and the thyroid anterior capsule. During the RFA procedure, the smaller lesion was ablated first.

RFA procedure was performed using trans-isthmic approach and moving-shot technique. To prevent thermal injury, hydrodissection technique was performed by injection of normal saline to separate the target tumor from critical structures (trachea, carotid artery, jugular vein, esophagus and recurrent laryngeal nerve). Normal saline was injected using another needle (23 gauge) to form at least 1 cm distance between the tumor and the critical structure (13, 14).

The initial RFA power was 3 W and was increased to 5 to 9 W if a transient hyperechoic zone did not form at the electrode tip in 10 s. To prevent marginal residue and recurrence, we enlarged the ablation area which exceeded the tumor edge (at least 3–5 mm) (21, 22). CEUS was performed immediately after the RFA procedure to assess the ablation area. If any enhancement existed, a complementary RFA should be applied.

Post-Ablation Assessment

Patients were followed up at 1, 3, 6 months and every 6–12 months thereafter by US, CEUS and chest CT. At 3 or 6 months after RFA, the ablated area was evaluated by CNB, which was performed to the central zone, the peripheral zone and surrounding thyroid parenchyma (22–24). The development of metastatic LNs and the suspicious new lesions were submitted to biopsy. The volume reduction rate (VRR) was calculated by the equations:

$$\mathrm{VRR} = \frac{(\text{initial volume} - \text{final volume})}{\text{initial volume}} \times 100\,\%$$

RFA was considered to successful when one of the criteria were met (25): (1) the ablated tumor was completely disappearance;

(2) the ablated tumor remained as scar-like on US but absence of enhancement on both arterial and venous phase on CEUS; (3) If the ablation area still existed, no malignant cells was confirmed by CNB. Local tumor recurrence was defined to include two situations (26): (1) new lesion was confirmed to be PTMC after CNB; (2) cervical LN metastasis was confirmed after biopsy. Distant metastasis was diagnosed by CT, positron emission tomography or bone scan when there were suspicious symptoms. Delayed surgery is defined as that patients received surgery due to tumor progression or anxiety during the follow-up.

Statistical Analysis

Statistical analysis was performed using the SPSS statistical software (Version 25.0). Continuous data were presented as mean ± SD (range). Non-parametric Wilcoxon signed-rank tests were used to compare the pre-ablation with post-ablation volume as each follow-up period. A P <0.05 was considered as statistically significant.

RESULTS

Clinical characteristics of patients before RFA are shown in **Table 1**. Among the 47 patients, 41 had two tumors and six had three tumors. The mean diameter was 4.82 ± 1.57 mm and the mean volume was 75.22 ± 73.87 mm^3. The volume of dominant tumor was 108.77 ± 87.08 mm^3.

TABLE 1 | Clinical characteristics of patients.

Characteristics		Data
No. of patients		47
No. of tumors		100
	Patients with two tumors, n (%)	41 (87.23)
	Patients with three tumors, n (%)	6 (12.77)
Age (years)		43.39 ± 9.26 (23–63)
Female (%)		37 (78.72)
Mean diameter (mm)		4.81 ± 1.57 (0.20–0.93)
Mean Volume (mm^3)		75.22 ± 73.87 (4.19–424.10)
Volume of dominant tumor (mm^3)		108.77 ± 87.08 (8.12–424.10)

Data are expressed as mean ± SD (range).

For each tumor, the mean power was 3.92 ± 0.98 W. The mean RFA time was 224.09 ± 156.68 s and the mean energy was 853.64 ± 614.39 J.

Efficacy

The changes of volume and VRR after RFA at each follow-up visit are presented in **Table 2**. The mean follow-up period was 47.77 ± 11.54 months (range 24–76 months). The mean volume of the ablation areas was significantly larger than the initial volume at first 3 months (P <0.001) because of the enlarge ablation, which was gradually decreased from 6 months after RFA (**Figure 1**). The mean VRR was 99.94 ± 0.28% (**Figure 2**) and the overall complete disappearance rate was 92.00% (92/100). The numbers of completely disappearance were 1 (1.00%), 12 (12.00%), 21 (21.00%), 26 (26.00%), 18 (18.00%), 10 (10.00%) and 4 (4.00%) at 1, 3, 6, 12, 18, 24, and 36 months after RFA, respectively. A representative case underwent RFA is presented in **Figure 3**.

Local Tumor Recurrence

Because 13 tumors disappeared in the first 3 months and another six tumors disappeared at 6 months, a total of 81 tumors underwent post-ablation CNB and the results were all negative.

The incidence of LN metastasis and of recurrence PTMC was 2.13% (1/47) and 4.26% (2/47), respectively. No distant metastasis was detected. No patient underwent delayed surgery during the follow-up. The clinical characteristics and outcomes of PTMC patients with local tumor recurrence are showed in **Table 3**. One patient developed LN metastasis in the central compartments at 12 months after RFA with a volume of 100.53 mm^3. Two patients had recurrent PTMC and the volume was 18.85 mm^3 and 153.93 mm^3, respectively. All of these three patients underwent additional RFA. Two recurrent PTMCs were completely disappeared during the follow-up. The metastatic LN shrunk to 37.70 mm^3 after 1-year follow-up. This lesion underwent CNB and demonstrated no malignancy.

Safety

All the 47 patients were tolerable to RFA. Four patients underwent local pain or discomfort and they all resolved spontaneously within 3 days. No patients had major or delayed complications.

TABLE 2 | Changes of the volume and VRR after RFA at each follow-up.

Time	Volume (mm^3)		*p* value (*Vs* initial volume)	VRR (%)	
	Mean ± SD	range		Mean ± SD	range
initial	75.22 ± 73.87	4.19–424.10	–	NA	
After RFA	664.13 ± 410.00	109.95–1,858.20	<0.001	NA	
1 month	314.35 ± 331.09	10.47–2,205.33	<0.001	−511.78 ± 569.06	−2,600–100
3 months	114.02 ± 231.45	0–1,910.03	<0.001	−76.40 ± 227.17	−985.71–100
6 months	44.31 ± 105.58	0–680.66	<0.001	43.01 ± 123.00	−585.71–100
12 months	21.11 ± 64.77	0–376.98	<0.001	77.85 ± 62.28	−255.56–100
18 months	9.76 ± 37.86	0–241.90	<0.001	84.97 ± 62.85	−350.00–100
24 months	3.29 ± 11.97	0–75.40	<0.001	96.97 ± 12.84	3.57–100
36 months	0.25 ± 1.42	0–9.42	<0.001	98.78 ± 1.28	91.43–100
48 months	0.09 ± 0.44	0–2.09	<0.001	99.94 ± 0.28	98.64–100

NA, not applicable.

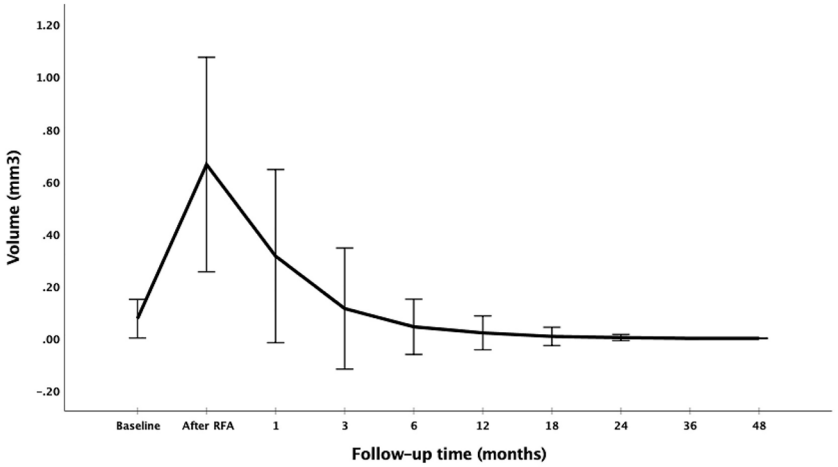

FIGURE 1 | Changes of volume at each follow-up period after RFA.

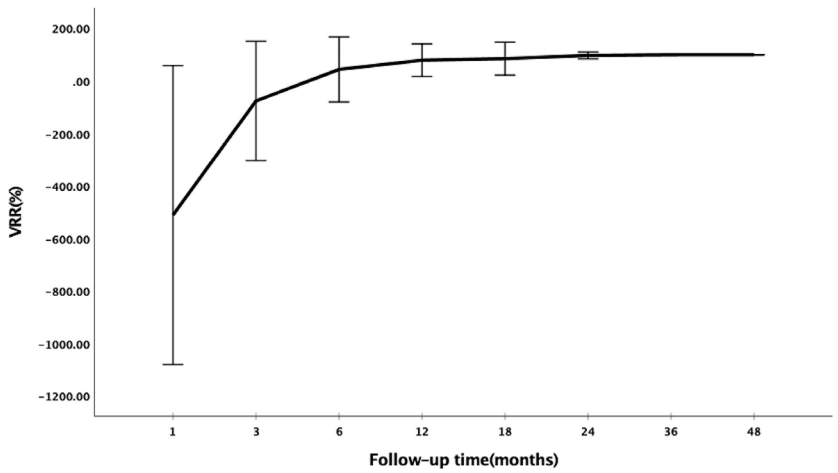

FIGURE 2 | Changes of VRR at each follow-up period after RFA.

DISCUSSION

To date, no study has been evaluated the clinical application of RFA for bilateral PTMC. In this study, after a mean follow-up period of 47.77 ± 11.54 months, the mean volume of bilateral PTMC decreased from 75.36 ± 73.86 mm^3 to 0.09 ± 0.43 mm^3 with a mean VRR of 99.94 ± 0.28%. A total of 92 tumors disappeared completely. The incidences of LN metastasis and of recurrent PTMC were 2.13 and 4.26%, respectively. All recurrent lesions were successfully treated with an additional RFA. No major complications or sequelae were observed.

Bilaterality has been observed in approximately 10–30% of patients with PTMC (6). It refers to the presence of multiple synchronous primary tumors, arising from independent clones, instead of intraglandular metastasis from a single primary tumor *via* intraglandular lymphatics (27, 28). However, the prognostic value of bilateral PTMC remains controversial. Studies recommended more aggressive treatments such as total thyroidectomy with central neck dissection and subsequent radioactive iodine ablation therapy for bilateral PTMC, which has an increased loco-regional recurrence rate (29, 30). In contrast, Choi et al. (7) found that bilateral PTMC was not an important prognostic factor in PTMC patients, but in the non-PTMC patients. Zhou et al. (6) also reported that bilateral PTMC was significantly associated with central LN metastasis on the univariate analysis. However, this was not an independent risk factor after multivariate logistic regression analysis. The conflicting results were likely due to the early detection and treatment of bilateral lesions, which did not fully exhibit its biological behavior.

Although thermal ablation is not the first-line treatments for PTMC, it has been applied to unifocal low-risk PTMC patients

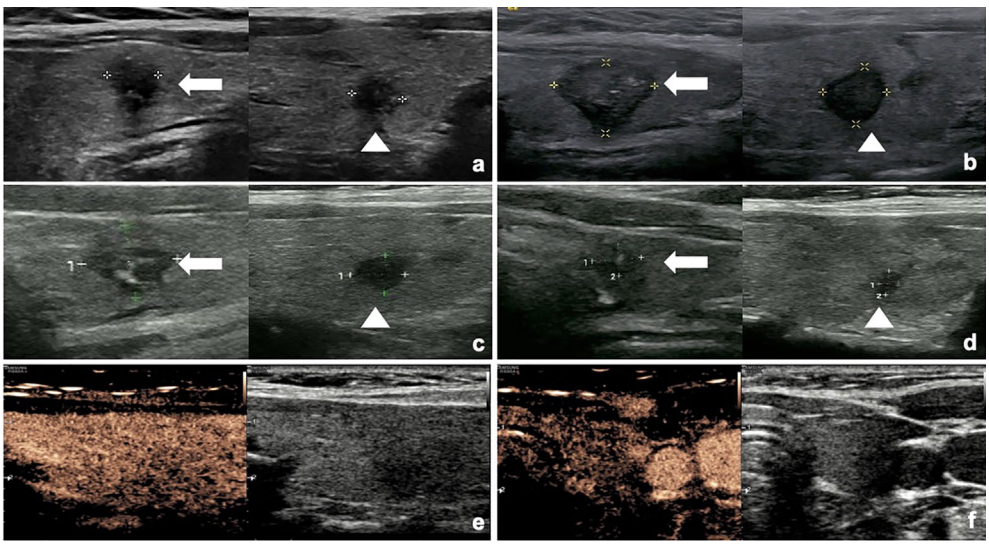

FIGURE 3 | The US and CEUS images of a 32-year-old female with bilateral PTMC during the follow-up. **(A)** Before RFA, two PTMC lesions were confirmed by CNB. One tumor was located in the left lobe with an initial volume of 78.54 mm^3 (arrow) and the other one was in right lobe with an initial volume of 65.45mm^3 (arrowhead). **(B)** At 1 month after RFA, the volume of left tumor (arrow) was 898.47 mm^3 and the volume of right tumor (arrowhead) was 234.57 mm^3. **(C)** At 3 months after RFA, the volume of left tumor (arrow) was 226.19 mm^3 and the volume of right tumor (arrowhead) was 78.54 mm^3. **(D)** At 6 months after RFA, the volume of left tumor (arrow) was 50.26 mm^3 and the volume of right tumor (arrowhead) was 12.57 mm^3. **(E, F)** At 12 months after RFA, these two ablated tumors both disappeared.

TABLE 3 | The clinical characteristics and outcomes of patients with local tumor recurrence.

	No. of patients	Sex/ age	No. of PTMC lesions	Dominant tumor Location/Volume (mm^3)	Developed Time (months)	Location	Volume (mm^3)	Treatment	Outcomes
LN metastasis (N = 1)	1	F/34	2	Isthmus/150.79	12	Right, Level VI	100.53	RFA	37.70[a]
Recurrent PTMC (N = 2)	1	F/43	2	Left/43.33	6	Right lobe	18.85	RFA	Disappeared at 12-month after additional RFA
	2	F/32	2	Right/53.33	12	Right lobe	153.93	RFA	Disappeared at 12-month after additional RFA

[a]*Data are represented as the volume at last follow-up (mm^3).*

concerned about active surveillance or complications after surgery (17, 25, 31–38). A few patients with multifocal or bilateral PTMC were also treated with ablation, but the clinical outcomes were not reported separately (14–16, 39). The viability of RFA as an alternative for bilateral PTMC patients who refuse surgery or are unsuitable for surgery is unknown. This study included 100 bilateral PTMC lesions in 47 patients who were unsuitable for surgery or refused surgery. This was the first study to evaluate the clinical results of RFA for bilateral PTMC. After a mean follow-up period of 47.77 ± 11.54 months, the VRR was 99.94 ± 0.28% and 92% of tumors completely disappeared. This was consistent with previous studies on RFA for unifocal PTMC, which reported a VRR of 90–100%, with a complete disappearance rate of 15.22–100% (17, 25, 31–38). This demonstrated that the efficacy of RFA for bilateral PTMC was comparable to that of unifocal PTMC.

In terms of safety, a meta-analysis reported that the pooled proportion of overall complications after thermal ablation was 3.1% and major complications occurred in 0.7% (20). The pooled proportion of complications after RFA was 1.7% (21). In this study, only four patients experienced local pain or discomfort. None of the patients experienced major complications. Several strategies were related to the low incidence of complications. First, RFA was performed by an experienced physician. A detailed preoperative evaluation and adequate knowledge of neck anatomy on US could minimize the incidence of complication (40). Second, during the RFA procedure, smaller lesion was usually treated first and the needle tip was monitored continuously and cautiously *via* US. Third, safe precautions against thermal injuries, such as the moving-shot technique, trans-isthmic approach and hydrodissection technique, were also performed during the RFA procedure (40).

The local tumor recurrence rate after ablation for unifocal PTMC is low. A previous study showed that the incidence of LN metastasis and recurrent PTMC following unifocal PTMC ablation were 0.84–2.98 and 1.19–2.78%, respectively (25, 34–38). A similar incidence of LN metastasis (2.13%) was observed in this study. However, the incidence of recurrent PTMC for bilateral PTMC was 4.26%, which was higher than that for unifocal PTMC. This was likely due to the low sensitivity of US in detecting multiple tumors. Thus, occult tumor foci may have been missed by preoperative evaluation. Although all recurrent lesions were successfully treated by additional RFA, sufficient preoperative evaluation was crucial in identifying the number and location of tumors and formulating an appropriate treatment strategy. Surgery remains the first-line treatment for bilateral PTMC. However, patients who refuse or are ineligible for surgery can opt for RFA for palliative purposes, with fully informed consent and thorough follow-up management.

This study had some limitations. First, it was a single-center retrospective study. Second, the sample size of bilateral PTMC cases was relatively small. Third, the follow-up period was relatively short. Given the good prognosis of PTMC, further studies with a larger number of bilateral PTMC patients and a more extended follow-up period are needed. Fourth, this study did not compare RFA with surgery for the treatment of bilateral PTMC.

In conclusion, with sufficient preoperative evaluation, RFA might be a promising treatment for bilateral PTMC patients who were unsuitable for surgery or refused surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of Chinese PLA General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LY interpreted the patient data and drafted the manuscript. YKL performed RFA procedure, and conceived of the study and coordination. MBZ, QS, JX, and YZ collected and analyzed the patient data. All authors contributed to the article and approved the submitted version.

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