



Review Article

Radiofrequency for benign and malign thyroid lesions

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KEYWORDS

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Abstract *Background:* Thermal ablation of thyroid nodules is new modality for the management of the benign and malign lesions. This minimally invasive treatment is performed as an outpatient, local anesthetic, single professional procedure that can treat neoplastic lesions without removing normal thyroid tissue and thus avoiding hypothyroidism.

Method: A comprehensive review of the most relevant literature regarding the thermal ablation of benign and malign nodules was performed in order to currently define its role on the management of the nodular thyroid disease. The data was divided into benign and malign literature.

Results: The benign nodules can be effectively treated by radiofrequency ablation (RFA) but some limitation exists regarding the nodule's size but not nodules characteristics. The RFA of primary malign tumors of the thyroid recently demonstrated positive and safe long-term follow-up and encouraged additional investigation and possibly a definitive role in the management of these low risk nodules.

Conclusion: RFA is a safe, cost-effective minimally invasive procedure that avoids thyroid tissue removal while destroying neoplastic one thus, preventing hypothyroidism.

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Background

Thyroid nodules are ubiquitous and can be presented as benign or malign lesions. The majority of this nodules are benign and just a small portion eventually grow (15.4% of the cases in a five year follow up) to a point that symptoms or esthetic problems may emerge.¹ The common management of these benign cases are observation with subsequent ultrasound exams until the patient complains of neck bulging or swallowing problems, when surgery should be offered.²

Malign lesions are usually treated with surgery. The extend of surgery is debatable with total thyroidectomy or lobectomy being valid options of treatments.² Although, recent trials introduced the possibility of active surveillance of small selected papillary carcinoma.³ This new disruptive treatment option is under evaluation in several centers to reproduce the results obtained.^{3–5} Concomitantly, radiofrequency is being evaluated for the treatment of initial papillary carcinoma.

Radiofrequency ablation of tumors is a well established technique used in other organs for decades. Mainly used to treat metastatic lesions of the liver or lungs it can also be used to treat the kidneys, bone and uterus. The energy is delivered through a cooled-tip electrode inserted into the nodule. As the tissue is heated cells are destroyed instantly causing a coagulative necrosis⁶ and along the follow-up tissue will be reabsorbed. Thus, the availability of the technology relatively high in several centers and thus it can be easily implemented.

Benign lesions

Rational

The symptomatic or esthetic benign nodules can be safely diagnosed by ultrasound exams and fine needle aspiration biopsies (FNAC) and once defined as benign, the risk of malignity is below 2%.^{2,7} Also, the risk of one of these nodules becoming a malignant is bleak.¹ Thus, the common management of these nodules is offering some sort of thyroid surgery to amend the patients' complains.²

Granting the necessity of some sort of treatment, the option of thyroid surgery is an asymmetrical one. Since, in order to solve the problems caused by the enlarged thyroid or nodule patients have to weight some risks such as vocal cord paralysis, hypoparathyroidism, general anesthesia, bleeding and infection or to burden side effects of the surgery itself such as hypothyroidism or a scar on the neck.^{8–10}

Thus, a minimally invasive therapy could be an option for benign nodules if it could decrease the limitations that conventional therapy has and effectively treat the esthetic and compressive symptoms. And, as the cost-effectiveness

is proven, beyond the quality of live indicators, the incorporation of this technology is ought to be.

Results

Radiofrequency ablation (RFA) is an ultrasound guided minimally invasive technique that is performed with or without sedation as an outpatient procedure. The characteristic of the procedure, as mentioned, is the ablation through heat delivered to the nodule thus causing coagulative necrosis.⁶ Consequently, no amount of the nodule's tissue is removed during RFA, although the nodule can be aspirated immediately before the procedure. Because of that, when treating solid nodules, no immediate size reduction is expected. On the contrary, some swelling is observed after the procedure.¹¹

The composition of the nodule does not affect the effectiveness of the RFA. Although, cystic nodules will experience an initial abrupt reduction in volume, due to aspiration of liquid, all nodules will have about the same volume reduction rate (VRR) after 6 months.¹² Divergently, predominantly cystic lesion could be effectively treated by Ethanol Ablation (EA) with a fraction of the cost of RFA. As the proportion of the nodules' solid part increases less effective EA is compared to RFA.¹¹

In a recent metanalysis RFA showed volume reduction rate (VRR) in 6, 12, 24 months of 68%, 75% and 87% respectively and that was significantly better than Laser Ablation.¹³ Also, they showed in their supplement appendix an increase of VRR proportionally to year of publication thus showing an improvement in the ablation technique.¹³ The results demonstrated a persistent (2–3 years) reduction in volume and patients complains following either one session of RFA or subsequent RFA sessions (Fig. 1).¹³

Some factors may decrease efficiency of RFA such as nodules close to the carotid artery, the danger triangle or peripheral blood flow on Color-Doppler at the end of the procedure (Fig. 2).¹⁴ Other authors correlate the initial volume of the nodule with the final VRR and sizes greater than 30 cc are reported to worst outcomes.^{15,16}

Regarding complications, the incidence is quite small although some of them are specific for thermal ablation's procedures. Looking into the data of a metanalysis and over 12 trials of RFA (1186 nodules) most of complications were minor and the commonest was local pain (mild to moderate). Additionally, bleeding on the subcutaneous or rupturing the nodules occurred at 3.38% of the time. Major complications were rarer and recurrent laryngeal nerve/voice change was the most common (1.1%). Other complications are dismal and generally temporary.¹³

Finally, the fact that RFA can achieve stable results and present low incidence of complications makes it a promising new approach to benign thyroid nodules. As the technique develops and it is incorporated into guidelines

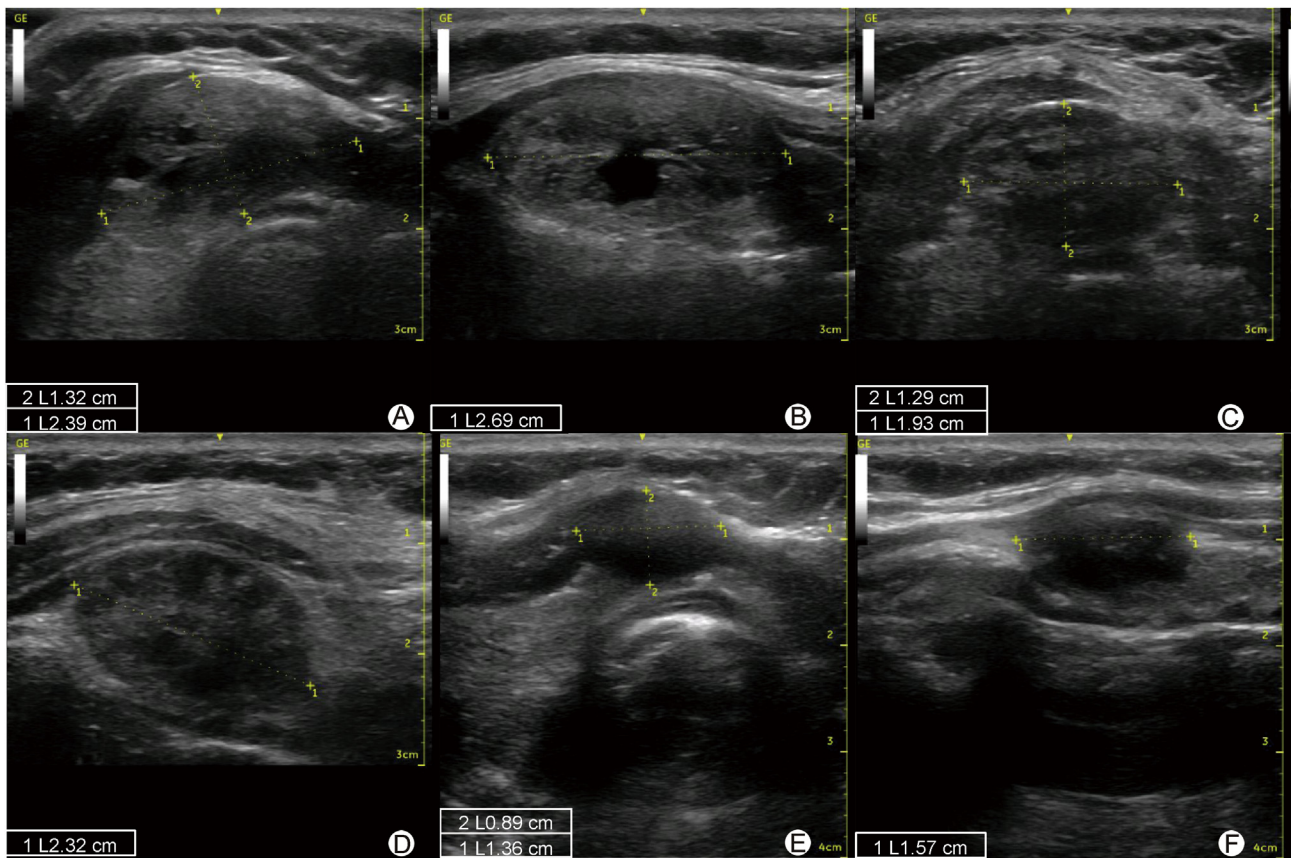


Fig. 1 Evolution of Thyroid Nodule after RFA A, B: transverse and sagittal sections before RFA, volume of 441 mm³; C, D: transverse and sagittal sections after one month of RFA and volume of 300 mm³; E, F: transverse and sagittal sections after six months of RFA and volume of 98 mm³ and global reduction of 78%.

one important question is the role of RFA in the growing asymptomatic thyroid nodules.

Malign lesions

Rational

The number of well differentiated thyroid carcinomas (WDTC) are increasing worldwide and the highest proportion of the cases are at the initial stage. The mortality attributed to these cases are dismal and the treatment's complications greatly exceed it. The treatment of the thyroid cancer is based on the resection of all malignant tissue through conventional surgery.

Currently the option of active surveillance is under evaluation in different centers of the world as an option to minimize the impact of the treatment. The rational for this approach is existence of a high incidence of micropapillary carcinomas that will never develop clinically hence, no medical intervention would be necessary.

These two alternatives are diametrically opposite regarding complications and applied treatment. The possibility of a minimally invasive treatment might be an option for low risk patients unwilling to undergo

surgery but not comfortable to observe a malignant diagnosis.

Results

The firsts series of papillary carcinomas treated with thermal ablation showed important volume reduction with either one or two sessions, without regrowth within the first year and without long-term complications.^{17,18} Additional data by Valcavi et al¹⁹ corroborated the feasibility of the procedure by performing thermal ablation immediately before surgery and found destruction of the tissue with complete loss of TTF1 and antimitochondrial antibody expression.

Recently, three papers addressing long-term follow-up came out with important results. Cho et al²⁰ described retrospectively 84 malignant thyroid nodules and followed them for 72 months resulting in a 100% reduction rate with 60 months. Additional ablation was necessary in 15.4% of the cases, also 3 out of 74 patients discovered new papillary carcinoma foci and were treated with RFA. During the follow-up no recurrences, no progression, no lymph nodes or distant metastasis were identified nor delayed surgery was necessary. Wu et al²¹ described a retrospective analysis

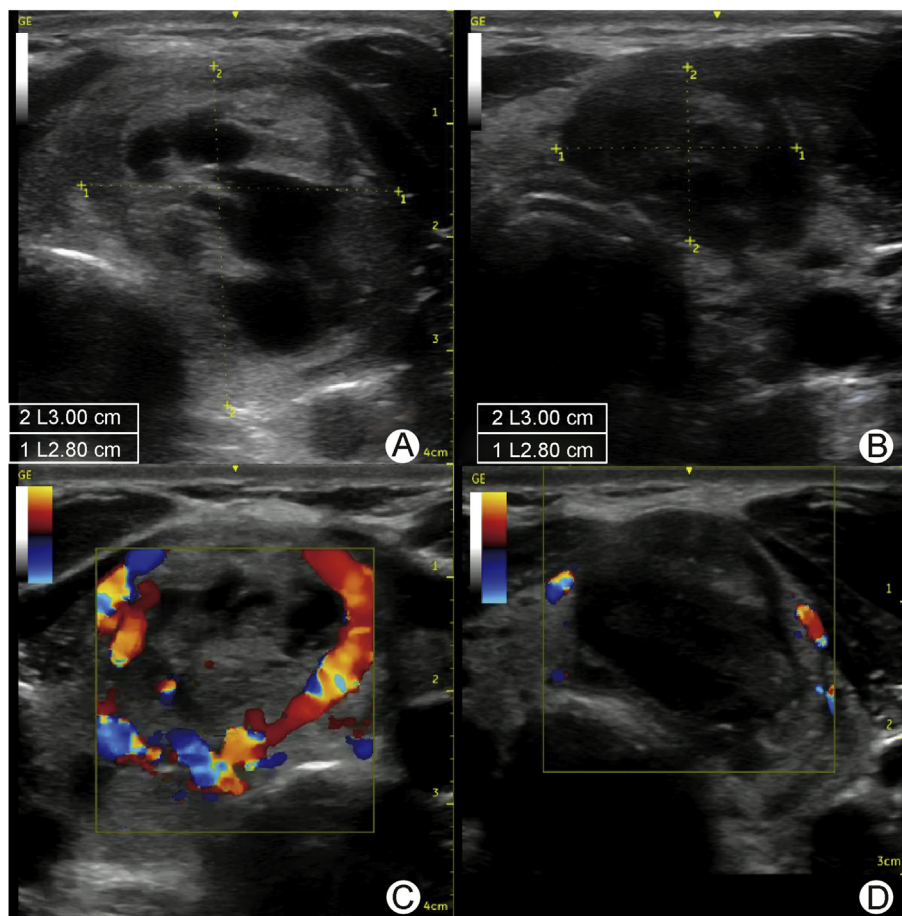


Fig. 2 Evolution of autonomous hypervascularized nodule A: pre-ablation aspect of the thyroid nodule; B: 3rd month aspect of the nodule with reduction with reduction of 75%; C: vascularization aspect before RFA; D: vascularization after RFA.

of 198 patients without major complications, four local pain and five temporary hoarseness. The reduction rate achieved with the procedure was $(99.8 \pm 1.0) \%$ within 24 months ($P = 0.005$).

Lastly, Zhang et al²² compared prospectively similar patients with PTMC that were allocated into RFA and surgery group. The surgery group had a longer procedure time, longer hospitalization and higher treatment costs compared to RFA group. Three patients had complications on the surgery group and none on the RFA, all complications occurred in patients with Central level neck dissection. The THYCA-Qol questionnaire showed a better outcome for RFA than surgery (13.1 ± 0.36 vs. 14.7 ± 2.01 , $P < 0.001$). In the surgery group final pathology confirmed additional PTMC foci not detected before surgery in 9 patients (11.3%). Also 9 patients presented with central lymph node metastases (one LN in four patients, two LN in four patients and one patient with five LN).

Complications after thermal ablation are infrequent and mostly transient. The most common one is pain, ranging from 2% to 60% although severe pain is unusual.^{20,23–26} Some authors use sedation to perform more extensive ablation. Direct damage to critical structures of the neck is a risk during ablation procedures and its likelihood depends on the size and position of the lesion. Lesions located on the dorsomedial portion of the thyroid are at most risk, as

malignant nodules compared to benign ones. The incidence of vocal cord paralysis on malignant lesions may be expected around 5% of the cases.²⁷

Other complications are described and result of the kind of method used and the surgeon's experience. Full thickness skin burns are a rare but extremely unwanted complication for a minimally invasive procedure.²⁸ Horner's Syndrome, Spinal accessory nerve and brachial plexus injury are reported and relate to primary lesion anatomical position, reoperation status, the use of hydrodissection and experience.

Discussion

Treatment of benign thyroid nodules may experience a disruptive change regarding its management. The conventional approach to this problem is, once the benignity nature is confirmed, dichotomous: refer to surgery due to compressive or esthetic symptoms or wait and follow the natural history of the disease and wait for the symptoms to flourish. The thermal ablation can reduce the volume of these symptomatic benign nodules between 80% and 90% thus, solving the esthetic or compressive complains.^{12,16,29}

Thermal ablation can outperform surgery for these cases regarding complication rate, costs and quality of life.^{5,12,30,31} A minimally invasive, outpatient, simple professional procedure that can treat more than one nodule in one session with

Table 1 Cancer ablation literature. Type of energy used, follow-up, reduction and recurrences.

Ref	Technique	Patients (N)	Nodules (N)	Initial vol (mm ³)	Reduction (%)	FU (m)	Recurrence (N)	New foci (N)
Zhang, M et al 2020 ²²	RFA	94	94	175.9 ± 228.3	—	72	1	0
Wu, R et al 2020 ²¹	RFA	198	204	99.4 ± 82	99.8 ± 1	25.9	—	—
Cho, SJ et al 2020 ²⁰	RFA	74	84	20 (1–234)	100	60	0	4
Yue, W et al 2014 ³³	MWA	18	18	89.5 ± 20.1	90	12	0	0
Cui, T et al 2019 ³⁴	MWA	185	206	100.1 ± 92.9	98.6 ± 3.6	36	0	1
Zhang et al 2018	LA	64	64	41 ± 40	100	25.7	0	0

RFA: radiofrequency ablation; MWA: microwave ablation; LA: laser ablation.

minimal risk for the patient ought to be incorporated in management of thyroid nodules guidelines in the future. Since, size matters for thermal ablation as nodules larger than 30 ml will experience slighter volume reduction rates than the smaller ones consequently, once the benignity of the nodule is assured there is an interval of opportunity for performing RFA and achieve the optimal result.

The malignant thyroid lesions are a public health problem and the number of cases increase continually. The majority of these new cases are small papillary carcinomas. The current treatment consists of conventional surgery followed by Radioactive Iodine ablation that accompany a number of complications, cost and burden to the patient. The option of a minimally invasive treatment started to be investigated since the thermal ablation technique for benign nodules had been established and mastered.

Thermal ablation's early results,^{19,32} on selected patients, encouraged prospective trials^{20,22} to investigate the long-term results of the PTMC treatment. These manuscripts demonstrated lower incidence of complications, morbidity and cost when compared to surgery. These low risk patients experienced an uneventful follow-up since the risk of locoregional recurrences was exiguous upfront. The comparison to surgery raised question regarding micro metastasis in the central compartment and the previously unidentified microcarcinoma foci.

In order to answer that question, larger and longer trials should be promoted and address the recurrence and multifocality of papillary carcinoma. The results of surgical patients will vary accordantly to the regional management of the PTMCs since some eastern colleagues will perform total thyroidectomy with or without central neck dissection or lobectomy with or without central neck dissection. Differently from how western surgeons would typically manage these cases and thus differing on the incidence of micro metastasis and multifocality.

Finally, the prospect of treating PTMC with thermal ablation is promising since the results achieved so far seem excellent and lasting. The treatment of benign lesions has broad literature with guidelines support with cost-effective and quality of life analysis favoring the minimally invasive treatment (Table 1).

Conclusion

Radiofrequency ablation of benign nodules presents as a viable option for symptomatic, esthetic concerning or continuous growing nodules. As it can significantly reduce

the nodule's volume without damaging the surrounding normal thyroid tissue thus, avoiding hypothyroidism. The use of this technique on low risk, small malign lesions is promising with encouraging recent long-term follow-up. Additional studies will be necessary to corroborate that datum and future incorporation of that technique into the thyroid guidelines. Thermal ablation became a focus of interest of the thyroidology community and in the future the most available, cost-effective and efficacious source of energy will be the energy source of choice.

Declaration of competing interest

Ralph P Tufano, Speaker for Medtronic and Hemostatix. None of the other authors have anything to disclose.

References

- Durante C, Costante G, Lucisano G, et al. The natural history of benign thyroid nodules. *JAMA*. 2015;313:926–935.
- Haugen BR, Alexander EK, Bible KC, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1–133.
- Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. *World J Surg*. 2016;40:516–522.
- Ho AS, Chen I, Melany M, Sacks WL. Evolving management considerations in active surveillance for micropapillary thyroid carcinoma. *Curr Opin Endocrinol Diabetes Obes*. 2018;25(5):353–359.
- Deandrea M, Trimboli P, Garino F, et al. Long-term efficacy of a single session of RFA for benign thyroid nodules: a longitudinal 5-year observational study. *J Clin Endocrinol Metab*. 2019;104:3751–3756.
- Goldberg SN. Radiofrequency tumor ablation: principles and techniques. *Eur J Ultrasound*. 2001;13:129–147.
- Stangl R, Szijártó A, Ónody P, et al. Reduction of liver ischemia-reperfusion injury via glutamine pretreatment. *J Surg Res*. 2011;166:95–103.
- Choi Y, Jung SL, Bae JS, et al. Comparison of efficacy and complications between radiofrequency ablation and repeat surgery in the treatment of locally recurrent thyroid cancers: a single-center propensity score matching study. *Int J Hypertherm*. 2019;36(1):359–367.
- Best AR, Shipchandler TZ, Cordes SR. Midcervical scar satisfaction in thyroidectomy patients. *Laryngoscope*. 2017;127:1247–1252.
- Felix C, Russell JO, Juman S, Medford S. Cervical scar satisfaction post conventional thyroidectomy. *Gland Surg*. 2019;8:723–728.

11. Kim JH, Baek JH, Lim HK, et al. 2017 thyroid radiofrequency ablation guideline: Korean society of thyroid radiology. *Korean J Radiol.* 2018;19(4):632–655.
12. Lee GM, You JY, Kim HY, et al. Successful radiofrequency ablation strategies for benign thyroid nodules. *Endocrine.* 2019;64(2):316–321.
13. Trimboli P, Castellana M, Sconfienza LM, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: a systematic review and meta-analysis. *Endocrine.* 2020;67:35–43.
14. Zhao CK, Xu HX, Lu F, et al. Factors associated with initial incomplete ablation for benign thyroid nodules after radiofrequency ablation: first results of CEUS evaluation. *Clin Hemorheol Microcirc.* 2017;65(4):393–405.
15. Sim JS, Baek JH, Cho W. Initial ablation ratio: quantitative value predicting the therapeutic success of thyroid radiofrequency ablation. *Thyroid.* 2018;28:1443–1449.
16. Sim JS, Baek JH. Long-term outcomes following thermal ablation of benign thyroid nodules as an alternative to surgery: the importance of controlling regrowth. *Endocrinol Metab.* 2019;34(2):117–123.
17. Jeong SY, Baek JH, Choi YJ, et al. Radiofrequency ablation of primary thyroid carcinoma: efficacy according to the types of thyroid carcinoma. *Int J Hyperther.* 2018;34:611–616.
18. Zhou W, Jiang S, Zhan W, Zhou J, Xu S, Zhang L. Ultrasound-guided percutaneous laser ablation of unifocal T1N0M0 papillary thyroid microcarcinoma: preliminary results. *Eur Radiol.* 2017;27(7):2934–2940.
19. Valcavi R, Piana S, Bortolan GS, Lai R, Barbieri V, Negro R. Ultrasound-guided percutaneous laser ablation of papillary thyroid microcarcinoma: a feasibility study on three cases with pathological and immunohistochemical evaluation. *Thyroid.* 2013;23:1578–1582.
20. Cho SJ, Baek SM, Lim HK, Lee KD, Son JM, Baek JH. Long-term follow-up results of ultrasound-guided radiofrequency ablation for low-risk papillary thyroid microcarcinoma: more than 5-year follow-up for 84 tumors. *Thyroid.* 2020;8.
21. Wu R, Luo Y, Tang J, et al. Ultrasound-guided radiofrequency ablation for papillary thyroid microcarcinoma: a retrospective analysis of 198 patients. *Int J Hyperther.* 2020;37(1):168–174.
22. Zhang M, Tufano RP, Russell JO, et al. Ultrasound-guided radiofrequency ablation versus surgery for low-risk papillary thyroid microcarcinoma: results of over 5 years' follow-up. *Thyroid.* 2020;30:408–417.
23. Bonichon F, Buy X, Godbert Y, et al. Local treatment of metastases from differentiated thyroid cancer. *Ann Endocrinol.* 2015;76(1 Suppl 1):1S40–1S46.
24. Che Y, Jin S, Shi C, et al. Treatment of benign thyroid nodules: comparison of surgery with radiofrequency ablation. *AJNR Am J Neuroradiol.* 2015;36(7):1321–1325.
25. Chung SR, Baek JH, Choi YJ, Lee JH. Longer-term outcomes of radiofrequency ablation for locally recurrent papillary thyroid cancer. *Eur Radiol.* 2019;29:4897–4903.
26. Chung SR, Suh CH, Baek JH, Park HS, Choi YJ, Lee JH. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. *Int J Hyperther.* 2017;33(8):920–930.
27. Nixon IJ, Angelos P, Shaha AR, Rinaldo A, Williams MD, Ferlito A. Image-guided chemical and thermal ablations for thyroid disease: review of efficacy and complications. *Head Neck.* 2018;40:2103–2115.
28. Bernardi S, Lanzilotti V, Papa G, et al. Full-thickness skin burn caused by radiofrequency ablation of a benign thyroid nodule. *Thyroid.* 2016;26:183–184.
29. Stabenow E, Rangel LJ. Radiofrequency ablation of benign thyroid nodules: evaluation of the safety and preliminary results. *Arch Endocrinol Metab.* 2019;63(suppl 2):1.
30. Vuong NL, Dinh LQ, Bang HT, Thuy TTM, Bac NH, Vy TT. Radiofrequency ablation for benign thyroid nodules: 1-year follow-up in 184 patients. *World J Surg.* 2019;43:2447–2453.
31. Jung SL, Baek JH, Lee JH, et al. Efficacy and safety of radiofrequency ablation for benign thyroid nodules: a prospective multicenter study. *Korean J Radiol.* 2018;19(1):167–174.
32. Papini E, Guglielmi R, Pacella CM. Laser, radiofrequency, and ethanol ablation for the management of thyroid nodules. *Curr Opin Endocrinol Diabetes Obes.* 2016;23:400–406.
33. Yue W, Wang S, Yu S, Wang B. Ultrasound-guided percutaneous microwave ablation of solitary T1N0M0 papillary thyroid microcarcinoma: initial experience. *Int J Hyperther.* 2014;30(2):150–157. <https://doi.org/10.3109/02656736.2014.885590>.
34. Cui T, Jin C, Jiao D, Teng D, Sui G. Safety and efficacy of microwave ablation for benign thyroid nodules and papillary thyroid microcarcinomas: a systematic review and meta-analysis. *Eur J Radiol.* 2019;118:58–64. <https://doi.org/10.1016/j.ejrad.2019.06.027>.