Seminar | Thyroid

eISSN 2005-8330
https://doi.org/10.3348/kjr.2021.0093
Korean J Radiol 2021;22(8):1436-1440

Check for updates

Korean Journal of Radiology
KJR

Unresolved Clinical Issues in Thermal Ablation of Benign Thyroid Nodules: Regrowth at Long-Term Follow-Up

Jung Suk Sim[1], Jung Hwan Baek[2]

[1]Department of Radiology, Withsim Clinic, Seongnam, Korea; [2]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Laser ablation (LA) for the treatment of symptomatic benign thyroid nodules was first introduced in the early 2000s [1]. In Korea, radiofrequency ablation (RFA) began in 2002, and a large population study was published in 2008 [2]. Other thermal ablation (TA) techniques, such as microwave ablation and high-intensity focused ultrasound, are also used in clinical practice. The Korean Society of Thyroid Radiology (KSThR) published its first thyroid RFA guideline in 2012, which was revised in 2018 [3,4]. These guidelines have greatly contributed to the establishment and spread of TA worldwide. Early experiences with TA showed promising short-term results, with early studies suggesting that the primary purpose of RFA for benign thyroid nodules was debulking to reduce pressure symptoms, rather than complete ablation [5]. However, Huh et al. [6] reported regrowth of nodules from unablated peripheral regions and suggested repeat treatment with a moving-shot technique, which is a safer method of ablating peripheral portions of the nodule. As long-term follow-up results have been released, issues surrounding regrowth and multiple treatments have emerged. Thus, the need for setting new treatment goals has increased [7].

Received: January 28, 2021 **Revised:** March 4, 2021
Accepted: March 9, 2021
Corresponding author: Jung Hwan Baek, MD, PhD, Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
• E-mail: radbaek@naver.com
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Excellent Short-Term Efficacy of TA

Generally speaking, short-term results are based on follow-up periods of less than one to two years. Four representative short-term follow-up studies from Korea and Europe achieved excellent volume reduction rates (79–84%) with improvements in nodule-related symptoms and cosmetic problems (Table 1) [2,8-10]. Symptoms and cosmetic problems are significantly improved when the volume reduction ratio (VRR) is more than 50% [1,2]. Many researchers have treated target nodules with a focus on the central safe area, as aggressive treatment of the nodule margin can cause thermal damage to surrounding critical structures, especially the recurrent laryngeal nerve. Therefore many doctors insist on debulking the nodule rather than complete treatment, and single-session treatment focusing on the safe central portion of the nodule is the therapeutic goal of TA. In a randomized trial of LA, Døssing et al. [11] reported that they gained only 13% additional VRR from additional sessions (single vs. three sessions, 45% vs. 58%), and suggested the limited efficacy of additional LA. In a randomized trial using RFA (single vs. two sessions), Huh et al. [6] reported that single-session RFA was effective for improving cosmetic and symptomatic problems in most patients as it achieved an excellent VRR (70.2%); however, for large nodules, especially those greater than 20 mL, additional RFA may be required to resolve persistent symptoms. After the trials, some centers started to apply multiple treatment sessions to treat nodules completely, especially for large nodules [12-14]. However, the necessity of multiple treatments remains debatable.

Copyright © 2021 The Korean Society of Radiology

Korean Journal of Radiology
KJR

Table 1. Short-Term Results of Thermal Ablation for Benign Thyroid Nodules

	Jeong et al. [2]	Spiezia et al. [8]	Dobnig and Amrein [9]	Jung et al. [10]
Year	2008	2009	2018	2018
Patient number	236	66	222	276
Study design	Retrospective Single center	Prospective Single center	Prospective Single center	Prospective Multicenter
Country	Korea	Italy	Austria	Korea
Modality	RFA	RFA	RFA	RFA
Device	Internally cooled	Umbrella	Thyroid-dedicated Internally cooled	Thyroid-dedicated Internally cooled
Mean volume, mL	6.1	21.1	14.1	14.2
Follow-up, months	1–41 (12.3)	1–24	12	12
12-month VRR, %	84.1	79.4	80.0	80.4

RFA = radiofrequency ablation, VRR = volume reduction ratio

Regrowth and Repeat Treatments

Unfortunately, excellent short-term results do not guarantee long-lasting effects. As follow-up results over 3 years have been published, regrowth issues have become evident [15]. Regrowth causes recurrence of symptoms and can even require surgery. Døssing et al. [16] reported the first 5-year follow-up results after LA; while they achieved an initial VRR of 51%, 29% of patients underwent surgery at a median follow-up duration of 38 months. Negro et al. [17] reported that 77.4% of LA-treated nodules showed regrowth when VRR was less than 50% after 1 year and 20.6% exhibited regrowth even when the VRR was greater than 50%.

With the regrowth seen during long-term follow-up, as described above, researchers who believe that TA could be an alternative to surgery have tried repeat treatments to obtain complete or near-complete ablation and minimize regrowth, with the ultimate aim of avoiding surgical intervention after TA. According to a meta-analysis by Cho et al. [18], over a follow-up duration of more than 3 years, patients treated with RFA achieved a better final VRR than those treated with LA (92.2% vs. 43.3%) (Fig. 1). Therefore, the RFA group showed less regrowth and less requirement for surgery. The authors suggested technical differences and completion of margin ablation as explanatory factors for the differences in clinical outcomes between the two ablation groups. For some researchers, repeated treatment is considered an unfavorable outcome [19]; however, other researchers have actively pursued multi-session treatment to achieve the maximum ablation effect [20]. The KSThR guidelines published in 2018, the consensus statement by the Italian minimally invasive treatment of the thyroid

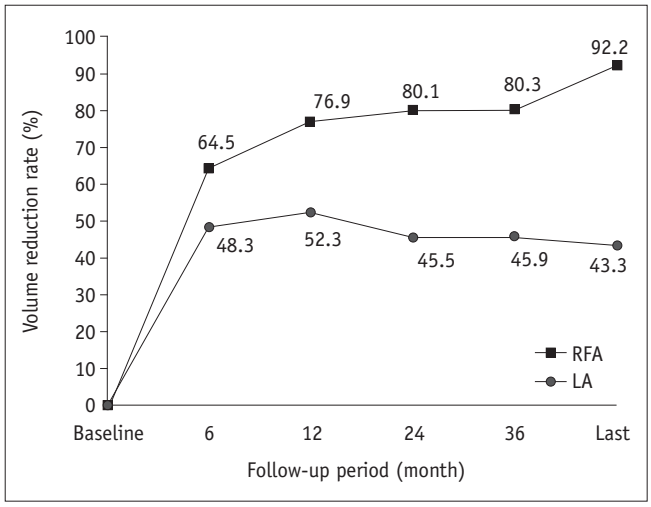

Fig. 1. Changes in volume reduction ratio over 5 years after RFA and LA for thyroid nodules. LA = laser ablation, RFA = radiofrequency ablation

group published in 2019, and the recommendations of the Asian Conference on Tumor Ablation Task Force all recommend that additional treatment is necessary [4,21,22].

Novel Strategies and Techniques to Control Regrowth

Recently, various attempts have been made to manage regrowth. One method involves a strategic approach, detecting regrowth earlier to perform additional ablation at the optimal time. If a viable nodule portion with vascularity is detected on color Doppler ultrasound images, additional treatment should be considered because the under-ablated portion with vascularity will have considerable potential for regrowth [23]. Sim et al. [15] suggested that early prediction of nodule regrowth is possible by calculating and

 https://doi.org/10.3348/kjr.2021.0093

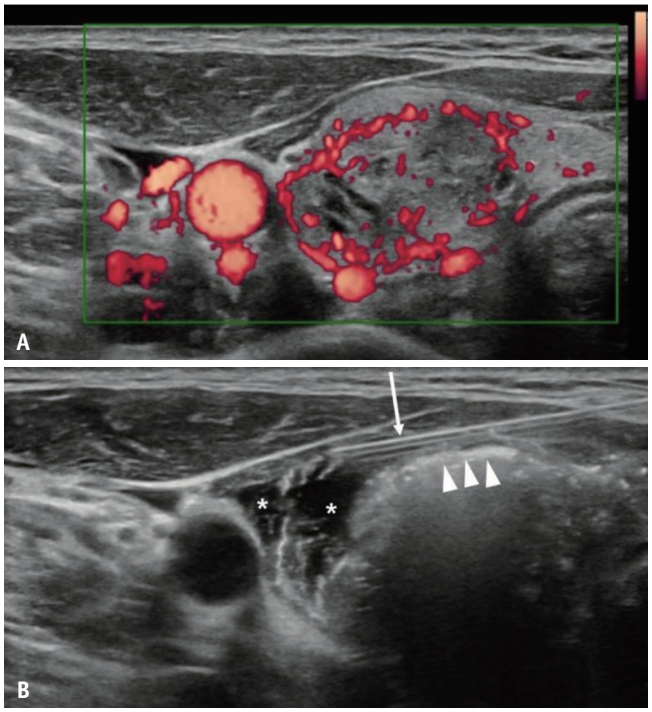

Fig. 2. Anterolateral hydrodissection and venous ablation techniques.
A. Blood vessels surrounding the nodule are clearly visible in the power Doppler ultrasonography image acquired before radiofrequency ablation. **B.** After completion of venous ablation, a compact filling of hot air bubbles is observed (arrowheads). A thin needle is inserted around the nodule for hydrodissection (arrow). An anechoic area was formed by the 5% dextrose injected for hydrodissection (*).

tracking the undertreated viable tissue volume. Negro et al. [17] reported that regrowth and time to regrowth can be predicted through a 1-year VRR. Sim et al. [24] introduced the initial ablation ratio, an index representing the performance of the procedure calculated from the ultrasound images acquired at the first follow-up and suggested that this initial ablation ratio could be a predictive factor for regrowth [25,26]. These efforts indicate a transition from a passive approach of re-treatment after regrowth to an active approach that minimizes the possibility of regrowth by performing controlling measures before regrowth occurs, thereby keeping the effect of treatment permanent, such that it can be compared with surgery [7].

Another approach involves technical development. Regrowth mainly originates from under-treated marginal tissue. Undertreated tissue may be intentionally left to avoid thermal damage to the surrounding critical structures. Therefore, targeting and treatment of margins is considered the key to retreatment. To ablate marginal undertreated tissue, it is essential to maximize maneuverability by using a modified internally cooled electrode and the moving-shot technique [4,18,22]. In addition, Park et al. [27] reported that the introduction of new techniques, such as vascular ablation and hydrodissection, provided advantages with respect to minimizing marginal tissue (Fig. 2).

Finally, innovations in ablation devices can minimize regrowth. Small active tips (0.4 or 0.5 cm) are useful for treating small amounts of remnant peripheral nodule tissue, and a recent publication showed that an adjustable electrode could treat the central safe area rapidly using a large active tip, and then safely treat the more dangerous peripheral area using a small active tip [28].

CONCLUSION

Over the past 20 years, TA has been used to successfully treat benign thyroid nodules without significant complications. Short-term results showed that reducing nodule volume resulted in considerable improvement in patient symptoms. However, such short-term effects do not guarantee long-lasting effects because of marginal regrowth. From this perspective, we propose "permanent avoidance of surgery" as a new clinical goal for the treatment of benign thyroid nodules. This new goal will only be achieved by complete or near-complete ablation of nodule tissue and control of regrowth.

Key words
Benign; Thyroid nodule; Thermal; Radiofrequency; Ablation; Therapy; Long-term outcome; Regrowth

Conflicts of Interest
Jung Hwan Baek's financial activities are not related to the present article (patent holder of a unidirectional ablation electrode); he has been a consultant to two radiofrequency companies, STARmed and RF Medical, since 2017. Jung Suk Sim has nothing to declare.

Author Contributions
Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Methodology: all authors. Supervision: Jung Hwan Baek. Validation: all authors. Writing—original draft: Jung Suk Sim. Writing—review & editing: all authors.

ORCID iDs
Jung Suk Sim
https://orcid.org/0000-0001-6803-3544

https://doi.org/10.3348/kjr.2021.0093

Korean Journal of Radiology
KJR

Jung Hwan Baek
https://orcid.org/0000-0003-0480-4754

REFERENCES

1. Døssing H, Bennedbaek FN, Karstrup S, Hegedüs L. Benign solitary solid cold thyroid nodules: US-guided interstitial laser photocoagulation--initial experience. *Radiology* 2002;225:53-57
2. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. *Eur Radiol* 2008;18:1244-1250
3. Na DG, Lee JH, Jung SL, Kim JH, Sung JY, Shin JH, et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. *Korean J Radiol* 2012;13:117-125
4. Kim JH, Baek JH, Lim HK, Ahn HS, Baek SM, Choi YJ, et al. 2017 thyroid radiofrequency ablation guideline: Korean Society of Thyroid Radiology. *Korean J Radiol* 2018;19:632-655
5. Deandrea M, Limone P, Basso E, Mormile A, Ragazzoni F, Gamarra E, et al. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. *Ultrasound Med Biol* 2008;34:784-791
6. Huh JY, Baek JH, Choi H, Kim JK, Lee JH. Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session--prospective randomized study. *Radiology* 2012;263:909-916
7. 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 (Seoul)* 2019;34:117-123
8. Spiezia S, Garberoglio R, Milone F, Ramundo V, Caiazzo C, Assanti AP, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. *Thyroid* 2009;19:219-225
9. Dobnig H, Amrein K. Monopolar radiofrequency ablation of thyroid nodules: a prospective Austrian single-center study. *Thyroid* 2018;28:472-480
10. Jung SL, Baek JH, Lee JH, Shong YK, Sung JY, Kim KS, et al. Efficacy and safety of radiofrequency ablation for benign thyroid nodules: a prospective multicenter study. *Korean J Radiol* 2018;19:167-174
11. Døssing H, Bennedbaek FN, Hegedüs L. Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules: one versus three treatments. *Thyroid* 2006;16:763-768
12. Aldea Martínez J, Aldea Viana L, López Martínez JL, Ruiz Pérez E. Radiofrequency ablation of thyroid nodules: a long-term prospective study of 24 patients. *J Vasc Interv Radiol* 2019;30:1567-1573
13. Hong MJ, Sung JY, Baek JH, Je MS, Choi DW, Yoo H, et al. Safety and efficacy of radiofrequency ablation for nonfunctioning benign thyroid nodules in children and adolescents in 14 patients over a 10-year period. *J Vasc Interv Radiol* 2019;30:900-906
14. Pacella CM, Mauri G, Achille G, Barbaro D, Bizzarri G, De Feo P, et al. Outcomes and risk factors for complications of laser ablation for thyroid nodules: a multicenter study on 1531 patients. *J Clin Endocrinol Metab* 2015;100:3903-3910
15. Sim JS, Baek JH, Lee J, Cho W, Jung SI. Radiofrequency ablation of benign thyroid nodules: depicting early sign of regrowth by calculating vital volume. *Int J Hyperthermia* 2017;33:905-910
16. Døssing H, Bennedbæk FN, Hegedüs L. Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. *Eur J Endocrinol* 2011;165:123-128
17. Negro R, Greco G, Deandrea M, Rucco M, Trimboli P. Twelve-month volume reduction ratio predicts regrowth and time to regrowth in thyroid nodules submitted to laser ablation: a 5-year follow-up retrospective study. *Korean J Radiol* 2020;21;764-772
18. Cho SJ, Baek JH, Chung SR, Choi YJ, Lee JH. Long-term results of thermal ablation of benign thyroid nodules: a systematic review and meta-analysis. *Endocrinol Metab (Seoul)* 2020;35:339-350
19. Negro R, Greco G. Unfavorable outcomes in solid and spongiform thyroid nodules treated with laser ablation. A 5-year follow-up retrospective study. *Endocr Metab Immune Disord Drug Targets* 2019;19:1041-1045
20. Lim HK, Lee JH, Ha EJ, Sung JY, Kim JK, Baek JH. Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. *Eur Radiol* 2013;23:1044-1049
21. Papini E, Pacella CM, Solbiati LA, Achille G, Barbaro D, Bernardi S, et al. Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT) group. *Int J Hyperthermia* 2019;36:376-382
22. Ha EJ, Baek JH, Che Y, Chou YH, Fukunari N, Kim JH, et al. Radiofrequency ablation of benign thyroid nodules: recommendations from the Asian Conference on Tumor Ablation Task Force. *Ultrasonography* 2021;40:75-82
23. Chung J, Lee YJ, Choi YJ, Ha EJ, Suh CH, Choi M, et al. Clinical applications of Doppler ultrasonography for thyroid disease: consensus statement by the Korean Society of Thyroid Radiology. *Ultrasonography* 2020;39:315-330
24. Sim JS, Baek JH, Cho W. Initial ablation ratio: quantitative value predicting the therapeutic success of thyroid radiofrequency ablation. *Thyroid* 2018;28:1443-1449
25. Sim JS. Letter: twelve-month volume reduction ratio predicts regrowth and time to regrowth in thyroid nodules submitted to laser ablation: a 5-year follow-up retrospective study. *Korean J Radiol* 2021;22:291-292
26. Park SI, Baek JH. How to monitor and manage nodule

 https://doi.org/10.3348/kjr.2021.0093

regrowth after thermal ablation of benign thyroid nodules. *Korean J Radiol* 2021;22:293-295
27. Park HS, Baek JH, Park AW, Chung SR, Choi YJ, Lee JH. Thyroid radiofrequency ablation: updates on innovative devices and techniques. *Korean J Radiol* 2017;18:615-623
28. Lee J, Shin JH, Hahn SY, Park KW, Choi JS. Feasibility of adjustable electrodes for radiofrequency ablation of benign thyroid nodules. *Korean J Radiol* 2020;21:377-383

https://doi.org/10.3348/kjr.2021.0093