



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

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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].

## 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.

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

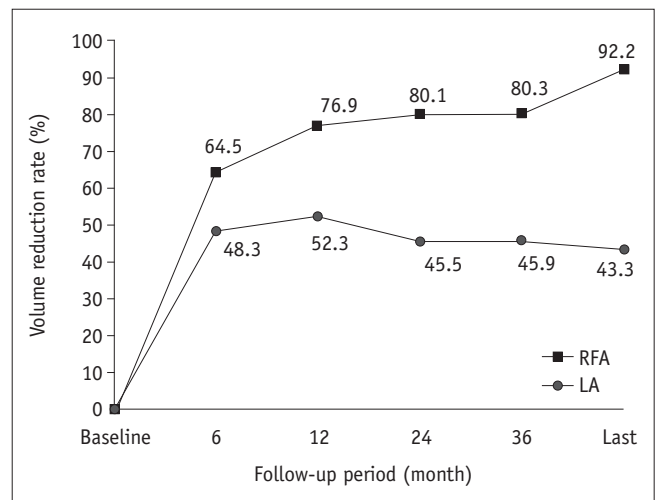
	Jeong et al. [2]	Spiezia et al. [8]	Dobnig and Amrein [9]	Jung et al. [10]
Year	2008	2009	2018	2018
Patient number	236	66	222	276
Study design	Retrospective Single center	Prospective Single center	Prospective Single center	Prospective Multicenter
Country	Korea	Italy	Austria	Korea
Modality	RFA	RFA	RFA	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

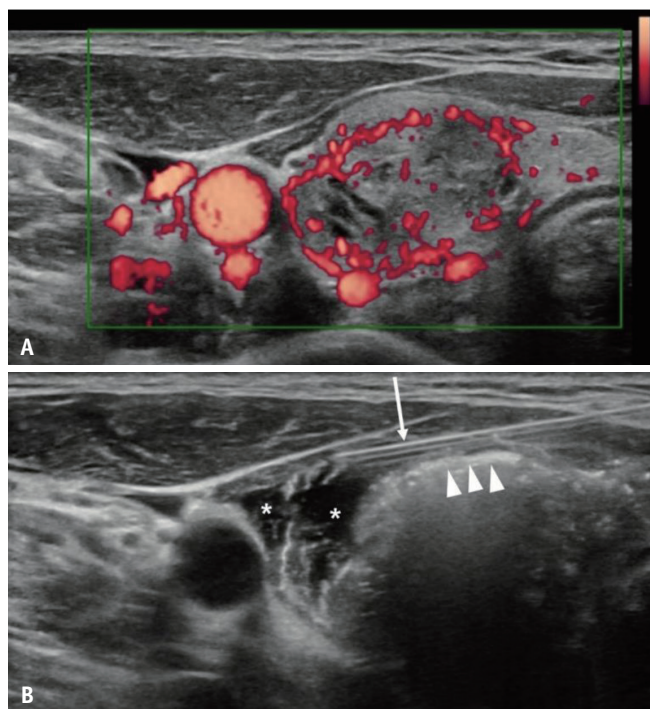


**Fig. 1. Changes in volume reduction ratio over 5 years after RFA and LA for thyroid nodules.** LA = laser ablation, RFA = radiofrequency ablation

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



**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.

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