THYROID
Volume 25, Number 8, 2015

DOI: 10.1089/thy.2015.0133

Efficacy and Safety of Radiofrequency Ablation Versus Observation for Nonfunctioning Benign Thyroid Nodules: A Randomized Controlled International Collaborative Trial

Maurilio Deandrea,[1] Jin Yong Sung,[2] Paolo Limone,[1] Alberto Mormile,[1] Francesca Garino,[1] Federico Ragazzoni,[1] Kyu Sun Kim,[2] Ducky Lee,[3] and Jung Hwan Baek[4]

Background: Percutaneous radiofrequency thermal ablation (RFA) has been reported as an effective tool for the management of benign thyroid nodules (BTN). However, large, randomized controlled trials (RCTs) are lacking.
Objective: The aims of this study were to assess the volume reduction of BTN after a single RFA performed using the moving-shot technique and to compare the volume reduction obtained in patients treated in two centers with different experience of the moving-shot technique.
Method: This study was an international prospective RCT. It was carried out at the Mauriziano Hospital (Turin, Italy) and the Asan Medical Center (Seoul, Korea). Eighty patients harboring solid, compressive, nonfunctioning BTN (volume 10–20 mL) were enrolled. Twenty patients in each country were treated by RFA using a 18-Gauge internally cooled electrode (group A); 20 nontreated patients in each country were followed as controls (group B).
Results: At six months, BTN volume significantly decreased in group A (15.1 ± 3.1 mL vs. 4.2 ± 2.7 mL; $p < 0.0001$), whereas it remained unchanged in group B (14.4 ± 3.3 mL vs. 15.2 ± 3.5 mL). The baseline volume was larger in the Italian series (16.4 ± 2.5 mL vs. 13.9 ± 3.3 mL, $p = 0.009$). However, at six months, there was no significant difference between the Korean group and the Italian group (3.7 ± 2.9 mL vs. 5.5 ± 2.2 mL). Both cosmetic and compressive symptoms significantly improved (3.6 ± 0.5 vs. 1.7 ± 0.4 and 3.6 ± 1.9 vs. 0.4 ± 0.7, respectively; $p < 0.001$). No side effects occurred.
Conclusions: RFA was effective in reducing the volume of BTN. The outcome was similar in centers with different experience in the moving-shot technique.

Introduction

Thyroid nodules are very common in the general population, with a prevalence of about 50% in subjects older than 60 years of age undergoing neck ultrasound (US) examination (1). In the majority of cases, thyroid nodules are benign, but they can be responsible for compression of local structures, which can result in discomfort and a decreased quality of life. Large compressive benign thyroid nodules (BTN) may also result in life-threatening conditions, due to the possible onset of acute respiratory crisis. Surgery and radioiodine therapy are the main therapeutic approaches for compressive or toxic nodules (1–3). However, surgery is charged by the possibility of immediate complications such as wound infection and compressive hematomas (requiring re-intervention) in 0.2–2.7% of cases, and by laryngeal recurrent nerve palsy and hypoparathyroidism, which can either be transient (in 2–28% of cases) or permanent (in 0.2–3% of cases) (4–7). Moreover, in the case of surgery for recurrent goiter, the frequency of such complications increases further (up to 37% for transient and 7.8%, for permanent damage) (4–7). In addition, a number of patients with BTN with an indication for surgery refuse this approach. In some of these cases, radioiodine therapy may be ineffective, especially in large nonfunctioning nodules (8,9).

Minimally invasive therapeutic options have been proposed to treat BTN when surgery or radioiodine is refused, contraindicated, or ineffective (10). Percutaneous radiofrequency ablation (RFA) is a minimally invasive procedure that has been used to treat both malignant and benign tumor nodules in many organs (11–15). RFA also represents a

[1]Endocrinology, Diabetes, and Metabolism Unit, A.O. Ordine Mauriziano di Torino, ''Umberto I'' Hospital, Turin, Italy.
Departments of [2]Radiology and [3]Internal Medicine, Thyroid Center, Daerim St. Mary's Hospital, Seoul, Korea.
[4]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

promising new approach for the management of BTN, as shown in previous studies (16–18) that demonstrated the efficacy and safety of RFA in the treatment of large nodules with local pressure symptoms (16,17). In a large series of elderly subjects, a two-year follow-up showed that RFA is highly effective in achieving long-term shrinkage of large solid BTN, as well as in controlling compressive symptoms (18). At the same time, some radiologists from Korea investigated the role of RFA in patients with BTN (19–22), but only two studies evaluated the effectiveness of RFA in a comparative setting (23,24). Baek *et al*. (23) performed RFA using a single-hook 18-Gauge needle in 15 patients with benign, nontoxic, predominantly solid nodules, and a six-month follow-up highlighted that the observed nodule volume reduction was related to RFA activity rather than to spontaneous shrinkage (23). In another comparative study, Faggiano *et al*. confirmed the excellent results both in toxic and nontoxic BTN, using a 14-Gauge needle with four expandable hooks (24).

The treatment technique proposed by Baek *et al*. differs from that used in Europe, where the electrode is fixed in position during treatment. Indeed, the Korean electrode, which is thinner and shorter than the devices used in Europe, is introduced through a transisthmic approach and moved back and forth inside the nodule according to parallel layers to ablate small conceptual tissue units in succession (23). This approach is called the moving-shot technique.

A randomized controlled trial (RCT) was therefore carried out involving two centers in two countries (Italy and Korea), with the aim of evaluating the efficacy of RFA performed by the moving-shot technique in BTN selected with the same criteria, and to compare the outcomes achieved by two groups of operators with a different level of experience with this technique.

Materials and Methods

Study design

This study is an international RCT performed in two centers: the Daerim St Mary's Hospital (Seoul, Korea) and the Mauriziano Hospital (Turin, Italy). The study protocol was approved by the Institutional Review Board of both hospitals. From May 6, 2010, to September 8, 2012, 80 patients (40 patients from each country) who met the eligibility criteria and gave written informed consent were randomly assigned to one of two groups of 40 patients to undergo either observation or RFA, with a 1:1 ratio. The enrolled patients were assigned to the group using a random allocation sequence as follows: 40 patients (20 patients from each country) were treated with a single RFA session, and 40 patients (20 patients from each country) did not receive any treatment and were only followed up as a control group. This protocol is similar to that adopted in another recently published randomized study in which laser thermal ablation was performed (25).

The inclusion criteria were as follows: (a) older than 18 years of age; (b) presence of a solid thyroid nodule (solid portion >70%) with a volume between 10 and 20 mL; (c) presence of pressure symptoms or cosmetic problems for which all patients specifically requested treatment; (d) confirmation of benign findings in at least two separate US-guided core needle or fine-needle aspiration (FNA) biopsies (i.e., two biopsies performed with an interval of several months); and (e) normal serum levels of thyroid hormones, thyrotropin (TSH), and calcitonin. The exclusion criteria were (a) nodules showing US features suggestive of malignancy (i.e., taller than wide, spiculated margin, markedly hypoechoic, micro- or macrocalcifications), and (b) treatments for the thyroid nodule in the six months prior to enrollment in this study.

Pretreatment assessment

US, US-guided biopsy, and laboratory and clinical results were evaluated before treatment. In Korea, two investigators (K.S.K. and J.Y.S., with 10 and 12 years' experience respectively in thyroid US) performed US and US-guided FNA by using a 10 MHz linear probe and a real-time US system (Aplio SSA-770A; Toshiba Medical Systems, Otawara-shi, Japan).

In Italy, two investigators (A.M. and M.D., with 13 and 15 years' experience respectively in thyroid US) performed US and US-guided FNA by using a 7.5–12 MHz linear probe equipped with CD and PD modules (MyLab70XVG Esaote; Biomedica, Genova, Italy).

On US examination carried out before the treatment, three orthogonal diameters (i.e., the largest diameter and two other mutually perpendicular diameters) of each nodule were measured, and the volume of the nodules was calculated with the following equation: $V = 0.524 \times abc$ (where V is volume, a is the largest diameter, and b and c are the other two perpendicular diameters) (17).

Serum concentrations of TSH, free thyroxine (fT4), thyroglobulin, and calcitonin, as well as titers of antithyroglobulin (TgAb) and antithyroperoxidase antibodies (TPOAb), were measured at baseline.

The Bethesda reporting system was used for cytological classification: patients with Bethesda Class II findings were enrolled (26). Before treatment, the patients were asked to rate their symptoms on a 10 cm visual analog scale (scale 0–10), and the investigator recorded a cosmetic score, as previously reported (score 1, no palpable mass; score 2, no cosmetic problem but a palpable mass; score 3, cosmetic problem only on swallowing; and score 4, readily detected cosmetic problem) (23).

RFA procedures

RFA was performed with the patient in the supine position and with mild neck extension. All procedures were performed under US guidance. To prevent serious hemorrhage, vessels located along the approach route were carefully evaluated by using Doppler US. The puncture site was anesthetized with 2% lidocaine (in Korea) and 1% mepivacain (in Italy), and the skin was not incised to prevent unnecessary scar formation. The skin was punctured by using the transisthmic approach method, in which the electrode is inserted through the short axis of the target nodule from the isthmus. This method allows the electrode to pass through a sufficient amount of thyroid parenchyma (23). This technical approach has several advantages. It can prevent the needle or electrode from moving when the patient is swallowing or talking during ablation and can also prevent fluid leakage (i.e., injected ethanol or ablated hot fluid of the cystic portion of thyroid nodules) outside the thyroid gland. This approach also allows continuous US monitoring of the nodule and the space

Table 1. Demographic Data of Study Population

	Korea		*Italy*		
	RF	*Control*	*RF*	*Control*	p-*Value**
Sex (M:F)	2:18	1:19	4:16	1:19	0.71
Mean age	39.5 ± 9.6 (26–60)	52.2 ± 10.3 (35–71)	54.3 ± 13.3 (34–83)	62.5 ± 12.7 (37–82)	0.05
Nodule largest diameter (cm)	4.0 ± 0.5 (3.1–4.9)	2.8 ± 0.3 (2.2–3.2)	4.0 ± 0.4 (3.4–4.6)	3.9 ± 0.5 (3.0–5.2)	0.95
Nodule volume (mL)	13.9 ± 3.1 (10–19.7)	13.7 ± 3.2 (10–19.8)	16.4 ± 3.4 (12.6–25.1)	15.0 ± 3.2 (9.4–20.2)	0.009
Symptom score	3.4 ± 0.9 (2–5)	3.1 ± 0.8 (2–5)	4.0 ± 2.7 (0–8)	3.9 ± 2.1 (0–7)	0.001
Cosmetic score	4.0 ± 0	4.0 ± 0	3.2 ± 0.7 (2–4)	2.8 ± 0.7 (1–4)	0.001

Values are reported as mean ± standard deviation (*SD*). Range is reported in parentheses.
*Comparison between Korean and Italian RFA groups.

between the needle or the electrode tip to the expected location of the recurrent laryngeal nerve, thus minimizing the risks of injury to the nerve and/or to the esophagus. At the end of the procedure, an ice pack was applied to the patient's neck with mild compression, and the patient underwent observation for about two hours.

Follow-up

The outcomes were assessed by investigators (J.Y.S. and K.S.K. in Korea; F.R. and F.G. in Italy) who were blinded to the group allocation. US examination was performed in order to measure the nodule volume (and also the cystic area volume), and compressive and cosmetic scores were recorded in both treated and untreated subjects at one month and six months after enrollment. Moreover, serum concentrations of TSH, fT4, thyroglobulin, and calcitonin, as well as the titers of TgAb and TPOAb, were measured in both treated patients and in controls at a six-month follow-up.

Study end points

The primary end points of the current study were (a) the quantitative volume reduction ratio of BTN between control (40 patients) and RFA (40 patients) at six months after the procedure, and (b) the comparison of the volume reduction ratio of the patients (20 vs. 20) of two centers after RFA. The Korean center (the ''more experienced group'' in this field) had an experience of about 3000 cases of thyroid RFA; the Italian center (the ''less experienced group'' in this field) had a significant experience in interventional US-guided therapies (both PEI and RFA by other devices), and had previously treated 50 cases of BTN with the moving-shot technique, after an initial instruction given by a Korean radiologist (J.H.B.).

The secondary end points for the clinical outcomes included the therapeutic success rate, in terms of improvement in symptoms and cosmetic problems, and the number of major complications.

Major and minor complications were defined according to the recommendations of the Society of Interventional Radiology (27).

Statistical analysis

Continuous variables describing patients and nodules were expressed as median with interquartile range; direct comparisons were performed with a nonparametric test for unpaired samples (Mann–Whitney *U*-test). Two-sided *p*-values of <0.05 were considered statistically significant. Analysis was performed using Analyse-it^{TM} Software v3.76.5 (Leeds, United Kingdom).

Sample size calculation for the study was performed as follows. Considering a volume reduction of 35% significance in the treated nodules in comparison with an expected maximum volume reduction of 5% in the control group, enrolment of 40 patients for each group could guarantee statistical power of more than 80%.

Thirteen percent was chosen as the clinically relevant difference between the experienced and less experienced group, according to previous data of US measurement–remeasurement variability (the results of previous studies were 5.1–6.6%, and relevant difference in the primary endpoint was set as 13%, which is double 6.6%) (28,29).

Results

Baseline characteristics of patients in group A and group B are shown in Table 1. BTN volume, function, and US characteristics

Table 2. Treatment Parameters of RFA

	Korea (n = *20*)	*Italy* (n = *20*)	p-*Value*
Mean ablation time (s)	435.8 ± 142.4	819.5 ± 225.9	**0.0001**
Mean RF power (Watt)	75.3 ± 10.4	49.7 ± 4.7	**0.0001**
Total energy (Joule)	33,068.0 ± 13,800.5	40,364.7 ± 10,801.1	0.72
Energy/mL (J/mL)	2436.3 ± 916.2	2521.7 ± 803.6	0.84

Values are reported as mean ± *SD*. Significant values are shown in bold.
RFA, radiofrequency ablation.

Table 3. Comparison of Clinical Characteristics Between RFA and Control Groups at Six Months

Outcome	*RFA* (n = *40*)	*Controls* (n = *40*)	p-*Value*
% Volume reduction [IQR]	71 [21]	−3 [23]	0.0001
Symptom score	0.4 ± 0.7	3.3 ± 1.7	0.0001
Cosmetic score	1.7 ± 0.8	3.5 ± 0.7	0.0001
TSH (μIU/mL)	0.9 ± 0.8	1.0 ± 0.9	0.190
fT4 (pg/mL)	10.8 ± 2.9	11.9 ± 2.0	0.05
Thyroglobulin (ng/mL)	31.5 ± 38	13.6 ± 22	0.02

Values are mean ± SD; volume reduction values are reported as median.

IQR, interquartile range; TSH, thyrotropin; fT4, free thyroxine.

did not significantly differ between the groups at baseline (Table 1). The F/M ratio was similar in the two countries, while the group of patients from Korea was younger than the group of patients treated in Italy (Table 1).

Hormonal evaluation

All the patients were euthyroid at baseline, and showed normal calcitonin levels. After treatment, thyroid function, as well as calcitonin levels, did not change. Thyroglobulin was elevated at baseline, and decreased significantly after treatment but did not normalize (Table 1). A minority of patients in both countries (8/40) had elevated titers of thyroid autoantibodies (more than twice the minimum value adopted for every laboratory), and the pattern did not change over time in either the treated or the control group.

Treatment modality

The treatment protocol described above allowed us to supply the same energy per milliliter of nodule volume in both countries (p = n.s.). However, the treatment method was different: while in Korea the operators distributed more power in a shorter time, in Italy the treatment was longer and less powerful (Table 2).

In all patients, RFA was safe and well tolerated. No significant side effects were observed, and no patient needed hospitalization after treatment. Local anesthesia prevented pain on needle insertion and electrode positioning. During the procedure, all patients were asymptomatic, with the exception of a mild sensation of heat in the neck, which did not require interrupting the treatment. After the procedure, no local edema, pain, or other adverse effects were detected (Table 2).

Nodule volume

After treatment, the BTN volume significantly decreased in the treated patients as a whole (group A; 15.1 ± 3.1 at baseline, 8.3 ± 2.9 mL at 1 month, 4.2 ± 2.7 mL at 6 months; $p < 0.0001$), whereas it remained unchanged in group B (14.4 ± 3.3 mL at baseline, 14.8 ± 3.5 mL at 1 month, 15.2 ± 3.5 mL at 6 months; p = n.s.; Table 3).

When the results obtained in the Korean and the Italian centers were compared, although the baseline nodule volume was larger in the Italian series ($p = 0.009$ vs. Korean), in both countries shrinkage was important, and no significant difference in volume reduction was seen at either the one-month or six-month evaluation (RFA group Korea 13.9 ± 3.3 at baseline, 7.0 ± 2.6 mL at 1 month, 3.7 ± 2.9 mL at 6 months; RFA group Italy 16.4 ± 2.5 at baseline, 9.9 ± 2.7 mL at 1 month, 5.5 ± 2.2 mL at 6 months; p = n.s.). Thirty-eight out of 40 treated nodules showed shrinkage of >50%. Data and results in the different groups are shown in Table 4.

Symptom score and clinical evaluation

The symptom score progressively improved in the treated patients both for compressive and for cosmetic symptoms. In group A, the compressive score decreased from 3.6 ± 1.9 at baseline to 0.4 ± 0.7 at the six-month evaluation ($p < 0.0001$), and the cosmetic score decreased from 3.6 ± 0.5 at baseline to 1.7 ± 0.84 at the six-month evaluation ($p < 0.0001$). The results were similar in the treated groups in both Korea and Italy. However, group B showed no change in the follow-up period (Table 4).

Discussion

US-guided minimally invasive procedures represent an alternative to surgery for the treatment of benign thyroid nodules, which grow and become symptomatic due to compressive symptoms. These treatments achieve the relief of neck complaints in most cases, are less expensive than surgery, preserve thyroid function, and can be performed on an outpatient basis. The percutaneous ethanol injection is the treatment of choice for thyroid cysts or predominantly cystic nodules due to its efficacy and the scarcity of adverse effects (30). Laser thermal ablation is a consolidated technique

Table 4. Comparison of Treatment Outcomes Six Months Following RFA Between Korea and Italy

Outcomes	*Korea* (n = *20*)	*Italy* (n = *20*)	p-*Value*	*Difference* [CI]*
Primary end point				
% Volume reduction [IQR]	77 [25]	66 [24]	0.07	6.23 [−3.67 to 16.13]
Secondary end points				
Symptom score	0.4 ± 0.6	0.6 ± 1.18	0.529	
Cosmetic score	2.05 ± 0.75	1.4 ± 0.9	0.429	
Therapeutic success (%)	90	100		
Major complications	None	None	> 0.99	

Values of secondary end points are expressed as mean ± *SD*. Therapeutic success is considered as an improvement in symptoms and cosmetic problems.

*Comparison of RF ablation groups between Korea and Italy.

proposed for treating solid BTN. Laser ablation induces a 40–60% decrease in the size of BTN over a six-month period and is long lasting (31–34). Laser ablation is minimally invasive. Indeed, 21-Gauge needles are used to insert the fiber into the nodule, but more than one session and/or the insertion of multiple optic fibers may be required for treating large BTN. RCTs carried out in homogeneous groups of patients have provided strong evidence of efficacy of laser thermal ablation and of a rather close relationship between the delivered energy dose and the extent of shrinkage (10).

RFA has been used since 2005 to treat compressive thyroid nodules, mostly in Korea and in Italy (16–24). The published data show good results in both countries, but with differences in patient selection and devices. In Italy, the authors, working with Dr. Spiezia's group, initially treated patients using a 14-Gauge needle with four or nine expandable hooks for the treatment of large solid or predominantly solid nodules (cystic component <30%), both toxic and nontoxic (16–18,24). In Korea, Baek *et al.*, as well as other thyroid radiologists, used an 18-Gauge internally cooled single needle to treat nodules that were smaller and had a greater cystic component than those treated in the Italian published series (19–23).

Until now, some prospective studies aimed at assessing the efficacy of RFA in cold and hyperfunctioning nodules have been published (19,21–24), but RCTs are lacking. The present study is the first international RCT aimed at evaluating the efficacy and safety of RFA in the treatment of benign medium-sized thyroid nodules responsible for moderate compressive or cosmetic discomfort, for which the patients requested treatment. To assess these two points, the less invasive 18-Gauge needle was used to perform only one session of treatment, in order to investigate a homogeneous series of solid nodules, thus avoiding the bias related to the cystic component. A further important issue was to assess the efficacy of RFA performed by groups of operators from different countries with different experience levels in the moving-shot technique.

The main finding of this study was that patients treated by RFA experienced a significant decrease in BTN volume, as demonstrated by US, and a rapid relief of compressive symptoms when compared to untreated subjects. It cannot be excluded that the patient's evaluation of compressive symptoms after RFA could have been influenced by the awareness of having received a treatment aimed at reducing their discomfort, and that this could have generated a bias. However, the possibility of such bias is common to all studies in which invasive approaches, including surgery, are performed on humans, and where a comparison with a ''sham operation'' cannot be made. Furthermore, the cosmetic score (as well US report), which, unlike the compressive score, was evaluated by operators who were blinded to the patients' group allocation, also showed a significant improvement after RFA. The results in terms of volume reduction were impressive in the treated group, both in Italy and Korea, with a slightly greater efficacy in the latter group where experience in the moving-shot technique is consolidated, but without a significant difference between the two countries. Further analysis of the data showed that a more intense and shorter treatment applied in Korea can obtain a quicker shrinkage than a less powerful and longer treatment session, as applied in Italy, but the long-term results were similar in both series. It can be speculated that the main factor responsible for long-term shrinkage is the delivered energy/mL of the treated tissue, which was not significantly different in the two series, while the time of treatment and the RFA power are not crucial.

With regard to the possible differences in the efficacy between radiofrequency and laser thermal ablation, they cannot be inferred from the present data. However, if the results obtained here are compared with those reported by Papini *et al*. in which patients with nodules of a comparable volume were treated by laser ablation, a greater efficacy of RFA can be argued for, compared with laser ablation in the treatment of 10–20 mL solid nodules (25). Indeed, in the present series, the mean volume reduction at six-month follow-up was $71 \pm 21\%$, and almost all nodules (38/40) showed shrinkage of >50%, while in the series by Papini *et al*., the mean reduction at the same follow-up time was $49 \pm 22\%$, and the volume reduction was >50% in only 67.3% of cases. However, it must be emphasized that in the long-term follow-up, a further reduction of up to $57 \pm 25\%$ was reported in the trial by Papini *et al*. (25). Ha *et al*. recently attempted to compare the relative efficacy of laser and radiofrequency ablation in the treatment of BTN. The results of their analysis, based on literature data, gave evidence for a greater efficacy of radiofrequency than laser ablation (35). However, only comparative studies specifically investigating this issue will allow a definitive answer to be given to this question.

In conclusion, the results of this RCT demonstrate in an unequivocal manner that RFA, when performed in experienced centers, is a rapid, inexpensive, and safe method for inducing a clinically significant nodule volume reduction. Thus, RFA represents a valid approach in patients with BTN who are not candidates, who refuse, or who failed to be cured by conventional treatments, and it can be considered a safe and effective therapeutic option together with laser ablation. Larger clinical trials are needed to assess the risk of nodule regrowth, the frequency of nonresponders, the optimal number of sessions needed to achieve better shrinkage according to the index nodule volume, the optimal treatment modality, and the duration of shrinkage in long-term follow-up. Furthermore, new trials should evaluate the benefit of RFA, as an alternative to surgery, in very large nodules, which are responsible for important compressive symptoms.

Author Disclosure Statement

The authors have nothing to disclose.

References

1. Gharib H, Papini E 2007 Thyroid nodules: clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am **36:**707–735, vi.
2. Mazzaferri EL 1993 Management of a solitary thyroid nodule. N Engl J Med **328:**553–559.
3. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, Duick DS, Guglielmi R, Hamilton CR, Zeiger MA, Zini M 2010 American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis

and management of thyroid nodules. Endocr Pract **12:** 63–102.
4. Christou N, Mathonnet M 2013 Complications after total thyroidectomy. J Visc Surg **150:**249–256.
5. Puzziello A, Rosato L, Innaro N, Orlando G, Avenia N, Perigli G, Calò PG, De Palma M 2014 Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. Endocrine **47:**537–542.
6. Rosato L, Avenia N, Bernante P, De Palma M, Gulino G, Nasi PG, Pelizzo MR, Pezzullo L 2004 Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg **28:**271–276.
7. Miccoli P, Frustaci G, Fosso A, Miccoli M, Materazzi G 2014 Surgery for recurrent goiter: complication rate and role of the thyroid-stimulating hormone-suppressive therapy after the first operation. Langenbeck's Arch Surg **400:** 253–258.
8. Lippi F, Ferrari C, Manetti L, Rago T, Santini F, Monzani F, Bellitti P, Papini E, Busnardo B, Angelini F, Pinchera A 1996 Treatment of solitary autonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group. J Clin Endocrinol Metab **81:**3261–3264.
9. Shetty KR, Duthie EH 1995 Thyroid disease and associated illness in the elderly. Clin Geriatr Med **11:**311–325.
10. Hegedüs L 2009 Therapy: a new nonsurgical therapy option for benign thyroid nodules? Nat Rev Endocrinol **5:**476–478.
11. Ohtani S, Kochi M, Ito M, Higaki K, Takada S, Matsuura H, Kagawa N, Hata S, Wada N, Inai K, Imoto S, Moriya T 2011 Radiofrequency ablation of early breast cancer followed by delayed surgical resection—a promising alternative to breast-conserving surgery. Breast **20:**431–436.
12. Livraghi T, Goldberg SN, Monti F, Bizzini A, Lazzaroni S, Meloni F, Pellicanò S, Solbiati L, Gazelle GS 1997 Saline-enhanced radio-frequency tissue ablation in the treatment of liver metastases. Radiology **202:**205–210.
13. Lane MD, Le HBQ, Lee S, Young C, Heran MKS, Badii M, Clarkson PW, Munk PL 2011 Combination radiofrequency ablation and cementoplasty for palliative treatment of painful neoplastic bone metastasis: experience with 53 treated lesions in 36 patients. Skeletal Radiol **40:**25–32.
14. Teh HS, Tan S-M 2010 Radiofrequency ablation - a new approach to percutaneous eradication of benign breast lumps. Breast J **16:**334–336.
15. Chan MD, Dupuy DE, Mayo-Smith WW, Ng T, DiPetrillo TA 2011 Combined radiofrequency ablation and high-dose rate brachytherapy for early-stage non-small-cell lung cancer. Brachytherapy **10:**253–259.
16. Spiezia S, Garberoglio R, Di Somma C, Deandrea M, Basso E, Limone PP, Milone F, Ramundo V, Macchia PE, Biondi B, Lombardi G, Colao A, Faggiano A 2007 Efficacy and safety of radiofrequency thermal ablation in the treatment of thyroid nodules with pressure symptoms in elderly patients. J Am Geriatr Soc **55:**1478–1479.
17. Deandrea M, Limone P, Basso E, Mormile A, Ragazzoni F, Gamarra E, Spiezia S, Faggiano A, Colao A, Molinari F, Garberoglio R 2008 US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. Ultrasound Med Biol **34:**784–791.
18. Spiezia S, Garberoglio R, Milone F, Ramundo V, Caiazzo C, Assanti AP, Deandrea M, Limone PP, Macchia PE, Lombardi G, Colao A, Faggiano A 2009 Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid **19:**219–225.
19. Baek JH, Moon W-J, Kim YS, Lee JH, Lee D 2009 Radiofrequency ablation for the treatment of autonomously functioning thyroid nodules. World J Surg **33:**1971–1977.
20. Kim Y-S, Rhim H, Tae K, Park DW, Kim ST 2006 Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. Thyroid **16:**361–367.
21. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, Lee D 2008 Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol **18:**1244–1250.
22. Baek JH, Jeong HJ, Kim YS, Kwak MS, Lee D 2008 Radiofrequency ablation for an autonomously functioning thyroid nodule. Thyroid **18:**675–676.
23. Baek JH, Kim YS, Lee D, Huh JY, Lee JH 2010 Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. AJR Am J Roentgenol **194:**1137–1142.
24. Faggiano A, Ramundo V, Assanti AP, Fonderico F, Macchia PE, Misso C, Marciello F, Marotta V, Del Prete M, Papini E, Lombardi G, Colao A, Spiezia S 2012 Thyroid nodules treated with percutaneous radiofrequency thermal ablation: a comparative study. J Clin Endocrinol Metab **97:**4439–4445.
25. Papini E, Rago T, Gambelunghe G, Valcavi R, Bizzarri G, Vitti P, De Feo P, Riganti F, Misischi I, Di Stasio E, Pacella CM 2014 Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial. J Clin Endocrinol Metab **99:**3653–3659.
26. Cibas ES, Ali SZ 2009 The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol **132:** 658–665.
27. Burke DR, Lewis CA, Cardella JF, Citron SJ, Drooz AT, Haskal ZJ, Husted JW, McCowan TC, Van Moore A, Oglevie SB, Sacks D, Spies JB, Towbin RB, Bakal CW 2003 Quality improvement guidelines for percutaneous transhepatic cholangiography and biliary drainage. J Vasc Interv Radiol **14:**S243–246.
28. Bennedbaek FN, Nielsen LK, Hegedüs L 1998 Effect of percutaneous ethanol injection therapy versus suppressive doses of L-thyroxine on benign solitary solid cold thyroid nodules: a randomized trial. J Clin Endocrinol Metab **83:** 830–835.
29. Døssing H, Bennedbaek FN, Hegedüs L 2005 Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules—a randomised study. Eur J Endocrinol **152:**341–345.
30. Bennedbaek FN, Hegedüs L 2003 Treatment of recurrent thyroid cysts with ethanol: a randomized double-blind controlled trial. J Clin Endocrinol Metab **88:**5773–5777.
31. Valcavi R, Riganti F, Bertani A, Formisano D, Pacella CM 2010 Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. Thyroid **20:**1253–1261.
32. Spiezia S, Vitale G, Di Somma C, Pio Assanti A, Ciccarelli A, Lombardi G, Colao A 2003 Ultrasound-guided laser thermal ablation in the treatment of autonomous hyperfunctioning thyroid nodules and compressive nontoxic nodular goiter. Thyroid **13:**941–947.

33. Papini E, Guglielmi R, Bizzarri G, Pacella CM 2004 Ultrasound-guided laser thermal ablation for treatment of benign thyroid nodules. Endocr Pract **10:**276–283.
34. Døssing H, Bennedbaek FN, Hegedüs L 2006 Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules: one versus three treatments. Thyroid **16:**763–768.
35. Ha EJ, Baek JH, Kim KW, Pyo J, Lee JH, Baek SH, Døssing H, Hegedüs L 2015 Comparative efficacy of radiofrequency and laser ablation for the treatment of benign thyroid modules: systematic review including traditional pooling and Bayesian network meta-analysis. J Clin Endocrinol Metab **100:**1903–1911.

Address correspondence to:
Jung Hwan Baek, MD
Department of Radiology and Research
Institute of Radiology
University of Ulsan College of Medicine
Asan Medical Center
86 Asanbyeongwon-Gil
Songpa-gu
Seoul 138-736
Korea

E-mail: radbaek@naver.com