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ENDOCRINE METHODS AND TECHNIQUES

High-intensity focused ultrasound (HIFU) therapy for benign thyroid nodules without anesthesia or sedation

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Abstract

Background Thermal ablation of thyroid nodules has gained momentum due to the possibility to avoid surgery. High-intensity focused ultrasound (HIFU) allows thermal treatment by energy ultrasound beam inside the targeted zone. Aim of our study was to evaluate the effects of HIFU treatment using Beamotion mode without anesthesia.

Methods Since 2016, patients with normal thyroid function, benign thyroid nodules with diameter no larger than 4 cm, and presenting local discomfort and/or compressive symptoms were treated by HIFU. We performed Beamotion HIFU and did not use anesthesia. Nodule size and thyroid function were evaluated before HIFU and 6 and 12 months later. Complications to therapy and tolerability of patients were also recorded. According to local ethical committee, for this retrospective study formal consent was not required.

Results The final series included 26 nodules from 26 patients with estimated volume of 2.81 ± 2.04 mL, treated by a power of 33.3 ± 10.3 W/site and energy of 2.1 ± 1.1 kJ. Nodules volume was significantly ($p < 0.0001$) reduced at 6 months of follow-up (1.83 ± 1.63 mL), and further at 1 year (1.57 ± 1.47 mL). Mean percentage of reduction over time of nodules was 48%. A 73% of patients described good comfort during treatment, 100% experienced good comfort just after therapy, and tolerability was high. No complications were recorded. At one 1 year of follow-up, 85% of subjects reported a reduction of local symptoms.

Conclusions HIFU therapy is effective in reducing size of thyroid nodules with major diameter below 4 cm and can be performed without anesthesia.

Keywords Thyroid · thermal ablation · high-intensity focused ultrasound (HIFU)

Introduction

The prevalence of thyroid nodules is recognized as very high and only up to 5% of these lesions is cancer [1, 2]. While thyroid removal is mandatory in patients with malignant lesions, those patients with benign nodules require treatment only in the presence of compression symptoms and/or cosmetic concerns. In the past decade, non-surgical options to treat benign thyroid nodules, such as laser, radiofrequency, microwaves, and high-intensity focused ultrasound (HIFU) have gained momentum due to the possibility to reduce the nodule's volume avoiding surgery and its potential complications [3]. It is well recognized that a temperature above 55 °C maintained held for more than 1 s induces the non-reversible enzymatic denaturation and leads to coagulative necrosis and cell death [4, 5]. Thus, all these thermal therapies aim to achieve this temperature threshold. As the more recently introduced therapy, HIFU allows the thermal tissue treatment by directing energy ultrasound beam inside the targeted nodule with neither needles nor other invasive instruments. This new method has been already applied in several organs [6], and a good performance of HIFU has been also recorded in thyroid goiter [7–15]. To date, no major complications have

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been recorded and some minor transient adverse effects (such as local edema, skin redness, skin micro-blisters, and vocal cord paresis) were observed [7–16]. Interestingly, patient's discomfort during therapy increased proportionally with the increasing delivered energy [9] and pain levels seemed to be independent on the dose of anesthetic or sedation [12]. Some potential disadvantages of HIFU with respect to radiofrequency and laser should be considered: higher costs, reduced efficacy in very large nodules, and longer treatment times. Then, only radiofrequency and laser can be considered for the treatment of large goiter. On the other hand, HIFU might be useful in those patients with no significantly large lesions (i.e., major diameter below 4 cm), determining local symptoms and perform radiofrequency and laser might be difficult.

Notably, it was recently demonstrated that, in silico phantom, a very low power of HIFU (i.e., 5 W per pulse) allows to achieve the temperature cutoff of 55 °C within 1 s and maintained it for some seconds [17]. These findings prompted us to verify if HIFU therapy with low power can be used to treat patients with compressive neck symptoms determined by a benign thyroid nodule. Specifically, the present study was undertaken as a proof of concept in clinical practice and aimed to evaluate if Beamotion HIFU allows to obtain a significant decrease of nodule size and a reduction of local subjective symptoms. Also, data of patient's comfort with and tolerability of low-dose HIFU were collected and evaluated.

Material and methods

Selection of patients

Since 2016, patients with thyroid nodules diagnosed at our Thyroid Center were considered for HIFU therapy when there was normal thyroid laboratory (TSH, fT3, fT4, Calcitonin, TgAb, and TPOAb) and local compressive symptoms specifically due to thyroid nodules with major diameter no larger than 4 cm. Initially, we selected patients with neck symptoms or cosmetic concerns specifically determined by thyroid nodule. As the main inclusion criterion, only patients with solid nodules at ultrasound could be eligible. Nodules with cystic changes (i.e., >30% of the targeted nodule), micro- and macrocalcifications, and difficult HIFU accessibility (lesions too deep or close to skin, trachea, and carotid) were excluded from this treatment option. Also, patients with vocal cord disease or significant alterations of the skin anterior to thyroid were initially assessed as no eligible for HIFU. Finally, all patients underwent fine needle aspiration cytology (FNAC) and only cases with benign report were enrolled for HIFU. The selection of patients for HIFU was done by two expert thyroidologists (P.T. and L.G.). According to local ethical committee, for this retrospective study formal consent was not required.

HIFU procedure

At our Thyroid Center, HIFU therapy was performed by using the EchoPulse system (Theraclion®, Paris, France). This equipment included an energy generator, an articulated harm, and a treatment head including an ultrasound probe and a cooling system. The system was also equipped by a touch screen echographic monitor essential to plan and monitor the treatment; by the latter, therapy could be planned directly on the monitor, target nodule identified and selected by a specific pen for touch screen display, and trachea, carotid, and skin well documented. After this preliminary procedure, the system calculated the number of pulses (i.e., sites) necessary to treat the target. Importantly, each pulse had duration of 8 s, and the acoustic power could be modified by the operator. At the end of the treatment, the system gave all details of the procedure (i.e., total duration, volume area and sites treated, total delivered energy, and energy delivered for each site). All treatments were performed by the above physicians.

In all patients, the first HIFU pulse was performed at a fixed dose of 45 W/site. This power was maintained for next pulses only when patient had good comfort. In case of patient's discomfort, the power of the subsequent pulses was tailored according to the patient's tolerability, with a range from 19 to 35 W/site. No anesthesia was administrated for the therapy, and no specific method for pain control was necessary. The effective duration of the procedure was considered as the time passed between the first pulse and the last one.

Evaluation of objective response to treatment

All cases were evaluated before HIFU therapy and at 6 and 12 months after the treatment. During each visit, all three diameters of nodules were measured and lesion's volume calculated by ellipsoid volume formula (transverse diameter × anterior–posterior diameter × longitudinal diameter × 0.52) and expressed in milliliters (mL). Ultrasound examination was performed by the same two operators (P.T. and L.G.). In addition, the complete thyroid laboratory assessment (TSH, fT3, fT4, Calcitonin, TgAb, and TPOAb) was performed at 6 and 12 months after the treatment.

Evaluation of subjective response to treatment (satisfaction of patient)

Data of patient's comfort with and tolerability of HIFU, and reduction of local compressive symptoms, were systematically collected by a specific questionnaire. Just after HIFU treatment (10 min later), each patient was asked to answer to the following multiple choice three questions: 1. how was your comfort during HIFU also considering the complete absence of anesthesia (good or not); 2. how was your comfort 10 min after HIFU (good or not); 3. how was your tolerability of HIFU therapy in a scale from 1 (low) to 10 (high). At 1 year of follow-up, we also asked patients if they experienced a reduction of symptoms correlated to the presence of nodule treated by HIFU (patients could answer yes or not).

Statistical analysis

Mean and standard deviations (SD) of nodules estimated volume and TSH levels recorded before and after HIFU were compared by paired *t* test. Statistical analysis was performed by GraphPad Prism 7 (GraphPad Software, Inc., La Jolla, CA 92037 USA).

Results

The final series included 26 nodules from 26 patients (21 females and 5 males) with mean age of 62 ± 19 years. These subjects had cytologically benign thyroid nodules with a size comprised from 15 and 35 mm in major diameter and a mean nodule's estimated volume of 2.81 ± 2.04 mL. The HIFU treatment was performed with a mean power of 33.3 ± 10.3 W/site and the mean energy delivered was 2.1 ± 1.1 kJ. The effective duration of the procedure was 9 ± 4 min (ranging from 3 to 18).

At the end of clinical and ultrasound follow-up (12 months after HIFU therapy), all lesions showed dimensional reduction. Specifically, nodule's size was significantly ($p < 0.0001$) reduced at 6 months of follow-up (1.83 ± 1.63 mL), and further reduced at final follow-up (1.57 ± 1.47 mL); when we analyzed the percentage of reduction over time, nodule's volume was decreased by 40% at 6 months and 48% at 1 year with respect to the initial data. Figure 1 compares the estimated nodule's volume recorded before HIFU and 1 year later. Figure 2 illustrates the ultrasonographic examination of a lesion before HIFU and 6 months later. In addition, significant changes in echogenicity and intranodular vascularization were observed in all nodules; 23 lesions become more hypoechoic and 3 showed the appearance of cystic changes (Fig. 3). All lesions had reduction of intranodular vascular signal.

When we evaluated the patient's comfort with and tolerability of HIFU, we found that 19/26 (73%) subjects described good comfort during treatment, 26/26 (100%) experienced good comfort just after therapy, and mean result of tolerability scale assessment was 8.1 ± 2.9. Neither

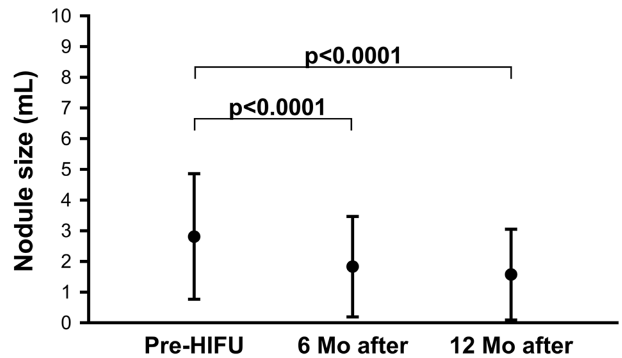

Fig. 1 Trend of nodule size after HIFU. Dimensional trend of the lesions treated by HIFU and then followed up 6 and 12 months later. Points illustrate means of nodule estimated volume, and bars indicate standard deviations

minor neither major complications were recorded. At one 1 year of follow-up, 22/26 (85%) patients reported a reduction of local cervical compressive symptoms. No significant difference was recorded in thyroid laboratory before and after HIFU treatment.

Discussion

Our preliminary data indicate that patients with local symptoms determined by the presence of a thyroid nodule below 4 cm can achieve a significant reduction of symptomatology by HIFU therapy. Furthermore, the HIFU treatment with lower mean energy we performed provided good patient's comfort and excellent tolerability with no anesthesia, and no complication nor thyroid function alteration were found. Therefore, HIFU treatment should be considered as effective and safe in patients with local symptoms due to no actual large nodules. Our results show that Beamotion mode allows to use HIFU system with low energy.

HIFU therapy was recently introduced as non-surgical treatment options for thyroid nodules with proven benignancy at FNAC. Several potential technologic advancements of ultrasound use have been reported in the last years [18], and this probably contributes to develop a ultrasonographic treatment. The results of HIFU in thyroid nodules reported in the literature are encouraging [11, 13, 14, 16] and rare minor and transient complications, probably correlated to high energy delivered, have been reported [15]. The present study corroborates the results of other authors. Solid thyroid nodules treated by HIFU show a significant reduction of their volume and this decrease is recordable at least up to 12 months since treatment. Specifically, similarly to the other researchers, nodules we treated had a reduction by about 50%. The main difference between the present study and other previous reports is represented by the energy delivered. In fact, the delivered energy used in our

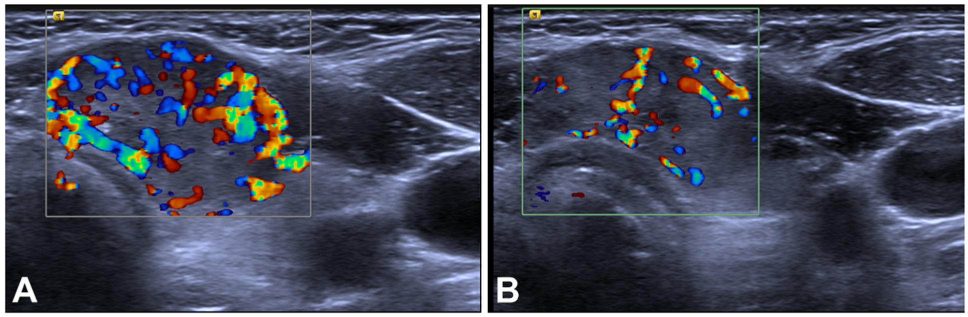

Fig. 2 Ultrasound images of a solid nodule before HIFU treatment (**a**) and 6 months later (**b**); a significant reduction of its size is evident

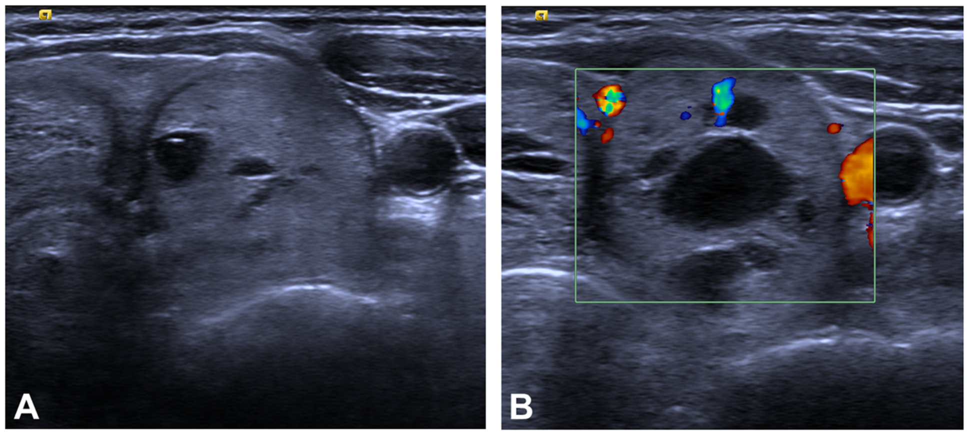

Fig. 3 Cystic changes of echostructure of a nodule after HIFU therapy: **a** at pre-HIFU ultrasonography, the lesion appears as quite entirely solid with size of 24 × 23 × 24 mm and volume of 6.62 mL; **b** after 12 months since HIFU, the nodule presents several anechoic/cystic areas and measures 20 × 19 × 26 mm with a volume of 4.94 mL (reduction of 25%). Patient declared a significant improvement of local compressive symptoms

Thyroid Center appears lower than that reported in some other studies [12–14]. These findings should be due to the herein used Beamotion mode. The specific parameters to be considered in HIFU therapy are the following: frequency, exposure time, transducer characteristics, acoustic power, pressure, and/or intensity (energy flux through a unit area in $J/s{\cdot}cm^2$), heat energy deposition rate (energy flux through a unit volume in $J/s{\cdot}cm^3$) and energy delivery mode (single shots, scanned exposures, etc.). Ultrasounds administrated in a target area produce cellular changes by several pathways, being the thermal effect and the acoustic cavitation the most significant ones [17]. The temperature elevation of biological tissue after ultrasound absorption is theoretically linearly proportional to ultrasonic intensity [19] but other relevant parameters need to be defined [20]. Recently, it was showed that in silico phantom a very low energy delivered by HIFU can be effective to achieve the temperature cutoff of cellular protein denaturation and subsequent cellular necrosis [17]. In the present study, we can confirm, by using Beamotion mode, that findings in clinical practice. In addition, we observed good satisfaction of patients.

The main limitations of thyroid HIFU are usually constituted by the need of general/deep patient's sedation and the consequent long duration of the treatment. These aspects probably have reduced the diffusion of this therapy. By the herein proposed approach, we can skip the above problems and record a significant reduction of nodule's size with no complications. The good tolerability of HIFU we recorded may be related to the short treatment duration and small nodule volumes we treated. Also, remarkably, the present proposal should be consequent to the recent advancements of HIFU technology, which have allowed us to treat a larger volume target per pulse. To date, minor transient complications were observed and the treatment was interrupted in some cases due to pain; also, the patient's pain levels seemed to be independent of the dose on anesthetic or sedation [7–16]. It has to be stressed that the aim of thermal therapies is to reduce the discomfort of patient, such as cervical compressive symptoms or cosmetic concerns; this theoretically lack of complications is the pivotal reason by which a thermal treatment could be preferred to surgery by a patient with a benign goiter [17]. Honestly, we should discuss that the reduction observed in our study was a little bit inferior to that recorded by other thermal therapies [21–24]. Therefore, in the future, a combination of energy treatment (i.e., moderate energy HIFU for safe area, but low dose around danger triangle) is necessary to increase efficacy and reduce complication. As illustrated in Table 1, HIFU therapy has been used in thyroid lesions with no actual large volume with respect to those treated by other thermal options [25]. On one hand, this could influence the good results that depend significantly on the pre-treatment nodule's size; in fact, small pre-ablation volume was shown

Table 1 Technical details reported in studies using HIFU to treat benign thyroid lesions

First author (ref.)	Patients (n)	Nodules volume (mL)	Mean energy (kJ)	Mean energy/site (J)	Mean energy/mL (kJ)
Korkusuz [12]	10	3.18[b]	8.4[b]	157.9[b]	N/A
Kovatcheva [13]	20	4.96 ± 2.79	16.4	N/A	3.8
Lang [14][a]	31	<10	10.4	N/A	2.03
	27	10–30	17.3	N/A	1.13
	15	>30	24.5	N/A	0.61
Sennert [16]	19	2.56	N/A	N/A	N/A
Trimboli (present)	26	2.81 ± 2.04	2.1 ± 1.1	214 ± 49	0.75

N/A not available data

[a]The paper by Lang et al. [14] reported three groups of patients

[b]Median value

as significant favorable factor for ablation success [14]. On the other hand, data reported in the literature do not allow a perfect comparison between HIFU and other thermal ablation options. In particular, the energy per mL reported in published studies is quite variable and this should be considered in the analysis of our results. Also, the treatment time we reported (from the first pulse to the last one) is not perfectly comparable with that reported in other studies (into out-office period); anyway, the treatment time depends on several variable, being the major one the nodule's volume. Interestingly, a recent report suggests that patients with thinner neck show more cosmetic problem than patients with thicker neck, regardless of volume of their nodules [26]. AACE/ETA/AME guidelines [27] on thyroid nodules indicate surgical removal when local pressure symptoms are clearly associated with the nodules and thermal ablation when solid or complex lesions enlarge, are symptomatic, or cause cosmetic concern. The selection we adopted in the present study is well in line with these recommendations. All in all, in our opinion, HIFU may be a good option in benign thyroid nodules with no actually large volume (i.e., 3–5 mL), while radiofrequency and laser should be considered the optimal choice in those lesions larger.

As a potential limitation of the present data, here we reported the results at 12 months of follow-up after HIFU and we cannot know the subsequent trend of nodule's size. In addition, this HIFU approach should be verified in future studies. To date, there are no specific guidelines in thyroid HIFU, while other thermal treatments are well assessed [28]; however, other thermal options, such as radiofrequency, have been significantly improved by the introduction of new approaches and/or devices [29], and the present study could influence the progress in HIFU therapy. In this context, a combination of other thermal techniques has been proposed [30] and HIFU has not yet.

In conclusion, we can corroborate and extend the results described until now about the HIFU treatment of solid thyroid nodules. According to our present results, HIFU therapy is effective in reducing size of thyroid nodules with major diameter below 4 cm and the related local symptoms. In these cases, Beamotion mode can be performed with no local anesthesia or sedation, with good tolerability and patient's comfort, and the procedure is free from complications. The recent advancements of HIFU technology could have significantly improved the HIFU therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Also, for this retrospective study, formal consent was not required.

References

1. L. Hegedüs, S.J. Bonnema, F.N. Bennedbaek, Management of simple nodular goiter: current status and future perspectives. Endocr. Rev. **24**, 102–132 (2003)
2. M.F. Erdogan, A. Gursoy, G. Erdogan, Natural course of benign thyroid nodules in a moderately iodine-deficient area. Clin. Endocrinol. **65**, 767–771 (2006)
3. H. Gharib, L. Hegedüs, C.M. Pacella, J.H. Baek, E. Papini, Clinical review: nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. J. Clin. Endocrinol. Metab. **98**, 3949–3957 (2013)
4. G.T. Haar, C. Coussios, High intensity focused ultrasound: physical principles and devices. Int. J. Hyperth. **23**, 89–104 (2007)
5. C.M. Pacella, G. Bizzarri, R. Guglielmi, V. Anelli, A. Bianchini, A. Crescenzi et al.. Thyroid tissue: US-guided percutaneous interstitial laser ablation-a feasibility study. Radiology **217**, 673–677 (2000)
6. Y.F. Zhou, High intensity focused ultrasound in clinical tumor ablation. World J. Clin. Oncol. **2**, 8–27 (2011)
7. O. Esnault, B. Franc, J.P. Monteil, J.Y. Chapelon, High-intensity focused ultrasound for localized thyroid-tissue ablation: preliminary experimental animal study. Thyroid **14**, 1072–1076 (2004)
8. O. Esnault, B. Franc, J.Y. Chapelon, Localized ablation of thyroid tissue by high-intensity focused ultrasound: improvement of noninvasive tissue necrosis methods. Thyroid **19**, 1085–1091 (2009)
9. O. Esnault, B. Franc, F.F. Ménégaux, A. Rouxel, E. De Kerviler, P. Bourrier et al.. High intensity focused ultrasound ablation of thyroid nodules: first human feasibility study. Thyroid **21**, 965–973 (2011)
10. O. Esnault, A. Rouxel, E. Le Nestour, G. Gheron, L. Leenhardt, Minimally invasive ablation of a toxic thyroid nodule by high-

intensity focused ultrasound. Am. J. Neuroradiol. **31**, 1967–1968 (2010)
11. H. Korkusuz, N. Fehre, M. Sennert, C. Happel, F. Grünwald, Volume reduction of benign thyroid nodules 3 months after a single treatment with high-intensity focused ultrasound (HIFU). J. Ther. Ultrasound **3**, 4 (2015)
12. H. Korkusuz, N. Fehre, M. Sennert, C. Happel, F. Grünwald, Early assessment of high-intensity focused ultrasound treatment of benign thyroid nodules by scintigraphic means. J. Ther. Ultrasound **2**, 18 (2014)
13. R.D. Kovatcheva, J.D. Vlahov, J.I. Stoinov, K. Zaletel, Benign solid thyroid nodules: US-guided high-intensity focused ultrasound ablation-initial clinical outcomes. Radiology **276**, 597–605 (2015)
14. B.H. Lang, Y.C. Woo, K.W. Chiu, Single-session high-intensity focused ultrasound treatment in large-sized benign thyroid nodules. Thyroid **27**, 714–721 (2017)
15. B.H. Lang, Y.C. Woo, K.W. Chiu, Vocal cord paresis following single-session high intensity focused ablation aHIFUa treatment of benign thyroid nodules - incidence and risk factors. Int. J. Hyperthermia **33**, 888–894 (2017)
16. M. Sennert, C. Happel, Y. Korkusuz, F. Grünwald, B. Polenz, D. Gröner, Further investigation on high-intensity focused ultrasound (HIFU) treatment for thyroid nodules: effectiveness related to baseline volumes. Acad. Radiol. **25**, 88–94 (2018)
17. F. Bini, P. Trimboli, F. Marinozzi, L. Giovanella, Treatment of benign thyroid nodules by high intensity focused ultrasound (HIFU) at different acoustic powers: a study on in-silico phantom. Endocrine (2017). https://doi.org/10.1007/s12020-017-1350-1
18. P. Trimboli, F. Bini, M. Andrioli, L. Giovanella, M.F. Thorel, L. Ceriani et al. Analysis of tissue surrounding thyroid nodules by ultrasound digital images. Endocrine **48**, 434–438 (2015)
19. J.C. Bamber, C.R. Hill, Ultrasonic attenuation and propagation speed in mammalian tissues as a function of temperature. Ultrasound Med. Biol. **5**, 149–157 (1979)
20. J. Civale, I. Rivens, G. ter Haar, Quality assurance for clinical high intensity focused ultrasound fields. Int. J. Hyperth. **31**, 193–202 (2015)
21. R.D. Kovatcheva, K. Zaletel, High-intensity focused ultrasound for thyroid nodule ablation: the evidence to date. Rep. Med. Imaging **10**, 9–16 (2017)
22. J.H. Baek, J.H. Lee, R. Valcavi, C.M. Pacella, H. Rhim, D.G. Na, Thermal ablation for benign thyroid nodules: radiofrequency and laser. Korean J. Radiol. **12**, 525–540 (2011)
23. Y.L. Yang, C.Z. Chen, X.H. Zhang, Microwave ablation of benign thyroid nodules. Future Oncol. **10**, 1007–1014 (2014)
24. H.S. Park, J.H. Baek, A.W. Park, Values and limitations of the comparing thyroid radiofrequency and microwave ablation using propensity score. Endocrine **56**, 681–682 (2017)
25. R. Cesareo, V. Pasqualini, C. Simeoni, M. Sacchi, E. Saralli, G. Campagna, R. Cianni, Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules. J. Clin. Endocrinol. Metab. **100**, 460–466 (2015)
26. S.U. Park, J.H. Baek, N.D. Gyu, Benign thyroid nodules treatment using percutaneous laser ablation (PLA) and radiofrequency ablation (RFA). Int. J. Hyperth. **33**, 953–954 (2017)
27. H. Gharib, E. Papini, R. Paschke, D.S. Duick, R. Valcavi, L. Hegedüs, P. Vitti, AACE/AME/ETA Task Force on Thyroid Nodules, American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. J. Endocrinol. Invest. **33**, 51–56 (2010)
28. D.G. Na, J.H. Lee, S.L. Jung, J.H. Kim, J.Y. Sung, J.H. Shin et al.. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: consensus statement and recommendations. Korean J. Radiol. **13**, 117–125 (2012)
29. H.S. Park, J.H. Baek, Y.J. Choi, J.H. Lee, Innovative techniques for image-guided ablation of benign thyroid nodules: combined ethanol and radiofrequency ablation. Korean J. Radiol. **18**, 461–469 (2017)
30. H.S. Park, J.H. Baek, A.W. Park, S.R. Chung, Y.J. Choi, J.H. Lee, Thyroid radiofrequency ablation: updates on innovative devices and techniques. Korean J. Radiol. **18**, 615–623 (2017)