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Research Article

Efficiency of Bipolar Radiofrequency Ablation in Benign Thyroid Nodules of Different Morphologies after a 3-Month Follow Up

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Abstract

Background and Aim: The purpose of this study was to determine the efficiency of bipolar Radiofrequency Ablation (RFA) for volume reduction in solid, complex solid, and complex cystic benign thyroid nodules in order to assess whether the therapy response depends on the nodule morphology - since it could be observed that the efficiency of thermo ablative techniques depends on the tissue properties.

Materials and Methods: This study analyzed the clinical data of all patients, who received RFA for treating benign symptomatic thyroid nodules at Frankfurt University Hospital from 2014 to 2016. Exclusion criteria were nodules that were in contact to vulnerable structures and nodules showing malignancy. Postablative efficiency was measured 3 months after bipolar RFA while examining changes in thyroid nodule volume using ultrasound and comparing the response of solid, complex solid, and complex cystic nodules. Possible complications such as bleeding or hematoma were examined by ultrasound and patients' complaints, such as the pain felt during ablation, were noted by the clinician in the patient documentation.

Results: 53 patients (16 men, 37 women) with a mean age of 53 (range: 33-73 years) with total of 55 nodules (12 solid nodules, 28 complex solid nodules and 15 complex cystic nodules) underwent bipolar RFA on an outpatient basis, and the nodule volume ranged from 6 ml to 150 ml (mean ± SD:31ml ± 29 ml).

Bipolar RFA resulted in a significant decrease of nodule volume from 31 ml ± 29 ml before therapy to 16 ml ± 17 ml after 3 months (Wilcoxon matched-pairs signed rank tests, $p < 0.0001$), representing an overall mean relative volume reduction of 51 % ± 18 % in general. The relative volume reduction (± absolute SD) was 56 % ± 23 % for solid nodules, 49 % ± 17 % for complex solid nodules and 50 % ± 16 % for complex cystic nodules. Bipolar RFA was well tolerated by all patients and complications such as bleeding could be excluded by ultrasound.

Conclusion: Bipolar RFA is an effective and safe method to decrease the volume of benign thyroid nodules with different morphologies, with comparable efficiency in different nodule consistencies.

Introduction

Thyroid nodules are commonly found and are among the most frequently occurring changes of the thyroid [1,2]. Abnormal findings (goiter and/or thyroid nodules > 0.5 cm) are observed in 33% of the normal population in Germany, with the prevalence of thyroid pathologies increasing with age [1,3]. Although most thyroid nodules are benign, some may cause cosmetic problems or symptoms such as pressure occurring alongside dysphagia or hoarseness. Furthermore, 5 -10% of nodules turn out to be malignant [4]. For these nodules, the treatment of choice is surgery, which is not only invasive but also may be associated with cosmetic defects such as scarring; in addition, it may affect thyroid function, which could require thyroid hormone therapy [3]. If any contraindication exists or patients refuse surgery, non-surgical techniques for treatment have to be considered. An alternative method to treat thyroid nodules is thermoablation [5], which includes Radiofrequency Ablation (RFA), Microwave Ablation (MWA), High-Intensity Focused Ultrasound (HIFU), and Percutaneous Laser Ablation (PLA).

High-intensity focused ultrasound produces heat by absorption of acoustic energy and conversion into thermal energy [6]. In comparison to other thermal ablative treatments, it is a noninvasive method for volume reduction of thyroid nodules and it is suitable for pain sensitive patients, as it works without skin incisions. HIFU is an effective method for treating benign solid and complex thyroid nodules and for preserving thyroid function but due to its long ablation time, HIFU is only used for small nodules [6,7,8,9,10]. Microwave ablation generates heat by creating a homogeneous electromagnetic field and homogeneous lesions [11]. Cooled microwave ablation leads to a significant decrease of blood circulation and nodule echogenicity, and to a significant increase in elasticity; therefore, it is also an effective method for the treatment of thyroid nodules, especially large and deep-seated nodules [12,13]. However, solid nodules require more energy than cystic nodules, which increase the conversion of electromagnetic energy into heat [11,12,13]. Percutaneous laser ablation directs collimated, monochromatic, and coherent light energy to the nodule, so the tissue gets destroyed by energy absorption [14]. Although PLA is effective in shrinking benign thyroid nodules, the efficacy of RFA appears to be superior to that of PLA [14,15]. Besides the techniques of thermoablation, an alternative treatment option for benign thyroid nodules is Percutaneous Ethanol Injection (PEI). PEI represents a safe and effective treatment option resulting in significant nodule reduction and normalization of thyroid function in hyper functioning nodules [16]. Moreover, PEI has shown effectivity in volume reduction of simple cystic thyroid nodules; however, complex cystic nodules and solid non-functioning nodules are associated with a lower response [16,17].

A further alternative treatment option is a radioiodine therapy, which is the classical approach to the treatment of uni focal autonomous adenomas [18]. Yet, benign nodules, in particular cold nodules, do not take up enough iodine for a successful radioiodine therapy; therefore, bipolar RFA can be used as a radiation-free possibility for volume reduction. In addition, bipolar RFA is less invasive than surgery, which is often recommended if both lobes of the thyroid gland are involved [19]. Besides, surgery entails the risk of hyperparathyroidism and recurrent laryngeal nerve palsy [19], in addition to those associated with the use of general anesthesia. Moreover, surgery is performed on an in-patient basis, resulting in greater costs.

RFA induces irreversible cell death by applying heat through a bipolar electrode, resulting in thyroid tissue necrosis which can be degraded by the patient´s own immune system, thus achieving a reduction of nodule volume [20,21,22]. The effectivity, safety, and suitability of RFA, as a minimally invasive modality to treat benign thyroid nodules, have been demonstrated in recent studies [23,24,25,26,27,28,29]. Although these studies have shown that thyroid nodule volume decreased significantly after RFA, no study has compared its efficacy in shrinking thyroid nodules of different consistency through bipolar RFA. Thyroid nodules differ in their morphology and, thus, have different proportions of solid and liquid components.

A study investigating the energy requirement per ml volume reduction in MWA of benign thyroid nodules showed that solid nodules required more energy per volume than cystic nodules, indicating that the consistency of thyroid nodules should be taken into account when calculating the energy requirement, at least for MWA [11]. This result was explained by the fact that the higher water content of cystic nodules increases the conversion of electromagnetic energy into heat, which can be distributed more homogeneously in complex nodules than in solid parts [11,30,31], suggesting that the efficiency of Thermoablation depends on the tissue properties. Therefore, the purpose of this study was to evaluate the volume reduction of thyroid nodules, depending on their morphology, after RFA treatment and over the following 3 months. This study is intended to analyse whether the different nodule morphologies respond similarly to RFA therapy or whether a certain morphology shows a better response. The purpose of this is to assess whether RFA should be indicated for a particular nodule. Specifically, thyroid nodules were categorized as solid, complex solid, or complex cystic, following the categorization criteria used in previous studies [17,32], and thyroid nodule reduction and side effects were examined.

Materials and Methods

Patients

This retrospective study includes all patients who received bipolar RFA for treating benign symptomatic thyroid nodules at Frankfurt University Hospital from 2014 to 2016. Criteria that had to be fulfilled for an RFA treatment were benign thyroid nodules that caused cosmetic problems or symptoms such as pressure, hoarseness, dysphagia, or foreign body sensation. Further criteria were the patient´s rejection to surgery or radioiodine therapy, high surgical risk, or contraindications to surgery. Exclusion criteria for treatment were nodules that were in contact with vulnerable structures such as vessels, trachea, esophagus, and nerves, and nodules which, according to the European Thyroid Association Guidelines, have a high risk of malignancy and therefore correspond to EU-TIRADS category 5 (at least one of the following features: irregular shape, irregular margins, micro calcifications, marked hypoechogenicity)[33]. Thyroid nodules were categorized, according to their consistency, as solid (solid tissue > 80%), complex solid (solid tissue > 50%), and complex cystic (cystic tissue > 50%), following the categorization criteria used in previous studies [17,32]. The nodule volumes and their development in each group were analyzed after a period of 3 months after RFA, because the main effect (nodule volume reduction) is evident after this period of time [34,35]. Laboratory research, including a thyroid function test (free thyroxine, triiodothyronine, thyroid-stimulating hormone, thyroglobulin, antibodies), was performed before and after thermal ablation and the values were checked after 3 months. Patients were asked about the pain they felt through the bipolar RFA treatment using a numeric rating 10-point scale which reaches from 0(= no pain) to 10(= most imaginable pain).

The study was approved by the Goethe University ethics committee.

Bipolar RFA

A generator with a maximum output of 250W at a frequency of 470 ± 10 kHz (POWER System, Olympus Hamburg, Germany) with an internally cooled 15-gauge electrode with an active tip of 20 to 40mm (Celon ProSurge, Olympus Hamburg, Germany) was used for treatment. Before RFA, a 0.9% NaCl infusion with 2mg Metamizole (Novaminsulfon-ratiopharm, Ulm, Germany) was applied for analgesia. Then, the position of the nodule was marked on the skin and a local anaesthetic (mepivacaine hydrochloride 1% (AstraZeneca, Wedel, Germany)) was injected subcutaneously under ultrasound guidance. In this way, the pain of the patients during the skin incision and insertion of the electrode could be reduced. Then, a 2mm skin incision was made to set the RFA electrode into the nodule using a transisthmic approach.

This approach was chosen because of the optimal visualization of the electrode and the possibility of keeping enough distance from vulnerable structures such as vagus nerve, jugular veins, carotid arteries, and the recurrent laryngeal nerve [36,37]. To make that the electrode is located in the right area, ultrasound was used.

Bipolar radiofrequency ablation was achieved using a multiple overlapping shot technique in which the ablation begins at the deepest point of the nodule and afterwards, the electrode gets repositioned, thus creating multiple overlapping ablation zones [23,32,37,38,39]. The generation of hyperechogenic dots, called micro bubbles, was used to evaluate the spread of heat during therapy, as microbubble formation represents tissue heating during RFA [40].

Since the recurrent laryngeal nerve is located in topographic proximity to the ablation area, the patient is asked to speak at times during the procedure in order to detect thermal damage to the nerve in time. A control ultrasound was performed to ensure that the thyroid nodule was treated successfully; furthermore, Doppler flow imaging, elastography, and echogenity were also used to monitor the procedure and to evaluate the tissue reaction before the electrode was removed. The treatment was completed in all cases.

Assessment of efficacy

The volume of the nodules was measured by ultrasound before RFA and 3 months after treatment, because the main effect, in the sense of a nodule volume reduction, has been reported to be evident after this period of time [34,35]. The comparison to the baseline values allows the evaluation of the absolute and the relative nodules volume reduction after therapy. Ultrasound data were generated by the Sonix TOUCH system (Ultrasonix Medical Corporation, Richmond, BC, Canada).In addition, procedure characteristics including power, number of shots, and total energy delivered per patient were recorded.

Statistical analysis

All data were recorded using Microsoft Excel 2013. Statistical analysis was performed using BiAS Version 11.06. for Windows. Wilcoxon matched-pairs signed rank tests were performed to compare the volumes of the nodule before and after treatment for significance of reduction. Since a Kolmogorov-Smirnov test showed that the observations are not normally distributed, a Kruskal-Wallis test was used as non-parametric analysis of variance (ANOVA) to compare the relative volume reduction across the three nodule types. For assessment of significance, a threshold of p=0.05 was chosen.

Results

53 patients (16 men, 37 women) with a mean age of 53 (range: 33-73 years) and a total of 55 nodules (12 solid nodules, 28 complex solid nodules and 15 complex cystic nodules) underwent bipolar RFA on an outpatient basis. The mean nodule volume was 31 ml ± 29 ml, within a range of 6 ml to 150 ml. The required power for the RFA ranged from 25 W to 45 W (median 25 W), number of shots from 1 to 16 (median 5.5), and energy delivered per patient from 1.2 kJ to 182 kJ (median 13.3 kJ).

Bipolar RFA resulted in a significant decrease of nodule volume, from 31 ml ± 29 ml before therapy to 16 ml ± 17 ml after therapy ($p < 0.001$, Wilcoxon matched-pairs signed rank test; Figure 1) and in an overall mean relative volume reduction of 51 % ± 18 % after 3 months. The volume of all treated nodules decreased.

The mean volume of solid nodules decreased from 24ml ± 21 ml before RFA to 10ml ± 9 ml after RFA, that of complex solid nodules decreased from 31 ml ± 25 ml to 16 ml ± 14 ml, and that of complex cystic nodules decreased from 37ml ± 41ml to 20ml ± 25ml. Thus, the relative volume reduction was comparable across all nodule types, with 56 % ± 23 % for solid nodules, 49 % ± 17 % for complex solid nodules and 50 % ± 16 % for complex cystic nodules (Table 1, Figure 2).

One shot Kolmogorov-Smirnov tests for every group showed

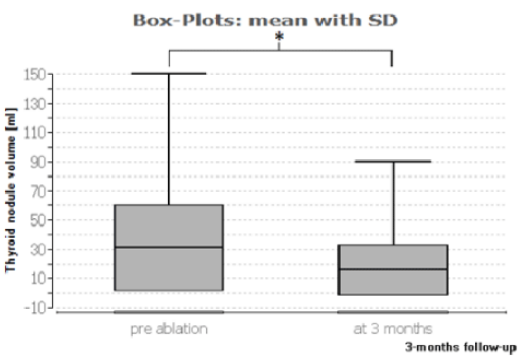

Figure 1: Comparison of thyroid nodule volumes pre and 3 months post bipolar RFA.

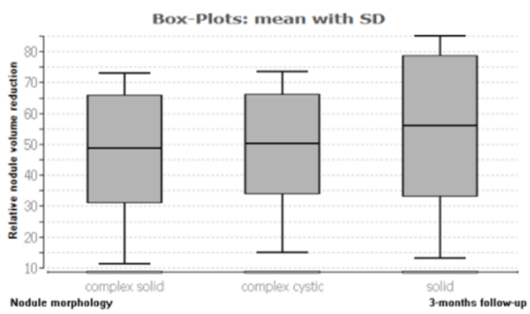

Figure 2: Comparison of relative nodule volume reduction in complex solid, complex cystic, and solid nodules after 3 months.

Table 1: Overview of results.

Nodule morphology	Initial nodule volume (ml)	Nodule volume after 3 months (ml)	Relative nodule volume reduction (%)
solid	24 ± 21	10 ± 9	56 ± 23
complex solid	31 ± 25	16 ± 14	49 ± 17
complex cystic	37 ± 41	20 ± 25	50 ± 16

Table 2: Side effects: pain level in n = 53 patients.

pain level (1 - 10)	n (%)
1	2 (4%)
2	40 (75%)
3	9 (17%)
4	1 (2%)
5	0 (0%)
6	1 (2%)
7	0 (0%)
8	0 (0%)
9	0 (0%)
10	0 (0%)

that the observations are not normally distributed ($p < 0.0001$ each). Thus, a Kruskal-Wallis test has been used to test whether the three groups' observations follow the same distributions. The test shows that the null hypothesis, i.e. that all groups' observations follow the same distribution, cannot be rejected ($p = 0.3829$). Concluding, no significant differences between the three nodule types in terms of RFA treatment have been observed.

Side-effects and complications such as bleeding, hematoma, and nodule rupture were examined by ultrasound and patient complaints (experienced pain) were documented. Symptoms such as voice changes, infections, skin burns, dysphagia, hoarseness, hematoma, nodule rupture, Horner's syndrome, and vagal reactions could be excluded in each patient by clinical examination and ultrasound immediately after RFA and at the 3-month follow-up. The experienced pain, during the bipolar RFA treatment, was assessed right after RFA treatment using a numeric rating 10 - point scale which reaches from 0 = no pain to 10 = most imaginable pain [Table 2]. Median pain level was 2 (range 1 to 6) but all complaints decreased without needing any treatment immediately after the procedure.

Discussion

The purpose of this study was to determine efficiency of bipolar Radiofrequency Ablation (RFA) in solid, complex solid, and complex cystic benign thyroid nodules.

The results showed that bipolar RFA induced significant reduction in nodule volume in all morphologies, showing comparable responses in solid, complex solid, and complex cystic nodules.

Since all three morphologies responded well to the therapy and the statistical analysis showed no difference in effectiveness, the data suggest that RFA could be recommended for all benign thyroid nodules equally. Furthermore, the study shows that bipolar RFA provides a safe treatment option with a low complication and pain rate [Table 2].

Because the electric current only flows between the two poles of the bipolar electrode and not undirected between the skin and a monopolar electrode, as is the case with monopolar RFA [28,36], it is possible to reach a higher energy density, a shorter term of ablation time, and a more predictable ablation zone while avoiding burns at the grounding pad site, since the electric current surrounds only the area of the bipolar electrode [36,41]. The heat, generated through the applied electric current, causes protein denaturation and irreversible cell death [20]. However, these damages are limited to the immediate area around the electrode and tissue distant from the electrode is only heated slowly [36,39,42].

As the above-mentioned study on thermal ablation has shown, the energy required to reduce nodule volume through MWA differs between various nodule morphologies [11], thus, a different response of the nodules (cystic nodules required less energy than solid nodules to achieve a therapy effect) to electromagnetic energy of the MWA can be assumed. The resulting hypothesis that thyroid nodules treated with bipolar RFA show a different response (depending on their morphology) to the energy generated by electric current in RFA could not be confirmed in our study. Although the energy required to reduce the volume of the various nodules was not the subject of this study, the compared nodule morphologies showed no significant difference in volume reduction after 3 months; whereby all nodules were treated until sonographic evidence of successful ablation was provided.

The fact that the composition of the nodule might have an influence on the therapeutic outcome in MWA, in contrast to RFA, could be explained by the different functional principles of these two thermoablative procedures. MWA creates electromagnetic energy to achieve a homogeneous heating of the tissue and a coagulation necrosis [43]. Heating occurs because the electromagnetic field forces water molecules in the tissue to oscillate and a part of the electromagnetic energy is absorbed and converted into heat [44]. The best heating effect is achieved in tissues with a high percentage of water while less heating occurs in tissues with low water content [44], suggesting a reduced efficiency of heating solid nodules.

RFA uses electric current producing heat-based thermal cytotoxicity [20]. Since the important tissue properties for RFA are electrical and thermal conductivity, its efficacy is limited in tissues with low electrical conductivity (e.g. adipose tissue) [43]. However, our study suggests that the tissue properties of the thyroid nodules do not determine the long-term outcome (at 3-month follow up) of RFA, possibly because only the immediate area around the bipolar electrode is heated and ablated [36,41], so that the heat conduction during nodule ablation has less influence on the outcome. Nevertheless, further investigations are needed to compare the different nodule morphologies with regard to the energy requirement for volume reduction.

Our study has several limitations as it has only a short-term follow-up period of 3 months, an overall limited number of patients, and a small number of nodules per group. Although post-ablative efficacy is proven by nodule volume reduction in all nodule types, further studies are necessary to evaluate the volumes of nodules with different consistencies in a longer time period. A longer follow-up period is also needed to investigate negative side-effects which occur later, such as induced autoimmune thyroiditis.

Furthermore, cosmetic and symptomatic scores were not evaluated in this study. However these clinical symptoms are usually correlated with a volume reduction of the nodule and improve once nodule and thyroid gland measurements decrease as described in previous studies [45].

Conclusion

Bipolar RFA was an effective method for decreasing the volume of benign thyroid nodules of different morphologies; solid, complex solid and complex cystic nodules exhibited comparable results.

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