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Radiofrequency Ablation of Benign Thyroid Nodules: Symptom Reduction and the Possibilities of Multiple Ablations

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Abstract

Background: This retrospective study evaluates the improvement of impairing symptoms of benign thyroid nodules after a single treatment with radiofrequency ablation. In addition, a second radiofrequency ablation was performed when severe symptoms persisted six months after the first treatment. This was intended to show how often a second thermal ablation of the same nodule is necessary for symptom reduction and whether it can be performed without an increased complication rate.

Methods: Our questionnaire was based on the ThyPRO (Thyroid-Related Quality of Life Measure). Patients were interviewed about the existing symptoms before the first treatment and three and six months later. To control possible complications, all patients had to be hospitalized for one night after the first and second radiofrequency ablations.

Results: Altogether 5 % of all patients (12 out of 240) received a second treatment. There of eight patients with hot and four patients with cold thyroid nodules. All twelve patients tolerated the second treatment as well as the first one and no serious or permanent complications such as infection or severe bleeding occurred.

Conclusion: For most patients, a single treatment with RFA appears to be enough to eradicate the symptoms. In our study, patients with hot thyroid nodules were more likely to receive a second treatment. Multiple radiofrequency ablations of the same nodule could be performed without any problems and seem to be a possibility for therapy after a single treatment with insufficient symptom reduction.

Key points:

- Most patients are free of symptoms after a single treatment with RFA
- Patients with hot thyroid nodules are more likely to need a second treatment than patients with cold nodules
- No complications occurred during a second treatment with RFA and it was tolerated well

Abbreviations: RFA: Radiofrequency Ablation; MWA: Microwave

Ablation; HIFU: High Intensity Focused Ultrasound; TSH: Thyroid Stimulating Hormone

Introduction

Thyroid nodules are a common phenomenon worldwide even in countries with sufficient iodine supply [1]. Most scintigraphically cold, non-functioning nodules are benign [2] but often cause problems such as difficulties in swallowing, complicated intubation in case of a necessary operation [3], respiratory problems -most notably under physical strain-, local pain, and cosmetic problems leading to psychic diseases right up to depressions [4,5]. Autonomously functioning nodules, i.e. those that produce excess thyroid hormone, often cause typical symptoms of hyperthyroidism such as tachycardia and nervousness [6]. It is easy to diagnose thyroid nodules by ultrasonography and to distinguish hot from cold nodules by ^{99m}Tc-scintigraphy [7,8], and benign from malign nodules by fine needle biopsy and ^{99m}Tc-MIBI scintigraphy [9,10]. Ultrasound elastography is a non-invasive way to evaluate thyroid nodules [11]. Some studies show that qualitative elastography could replace fine-needle aspiration in patients with soft thyroid nodules [12,13,14,15]. One of the standard treatments for patients suffering from symptomatic cold thyroid nodules is thyroidectomy [16]. Some patients decline the intervention because of the multitude of risks. Possible risks of a surgical treatment are damage of the parathyroid glands -which control the calcium level-, hoarseness, breathing problems by an injury of the recurrent laryngeal nerve, or acute bleeding [17,18,19], and the risks caused by general anesthesia are not to be neglected. According to previous studies, open surgery for treatment of benign thyroid nodules was “associated with significantly higher VAS scores, and significantly higher serum levels of hs-CRP, IL-6 and cortisol” compared to a treatment with thermal ablation [20]. In cases of hot thyroid nodules, the common procedure is radioiodine therapy [21]. Despite of the relatively minor amount of radiation, more and more patients decline the treatment with Radioiodine in fear of possible long-term effects [22]. In the last years, minimal-invasive local thermal ablation techniques such as Radiofrequency Ablation (RFA) and Microwave Ablation (MWA), as well as non-invasive thermal ablation techniques such as High Intensity Focused Ultrasound (HIFU), are used to treat benign, symptomatic thyroid nodules [23].

Thermal ablation had been used in other specializations long before it was appointed to treat thyroid nodules and is still used in other fields of expertise. These specializations include hepatology [24,25], gynecology [26], and oncology for the treatment of Liver Metastases, Hepatocellular Carcinoma, low-risk small papillary thyroid carcinoma and lung malignancies [27,28,29,30,36,41]. There are many publications proving the safety [31,32,33] and effectiveness of the treatment of benign thyroid nodules and Inoperable symptomatic recurrent thyroid cancers with Radiofrequency Ablation [34,35,37,38,39], Microwave Ablation [40,42,43] and High-Intensity Focused Ultrasound [44,45,46,47] which showed positive results [48]. Both autonomously functioning nodules [49] as well as cold thyroid nodules [50] can be treated with thermal ablation. By now, there are systematic reviews and meta-analyses that suggest that RFA leads to better outcomes and prognoses for patients with benign thyroid nodules [51,52]. In addition, a prospective multi-center study reported the safety and efficacy of radiofrequency ablation, by trained radiologists, for benign thyroid nodules, according to a unified protocol [53]. Also, combined treatments with thermal ablation and radioiodine therapy were used in the past if a radioiodine monotherapy was not practicable [54,55]. In addition, RFA may be an effective and safe alternative for the management of patients with small follicular neoplasm suspected on thyroid biopsy [56]. However, little research has been done to determine whether thermal ablation of thyroid nodes only needs to be performed once to achieve a sufficient reduction in clinical symptoms and whether multiple ablations are required in some cases. There are currently no guidelines on the multiple use of thermal ablative procedures in thyroid nodes and on how to proceed if the first therapy with RFA is unsuccessful.

Materials and methods

Study design

This is a retrospective analysis of all patients with scintigraphically cold and autonomously functioning thyroid nodules who fulfilled the inclusion criteria, did not have any exclusion criteria and received a radiofrequency ablation.

Setting

All thermal ablations took place at the same Institute. The

treatments were performed during a period of two and a half years, between January 2015 and June 2017. The same device and probes from the same manufacturer were used for all patients.

Exclusion criteria

No radiofrequency ablation was performed in case of malignancy and if the thyroid nodule could not be reached with a probe without endangering important structures such as trachea, oesophagus, large vessels, and nerves. Further, patients with disseminated thyroid autonomy were excluded from this study.

Inclusion criteria

All patients had to refuse surgery and Radioiodine Therapy. In addition, all patients had to consent to their data being evaluated anonymously for a study and had to agree to be treated with an alternative treatment method that was not included in the guidelines at that time.

Data sources/ measurement

The examiner systematically asked the patients about their current complaints. The questioned symptoms were based on the ThyPRO (Thyroid-Related Quality of Life Measure). Our questionnaire included: Goiter symptoms such as difficulty in swallowing, cosmetic complaints, hyperthyroid symptoms as nervousness, sensitivity to heat, and difficulty as well as psychological problems like depressivity and anxiety. All patients who were subsequently included in the study stated that they were significantly impaired in their daily lives by at least one of the symptoms or by the combination of symptoms. Due to the topographically close relationship to the trachea, an isthmus location seemed to cause discomfort even in case of smaller nodules. Previous studies have already shown the connection between goitre and laryngeal sensory neuropathy with chronic cough [57]. In the medical history of the patients there were no other conclusive reasons for the complaints. A medical report from an otolaryngologist was required to make sure the symptoms were not caused by vocal cord problems or other diseases of the nasopharynx.

Ultrasound was used to determine the size and position of the thyroid nodes. To classify into hot or cold nodules, all patients received a ^{99m}Tc-scintigraphy. To rule out

malignancy, every patient with cold thyroid nodules received a fine needle biopsy and ^{99m}Tc-MIBI scintigraphy.

Bipolar radiofrequency ablation was used for treatment. The same generator (POWER System) was used for all patients. Depending on the size and position of the nodule cooled 15 gauge electrodes (active tip: 20 to 40 mm; CelonProSurge) or un-cooled 18 gauge electrodes (active tip: 9 to 15 mm; CelonProSurge) made by Olympus Hamburg (Germany) were used. The generator had an output of 9 to 40 W (maximum 250 W) at a frequency of 470 ±10 kHz. A local anaesthesia (Mepivacaine hydrochloride 1%; Scandicain® injection solution, Astrazeneca, Wendel, Germany) was injected into the skin under ultrasound-guidance. A small incision was made with a scalpel, through which the probe was inserted. If the patients felt pain during the intervention, a 0.9% NaCl infusion with 2 mg Metamizole (metamizole sodium monohydrate, Novaminsulfon-ratiopharm® 1 g/2 ml injection solution, Ulm, Germany) was offered. To destroy as much tissue of the nodule as possible, a multiple overlapping shot technique was used [38]. To avoid critical structures, the heat was applied centrally inside the nodule with distance from the surrounding tissue.

The follow-ups for all 240 patients were three and six months after their thermal ablation. In each follow-up, the thyroid nodules were examined by ultrasound, the thyroid hormone blood levels were determined, and the symptoms were inquired. We provided a second treatment if the patients still had symptoms and severe impairments in everyday life six months after ablation because previous studies have shown that the main shrinking effects take place in the first three months after ablation [58], making it unlikely that still existing symptoms would further improve.

Before performing a second treatment, all eight patients with hot nodules additionally obtained another ^{99m}Tc-scintigraphy. In those cases, the scintigraphy proved remaining hot areas. For the second therapy, the same procedure was applied. In contrast to the previous ablation, the smallest cooled probes (15 gauge electrodes; active tip: 20 mm) were used given a reduced size of the nodes. Compared to the first treatment, there was a stronger resistance when the probe was inserted into the nodes, which was caused by scarring

of the previously ablated tissue. Nevertheless, the multisport technique could be performed without any problems.

To assess possible complications such as bleeding, pain or nerve injury, all patients who received radiofrequency ablation had to be admitted to hospital for one night. The patients agreed to get in touch with us if any signs of infection such as fever appeared in the first week after the intervention. For this purpose, they could contact the examiner by telephone at any time.

Statistical methods

Prism 7 for Windows (GraphPad Software, Inc.; La Jolla California USA) was used for statistical analysis. The pre-ablative volume of nodules with a single treatment and the pre-ablative volume of nodules which were treated a second time were compared using the Mann-Whitney test for non-parametric data. To compare the percentage of patients with non-functional nodules who received a second treatment and the percentage of those with autonomously functional nodules who were treated a second time, Fisher's exact test was used. We used an alpha level of 0.05 to define statistical significance.

Results

Participants

Altogether 240 patients (176 female and 64 male) between the age of 21 years and 78 years (median 51 years) with a total of 277 thyroid nodules were included in this study. The group of patients can be divided in 71 patients with a total of 80 scintigraphic hot nodules and 169 patients with a total of 197 scintigraphic cold nodules [Figure. 2]. The median pre-ablative volume of the nodules was 15.2 ml (0.5 ml - 174 ml). The median pre-ablative volume of the scintigraphic cold nodules

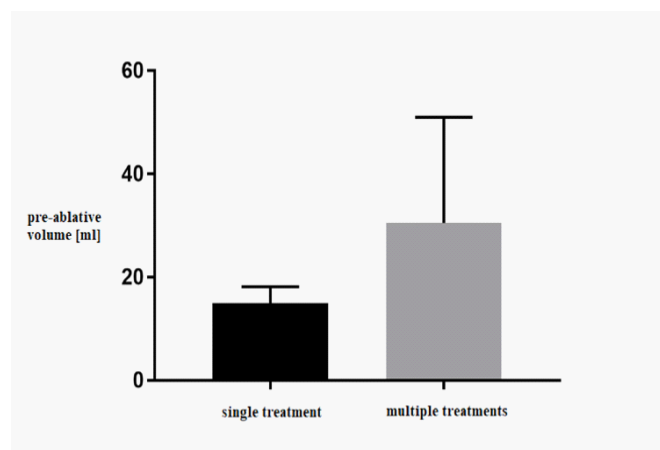


Figure 1: Median pre-ablative volume of nodules with a single treatment compared to median pre-ablative volume of nodules where a second treatment was implemented.

was 17 ml (0.5 ml - 150 ml) and The median pre-ablative volume of the autonomously functioning nodules was 10 ml (0.5 ml - 174 ml) [Table 1]. While all patients with cold nodules were euthyroid before the first treatment, most patients with hot thyroid nodules had a latent or manifest hyperthyroidism with a TSH <0.3 mE/l, also there were some patients with a relatively low TSH level of 0.3-1.0 mE/l who also showed symptoms of hyperthyroidism. A second blood test showed TSH levels between 0.006 mE/l and 0.8mE/l (reference values of our laboratory 0.3 - 4.0 mE/l for the patients with autonomously functioning nodes, who continued to show symptoms impairing everyday life and received a second treatment.

Descriptive data

The patient collective consisted primarily of people who came to our institute on their own initiative and with the desire for an alternative treatment to thyroidectomy or radiotherapy. All patients had indications for therapy. The social background of the study participants was not taken

Table 1: Autonomously functioning nodules and Non-functioning nodules.

Characteristics	Autonomously functioning nodules	Non-functioning nodules	Total
Number of patients	71	169	240
Male	17	47	64
Female	54	122	176
Median age [years]	51 (21 – 78)	50 (27-77)	51 (21 – 78)
Number of nodules	80	197	277
Median Pre-ablative volume [ml]	10 (0.5 – 174)	17 (0.5 – 150)	15.2 (0.5 – 174)
Number of patients with second RFA	8	4	12

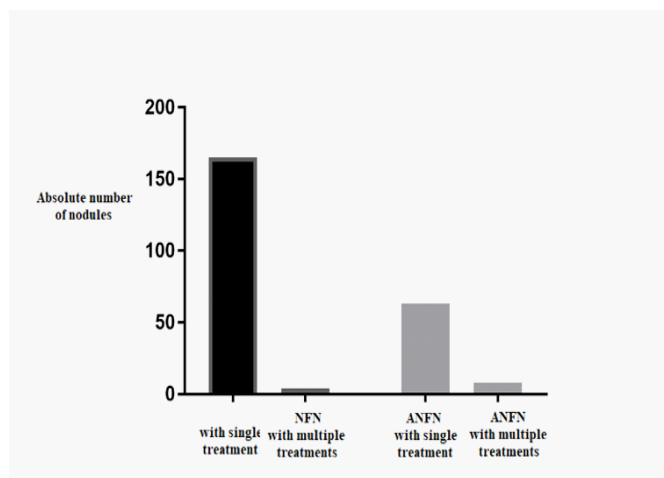


Figure 1: Absolute number of non-functional nodules (NFN) and autonomously functional (ANFN) which received a single treatment to multiple treatments.

into account. Most of the patients came from other cities in Germany, few patients came from abroad for radiofrequency ablation.

Outcome data

Twelve out of 240 patients (5 %) still suffered from symptoms after one treatment with RFA. The other 228 patients were free of symptoms six months after treatment

With 8 out of 71 (11.3 %) patients with hot thyroid nodules and only 4 out of 169 (2.4 %) patients with cold thyroid nodules, patients with hot nodules are significantly ($p < 0.05$) more likely to receive a second treatment to get rid of their symptoms than patients with cold thyroid nodules.

The median pre-ablative volume of the nodules with a second treatment was 30.5 ml (6.6 ml – 150 ml) [Figure 1]. Also, a significant ($p < 0.05$) correlation between the pre-ablative size of the nodules and a decrease of symptoms in respect of the symptoms six months after ablation was noticed.

Main results

The study shows that the majority of patients are content with the results of a single treatment with Radiofrequency ablation six months after RFA. Only 5 % of all 240 patients still suffered from symptoms six months after ablation and received a second treatment.

All twelve patients tolerated the second treatment as well

as the first one and no serious or permanent complications such as infection or severe bleeding occurred. After one ablation, the treated nodule was more solid, and the patients reported slightly more pressure when the probe was inserted.

Discussion

Key results

Twelve out of 240 patients reported continuing symptoms after six months, there from eight patients with hot and four patients with cold nodules. Those eight patients with hot suffered from persistent symptoms of hyperthyroidism, in particular: nervousness and palpitations. The four patients with cold nodules complained especially about a remaining and persistent desire to clear one's throat.

In our study, patients with hot nodules are more likely to receive a second treatment to get rid of their symptoms than patients with cold thyroid nodules. Overall 11.3 % (8 out of 71) of the patients with hot thyroid nodules and 2.4 % (4 out of 169) of the patients with cold thyroid nodules were treated a second time.

The second treatment was tolerated as well as the first one and no serious or permanent complications occurred. During the second thermal ablation of the same thyroid node, the performing physician reported a greater resistance when inserting the probe. Otherwise, there were no particular difficulties in performing multiple RFA of a node.

Limitations

Although all results were statistically significant for the respective group of subjects, the number of patients is too small to make generalized statements. However, this study can be groundbreaking for further research and suggests that multiple ablations of a thyroid node are possible and can further alleviate symptoms, with a single treatment being sufficient to minimize symptoms for many patients.

In the survey of symptoms, particular consideration was given to the limitation of patients in everyday life due to symptoms. Although we were able to rule out many other physical causes for the symptoms through a thorough medical history and prior consultation with an ear, nose and throat specialist, and the symptoms were usually explained by

hyperthyroidism or visible goiter, psychological factors may have been involved. Especially in the case of smaller nodes, knowledge of the thyroid node and possibly fear of developing cancer despite the low risk [63] may have increased the symptoms.

Since many patients came from other cities in Germany and partly from abroad travelling a long way to our clinic, the aftercare was taken over by the treating general practitioner or endocrinologist after six months. All patients were advised to have regular check-ups. None of the twelve patients who received a second therapy consulted us again with symptoms within one year after the first treatment. We remained in contact with all patients by telephone or e-mail for at least one year. Previous studies showed that thyroid nodules treated with radiofrequency ablation did not tend to increase in size after a period of two to four years, and the patients' quality of life often remains improved [59,60]. A longer follow-ups after single and multiple thermal ablations are necessary to find out whether the thyroid nodes grow again in the further course and whether the multiple therapy can provide permanently better results.

Interpretation

In our study, patients with larger thyroid nodes in particular have needed more than one treatment to reduce their symptoms six months after ablation. This result affirms another study which shows that nodule volume seems to be a significantly predictive factor for the efficacy of RFA in treating autonomously functioning thyroid nodules [61]. This can probably be explained by the fact that the symptoms of cold thyroid nodules can be improved by volume reduction [62], and a small amount of remaining nodule tissue does not cause any problems whilst the volume reduction does not necessarily improve the symptoms of hot thyroid nodules if hyperthyroidism persists. To treat autonomously functioning nodules, it is important that the percentage of maintained tissue is as small as possible because the edge regions of the nodules can continue to be scintigraphically hot and produce hormones, which can result in the persistence of hyperthyroidism.

During ablation, a multi shot technique was used and a proper distance to the capsule of the nodule was kept to

prevent damage to surrounding structures such as nerves and vessels and to keep the risk of complications at a minimum. Probably the remaining edge region of the nodules can be a reason for continuing symptoms and could be avoided with a more aggressive ablation technique at the cost of a higher risk of complications.

To ascertain predictive factors to reduce symptoms of benign thyroid nodules with RFA, further studies are necessary. Perhaps, alongside the mentioned factors that seem to have an impact of the efficacy such as the scintigraphic characteristics of the nodules and the ablation technique as well as possible factors as the pre-ablative nodule volume there could be other influences. Conceivably, the morphology or location of the thyroid nodule can affect the outcome of a single treatment with RFA. In view of future studies, a unified protocol could help to improve the comparability and point out the most effective ablation techniques with simultaneously the lowest possible risks for complications.

Whereas a strict treatment of autonomously functioning nodules to prevent severe complications as cardiovascular problems [64] is indisputable, it is a legitimate subject for debate if a second treatment of cold, benign thyroid nodules after six months is urgently needed as long as the remaining symptoms are mild.

Earlier studies have already shown that even after a thermal ablation of a thyroid node, further treatments such as radioiodine therapy are possible [65]. In addition, our study points out that multiple radiofrequency ablations of a single node can be performed without any problems if required.

Generalisability

As in many previous studies, this shows that a single treatment with radiofrequency ablation usually achieves good results. However, in the case of insufficient symptom reduction, it is possible to perform multiple radiofrequency ablations of a thyroid node. This could reduce the use of more invasive procedures such as surgery for inadequate symptom reduction after a single radiofrequency ablation.

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