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INTERVENTIONAL

Thermal ablation of thyroid nodules: are radiofrequency ablation, microwave ablation and high intensity focused ultrasound equally safe and effective methods?

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Abstract

Objectives This study compares volume reduction of benign thyroid nodules three months after Radiofrequency Ablation (RFA), Microwave Ablation (MWA) or High Intensity Focused Ultrasound (HIFU) to evaluate which of these methods is the most effective and safe alternative to thyroidectomy or radioiodine therapy.

Material and Methods Ninety-four patients (39 male, 55 female) with a total of 118 benign, symptomatic thyroid nodules were divided into three subgroups. HIFU was applied to 14 patients with small nodules. The other 80 patients were divided up into two groups of 40 patients each for RFA and MWA in the assumption that both methods are comparable effective. The pre-ablative and post-ablative volume was measured by ultrasound.

Results RFA showed a significant volume reduction of nodules of 50 % ($p<0.05$), MWA of 44 % ($p<0.05$) and HIFU of 48 % ($p<0.05$) three months after ablation. None of the examined ablation techniques caused serious or permanent complications.

Conclusion RFA, MWA and HIFU showed comparable results considering volume reduction. All methods are safe and effective treatments of benign thyroid nodules.

Key Points

- *Thermal Ablation can be used to treat benign thyroid nodules*
- *Thermal Ablation can be an alternative to thyroidectomy or radioiodine therapy*
- *Radiofrequency Ablation, Microwave Ablation, High Intensity Focused Ultrasound are safe and effective*

Keywords Thyroid nodules · Thermal ablation · Radiofrequency ablation · Microwave ablation · High intensity focused ultrasound

Introduction

Thyroid nodules are still a widely occurring phenomenon in many countries despite improved and area-wide supply with iodine [1]. Because of a persisting mild to moderate iodine deficiency in Germany "the goitre prevalence is about 30% in children as well as in adults" [2]. Nowadays it is easy to diagnose even small thyroid nodules by ultrasound. Even if most of them do not cause any symptoms, patients with big or multiple thyroid nodules often suffer from different issues such as difficulties in swallowing, local pain and cosmetic problems often caused by a goitre. A goitre can also be a problem in case of emergency because it can impede an intubation if it is necessary [3]. Furthermore, especially cold nodules can increase the risk of malignancy [4, 5]. In some cases, they can also cause hyperthyroidism. The standard treatments for patients with a goitre or big and multiple thyroid nodules are still thyroidectomy and radioiodine therapy. Many patients decline both treatments because of the multitude of risks. Possible risks of a surgical treatment are damage of the parathyroid glands which control the calcium level, hoarseness and breathing problems by an injury of the recurrent laryngeal

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nerve or acute bleeding and not negligible are the risks caused by general anaesthesia. Even the normally well-tolerated radioiodine therapy carries a few risks. Some people suffer from hypothyroidism after the treatment and need to take a thyroid hormone replacement therapy life-long [6]. There are also other side effects such as nausea. Many patients especially fear the fact that they have to incorporate a radioactive substance and need to be isolated [7]. A special caution applies to women who are pregnant or who are planning a pregnancy in the next months. This is why a great number of patients with thyroid nodules ask for alternative treatments without general anaesthesia or radioactive substances. Thermal ablation offers those people a minimal invasive way to get more life quality and to reduce their fears. Thermal ablation has been used to treat benign thyroid nodules for a few years after it was established in other specialisations such as hepatology [8–10], gynaecology [11] and oncology for the treatment of metastases [12–14] or different kinds of cancer [15–17]. In the past it also had been used for the treatment of well-differentiated thyroid malignancy [18] and inoperable symptomatic thyroid cancer [19]. There are many publications proving the effectiveness of radiofrequency ablation [20–23], microwave ablation [24] and high intensity focused ultrasound [25–27] and combined treatments with thermal ablation and radioiodine therapy [28–30] which showed positive results. The main concept is to destroy the tissue with high temperatures of above 60° Celsius. Conventionally those patients were treated with a total or near-total thyroidectomy. Meanwhile thermal ablation is the method of choice for patients with pre-existing diseases which lead to a high risk of post-operative death. It turned out that the combination of thermal ablation and radioiodine therapy can be beneficial in certain cases [31].

Material and methods

Study population

This study included 94 patients (39 male, 55 female) with a median age of 47 (range 22 – 82) years and a total of 118 benign thyroid nodules. The patients were subdivided up into three groups. The first group of 40 patients (18 male, 22 female) with altogether 55 nodules (0.3 ml – 90 ml) was treated with un-cooled or cooled bipolar RFA. The second group of 40 patients (19 male, 21 female) with 47 nodules (1.3 ml – 82 ml) was treated with un-cooled or cooled MWA. The third group of 14 patients (two male, 12 female) and altogether 16 nodules (0.3 ml – 7.6 ml) received a treatment with HIFU. Most nodules were cold and had mixed cystic/solid components. While HIFU was limited on patients with small nodules who were able to lie flat with reclined head for over thirty minutes without moving too much, RFA and MWA was practicable for all patients who met the inclusion criteria. The patients where HIFU was not usable were divided into two according groups without using any further discrimination.

All patients suffered from symptoms, which were indications for a surgery, but refused this intervention because of contraindications, a high risk of postoperative mortality or a high risk of complications. All patients with small nodules < 5 ml (n=62) suffered from the desire to clear one's throat or from cosmetic problems due to the location in front of the trachea on the thyroid isthmus or on the side of the trachea in the right or left thyroid lobe. The patients with bigger nodules > 5 ml (n=56) stated symptoms such as pressure, difficulties in swallowing or dyspnoea. Exclusion criteria were malignancy and an unsafe position of the nodule nearby important structures such as trachea, oesophagus, large vessels and nerves. The absence of malignancy was ensured by scintigraphy and fine needle aspiration biopsy.

Methods

The Bipolar RFA was conducted with a generator (POWER System) and 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). The generator had an output of 9 to 40 W (maximum 250 W) at a frequency of 470 ± 10 kHz. The MWA was accomplished with a generator by MedWaves Incorporated (Avecure MWG881, San Diego, CA, USA) and cooled or un-cooled 14 to 16 gauge electrodes. The output of the generator varied between 24 to 32 W at a frequency of 902 – 928 MHz. In all cases the temperature ranged between 75 and 85 °C. HIFU was accomplished with the Theraclion SA (Malakoff, France) with a probe that emitted pulses at 3 MHz and a maximum power of 125 W. The device was used without beamotion.

During intervention, a 0.9% NaCl infusion with 2 mg Metamizole (Novaminsulfon-ratiopharm, Ulm, Germany) was offered to the patients. Subsequently, the localisation of the nodule was determined again and a local anaesthesia (Mepivacainhydrochloride 1%; AstraZeneca, Wedel, Germany) was injected under ultrasound-guidance. In case of minimal-invasive methods such as RFA and MWA, the probe was inserted through a small incision. To destroy as much tissue of the nodule as possible, a multi-shot technique was used. By repositioning the electrode overlapping ablation zones arose. To stay away from critical structures, the heat was applied centrally inside the nodule and the border so that healthy tissue was spared. To enlarge the distance between the nodule and critical structures, a fluid like a glucose solution was injected, if necessary. For HIFU a probe emitting both the treatment and the guidance ultrasound was used. A robotic arm held the probe. Treatment was displayed during the whole time and it was possible to interfere every time. The

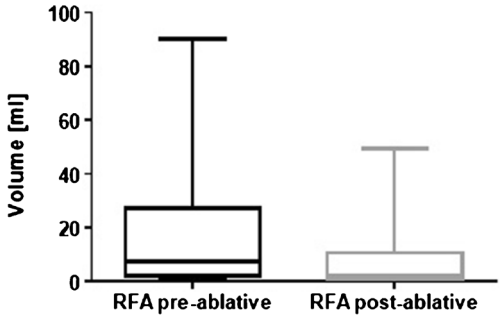

Fig. 1. Volume of thyroid nodules before and three to six months after RFA

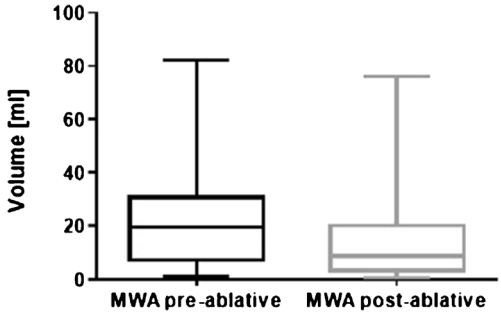

Fig. 2. Volumes of thyroid nodules before and three to six months after MWA

patients were asked to describe the pain intensity with a score between 0 and 10 where '0' means 'no pain' and '10' means 'intolerable pain'.

Statistical analysis

For statistical analysis, Prism 6 for Windows (GraphPad Software, Inc.; La Jolla California USA) was used. To compare the nodule volume before and after performing RFA, MWA and HIFU, Wilcoxon matched-pairs signed rank tests were applied. The volume reduction of RFA, MWA and HIFU was compared with ANOVA for non-parametric data. The results were significant with $p<0.05$.

Results

RFA

In this group the median pre-ablative volume of the nodules was 6.5 ml (range 0.3 ml to 90 ml) and post-ablative volume after three months was 2.1 ml (range 0.2 ml to 49.2 ml), as shown in Fig. 1. This result shows a significant decrease. The median volume reduction amounted to 50% (range 8.3 % to 89 %). Median application energy was 14 kJ in 7.8 minutes divided up into 6.2 shots. The median pain score during RFA was 3 (range 1 to 6). A mild haematoma occurred in 26 patients. No infections or injuries of nerves or vessels occurred.

MWA

Compared to RFA, MWA was used for nodules with a median pre-ablative volume of 19 ml (range 1.3 ml to 82 ml). The post-ablative volume after three months was 8.9 ml (range 0.3 ml to 76 ml) as shown in Fig. 2. This decrease amounted to a median volume reduction of 44 % (range 0.3 % to 82 %) and, thus, slightly less than the decrease after RFA treatment, although the median application energy was lower with 12 kJ in 10 minutes divided up into 2.6 shots. During treatment the median pain score was 4 (range 1 to 7). A mild haematoma after treatment was seen in 21 patients. No nerve or other lasting complications were reported.

HIFU

For HIFU only small and advantageous located nodules with a median pre-ablative volume of 2.8 ml (range 0.6 ml to 7.6 ml) were chosen. With a median post-ablative volume after three months being 1.6 ml (range 0.1 ml to 3.5 ml) as shown in Fig. 3, the median volume reduction amounted to 49 % (range 12 % to 77 %). With median 9.2 kJ per 30 minutes this treatment took the longest time while least energy was administered. The median pain score during ablation was 7 (range 3 to 8). All patients experienced mild pain up to two days after treatment. No haematomas occurred and no surrounding structures were injured.

Comparison

The RFA showed a slightly better mean volume reduction (50 %) than MWA (44 %) and HIFU (49 %) (Fig. 4) but the differences between RFA, MWA and HIFU were not significant ($p>0.05$). With a median energy of 0.03 kJ/s (30 W) in RFA, of 0.019 kJ/s (19 W) and 0.005 kJ/s (5 W), most energy per time was administered by RFA (Table 1).

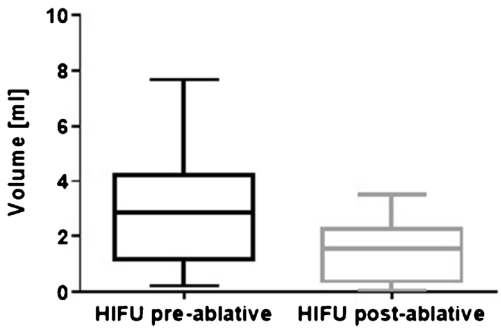

Fig. 3. Volumes of thyroid nodules before and three to six months after HIFU

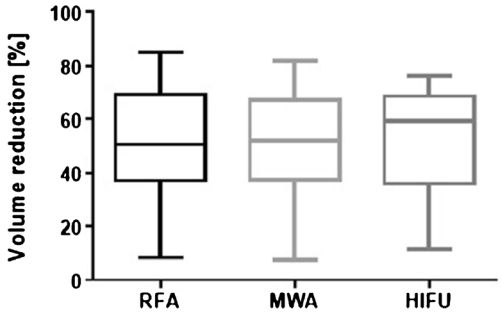

Fig. 4. Comparison of significant ($p < 0,01$) volume reduction three months after RFA, MWA and HIFU

Safety and treatment tolerance

Both RFA and MWA were tolerated well. Nevertheless, all patients reported a mild or rarely moderate pain radiating to the mandible, neck or shoulders. They also felt pressure during energy submission into the nodule. The discomfort got worse if the nodules were superficial. Deep or large nodules barely caused discomfort. Uncooled systems often caused slight first-degree skin burn [32, 33] and in some cases a cervical haematoma developed. Serious or permanent complications such as infection, injuries of nerves or nodule rupture did not occur. After HIFU the patients suffered from moderate pain. They also had no serious or permanent complications.

Discussion

Considering the results, RFA, MWA and HIFU represented safe and effective therapeutic options for patients suffering from benign thyroid nodules and indications for a thyroidectomy. The methods reached a mean volume reduction of 44-50 % within three months after ablation. The nodules in both groups with minimal-invasive treatments were equally distributed in virtue of various characteristics such as size, echogenicity and echotexture. HIFU was only used for small nodules. Notably the results of MWA with higher administered energy in less time supported the tendency showed in previous publications [34, 35]. The differences of median volume reduction between RFA, MWA and HIFU were not significant ($p>0.05$). A rate of 44-50 % volume reduction as shown in this study can relieve symptoms such as difficulty in swallowing considerably. Probably the symptoms will continue to decline within the following months as it happened in other cases before [36]. Perspectives on an ongoing volume reduction up to over 80 % after six months can be expected [37–39]. HIFU as well showed good results though it seems that RFA and MWA are more suitable for most patients. Although HIFU as none-invasive method has no risk of infection, it is questionable if it is preferable. RFA and MWA also have a very low risk of infection when accomplished under semi-sterile conditions [40]. Also, the cooled minimal-invasive methods are faster, more accurate and more comfortable than HIFU. Moreover, the use of HIFU is limited to very small nodules, which cause less symptoms than big ones.

In case of HIFU, no additional tool to speed up the treatment was used. There are more recent devices with beamotion which can shorten the therapy and make HIFU a more suitable procedure. In our study an older device was used. By further development of HIFU it seems possible to eliminate the limitations we observed so it is likely that this non-invasive technique could overtake the minimal-invasive techniques within a foreseeable period. In view of volume reduction, it is already equal to RFA and MWA. The second problem that occurred during therapy with HIFU was a subjectively experienced higher pain-intensity with a median pain score of 7.

However, the question if one of the two minimal-invasive methods is superior to the other one remains. In the past there was an ex vivo and in vivo study that investigated the effectiveness of MWA and RFA in a hepatic porcine model with single internally cooled probes to imitate the treatment of liver

Table 1 Comparison of median results of RFA, MWA and HIFU

	RFA	MWA	HIFU
Generator	Olympus (Germany)	MedWaves (California)	Theraclion SA (France)
Technical data	max. 250 W	max. 240 W	max. 125 W
Probes	15-18 gauge	14-16 gauge	none
Median pre-ablative nodule volume [ml]	6.5	19	2.8
Median post-ablative nodule volume after three months [ml]	2.1	8.9	1.6
Median volume reduction [%0] p<0.05	50	44	49
Median application energy [kJ]	14	12	9.2
Median energy [W]	30	19	5
Median application time [min]	7.8	10	30
Median number of shots	6.2	2.6	1

tumours [41]. The authors speculated that the potential to completely destroy the tissue of liver tumours may be higher for MWA than RFA. This guess would fit the fact that in this study more energy per time was administered by MWA.

Also, the complications were similar in both groups. No matter which generator was used, the ablation with uncooled probes provoked more pain and left skin burn (n=6) while all treatments with cooled probes were more pleasant and more effective for the patients [42]. If we split up the median pain score for all treatments with RFA (n=55; median pain score 3; range 1 – 6) the patients with smaller nodules < 5 ml and uncooled probes (n=34) showed a higher median pain score of 4 (range 2 – 6) than the patients with bigger nodules > 5 ml and cooled probes (n=21) with a median pain score of 2 (range 1 – 6). The median pain score for all ablations with MWA (n=47; median pain score 4; range 1 – 7) can be divided up in a median pain score of 5 (range 2 – 7) for small nodules < 5 ml and uncooled probes (n=13) and a median pain score of 4 (range 1 – 6) for bigger nodules > 5 ml and cooled probes (n=34). This shows that the treatment of bigger nodules with cooled probes is better tolerated. Looking at these results, it must be kept in mind that the treatment of smaller nodules < 5 ml seems to be more painful regardless of the use of cooled or uncooled probes and regardless of the used ablation technique. One possible explanation is that the ablation zone in small nodules is closer to the capsule of the nodule which is more sensible. There were no permanent or serious complications that do coincide with other studies [43]. Although thermal ablation is a comparatively safe procedure, beside the common and mild complications such as haematoma there is also a low risk for mild and even a very low risk for serious complications [44]. Comparable to potential complications of surgery including post-operative death [45], the ablation of thyroid nodules with MWA, RFA or HIFU is much safer than thyroidectomy.

As shown before in other separate studies about RFA [46–48], MWA [49] and HIFU [50, 51], all of these methods are effective to reduce the volume of thyroid nodules and offer safe treatment alternatives to standard procedures. The results also scientifically support the conclusion of other studies that cooled probes are better tolerated than uncooled probes [52]. Matching the findings of other studies, the RFA and MWA are equal in most aspects, and it may need more research to figure out if one of them is preferable [53]. Opposed to that, the used HIFU device without beamotion tends to be the second choice because of its limited possibilities and discomfort. Especially in view of RFA and MWA, there is a need of additional follow-up studies in the future. Just as well there is a urgent need of studies to analyse the possibilities of more recent HIFU devices. The current results are not very inclusive because of the limitations and low number of patients. In addition, follow-ups of more than three months for RFA, MWA and HIFU are necessary to figure out the progress of the volume reduction of nodules. The comparison in this study is limited by the short period of time that was observed. Eventually, it should be considered if other factors such as availability of generator and probes, wear of materials or handling are important factors for the choice of a method.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Hüdayi Korkusuz.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Ethical approval Institutional Review Board approval was obtained.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Methodology
- retrospective
- observational
- performed at one institution

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