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Percutaneous microwave ablation of thyroid nodules: efficacy evaluation with ^{99m}Tc - pertechnetate and ^{99m}Tc-MIBI functional imaging

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▶ ***Original article***

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ABSTRACT

Background*:** Local ablative treatments play an important role for patients who cannot be treated surgically. Radiofrequency ablation is a well-established alternative to surgical treatment of thyroid nodules, however it also has disadvantages. Microwave ablation (MWA) is a new minimally invasive treatment promising several improvements. The aim of this retrospective study was to evaluate the effects of microwave ablation on thyroid nodules by ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI scintigraphy. ***Materials and Methods*:** 30 patients with overall 40 nodules were treated. For the ablation of thyroid nodules, a microwave generator working with frequencies from 902 to 928 MHz was used. The ablation time ranged between 120 and 300 seconds per ablation zone. The target temperatures ranged between 60-80 °C. Pre- and post- interventional, the radionuclide uptake was determined using a thyroid specific scintillation camera. For 27 cold nodules ^{99m}Tc-MIBI was used for evaluation; 13 indifferent nodules were measured with ^{99m}Tc-pertechnetate. ***Results: The relative change of uptake was detected as a quotient of pre- and post- therapeutic uptake. The statistical analysis of scintigraphy data proved the efficacy of microwave ablation. ^{99m}Tc-pertechnetate scintigraphy showed an uptake reduction of 39% (range 9 to 85%). ^{99m}Tc-MIBI imaging showed a median reduction of 40% ($p<0.01$) (range 7 to 100%). ***Conclusion:*** The determined results show the effectiveness of MWA as a treatment option for benign thyroid nodules. With functional scintigraphy a significant activity decrease could be detected in the ablation zone; hence a verification of affectivity was possible after a short period of time.

Keywords: *Thyroid nodules, microwave ablation, ^{99m}Tc-pertechnetate scintigraphy, ^{99m}Tc-MIBI scintigraphy, functional imaging.*

INTRODUCTION

Thyroid nodules are a common clinical problem in the German population; they are detected in about 30 % (1). Despite this relatively high prevalence most nodules are benign, only 0.1 % of all malignant neoplasms are thyroid carcinomas (1). Nonetheless, benign nodules can cause problems as well, namely subjective symptoms, cosmetic concerns or even the fear of a malignant transformation (2). Ultrasound guided percutaneous microwave ablation (MWA) is a new minimally invasive treatment, which provides an alternative to conventional treatments for benign thyroid nodules such as surgical excision and radioiodine therapy, as well as for other thermal ablation techniques e.g. radiofrequency ablation (RFA) (3-5). Even though MWA represents a recent treatment approach in the field of thyroid nodules, it has already been used successfully for the treatment of other parenchyma as liver, lung and kidney (6). First encouraging results for volume reduction in thyroid nodules have already been presented in several studies [3–5]. Microwave ablation offers various advantages in comparison to other thermal ablation techniques as, for example, the ability to generate larger ablation zones, a shorter ablation time and a lower susceptibility to heat sinks [7–9].

While scintigraphy is well established in assessing the consistency of thyroid nodules [10], its usage for validation of thermal ablation has not been described so far. Different studies showed possible disadvantages of ultrasound in evaluating the effects of thermal ablation such as underestimating the size of the ablation area and representing a falsified conformation of this area [11, 12]. Evaluating the result of microwave ablation or of other thermal ablation techniques using scintigraphy imaging is a new approach. To our knowledge, there are no studies discussing the possible advantages of functional imaging for evaluation of MWA so far.

The aim of this study was to define observable alterations of thyroid tissue after microwave ablation by functional scintigraphy and to evaluate the feasibility of this diagnostic tool for follow-up of microwave ablated benign thyroid nodules.

MATERIALS AND METHODS

Patients

Thirty patients with overall forty benign thyroid nodules were treated with MWA (16 men, 14 women; median age 56 years, range 31 to 81 years). Inclusion criteria were: (a) nodule-related clinical problems such as throat tightness, hoarseness, swallowing disorders, neck pain, discomfort or thyrotoxicosis, (b) refusal of surgical treatment, (c) contraindications to surgery. This type of treatment can also be used for (d) cosmetic problems caused by thyroid nodules.

The following contraindications can be specified: Patients with (a) malignant nodules, (b) histological indication of follicular proliferation and (c) atypical findings in ^{99m}Tc-MIBI in cold thyroid nodules were excluded from treatment. Patients with (d) thyroid nodules in critical locations (positions of vessels, nerves, trachea and esophagus), (e) nodules with dominantly cystic composition were also excluded from participation.

The local Ethics Committee approved this retrospective study and a written informed consent was obtained from all patients before treatment.

MWA equipment

The generator used in this study (Avecure MWG881, Med Waves, Inc., San Diego, CA) is operating with frequencies within the range of 902 to 928 MHz. Three probes with ablation zones of different sizes (14-16 G) were used depending on nodule volume and individual anatomical conditions of each patient. The field size varied from 1 cm to 4 cm. In order to avoid overheating, the microwave probe possesses an integrated temperature sensor, which restrains a potential heating-up after the target temperature is reached. The ^{99m}Tc-MIBI imaging was performed using a thyroid specific gamma camera (Mediso Nucline ® TH/22) with an acquisition time of 500 s, an acquisition matrix of 256 × 256 × 16 and a LETH collimator. The same gamma camera was used for ^{99m}Tc-pertechnetate scintigraphy. The acquisition duration was 300 s, and an acquisition matrix of 128 × 128 × 16 was used.

Pre-ablation assessment

Prior to the actual microwave ablation, size, volume, consistency and the exact location of the nodules were determined by ultrasound. The nodules were categorized as echo-solid, echo-cystic or echo-complex (both solid and cystic). In addition the exact position, the capacity of ablation and the type of vagus nerve was identified [13]. Additionally, functional imaging of the nodule activity was performed by ^{99m}Tc-pertechnetate scintigraphy in all patients. 20 minutes after injection of 75 MBq ^{99m}Tc-pertechnetate, the guideline compliant imaging was accomplished. In thyroid nodules detected as cold by prior scintigraphy, a ^{99m}Tc-MIBI scintigraphy imaging and a fine needle aspiration cytology of the nodular tissue with subsequent pathological examination was performed to exclude malignancy. ^{99m}Tc-MIBI scans were taken 10 and 60 minutes after injection of 500 MBq ^{99m} Tc-MIBI. Quantitative ROI-analysis was performed using ROIs covering the global thyroid, the cold nodules and a background-ROI in the pre- and post-therapeutic images (software: Mediso Interview XP®). After area adapted background corrections of the count rates, the intranodular uptake was calculated pre- and post-therapeutically and related to the global uptake of the whole thyroid gland. Moreover, microwave induced percentage change of uptake was detected as a quotient of pre-and post-therapeutic (figure 1). Multiple benign nodules were assessed in the same scan.

MWA procedure

The intervention was performed under local anesthesia and aseptic conditions. Each patient was treated in a supine position with extended neck. In order to reduce possible pain, the patients received 40 drops of Novalgin. Before the ablation started, a local infiltration of Scandicain 1% was performed to reduce pain and to enlarge the distance between skin and ablation zone. The general approach of transithmic access was chosen in order to make the display of the whole length of the probe easier.

If it was not possible to reach the thyroid nodule through the transisthmic path, a craniocaudal access was chosen. The microwave probe was inserted under sonographic guidance. The ablation was performed starting from the deepest part of the thyroid nodule to the superficial zone. To reduce risks of treatment significantly, the moving-shot-technique was used [2]. Heating of the thyroid tissue leads to the emergence of transient hyperechoic zones (observable via ultrasound) which can be used as a control during the ablation procedure [14]. In case of perception of pain, target temperature was decreased during the ablation procedure.

Efficacy evaluation and follow-up

24 hours after ablation, the post-treatment thyroid imaging was performed. Patients with cold nodules received another ^{99m}Tc-MIBI imaging; patients with indifferent nodules (neither hot nor cold) another ^{99m}Tc-pertechnetate imaging. Additionally, B-mode ultrasound was performed to exclude any local complications. 3 monthsafter MWA volume changes were assessed.

Statistical analysis

All statistical analyses were performed with dedicated software (BiAS.® 10.04 for Windows, epsilon-Verlag).

The post-interventional radionuclide uptake of nodular tissue was compared in relation to the pre-interventional uptake. Due to non-symmetric distribution of ^{99m}Tc-MIBI- and ^{99m}Tc-pertechnetate uptake, non-parametric statistics was used on these data. Averaged measurements for the uptake-reduction are expressed as median. Significant differences of pre- and post-

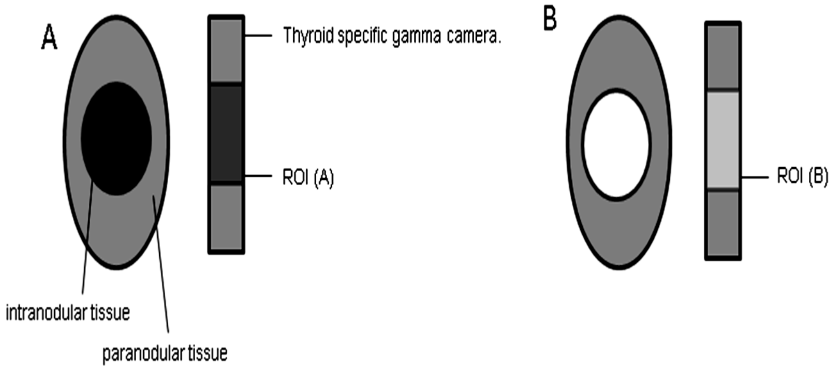

Figure 1. ROI Evaluation. The ROI **(I)** in figure A represents the intranodular and the paranodular uptake of 99m Tc. After microwave ablation the ROI **(II)** in figure B represents the paranodular uptake. The necrotic intranodular thyroid tissue (ROI II) in figure B has no uptake. The percentage change of 99mTc uptake was detected as a quotient of pre- and post-therapeutic 99mTc MIBI uptake.

interventional values, as well as volume reduction were evaluated by Wilcoxon-matched-pairs-test; percental reduction is given as median. Spearman's correlation test was used to analyse a possible correlation between volume reduction and uptake reduction. Results were considered to be significant at $p<0.05$.

RESULTS

In all ablation sessions, the therapy could be fully completed, and the entire nodule volume was ablated. Fifteen nodules were solid and twenty-five complex. Dominantly cystic nodules were excluded from this study. Twenty-seven cold and thirteen indifferent nodules were treated. The respective time of ablation ranged between 300 and 1500 seconds per patient and 120 and 300 seconds per ablation zone. On an average, each patient was treated for 600 seconds with a median output of 28 W (range 24 to 36 Watt). Post-interventional ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI scintigraphy showed that the uptake in ablated thyroid areas decreased (figure 2, figure 3). In case of cold nodules, post-interventional scintigraphy imaging determined a reduced tracer trapping ability: compared to the uptaking properties of surrounding intact thyroid tissue the nodular uptake decreased. Scintigraphy also showed a decrease of uptake in indifferent nodules. Before MWA the median storage in the ablation area was 14.1 % (range 2.5-45.6 %) in ^{99m}Tc-MIBI and 4.45 % (range 1.8-20.8 %) in ^{99m}Tc-pertechnetate scans. After MWA the median storage was 7.55 % (range 0.0-24.0 %) for ^{99m}Tc-MIBI and 2.55 % (0.6-8.1 %) for ^{99m}Tc-pertechnetate. In ^{99m}Tc-pertechnetate scintigraphy the median reduction of uptake was 39 % (range 3-85%) ($p<0.01$) (table 1, figure 4).

The ^{99m}Tc-MIBI measurements resulted in an average uptake-reduction of 40 % (range 7-100%) ($p<0.01$) (table 2, figure 5).

At a 3-month follow-up all patients showed a significant decrease of nodule volume. The median volume reduction was 7.8 ml or 50.34 % ($p < 0.01$).

A correlation between the uptake reduction in ^{99m}Tc-MIBI scans and volume reduction could not be allocated. A correlation between uptake reduction in ^{99m}Tc-pertechnetate scans and volume reduction could not be found either .

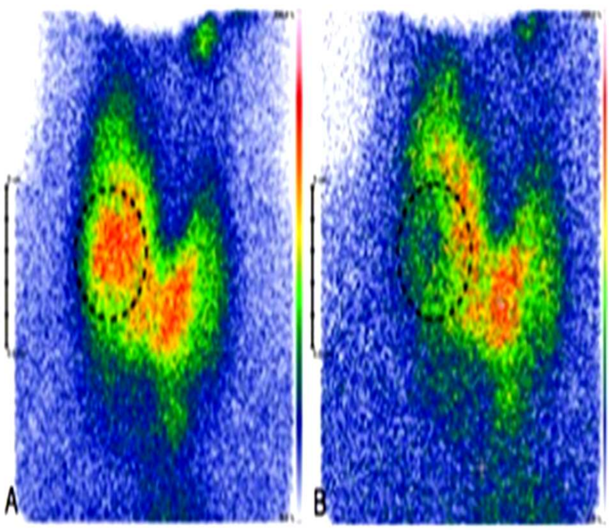

Figure 2. ^{99m}Tc-pertechnetate imaging before and after MWA. Scintigraphic imaging using ^{99m}Tc-pertechnetate prior to (A) and after microwave ablation (B). In the ablated area tracer uptake is decreased after MWA (circle).

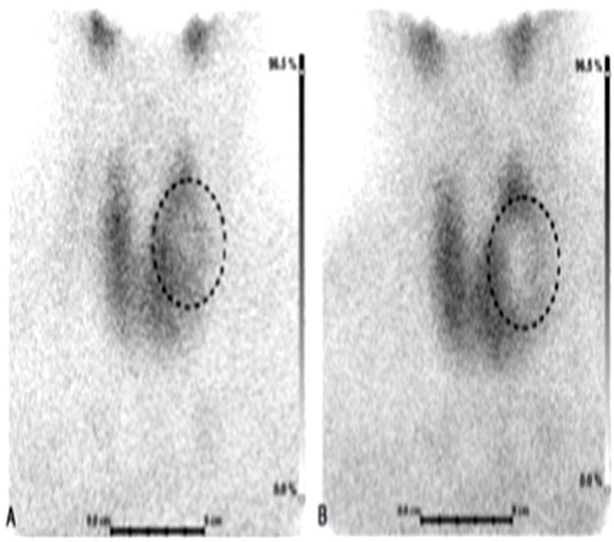

Figure 3. ^{99m}Tc-MIBI imaging before and after MWA. Scintigraphic imaging using ^{99m}Tc -MIBI prior to (A) and after microwave ablation (B). In the ablated areab tracer uptake is decreased after MWA (circle).

Table 1. Percental ^{99m}Tc-pertechnetate uptake in ablation zone prior to MWA, after MWA and reduction of tracer uptake in ablation zone [%].

Nodule No.	^{99m}Tc-pertechnetate uptake		
	pre [%]	post [%]	reduction[%]
1	1.8	0.8	55
2	4.0	0.6	85
3	3.6	2.2	39
4	5.0	1.3	75
5	2.5	2.3	9
6	2.3	1.4	36
7	8.7	7.1	19
8	20.8	8.1	61
9	5.0	3.3	33
10	7.5	3.3	56
11	6.1	4.2	31
12	6.1	5.4	12
13	4.9	4.7	3.0

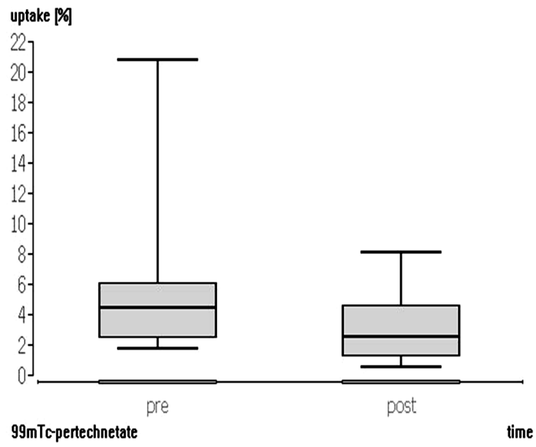

Figure 4. ^{99m}Tc-pertechnetate uptake reduction. Percental reduction ^{99m}Tc-pertechnetate uptake in ablation zone [%]. Median reduction after MWA was 39% ($p<0.01$).

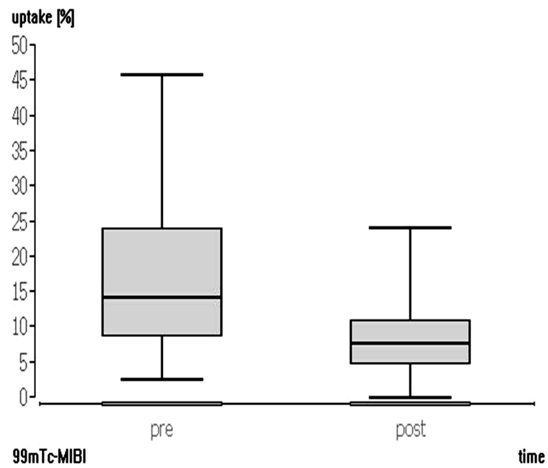

Figure 5. ^{99m}Tc-MIBI uptake reduction. Percental reduction ^{99m}Tc-MIBI uptake in ablation zone [%]. Median reduction after MWA was 40 % ($p<0.05$).

Table 2. ^{99m}Tc-MIBI uptake in ablation zone prior to MWA, after MWA and reduction of tracer uptake in ablation zone [%].

Nodule No.	^{99m}Tc-MIBI uptake		
	pre [%]	post [%]	reduction[%]
1	17.9	10.7	40
2	2.5	2.3	8
3	3.0	2.7	8
4	12.1	11.2	7
5	9.2	8.0	13
6	12.8	7.1	45
7	11.2	0	100
8	15.3	6.9	55
9	23.2	6.5	72
10	38.7	24	38
11	15.5	0	100
12	9.0	3.6	60
13	17.4	10.4	40
14	6.0	5.5	10
15	7.5	6.6	13
17	25.9	9.3	64
18	13.2	12.3	7
19	10.3	9.1	12
20	17.4	15.9	9
21	30.7	5.5	82
22	32.1	9.1	71
23	35.4	14.4	59
24	7.0	5.0	30
25	15.0	9.7	35
26	7.5	2.9	61
27	45.6	19.3	58

DISCUSSION

The findings of this study suggest, that functional imaging with ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI shows molecular-based and early-phase changes in the ablation area after microwave ablation of benign thyroid nodules. For both tracers, a significant uptake reduction could be shown. The effectiveness of MWA, as an alternative treatment option for benign thyroid nodules, has been shown in several studies before [3-5]. Therefore, the aim of this study was not to prove the effects of MWA on thyroid tissue in general but to evaluate how efficiently those effects can be detected and qualified using scintigraphy. In previous studies about RFA or MWA ultrasound or Doppler was used to assess treatment outcome. A significant advantage of using ultrasound in order to visualize treatment outcome of thermal ablation is the fact that sonography does not require any patient preparation. Furthermore, this method is easy to perform and cost-effective [15, 16], especially when compared to other imaging methods as MR scans or scintigraphy. Nevertheless, ultrasound can only detect morphological changes of thyroid nodules. A functional evaluation of the treated area is not possible. Subsequent to the ablation, a period of several months is required in order to degrade the necrotic ablated tissue endogenously. In addition, Andrioli *et al.* [17] stated that an immediate evaluation of lesions treated with radiofrequency or laser ablation by ultrasound is not possible "due to tissue infiltration by gas as a result of tissue vaporization". Sonography, and Doppler ultrasound, are susceptible to artefacts, so called "microbubbles", that appear in the ablation area during thermoablation [14, 18], limiting the diagnostic accuracy in early post-ablative phases.

Furthermore, studies show that B-mode ultrasound is not absolutely appropriate to assess MWA outcome. Zhou *et al.* [11] showed that sonography does not reflect the true conformation of lesions due to thermal ablation. Wiggermann *et al.* [16] stated that with ultrasound the necrotic area cannot be clearly defined whilst ablation due to poor contrast between untreated and treated tissue. Correa-Gallego *et al.* [12] even showed, that ultrasound and elastography significantly underestimate the size of the area treated with RFA as the degree of cell injury cannot be displayed with these methods. This study was on RFA in *in-vivo* porcine liver tissue; Pareek *et al.* [19] showed similar findings in kidney tissue.

Scintigraphy imaging still is a crucial device for the characterization of thyroid pathologies; even innovations in other diagnostic techniques have not been able to reduce the importance of scintigraphy in the diagnose of thyroid diseases [10, 20, 21].

In this study, two traces were used: ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI. ^{99m}Tc-pertechnetate is a substrate for the sodium iodine symporter in thyroid tissue [22]; like iodine itself ^{99m}Tc-pertechnetate is carried into iodine storing cells. The scintigraphy findings of this study show a significant decrease of tracer uptake after microwave ablation (figure 4). The uptake was reduced by 39 %. Temperatures during MWA rise above 43 ° C, causing injury to cell morphology and ion channels [23], the sodium iodine symporter and iodine storing tissue must be destroyed. Subsequently, scintigraphy shows a reduced tracer uptake in the ablation area (figure 2). Baek *et al.* [24] showed similar findings after RFA for autonomously functioning thyroid nodules.

For cold nodules, without any uptake of ^{99m}Tc-pertechnetate, ^{99m}Tc-MIBI was used for evaluation. A significant reduction of tracer uptake could be shown for ^{99m}Tc-MIBI as well (figure 5). For ^{99m}Tc-MIBI, the uptake reduced by 40 %. ^{99m99m}Tc-MIBI accumulates in sound mitochondria with an intact membrane potential [25]. As can be seen in figure 3, there is no ^{99m}Tc-MIBI uptake within the ablation area after MWA, the necrosis induced by MWA must have destroyed the mitochondrial membrane potential and mitochondria itself. The findings of this study show that ^{99m}Tc-MIBI enables a functional evaluation after thermal ablation even for cold nodules. A previously released case report confirmed these findings [26].

Functional imaging was used to detect effects within the early postablative period. As previously described [22, 25], tracer uptake is dependent on molecular processes. The molecular-based changes leading to an uptake reduction may display necrosis even before morphological changes can happen. Thus, by using ^{99m}Tc-MIBI or ^{99m}Tc-pertechnetate scintigraphy , it is possible to evaluate MWA almost instantly following the treatment, whereas sonography and ultrasound are not capable of detecting these early molecular changes. Moreover and contrary to sonography, scintigraphy offers the advantage of assessing the ablated thyroid tissue morphologically as well as functionally [26, 27]. The procedure supplies prompt information about the global functional status of the thyroid and the local activity within the area of the treated tissue [5, 26, 27). Another study by Klebe *et al.* (27) confirmed, that "scintigraphy is the only diagnostic method that can make a conclusive comparative analysis of results before and after microwave ablation during follow-up". As radioactive devices should be used reasonably, additional studies are required in order to confirm the efficacy of this method. Moreover, longer follow-up periods are needed to prove in how far scintigraphy can be considered as a conclusive diagnostic method for long-term treatment success.

CONCLUSION

Functional imaging shows early-phase and molecular-based changes of the ablation area, these cannot be seen in ultrasound measurement. Scintigraphy displays a potential device for functional verification of MWA. Further studies are necessary to prove the benefit of functional imaging.

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