Microwave Ablation of Symptomatic Benign Thyroid Nodules: Energy Requirement per ml Volume Reduction

Mikrowellenablation von symptomatischen, benignen Schilddrüsenknoten: Energiebedarf pro ml Volumenreduktion

Authors Y. Korkusuz[1], K. Kohlhase[1], D. Gröner[1], C. Erbelding[1], W. Luboldt[2], C. Happel[3], S. Ahmad[4], T. J. Vogl[5], F. Gruenwald[3]

Affiliations Affiliation addresses are listed at the end of the article.

Correspondence
Konstantin Kohlhase
Department of Nuclear
Medicine, University Hospital
Frankfurt
Theodor-Stern-Kai 7
60590 Frankfurt
Germany
Tel.: ++ 49/69/63 01 67 83
konstantin_k@hotmail.de

Zusammenfassung
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Hintergrund: Mikrowellenablationen (MWA) stellen eine neuartige thermoablative Behandlung für benigne Schilddrüsenknoten dar. Ziel war es, die benötigte Energie pro ml Volumenreduktion zu benutzen, um die benötigte Energie für ein volume-of-interest (VOI) abschätzen zu können.

Methode: 25 Patienten mit 25 Knoten (6 solide, 13 komplex und 6 zystisch) wurden durch MWA behandelt. Die übertragene Energie (E) wurde mit der Volumenveränderung (Δ V) nach 3 Monaten korreliert. Der Energiebedarf pro ml Volumenreduktion wurde durch E/Δ V bestimmt.

Ergebnisse: MWA zeigte eine signifikante (p < 0,0001) Volumenreduktion (Δ V) im Mittel von 12,4 ± 13,0 ml (range: 1,5 – 63,2 ml) und eine relative Reduktion von 52 ± 16 % (range: 22 – 77 %). Es zeigte sich eine positive Korrelation zwischen E und Δ V (r = 0,82; p < 0,05). Die mittlere E/Δ V war 1,52 ± 1,08 (range: 0,4 – 4,6) kJ/ml für alle Knoten und 2,30 ± 1,5 (0,9 – 4,6); 1,5 ± 0,9 (0,4 – 3,6); 0,75 ± 0,25 (0,4 – 1,2) kJ/ml für solide, komplexe und zystische Knoten mit einer signifikanten Differenz der in E/Δ V zwischen soliden und zystischen Knoten (p < 0,03).

Schlussfolgerung: Die benötigte Energie pro Volumen ist abhängig von der Knotenkomposition. Solide Knoten benötigen mehr Energie als zystische. Die abgeschätzte Energie für ein volume-of-interest sollte als zusätzlicher Parameter helfen, eine Über- oder Unterbehandlungen zu vermeiden.

Kernaussagen:
▶ Die abgeschätzte benötigte Energie für ein Volume-of-interest ist abhängig von der Knotenmorphologie.
▶ In soliden Knoten ist eine höhere Energie-Transmission empfohlen als bei zystischen Knoten.
▶ Die Energietransmission als zusätzlicher Parameter neben dem Ultraschall ist nützlich, die periprozedurale Überwachung zu verbessern.

Abstract
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Purpose: Microwave ablation (MWA) represents a novel thermal ablative treatment of benign thyroid nodules. The aim was to determine the energy required per ml volume reduction in order to match the required energy to the volume-of-interest (VOI).

Materials and Methods: 25 patients with 25 nodules (6 solid, 13 complex and 6 cystic) were treated by microwave ablation (MWA). The transmitted energy (E) was correlated with the volume change (Δ V) after 3 months. The energy required per ml volume reduction after 3 months was calculated by E/Δ V.

Results: MWA resulted in a significant (p < 0.0001) volume reduction (Δ V) with a mean of 12.4 ± 13.0 ml (range: 1.5 – 63.2 ml) and relative reduction of 52 ± 16 % (range: 22 – 77 %). There was a positive correlation between E and Δ V (r = 0.82; p < 0.05). The mean E/Δ V was 1.52 ± 1.08 (range: 0.4 – 4.6) kJ/ml for all nodules and 2.30 ± 1.5 (0.9 – 4.6), 1.5 ± 0.9 (0.4 – 3.6), 0.75 ± 0.25 (0.4 – 1.2) kJ/ml, respectively, for solid, complex and cystic nodules with a significant difference in E/Δ V for solid and cystic (p < 0.03).

Conclusion: The energy required per volume depends on the nodule consistency. Solid nodules require more energy than cystic ones. The estimation of the energy needed per volume-of-interest as an additional parameter should help to avoid under- or overtreatment.

Key Points:
▶ The estimated required energy for a volume-of-interest depends on the nodule consistency
▶ In solid nodules a higher energy transmission than in cystic nodules is recommended
▶ The energy transmission as an additional marker to ultrasound is helpful for improving periprocedural monitoring

Introduction
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Thermal ablative procedures like laser and radiofrequency ablation are already approved as new reasonable possibilities to treat symptomatic benign thyroid nodules [1–3], with radiofrequency ablation (RFA) representing the most common and best evaluated thermal procedure. Minimally invasive thermal ablation has been used in an attempt to prevent the drawbacks of conventional surgery, including large scars, difficulties in reoperation, iatrogenic hypoparathyroidism and general anesthesia. Although minimally invasive surgery has been developed as an alternative to conventional surgery and has shown advantages especially with respect to cosmetic score, it is still limited to a nodule size between 30–40 mm [4–6]. In contrast to surgery, thermal ablation is performed on an outpatient basis and only under local anesthesia. Sufficient ablation of large nodules (>40 mm) is also possible, because MWA permeates tissues that are even desiccated or evaporated. This differs from comparable thermal procedures like RFA, which is dependent on local resistance [7, 8]. As microwave ablation (MWA) generates heat by creating a homogeneous electromagnetic field that interacts with water dipoles [7] and creates homogeneous lesions, it is reported to be a safe and effective treatment of benign nodules [9]. Nonetheless, adequate monitoring during ablation is mandatory and is primarily performed using ultrasound [10, 11]. However, it is not possible to predict the approximate volume reduction right after ablation only on the basis of ultrasound imaging [10]. As the transmitted energy determines the generated heat and therefore influences the ablation itself, it has to be taken into account [8]. Until now, no calibration curve has been established to determine how much energy is necessary to destroy a given volume. Therefore, an energy-versus-efficacy calibration curve is desirable in order to match the required energy to the volume-of-interest (VOI) and avoid under- or overtreatment.

The purpose of the study was to establish an energy versus volume reduction calibration curve in order to better predict the microwave energy needed for a target volume-of-interest (VOI).

Materials and methods
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The retrospective study was approved by the ethics committee and written informed consent was obtained from all patients.

Patients

25 patients (mean age: 54 ± 13 years; 12 males, 13 females) with 25 nodules (mean initial volume: 25.2 ml ± 24.3 ml [range: 2.6–100 ml]; composition: 6 solid, 13 complex and 6 cystic) underwent microwave ablation on an outpatient basis. The inclusion criteria were symptoms requiring surgery (cosmetic problems; compressive symptoms like foreign body sensation, hoarseness and dysphagia) in patients who had refused radioiodine therapy or surgery or had contraindications to surgery. The exclusion criteria included excessive thyroid volume with retrosternal growth, critical adjacency to structures such as vessels, trachea, esophagus and nerves, limited ultrasound visualization ("macro-calcification" and no presentable capsule border) as well as malignancy.

The assessment before ablation included ultrasound imaging using B-mode, color Doppler sonography and elastography. All patients underwent ^{99m}Tc-pertechnetate scintigraphy. In the case of "cold" nodules, ^{99m}Tc-MIBI scintigraphy and fine-needle aspiration biopsy were performed to exclude signs of malignancy [12, 13].

Microwave ablation – summary of technique

A generator with a maximum output of 36 W at a frequency of 928 MHz was used (MedWaves Avecure™ Microwave Generator; San Diego, California) with an uncooled 14–16 gauge electrode. Prior to the procedure, a short infusion of 0.9 % NaCl with 2 mg Metamizole (Novaminsulfon-ratiopharm, Ulm, Germany) was administered. Under ultrasound guidance local anesthetic (mepivacaine hydrochloride 1 % (AstraZeneca, Wedel, Germany) was injected to reduce the pain during the skin incision and insertion of the electrode. When local anesthesia of the skin was achieved, a 2-mm incision was made to place the MW electrode into the nodule using a transisthmic approach [11]. This approach enables optimal visualization of the electrode as well as ensures the maximum safety margin with respect to vulnerable structures like the carotid arteries, jugular veins, nervus vagus and the recurrent laryngeal nerve, which is situated in the so-called "danger triangle" between the trachea and thyroid [11]. When a transisthmic approach was not possible, a cranio-caudal approach was chosen. The needle was positioned in the nodule under ultrasound guidance. In the case of cystic parts, the fluid was aspirated before MWA was performed [14]. Once the correct position was confirmed, microwave ablation was initiated using the predefined parameters such as power and target temperature. Treatment was started using a footswitch and monitored by ultrasound until the targeted area showed a decrease in echogenicity and/or hyperechogenic microbubbles to indicate vaporization [15] (○ Fig. 1). During this process ablation was fixed in one section, starting with the deepest part of the nodule. Ablation was performed either for 5 minutes, independent of the nodule composition, or until the safety margin was reached. Once ablation was completed, the probe was repositioned and another ablation procedure was performed, thus creating multiple overlapping ablation areas. This procedure, i. e., the multiple-shot technique, was repeated until the whole nodule was hollowed out or the safety margin was reached. The transmitted energy [kJ] was documented.

Measurements

The volume of the nodules was determined before and 3 months after treatment using ultrasound (SonixTOUCH, Ultrasonix Medical Corporation. Richmond. BC. Canada). The nodule volume and reduction rate were calculated using the following formula for ellipsoid bodies: $V = (\pi * a * b * c)/6$ (V = volume; a = largest diameter; b, c = perpendicular diameters). The nodules were categorized according to their consistency: primary solid (solid tissue >80 %), cystic (solid tissue <20 %) or mixed subgroups (complex).
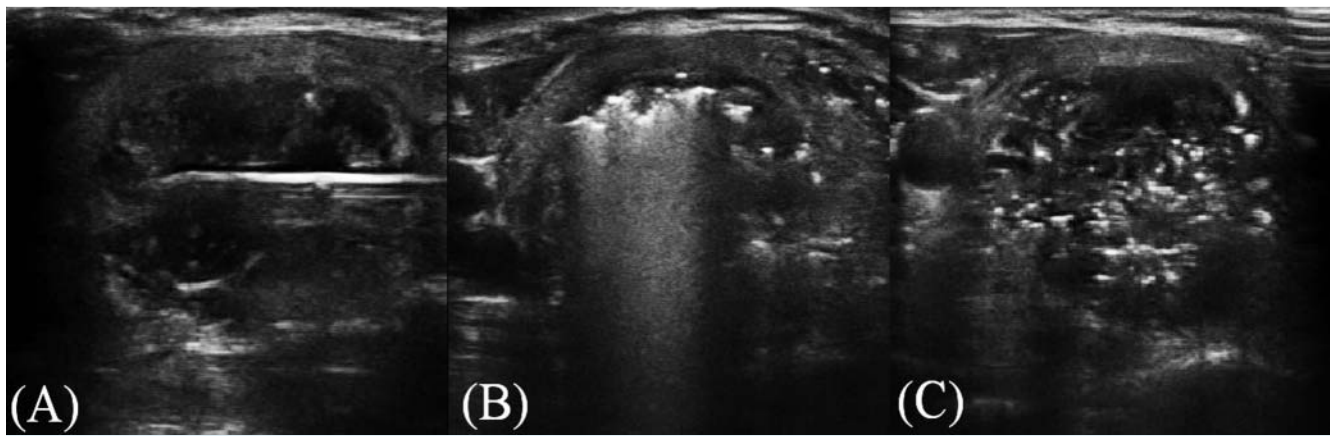
Fig. 1 Sonographic guidance of microwave ablation of a complex nodule with solid and cystic parts. **A** The probe is visualized before ablation to ensure, that the active tip is completely placed within the targeted area. **B** During ablation the heat is visualised by hyperechogenic "microbubbles" which are homogeneously distributed in the cystic regions. **C** Consecutive sonographic control after ablation shows hyperechogenic lesions within the ablated area.

Abb. 1 Sonografische Überwachung einer Mikrowellenablation eines komplexen Knotens mit soliden und zystischen Anteilen. **A** Die Sonde wird vor der Ablation sonografisch kontrolliert, wobei darauf geachtet wird, dass die active tip komplett in dem gewünschten Bereich liegt. **B** Während der Ablation ist die Wärmeentwicklung durch hyperechogene „microbubbles" darstellbar, die besonders in zystischen Regionen homogen verteilt sind, **C** Die anschließende sonografische Kontrolle nach der Ablation zeigt hyperechogene Läsionen im Bereich der Ablationszone.
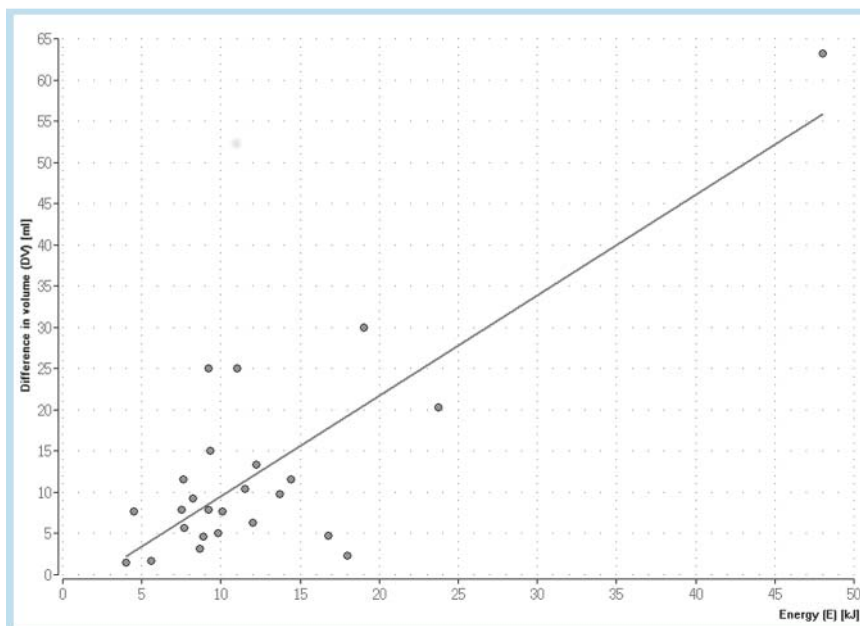

Fig. 2 Correlation between applied energy (E) and resulting difference in volume (ΔV) observed 3 months after microwave ablation (Pearson correlation coefficient r = 0.82).

Abb. 2 Korrelation zwischen der applizierten Energie (E) und der resultierenden Volumendifferenz (ΔV) 3 Monate nach der Mikrowellenablation (Pearson correlation coefficient r = 0,82).

Statistical analysis

Statistical analysis was performed with BiAS, version 10.04 (epsilon Verlag, 1989–2013, Frankfurt, Germany). The Wilcoxon matched pairs test was used to evaluate the significance in the volume change (ΔV). The Kruskal-Wallis test corrected by Bonferroni was used to evaluate the significance of differences under subgroups regarding the energy required per volume change (E/ΔV). The Pearson correlation coefficient was used to evaluate the correlation between the energy (E) and volume change (ΔV). Statistical significance was indicated with p-values < 0.05.

Results

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MWA resulted in a significant (p < 0.0001) volume reduction (ΔV) after 3 months with a mean of 12.4 ± 13.0 ml (range: 1.5 – 63.2 ml) corresponding to a relative reduction of 52 ± 16 % (range: 22 – 77 %) (○ **Table 1**, e.g. ○ **Fig. 3**). There was a positive correlation between E and ΔV (Pearson correlation coefficient r = 0.82 for all nodules (○ **Fig. 2**). The mean E/ΔV was 1.52 ± 1.08 (range: 0.4 – 7.65) kJ/ml for all nodules and 2.30 ± 1.50 (0.9 – 4.60), 1.5 ± 0.9 (0.4 – 3.6), 0.75 ± 0.25 (0.4 – 1.2) kJ/ml, respectively, for solid, complex and cystic nodules (○ **Table 1**) (p < 0.03).

Table 1 Analysis of microwave ablation in benign thyroid nodules in relation to the applied energy (E).

Tab. 1 Analyse der Mikrowellenablation benigner Schilddrüsenknoten in Relation zur applizierten Energie (E).

Nº	V_o [ml]	$V_{three\ month}$ [ml]	Δ V [ml]	applied energy (E) [kJ]	energy per ΔV E/ΔV [kJ/ml]	type
1	3.45	1.1	2.35	10.8	4.6	
2	7.2	4.0	3.2	8.6	2.7	
3	5.4	3.7	1.7	5.6	3.3	solid
4	10.4	2.5	7.9	7.5	0.9	
5	25.7	20.0	5.7	7.7	1.4	
6	33.5	20.2	13.4	12.2	0.9	
1	18.8	9	9.8	13.7	1.4	
2	15	3.4	11.6	14.4	1.2	
3	20.7	10.28	10.4	11.5	1.1	
4	28.7	8.43	20.3	23.8	1.2	
5	7.1	2.4	4.7	16.8	3.6	
6	19.3	11.6	7.7	10.1	1.3	
7	46	21	25.0	9.2	0.4	complex
8	20.3	8.7	11.6	7.6	0.7	
9	2.6	1.1	1.5	4	2.7	
10	16.6	8.9	7.7	4.5	0.6	
11	7.2	2.6	4.6	8.9	1.9	
12	15	10	5.0	9.8	2.0	
13	14.9	8.6	6.3	12	1.9	
1	85	21.79	63.2	48	0.8	
2	14.3	6.4	7.9	9.2	1.2	
3	14.8	5.5	9.3	8.2	0.9	
4	43	28	15.0	9.3	0.62	cystic
5	55	30	25.0	11	0.4	
6	100	70	30.0	19	0.6	
n = 25	25.2 ± 24.3	12.8 ± 14.6	12.4 ± 13.0	12.13 ± 8.67	1.52 ± 1.08	mean±SD
	2.6 – 100.0	1.1 – 70.0	1.5 – 63.2	4.0 – 48.0	0.4 – 4.6	range

Discussion

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This study shows that MWA is an effective method for reducing the volume of benign thyroid nodules (e.g. ○ **Fig. 3**). Our results are in accordance with Yue et al. [9] who reported a mean volume reduction of 41 % after 3 months and 65 % after 6 months. The long timescale of MWA's effects make prediction of treatment outcomes difficult. Therefore, an energy-versus-efficacy calibration curve seems to be beneficial in order to improve therapeutic handling and better match the expected volume reduction. This is especially necessary for MWA because it generates higher temperatures at a faster rate than comparable thermoablative methods such as RFA. Its energy output is relatively high in the confined space of the thyroid, which results in less controllability and predictability [16, 17]. Since an effect on surrounding nerves and vessels can't be excluded, the procedure has to be guided carefully [18]. Currently, guidance is primarily performed using conventional B-mode sonography with high-resolution transducers, which especially improves guidance with respect to superficial structures and facilitates the maintenance of a safety distance. Further imaging techniques, such as elastography and contrast-enhanced ultrasound (CEUS), are described, although these techniques are reported to be best suited for periprocedural guidance. Elastography as well as CEUS improve the differentiation between benign and malignant nodules, whereas only elastography is currently recommended for the thyroid in the EF-SUMB guidelines [19 – 23]. Recent studies also indicated positive effects of real-time elastography on the guidance of thermal abla-

tion and showed an improved delineation of the ablated area compared to B-mode sonography [24, 25]. As the study was performed in the liver, future studies should involve an evaluation of thyroid ablation to determine its clinical relevance. Nevertheless, elastography is highly dependent on the experience of the examiner, thus the transferability of these results is limited. In contrast, CEUS is not reliable for monitoring during thermal ablation, because MWA creates so-called microbubbles [14], which interfere with CEUS imaging. After ablation, CEUS is reported to predict successful treatment of soft tissue and is used to identify local recurrences of malignant neoplasia [21, 26]. In particular, the imaging of malignant lesions benefits from CEUS as success depends on exact ablation. An additional benefit to standard ultrasound imaging of benign thyroid nodules has not been evaluated. The positive correlation (r=0.82) between the applied energy and volume reduction enables an approximate prediction of volume reduction during ablation and should therefore improve periprocedural guidance in addition to standard ultrasound.

Our study shows a good correlation between energy and volume (r = 0.82) (○ **Fig. 2**) to estimate the required energy per ablative VOI using: E/ΔV × VOI with 2.30 ± 1.50 (0.9 – 4.6), 1.5 ± 0.9 (0.4 – 3.6), 0.75 ± 0.25 (0.4 – 1.2) kJ/ml, respectively, for solid, complex and cystic nodules.

Furthermore, our study shows that solid nodules require significantly more energy than cystic nodules (2.30 vs. 0.75 kJ/ml). This finding indicates that the consistency of the thyroid nodule must be taken into account when estimating the energy requirement. The fact that solid nodules require more energy than cystic ones
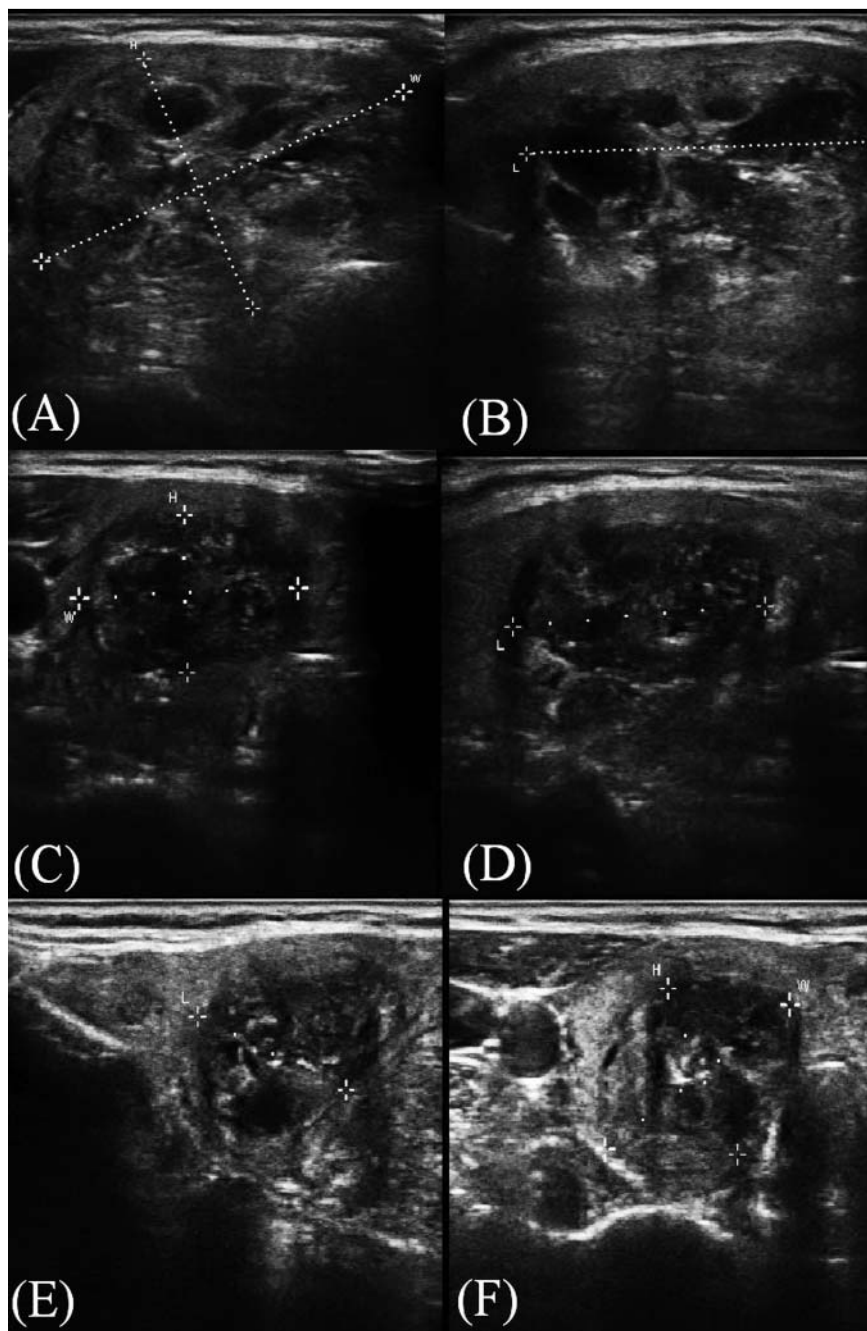
Fig. 3 Measurement of the nodule volume before ablation (**A** + **B**: Length (L): 40.85 mm; Heigh (H)t: 31.63 mm; Width (W): 46.41 mm; V: 28.72 cm^3), 3 months after ablation (**C** + **D**: L: 33.11 mm; H: 18.06 mm; W: 29.44 mm; V: 8.43 cm^3) and 12 months after ablation (**E** + **F**: L: 21.08 mm; H: 19.77 mm; W: 28.82 mm; V: 5.75 cm^3).

Abb. 3 Messung des Knotenvolumens vor der Ablation (**A** + **B**: Länge (L): 40,85 mm; Höhe (H)t: 31,63 mm; Breite (W): 46,41 mm; V: 28,72 cm^3), 3 Monate nach Ablation (**C** + **D**: L: 33,11 mm; H: 18,06 mm; W: 29,44 mm; V: 8,43 cm^3) und 12 Monate nach Ablation (**E** + **F**: L: 21,08 mm; H: 19,77 mm; W: 28,82 mm; V: 5,75 cm^3).

can be explained by the higher water content, which increases the conversion of electromagnetic energy into heat [8]. The distribution of microbubbles in the fluid areas of the complex nodule in ○ **Fig. 1** demonstrates the increasing temperature of these areas, which is more homogeneously distributed than in solid areas (○ **Fig. 1**). The homogeneous distribution of water results in homogeneous production of heat leading to homogeneous thermal ablation [14]. Furthermore, in cystic nodules there is no blood flow that carries the heat away (conduction) which further increases the efficiency of MWA in cystic nodules. The conduction of heat – the so called "heat-sink effect" [27, 28] – decreases the efficiency of thermal ablation, although microwave ablation seems to be less affected than other thermal ablation techniques [28 – 30]. Nevertheless, current research shows that the pattern of temperature increase during MWA depends on the distance between the probe and the blood vessel as well as on the flow rate inside the vessel, as shown in the liver [31]. Heat loss was reported to be negligible only when the distance to a vessel exceeds 20 mm. However, these results are not fully transferable to the thyroid as the hepatic vessels are significantly larger than those in the thyroid and the negative inferring effect of blood flow on microwave ablation has not been completely investigated yet. In addition to the greater heat conductivity, this phenomenon may explain why solid nodules require more energy for ablation than cystic nodules. Besides consistency, another predictor of the effectiveness of MWA could be the microwave frequency. Lower frequencies have a larger penetration depth and a slower heating rate [8]. Thus, 915 MHz MWA results in damage with a more long-ellipsoid shape, while 2.45 GHz MWA caused damage with a more spherical shape. Therefore, 915 MHz should be used for ellipsoid nodules while 2.45 GHz should be used for spherical ones [16, 32].

Non-thermal as well as thermal effects contribute to the efficacy of microwave ablation [3]. George et al. reported unfolding of enzymes caused by direct electromagnetic impacts either on protein structure or on hydration-water [33]. Furthermore, Yu and Yao reported an inhibition of DNA synthesis and proliferation arrest in rabbit lens cells, which led to apoptotic changes. Reduced intercellular communication through gap junctions as well as repairable induced DNA damage were also reported, both resulting in an altered cellular stress response [34]. An important finding was that the development of cataracts is not a stochastic but a deterministic effect that correlates with the power and duration of exposure. The energy-efficacy curve in our study (○ **Fig. 2**) cuts the x-axis at a value greater than zero, which indicates that there is a minimum energy required to have an effect. This threshold energy is typical of the transition from stochastic to deterministic effects, as in radiation therapy, for example. The intention of the study was to establish an energy-efficacy calibration curve in order to better estimate the energy needed per volume of ablation. Similar calibration has been established for radioiodine therapy. There is currently no comparable correlation between the transmitted energy and volume-of-interest in public research concerning thyroid nodules treated by MWA. Certainly, these results and values are not transferable to every patient and should therefore be seen as a reference point, which may improve therapeutic handling of MWA. Additional guidance via ultrasound is indispensable here and should still be the most essential part of guidance during ablation. Nonetheless, the transmitted energy should be taken into account and certainly improves therapeutic handling.

Conclusion
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Supplementary to ultrasound guidance and temperature measurements, the method for estimating the required energy per ablative volume provided by this study should help to improve the efficacy of MWA of benign thyroid nodules and to avoid under- or overtreatment.

Affiliations

[1] Department of Nuclear Medicine, Johann Wolfgang Goethe University Hospital, Frankfurt, Germany
[2] Radiology, Multiorgan Screening Foundation, Munich, Germany
[3] German Center for Thermoablation of Thyroid Nodules, Johann Wolfgang Goethe University Hospital, Frankfurt a. Main, Germany
[4] Department of General and Visceral Surgery, Agaplesion Elisabethenstift Darmstadt, Germany
[5] Department of Diagnostic and Interventional Radiology, Johann Wolfgang Goethe University Hospital, Frankfurt, Germany

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