Percutaneous microwave ablation of benign thyroid nodules

Functional imaging in comparison to nodular volume reduction at a 3-month follow-up

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Keywords

Microwave ablation, functional imaging, thyroid nodules, scintigraphy, ^{99m}Tc-pertechnetate, ^{99m}Tc-MIBI

Summary

Aim: Thyroid nodules represent a common clinical issue. Amongst other minimally invasive procedures, percutaneous microwave ablation (MWA) poses a promising new approach. The goal of this retrospective study is to find out if there is a correlation between volume reduction after 3 months and ^{99m}Tc-uptake reduction of treated thyroid nodules. Patients, methods: 14 patients with 18 nodules were treated with MWA. Pre-ablative assessment included sonographical and functional imaging of the thyroid with ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI. Additionally, patients underwent thyroid scintigraphy 24 hours after ablation in order to evaluate the impact of the treatment on a functional level and to ensure sufficient ablation of the targeted area. At a 3-month follow-up, ultrasound examination was performed to assess nodular volume reduction. Results: Mean relative nodular volume reduction after three months was 55.4 ± 17.9% ($p < 0.05$). ^{99m}Tc-uptake 24 hours after treatment was 45.2 ± 31.9% (^{99m}Tc-MIBI) and 35.7 ± 20.3% (^{99m}Tc-pertechnetate) lower than prior to ablation ($p < 0.05$). Correlating reduction of volume and ^{99m}Tc-uptake, Pearson's r was 0.41 ($p < 0.05$) for nodules imaged with ^{99m}Tc-MIBI and –0.98 ($p < 0.05$) for ^{99m}Tc-pertechnetate. According to scintigraphy 99.6 ± 22.6% of the determined target area could be successfully ablated. Conclusions: MWA can be considered as an efficient, low-risk and convenient new approach to the treatment of benign thyroid nodules. Furthermore, scintigraphy seems to serve as a potential prognostic tool for the later morphological outcome, allowing rapid evaluation of the targeted area in post-ablative examination.

Schlüsselwörter

Mikrowellenablation, funktionelle Bildgebung, Schilddrüsenknoten, Szintigraphie, ^{99m}Tc-Pertechnetat, ^{99m}Tc-MIBI

Zusammenfassung

Schilddrüsenknoten sind ein häufiges klinisches Problem. Wie andere minimal-invasive Techniken stellt die perkutane Mikrowellenablation (MWA) einen viel versprechenden neuen Therapieansatz dar. Das Ziel dieser retrospektiven Studie ist es herauszufinden, ob ein Zusammenhang zwischen Volumenabnahme nach drei Monaten und ^{99m}Tc-Uptake-Abnahme des therapierten Schilddrüsenknotens besteht. Patienten, Methoden: 14 Patienten mit 18 Knoten wurden mit MWA behandelt. Das prä-ablative Prozedere umfasste Ultraschalluntersuchung, funktionelle Bildgebung mit ^{99m}Tc-Pertechnetat und ^{99m}Tc-MIBI. Nach 24 Stunden wurde erneut ein Szintigramm angefertigt, um das Ergebnis der Behandlung auf funktioneller Ebene zu beurteilen. Nach drei Monaten erfolgte die Verlaufskontrolle, bei der sonographisch die Reduktion des Knotenvolumens erfasst wurde. Ergebnisse: Die relative Reduktion des Knotenvolumens betrug nach drei Monaten 55,4 ± 17,9% ($p < 0,05$). Der ^{99m}Tc-Uptake war 24 Stunden nach der Behandlung um 45,2 ± 31,9% (^{99m}Tc-MIBI) bzw. 35,7 ± 20,3% (^{99m}Tc-Pertechnetat) verringert ($p < 0,05$). Die statistische Korrelation von Volumenreduktion und ^{99m}Tc-Uptake ergab r-Werte von 0,41 (^{99m}Tc-MIBI) bzw. –0,98 (^{99m}Tc-pertechnetate) ($p < 0,05$). Zudem konnten gemäß Szintigraphie 99,6 ± 22,6% des definierten Zielareals abladiert werden. Schlussfolgerung: Die MWA kann als effizienter und risikoarmer neuer Therapieansatz zur Behandlung benigner Schilddrüsenknoten angesehen werden. Weiterhin scheint es möglich, die Szintigraphie als prognostisches Hilfsmittel und auch zur raschen post-ablativen Beurteilung des Zielvolumens heranzuziehen.

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Thyroid nodules pose a common clinical issue. Next to functional disorders, inflammation and an increase in size, nodules rank among the most frequent transformations of the thyroid. The prevalence in Germany, until 2005 representative for a region of relative iodine deficiency (17), is estimated to be up to 68%, depending on age and the way of detection (14, 38), with the incidence increasing with continuous improvement of sonographical imaging (30). Those nodules tend to be benign in most cases; the incidence of thyroid cancer in Europe is reported to be 2.2–12.4 / 100 000 (5), making it a relatively rare malignant event. An insufficient supply of the population with iodine in the past decades is accepted as the main reason for the strikingly high prevalence in contrast to the good alimentary situation today (6, 9, 13). Yet, benign nodules may potentially cause serious problems and thus require treatment due to

- cosmetic issues,
- subjective symptoms or
- patients' fear of malignancy (20).

This investigation addresses the question whether thermal microwave ablation (MWA) can provide a significant reduction of nodal volume in benign thyroid nodules and therefore prove as an effective way of treating this very common disease.

Surgical intervention and radioiodine therapy represent the current standard therapy options for thyroid nodules, regardless of both featuring a number of drawbacks and limitations. Given the constraints of these established therapeutic approaches, new image-guided, minimally invasive techniques of treating thyroid nodules have emerged, representing a promising alternative to the well-established methods (11). Radiofrequency ablation (RFA) has already shown positive results indicating RFA to be a convenient option for treatment of benign and malignant thyroid nodules (26, 34), yet presenting a number of drawbacks as well (1, 15). Other alternative therapies to be mentioned are the percutaneous ethanol injection for cystic and predominantly cystic nodules (21), ultrasound-guided laser therapy for mainly solid nodules (7, 37) as well as thermal microwave ablation.

MWA is a comparatively new thermal ablative technique that has already been successfully put to use in order to treat malignancies in other organs such as the liver (29). The limited number of clinical and experimental studies dealing with the use of MWA in the treatment of thyroid nodules has presented encouraging results featuring a favorable profile of adverse effects (8, 23, 24, 40), yet largely lacking an analysis of ablated nodules in terms of functional aspects.

Thyroid scintigraphy represents a useful diagnostic tool in terms of assessing the consistency and function of thyroid tissue (18), thus also making it an important device when it comes to the overall evaluation of a new therapeutic approach such as MWA. After all, further endeavours are indicated to consolidate MWA as a favourable and effective method of treating benign thyroid nodules. Therefore the aim of this retrospective study is to find out whether MWA can provide a significant decrease of nodular volume at a 3-month follow-up and if there is a correlation between post-ablative functional imaging, i.e. thyroid scintigraphy, and post-ablative nodular volume.

Patients, material, methods

Patients

In this retrospective study data from 14 patients (5 men, 9 women; mean age 57.0 years; median age 59.0 years; range 31–78 years) with 18 nodules who had received treatment with MWA were evaluated. Inclusion criteria for treatment were:

- cosmetic problems,
- symptomatic nodules (e. g. swallowing problems, hoarseness, distress),
- refusal of surgery or contraindications.

Exclusion criteria:

- excessive thyroid volume with retrosternal growth,
- lack of symptoms,
- histological evidence for follicular proliferation in terms of a malignant dysplasia,
- critical position of adjacent structures such as vessels, trachea, oesophagus and nerves.

Patients were treated on a compassionate use basis; written informed consent, clarifying possible risks and the experimental nature of the treatment, was obtained from all patients. Local ethics committee approved the study protocol and the retrospective evaluation of data.

MWA equipment

The system used in this study (Avecure MWG881, MedWaves, Inc., San Diego, CA) works in a frequency range of 902–928 MHz generating maximum temperatures of approximately 140°C. According to individual aspects of each patient three probes (uncooled tip, 14–16 G) with diverging ablation areas are available. The field size varies from 1 to 4 cm, all probes feature integrated temperature sensors. The target temperature was 60–95°C with an output of 24–36 W. The device was operated in power control mode with the microwave generator periodically delivering pre-adjusted peak energy.

Pre-ablative assessment

Before ablation all patients underwent ultrasound examination (▶Fig. 1), laboratory tests and scintigraphic thyroid imaging. Ultrasound examination was performed in order to evaluate volume, number and composition of the nodules. Volume (in ml) was calculated using the following equation (hight, width, depth in cm):

$$\text{volume} = (\text{hight} \times \text{width} \times \text{depth}) / 2$$

Additionally, the type of vagus nerve location (16) was identified in order to avoid potentially critical situations during actual ablation that might lead to an irritation or lesion of the vagus nerve. Nodules were classified as mainly solid, cystic or complex (both solid and cystic) depending on their relation of solid and cystic portion. Laboratory tests included a complete thyroid hormone status, blood count, coagulation diagnostic, C-reactive protein and blood glucose.

Patients with discretely increased ^{99m}Tc-uptake or with known indifferent nodules (as detected by earlier scintigraphy) received a thyroid scan with averagely 75 MBq ^{99m}Tc-pertechnetate (▶Fig. 2). Patients presenting known "cold" nodules underwent a thyroid scintigraphy with 500–557 MBq ^{99m}Tc-MIBI (▶Fig. 3) and additionally fine needle aspiration biopsy (FNAB), which has proven to be a safe method of excluding malignancy, especially when combined (12, 25, 31). In patients with cold and indifferent thyroid nodules both mentioned scintigraphy modalities were performed. Acquisition was conducted 20 minutes after administration of ^{99m}Tc-pertechnetate or, in case of ^{99m}Tc-MIBI scans, 10 and 60 minutes after, respectively. For this purpose a scintillation camera (Nucline TH/22, Mediso Medical Imaging Systems, Budapest, Hungary) equipped with a low energy collimator was used.

Procedure

The intervention was performed by an experienced physician during local anaesthesia and under aseptic conditions. Before the actual MWA intervention a local infiltration anesthesia (Scandicain 1%) was performed, on the one hand to eliminate or minimize pain during the process, hereby making the procedure more tolerable for the patient, on the other hand to enlarge the distance between skin and ablation area, thus increasing the patient's safety concerning skin burns. If realizable an access via transisthmic approach was chosen, hereby permitting the display of the microwave probe in its entire length and its current location in reference to vital vascular or nerval structures via ultrasound imaging. Besides, doing so, the heat stress on the vagus nerve can be kept as low as possible. If transisthmic approach was not accomplishable, a craniocaudal access path was chosen. After correct identification of vagus and recurrent laryngeal nerve the probe was placed directly in the nodule under sonographical guidance.

During ablation the operating physician had to pay attention to the occurrence of so-called microbubbles and hypoechogenic areas, both representing the direct effects of heat development in the ablation area that can be visualized sonographically (39). Afterwards, an ultrasound control of the ablation area was done due to ruling out

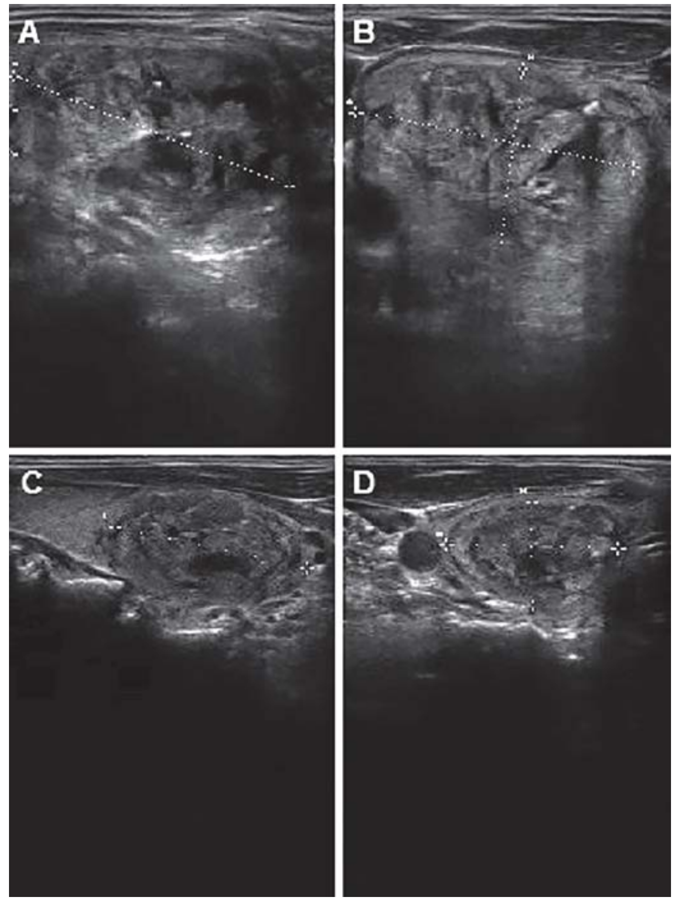

Fig. 1 Sonographic imaging before (A: sagittal, B: transversal) and after ablation (C: sagittal, D: transversal)

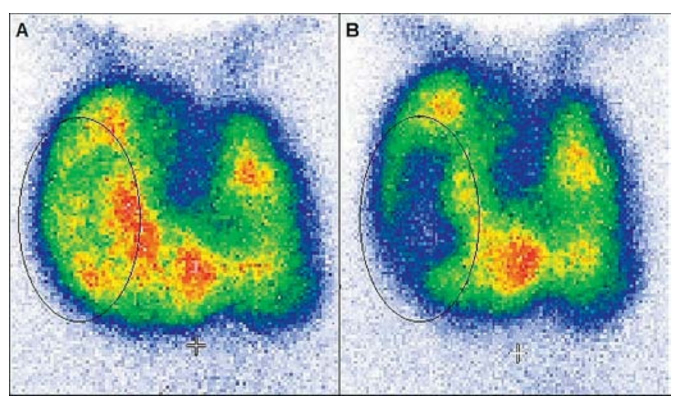

Fig. 2 Functional imaging with ^{99m}Tc-pertechnetate, before (A) and after (B) ablation: Notice the encircled areas, indicating the location of the nodule and the decreased ^{99m}Tc-uptake after ablation.

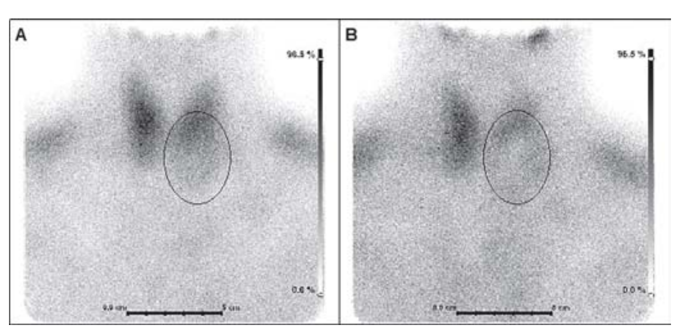

Fig. 3 Functional imaging with ^{99m}Tc-MIBI before (A) and after (B) ablation: Notice the encircled areas, indicating the location of the nodule and the decreased ^{99m}Tc-uptake after ablation.

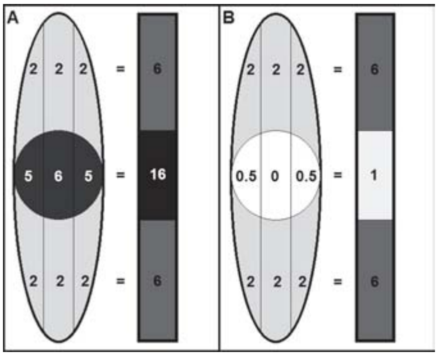

Fig. 4 Thyroid before (A) and after (B) ablation and the resulting scintigraphy: Ovals represent the thyroid in a sagittal view, inner circles represent the nodule (A) and the ablation zone (B). Numbers and brightness illustrate the ^{99m}Tc-uptake in an increasing manner going from white to black. The colour intensities of the scintigraphic image, depicted as columns, result from the addition of frontal layers by the scintillation camera.

local complications. If required, the probe was repositioned and other parts of the nodule were treated equally. Throughout the entire duration of the intervention the physician paid attention to the well-being of the patient and to the emergence of possible voice changes as a sign of recurrent laryngeal nerve stress. If nodules were found to be mainly cystic, an additional puncture for the purpose of aspirating fluid contents was done before actual ablation. This was done in order to both minimize the pre-procedural ablation volume and to exclude possible heat-sink effects resulting from cystic fluids (22).

24 hours after intervention each patient received a second thyroid scan using the same tracer as before ablation (▶Fig. 2, ▶Fig. 3) and ultrasound control was conducted to exclude focal complications. Additionally, laboratory blood tests were performed again to ensure no thyroid dysfunction had occurred after the procedure. Three months after treatment patients underwent another ultrasound examination of the ablation site in order to evaluate post-ablative nodular volume reduction (▶Fig. 1). No patient was re-treated.

Statistical analysis

Statistical results were obtained using BIAS., version 10.04 (epsilon Verlag, 1989–2013). Values were tested for normality of distribution and t-tests were performed to evaluate nodular volume and functional imaging findings with significance set at ≤ 0.05. Additionally, Pearson's r was calculated in order to find a possible correlation between nodular volume decrease and ^{99m}Tc-uptake reduction. Data is reported as mean ± standard deviation.

Results

Imaging

Mean pre-ablative nodular volume was 19.8 ± 21.3 ml, post-ablative volume was 8.9 ± 8.9 ml. This equals a mean absolute volume reduction of 10.8 ± 15.2 ml ($p < 0.05$) and a relative reduction of 55.4 ± 17.9% ($p < 0.05$). Mean pre-ablative ^{99m}Tc-uptake was 13.9 ± 9.7% (^{99m}Tc-MIBI; n = 13) and 15.3 ± 16.1% (^{99m}Tc-pertechnetate; n = 5), after treatment it was averagely reduced to 6.6 ± 6.2% (^{99m}Tc-MIBI) and 9.0 ± 9.6% (^{99m}Tc-pertechnetate), equivalent to a relative uptake reduction of 45.2 ± 31.9% (^{99m}Tc-MIBI) and 35.7 ± 20.3% (^{99m}Tc-pertechnetate), respectively ($p < 0.05$) (▶Fig. 4).

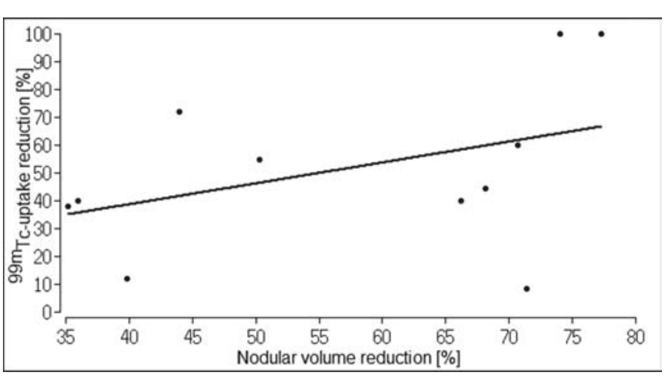

Fig. 5 Correlation of post-ablative ^{99m}Tc-MIBI scintigraphy and nodular volume reduction at the 3-month follow-up

Correlating relative reduction of volume and ^{99m}Tc-uptake, Pearson's r was 0.41 ($p < 0.05$) for nodules imaged with ^{99m}Tc-MIBI (▶Fig. 5) and –0.98 ($p < 0.05$) for ^{99m}Tc-pertechnetate, respectively. Four nodules, which were all found in one patient, could not be separately distinguished by sonography and subsequently were not taken into consideration in terms of correlating volume reduction and ^{99m}Tc-uptake reduction.

In order to evaluate whether nodules had been successfully hit during MWA, pre-ablative target areas were compared to actually ablated areas as determined by scintigraphy. According to scintigraphy, pre-ablative target areas had a mean pre-ablative size of 1252 ± 896 pixels, post-procedural ablation areas, i.e. areas in which an apparent change of ^{99m}Tc-uptake had occurred, had a mean size of 1252 ± 1020 pixels, which averagely equals 99.6 ± 22.6% of the area determined to be treated.

Complications

Slight pain and a feeling of pressure during the ablation were reported by all patients, yet the pain could be easily decreased by just reducing the temperature. No further treatment was required; the pain rapidly vanished after ablation. All patients developed first-degree skin burns at the puncture site. The burns did not need any specific treatment either and disappeared within days. One patient developed a cervical haematoma sized about 47 x 22 mm, yet colour duplex sonography did not deliver any hint towards an active bleeding source and the haemoglobin count remained at a normal level. Three patients reported dragging pain towards the mandibular angle and ear during the treatment. No swallowing difficulties, vagal reactions or voice changes were observed.

Serious complications like secondary haemorrhage, infections, nodule ruptures, deep haematomas or injuries of the vagus or recurrent laryngeal nerve did not occur. In one patient a slight hyperthyreosis with a T4 level of 207 nmol/l (reference range: 55–170 nmol/l) without elevated T3 was discovered after ablation, yet the thyroid function normalized within one week without occurrence of any further complications. Another patient with known diabetes mellitus presented a slightly increased blood glucose level of 118 mg/dl. All other patients presented a proper thyroid function after ablation. In the post-procedural observation period one patient who had received radioiodine therapy in addition to MWA developed Graves' disease. Retrospectively it is not apparent which therapy might be considered the inducing factor, however, self-limiting immunogenic hyperthyreosis is known to rarely occur in patients after radioiodine therapy. Yet, it is not possible to definitely exclude MWA as a potential (co-)factor.

Discussion

The aim of this study was to discover whether or not MWA is capable of delivering a significant volume reduction of benign thyroid nodules after a 3-month follow-up. Moreover its intention was also to find out if nodular volume reduction and the decrease of post-ablative ^{99m}Tc-uptake in treated areas of the thyroid could be related in terms of a statistical correlation. With a mean relative volume reduction of 55.4 ± 17.9% ($p < 0.05$) at a 3-month follow-up MWA might me assumed as capable of providing a significant volume reduction in thyroid nodules. Functional imaging revealed a decrease of post-ablative ^{99m}Tc-uptake, 45.2 ± 31.9% ($p < 0.05$) for ^{99m}Tc-MIBI and 35.7 ± 20.3% ($p < 0.05$) for ^{99m}Tc-pertechnetate. Additionally, a significant correlation of volume reduction and functional imaging could be discovered, both considering ^{99m}Tc-MIBI ($r = 0.41$) and ^{99m}Tc-pertechnetate ($r = –0.98$).

> Based on these findings, ^{99m}Tc-uptake might serve as a prognostic factor for the outcome in terms of nodular volume reduction.

Scintigraphy also revealed a good match (99.6 ± 22.6%) of pre-ablative target areas and areas showing a decrease of ^{99m}Tc-uptake after ablation. The congruency of these areas can be interpreted as a sign of successful ablation of the entire area determined to be ablated before the procedure. Although this approach is limited by the fact that only a two-dimensional scintigraphic image has been evaluated, which, after all, does not prove a sufficient ablation of the lesion, the comparison of pre- and post-ablative scintigraphy allows a rapid and pretty accurate estimation whether the distinguished target area was sufficiently hit by MWA in its entire extent in terms of a control of success.

In consideration of these results one may find a clear tendency to assessing MWA as an effective approach to treatment of benign thyroid nodules. Two other studies investigating on the volume reduction of benign thyroid nodules by MWA came to similar positive conclusions (8, 40). In their study, Feng et al. (8) observed a mean nodule volume reduction ratio of 46.0%, with longer follow-ups (> 3 months) tending to result in even superior outcomes. Yue et al., who evaluated the results of MWA at a 6-month follow-up, found a mean reduction ratio of 41% after 3 months and of 65% after 6 months (40). These findings coherently support the results of this study.

Although the exact mechanisms of MWA in vivo are not completely comprehended, there are several aspects that may be used in order to, at least partially, interpret these findings. Generally spoken, microwaves are known to have effects on living tissue that can be subdivided in such of thermal and non-thermal nature, respectively. On the one hand microwaves produce thermal energy by stimulating water molecules which are consecutively accelerated, inducing friction and subsequently heat. Heat, when applied to the tissue for an adequate period of time and in a degree as given in our case (60–95°C), induces necrosis by coagulation and denaturation of crucial cellular protein structures. This particular effect certainly may pose one main mechanisms of MWA leading to cellular death and therefore the desired clinical results in terms of nodular volume reduction. Yet, apart from this mere thermal effect microwaves are also known to have a degrading effect on lipid membranes which so far could only be verified ex vivo, but that could also be used to partly explain the observed results (32). Shamis et al. managed to reveal an impact of microwaves in a non-lethal thermal range on *E. coli* cells which led to a temporary destabilization and increase in permeability of the lipid membrane.

Banik et al. described another form of non-thermal interaction of microwaves with cellular proteins based on ion acceleration and collision as well as dipole rotation causing changes in protein structure (3). Other studies imply an immediate effect of microwave radiation on enzyme activity, which could affect critical thyroid structures as ion-transporters like the sodium/iodide symporter (NIS) as well (33). With ^{99m}Tc-pertechnetate being a substrate of NIS (2) and the uptake and accumulation of ^{99m}Tc-MIBI being dependent on the existence of intact mitochondria (2, 28), which – just like *E. coli* cells – may be subject to lipid membrane degradation, these non-thermal effects of MWA might also represent a cause of cellular death in nodular tissue. Eventually, this study cannot and does not aim to finally clarify which of the named thermal and non-thermal effects exactly cause the observed reduction of nodular volume and ^{99m}Tc-uptake. Still, it might be considered that the efficiency of MWA may result from an interaction of various thermal and non-thermal effects. Concerning the nodular volume reduction, Yue et al. propose that the final clinical outcome considerably depends on the nodular baseline volume, with a significant negative correlation between baseline volume and volume reduction ratio (40). Also, they discovered that the larger the cystic portion of the treated nodules had been, the greater the volume reduction ratio finally was.

As mentioned in the introduction, there have emerged a number of other ultrasound-guided ablative technologies over the past years. Studies about radiofrequency ablation (RFA) of benign thyroid nodules have revealed a volume reduction ratio of 71.4–93.3% at a 6-month follow-up (19, 35). Percutaneous ethanol injection was reported to create a mean volume reduction of 46–51% at 6-month follow-up (4) and of 85.6% after 12 months (36), respectively. Also percutaneous laser ablation was found to produce a significant reduction of nodular volume with a decrease of 42.7–44.0% at different follow-ups (30 weeks – 12 month) (10, 27). All values are based on the results of randomized controlled trials and therefore can be considered as fairly accurate. Given the longer follow-ups of the cited studies, MWA might be considered an at least equally efficient method for the treatment of benign thyroid nodules. Yet, due to the small number of cases subjected in this retrospective study further endeavours ought to be made in order to gain a better understanding of microwave ablation in vivo and of individual parameters leading to a favourable clinical result.

Conclusions

With a mean relative reduction of $55.4 \pm 17.9\%$ ($p < 0.05$) at a 3-month follow-up and in addition with the favourable profile of adverse effects during or after treatment and considering the small amount of time the treatment takes, with the ablation process itself (8–9 minutes per nodule), MWA can be considered not only as an effective but also as a convenient tool for the treatment of benign thyroid nodules in patients with nodular growth related symptoms.

Although the exact mechanism is not completely comprehended and given the limitations of this retrospective study, functional imaging with ^{99m}Tc-MIBI and ^{99m}Tc-pertechnetate seems to correlate with later nodular volume reduction. Based on this assumption, post-ablative scintigraphy might allow conclusions of the actual morphological outcome. Furthermore, scintigraphic thyroid imaging allows a fairly accurate evaluation of the ablated area in comparison to the distinguished target area, hereby revealing information about the extent of the ablation zone and whether the target area could be hit by MWA in its entire extent. Hence, it not only poses a crucial instrument for the pre-ablative assessment of thyroid nodules, regarding quantity and functional status, but also in terms of post-ablative assessment.

Conflict of interest

The authors declare that here is no financial conflict of interest.

References

1. Ahmed M, Brace CL, Lee FT, Goldberg SN. Principles of and advances in percutaneous Aablation. Radiology 2011; 258: 351–369.
2. Arbab AS, Koizumi K, Toyama K et al. Technetium-99m-tetrofosmin, technetium-99m-MIBI and thallium-201 uptake in rat myocardial cells. J Nucl Med 1998; 39: 266–271.
3. Banik S, Bandyopadhyay S, Ganguly S. Bioeffects of microwave – a brief review. Bioresour Technol 2003; 87: 155–159.
4. Bennedbaek FN, Hegedüs L. Percutaneous ethanol injection therapy in benign solitary solid cold thyroid nodules: a randomized trial comparing one injection with three injections. Thyroid 1999; 9: 225–233.
5. Cancer Research UK. Thyroid cancer incidence statistics – In Europe and worldwide. www.cancerresearchuk.org/cancer-info/cancerstats/types/thyroid/incidence/#geog. visited 15/05/2014.
6. Döbert N, Balzer K, Diener J et al. Thyroid sonomorphology, thyroid peroxidase antibodies and thyroid function. New epidemilogical data in unselected German employees. Nuklearmedizin 2008; 47: 194–199.
7. Døssing H, Bennedbæk FN, Hegedüs L. Interstitial laser photocoagulation (ILP) of benign cystic thyroid nodules-a prospective randomized trial. J Clin Endocrinol Metab 2013; 98: 1213–1217.
8. Feng B, Liang P, Cheng Z, et al. Ultrasound-guided percutaneous microwave ablation of benign thyroid nodules: experimental and clinical studies. Eur J Endocrinol 2012; 166: 1031–1037.
9. Gallowitsch HJ, Mikosch P, Kresnik E et al. Thyroid volume and iodine supply of 6 to 17 year old students. Results 3 years after the introduction of increased iodized salt. Nuklearmedizin 1994; 33: 235–238.
10. Gambelunghe G, Fatone C, Ranchelli A et al. A randomized controlled trial to evaluate the efficacy of ultrasound-guided laser photocoagulation for treatment of benign thyroid nodules. J Endocrinol Invest 2006; 29: 23–26.
11. Gharib H, Hegedüs L, Pacella CM et al. Nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. J Clin Endocrinol Metab 2013; 98: 3949–3957.
12. Giovanella L, Suriano S, Maffioli M et al. ^{99m}Tc-sestamibi scanning in thyroid nodules with nondiagnostic cytology. Head Neck 2010; 32: 607–611.
13. Gotthardt M, Stübinger M, Pansegrau J et al. Decrease of ^{99m}Tc-uptake in autonomous thyroid tissue in Germany since the 1970s. Clinical implications for radioiodine therapy. Nuklearmedizin 2006; 45: 122–125.
14. Guth S, Theune U, Aberle J et al. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest 2009; 39: 699–706.
15. Ha EJ, Baek JH, Lee JH. The efficacy and complications of radiofrequency ablation of thyroid nodules. Curr Opin Endocrinol Diabetes Obes 2011; 18: 310–314.
16. Ha EJ, Baek JH, Lee JH, Kim JK, Shong YK. Clinical Significance of vagus nerve variation in radiofrequency ablation of thyroid nodules. Eur Radiol 2011; 21: 2151–2157.
17. Hampel R, Bennöhr G, Gordalla A, Below H. Urinary iodide excretion in adults in Germany 2005 meets WHO target. Exp Clin Endocrinol Diabetes 2010; 118: 254–257.
18. Happel C, Truong PN, Bockisch B et al. Colour-coded duplex-sonography versus scintigraphy. Can scintigraphy be replaced by sonography for diagnosis of functional thyroid autonomy? Nuklearmedizin 2013; 52: 186–191.
19. Huh JY, Baek JH, Choi H et al. Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session--prospective randomized study. Radiology 2012; 263: 909–916.
20. Jeong WK, Baek JH, Rhim H et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol 2008; 18: 1244–1250.
21. Kim YJ, Baek JH, Ha EJ et al. Cystic versus predominantly cystic thyroid nodules: efficacy of ethanol ablation and analysis of related factors. Eur Radiol 2012; 22: 1573–1578.
22. Kim Y-S, Rhim H, Tae K et al. Radiofrequency ablation of benign cold thyroid nodules: Initial clinical experience. Thyroid 2006; 16: 361–366.
23. Korkusuz H, Happel C, Grünwald F. Ultrasound guided percutaneous microwave ablation of hypofunctional thyroid nodules: evaluation by scintigraphic ^{99m}Tc-MIBI imaging. Nuklearmedizin 2013; 52: N68.
24. Korkusuz H, Happel C, Heck K et al. Percutaneous thermal microwave ablation of thyroid nodules: Preparation, feasibility and efficiency. Nuklearmedizin 2014; 53: 123–130.
25. Leidig-Bruckner G, Cichorowski G, Sattler P et al. Evaluation of thyroid nodules-combined use of ^{99m}Tc-methylisobutylnitrile scintigraphy and aspiration cytology to assess risk of malignancy and stratify patients for surgical or nonsurgical therapy-a restrospective cohort study. Clin Endocrinol 2012; 76: 749–758.
26. Na DG, Lee JH, Jung SL et al. Radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: Consensus statement and recommendations. Korean J Radiol 2012; 13: 117–125.
27. Papini E, Guglielmi R, Bizzarri G et al. Treatment of benign cold thyroid nodules: a randomized clinical trial of percutaneous laser ablation versus levothyroxine therapy or follow-up. Thyroid 2007; 17: 229–235.
28. Piga M, Cocco MC, Serra A et al. The usefulness of ^{99m}Tc-sestaMIBI thyroid scan in the differential diagnosis and management of amiodarone-induced thyrotoxicosis. Eur J Endocrinol 2008; 159: 423–429.
29. Ratanaprasatporn L, Charpentier KP, Resnick M et al. Intra-operative microwave ablation of liver malignancies with tumour permittivity feedback control: a prospective ablate and resect study. HPB (Oxford) 2013; 15: 997–1001.
30. Ross DS. Non-palpable thyroid nodules – managing an epidemic. J Clin Endocrinol Metab 2002; 87: 1938–1940.
31. Saggiorato E, Angusti T, Rosas R et al. ^{99m}Tc-MIBI imaging in the presurgical characterization of thyroid follicular neoplasms: relationship to multidrug resistance protein expression. J Nucl Med 2009; 50: 1785–1793.
32. Shamis Y, Taube A, Mitik-Dineva N et al. Specific electromagnetic effects of microwave radiation on

Escherichia coli. Appl Environ Microbiol 2011; 77: 3017–3023.
33. Shamis Y, Croft R, Taube A et al. Review of the specific effects of microwave radiation on bacterial cells. Appl Microbiol Biotechnol 2012; 96: 319–325.
34. Spiezia S, Garberoglio R, Milone F et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid 2009; 19: 219–225.
35. Sung JY, Baek JH, Kim KS et al. Single-session treatment of benign cystic thyroid nodules with ethanol versus radiofrequency ablation: a prospective randomized study. Radiology 2013; 269: 293–300.
36. Valcavi R, Frasoldati A. Ultrasound-guided percutaneous ethanol injection therapy in thyroid cystic nodules. Endocr Pract 2004; 10: 269–275.
37. Valcavi R, Riganti F, Bertani A et al. Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. Thyroid 2010; 20: 1253–1261.
38. Vanderpump MPJ. The epidemiology of thyroid diseases. Br Med Bull 2011; 99: 39–51.
39. Wood MA, Shaffer KM, Ellenbogen AL, Ownby ED. Microbubbles during radiofrequency catheter ablation: composition and formation. Heart Rhythm 2005; 2: 397–403.
40. Yue W, Wang S, Wang B, et al. Ultrasound guided percutaneous microwave ablation of benign thyroid nodules: Safety and imaging follow-up in 222 patients. Eur J Radiol 2012; 82: 11–16.