Thyroid nodules represent a common clinical problem. Besides functional disorders, inflammation and an increase in size, nodules form part of the most frequent diseases of the thyroid gland. The prevalence ranks between 20 and 50% depending on the technique of detection (13, 30, 32, 33, 41), whereupon the incidence increases with continuous protection (13, 30, 32, 33, 41), whereupon the incidence increases with continuous improvement of sonographical capabilities (31).

In Germany, these nodules are benign in most cases; thyroid carcinomas only represent 0.1% of malignant degenerations (8). Yet, benign nodules can cause problems and thus require treatment due to subjec-
breast or lung, liver and kidneys (6). In contrast to the recommended techniques, microwave ablation (MWA) is a non-thermal technique. Ethanol is injected directly into the thyroid nodule producing necrosis. It has been used as a minimal invasive alternative for years showing a sound volume reduction (15, 19), but yet involving various complications and disadvantages (20, 38).

Microwave ablation (MWA) is a new thermal ablative technique to treat thyroid nodules and has been proved effective in individual studies (14, 45).

Until now, studies concerning this field in Europe are lacking. However, MWA is already used to treat malignancies in the lung, liver and kidneys (6). In contrast to RFA, MWA can offer several advantages like:

- larger ablation volumes,
- more homogenous dispersion of heat,
- missing heat sink effect.

Furthermore, MWA is described as less painful (5, 7, 36, 40). The aim of this study was the evaluation of indications, the feasibility of MWA to treat benign thyroid nodules and, moreover, highlight the benefit of functional nuclear medicine imaging to verify effectiveness.

Patients, material, methods

Patients

Eleven patients (6 men, 5 women; average age 62.3 years, range 39 to 81 years) with 18 nodules were treated with MWA.

- Inclusion criteria:
  - subjective symptoms: swallowing problems, a feeling of a ”lump in the throat”, distress,
  - cosmetic problems,
  - refusal of surgery,
  - contraindications,
  - cold nodules in \( ^{99m} \text{Tc} \)-pertechnetate scintigraphy.

- Exclusion criteria:
  - excessive thyroid volume with retrosternal growth,
  - missing symptomatology,
  - histological evidence for follicular proliferation or malignancy,
  - conspicuous \( ^{99m} \text{Tc} \)-MIBI uptake in cold nodules,
  - abnormal calcitonin measurement as evidence for medullary thyroid cancer,
  - critical position near to vessels, trachea, oesophagus or nerves.

Written informed consent was obtained from all patients. The study was approved by the local ethics committee (no. 243/13).

MWA equipment

Microwaves wavelengths ranging from 900 to 2450 MHz produce the desired effect. The microwaves are inserted directly into the nodule through a probe under sonographical guidance. By utilization of the dipole moment of water molecules oscillation and heat are created in the surrounding tissue. Thereby an irreversible coagulation necrosis is induced. The system used (Avecure MWG881, MedWaves, Inc. San Diego, CA) works in a frequency range 902–928 MHz and generates maximum temperatures of approximately 140°C. According to individual aspects of each patient three different probes (uncooled tip, 14–16 G) with diverging ablation areas can be used. The field size varies from 1 cm to 4 cm, all probes feature integrated temperature sensors. The target temperature was 60–80°C with an output of 24–28 W.

Preablation assessment

Prior to each ablation, all patients had ultrasonic examination, laboratory tests, fine needle aspiration biopsy (FNAB) and a \( ^{99m} \text{Tc} \)-pertechnetate thyroid scan. The ultrasound examination was done to evaluate size, number, composition and volume of the nodule. In addition the exact position, the capacity of ablation and the type of vagus nerve (16) was identified. The nodules were classified in mainly solid, cystic and complex (solid and cystic) (45). To exclude malignant thyroid nodules, FNAB, calcitonin measurement and \( ^{99m} \text{Tc} \)-MIBI-imaging were performed. There was no evidence for malignancy.

Laboratory tests included a complete thyroid hormone status, blood count and coagulation diagnostic. All patients received a thyroid scan with \( ^{99m} \text{Tc} \)-pertechnetate (11). Images were taken 20 minutes after injections of 75 MBq \( ^{99m} \text{Tc} \)-pertechnetate and were recorded using a gamma camera with a LETH collimator (Mediso Nuclinete TH/22).

Seven patients with cold nodules in \( ^{99m} \text{Tc} \)-pertechnetate imaging received a thyroid scan with \( ^{99m} \text{Tc} \)-MIBI and FNAB to exclude malignancy (Tab. 1). Scans were taken 10 and 60 minutes after injection of 500 MBq \( ^{99m} \text{Tc} \)-MIBI (Rotopharmaka AG, Dresden, Germany).

Clinical symptoms were assessed during, 24 hours and three months after treatment by a symptom score:

1. no discomfort,
2. moderate discomfort,
3. light discomfort,
4. distinct discomfort.

The following items were evaluated:

- feeling of pressure,
• neck constriction,
• cosmetic image,
• lump in the throat,
• swallowing problems.

Procedure

The intervention occurred under local anesthesia and aseptic conditions. The patient was put into a supine position with extended neck. Before each ablation the patient received 40 drops of Novalgin. At the beginning a local infiltration anaesthesia (Scandicain, 1%) took place, on the one hand to eliminate pain and on the other hand to enlarge the distance between skin and ablation area (Fig. 1). If possible, a transisthmic access was chosen, making it easier to display the whole length of the microwave probe and vital vascular or nerval structures via ultrasound imaging. Besides, the heat impact on the vagus nerve could be kept as low as possible (35). If this was impossible, a craniocaudal access has been chosen (Fig. 2). After identification of the vagus nerve and the so-called “danger triangle”, containing the recurrent laryngeal nerve in most instances (35), the probe was placed directly in the nodule under sonographical control. For this purpose an incision of approximately 2 mm was made. Once the probe was positioned correctly the generator was connected. Afterwards the ablation took place.

During the ablation so-called micro bubbles and hypoechochogenic areas (Fig. 1, Fig. 2) are formed, both display an expression of heat development in the ablation area and can be visualized via ultrasound (44). Thereafter, an ultrasound control of the ablation area was performed in order to expulse local complications. If necessary, the probe was repositioned and other parts of the nodule were treated. Throughout the whole intervention the physician paid attention to the well-being of the patient and possible voice changes.

Concerning cystic nodules, an additional puncture to aspirate contents was done before actual ablation as already described by Kim et al (20). Through this procedure the ablation volume minimizes before ablation.

24 hours after intervention, each patient underwent a thyroid imaging, an ultrasound control to exclude focal complications, laboratory tests and an assessment of the symptom score again. Thyroid scans before and after treatment were compared using CSFIS (center specific functional imaging score). The classification of the nodules by means of the scans in comparison to the surrounding parenchyma of the thyroid was made according to the uptake (none, less, indifferent/neutral, enhanced). On the basis of this classification the CSFIS was developed to illustrate the results of the visual control:
• no storing – 0 points,
• less storing – 1 point,
• indifferent – 2 points,
• exceeding storage – 3 points.

After three months a follow-up examination was performed; nodule volume,

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<tr>
<td>1</td>
<td>59/m</td>
<td>Tc-MIBI</td>
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<td>cold</td>
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<td>750</td>
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<td>85</td>
<td>4</td>
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<tr>
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<td>76/m</td>
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<td>indifferent</td>
<td>cold</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>600</td>
<td>28</td>
<td>85</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>69/f</td>
<td>Tc-Pert</td>
<td>hot</td>
<td>cold</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>720</td>
<td>24</td>
<td>80</td>
<td>4</td>
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<tr>
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<td>61/f</td>
<td>Tc-MIBI</td>
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<td>cold</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>750</td>
<td>24</td>
<td>70</td>
<td>4</td>
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<tr>
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<td>0</td>
<td>1</td>
<td>400</td>
<td>28</td>
<td>60</td>
<td>4</td>
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<tr>
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<td>0</td>
<td>1</td>
<td>300</td>
<td>28</td>
<td>75</td>
<td>4</td>
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<tr>
<td>7</td>
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<td>Tc-MIBI</td>
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<td>0</td>
<td>1</td>
<td>450</td>
<td>24</td>
<td>80</td>
<td>3</td>
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<td>0</td>
<td>1</td>
<td>600</td>
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<td>64/f</td>
<td>Tc-MIBI</td>
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<td>24</td>
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<td>3</td>
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<tr>
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<td>Tc-MIBI</td>
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<td>0</td>
<td>1</td>
<td>420</td>
<td>24</td>
<td>80</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>65/m</td>
<td>Tc-Pert</td>
<td>indifferent</td>
<td>cold</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1200</td>
<td>24</td>
<td>80</td>
<td>4</td>
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</table>
symptom score and laboratory test were reassessed. 3 of 11 patients did not participate and were not integrated in statistical analysis of symptom score change and volume reduction.

**Statistical analysis**

All statistical analyses were performed with dedicated software (Bias®, Windows, Version 10.04, epsilon Verlag, 1989–2013). Due to non-symmetric distribution of CSFIS, symptom score and volume variables non-parametric tests were used. Significant differences were evaluated by Wilcoxon matched pairs test. Ablation parameters (time, output, temperature), volume reduction and change of Symptom Score are given as mean ± standard deviation. Changes in CSFIS are given as median. Results were considered to be significant at p < 0.05.

**Results**

In all 11 sessions the whole volume of the 18 nodules could be ablated. The treatment was well tolerated by all patients, an interruption was not necessary. The time of ablation per nodule was 552 ± 224 s (range 300–1200 s), the output 25.1 ± 1.8 W (range 24–28 W), the temperature was 74.7 ± 9.2°C (range 60–85°C) (▶Tab. 1).

**Symptom score**

All patients reported less distinctive symptoms after treatment than after ablation. The mean change of the symptom score was 2.0 ± 1.1 points after 24 hours (range 0–3 points, p < 0.05) and 2.5 ± 0.93 points after 3 months (range 1–3 points, p < 0.05) (▶Tab. 1).

**Volume reduction**

Ultrasound examination showed a significant decrease of nodule volume in all patients. The mean volume reduction was 6.8 ± 3.8 ml (range 2.4–11.6 ml) or 54.2 ± 19.5% (range 19.9–77.3%) at the 3-month follow-up (p < 0.05).

**Safety and treatment tolerance**

The procedure was tolerated well by all patients, although there have been various adverse effects. All patients reported mild pain and a slight feeling of pressure during the ablation, whereas, no patient claimed to stop the procedure. The pain decreased with reduction of the temperature. No further treatment was required; the pain vanished after ablation. Two patients developed first-degree burns alongside the puncture channel. The burns did not need any treatment and disappeared within a couple of days. Mild superficial haematomas due to pressure of the ultrasound probe appeared in all patients and faded within the next few days. Ultrasound controls assured that these haematomas did not reach deeper tissue layers. Three patients experienced a dragging pain towards the mandibular angle and ear during the treatment.

There were no swallowing problems, vagal reactions or subjectively noticeable voice changes. Serious complications like secondary haemorrhage, infection, nodule ruptures, deep haematomas or injuries of the vagus or recurrent laryngeal nerve did not occur (▶Tab. 2). One patient with formerly established diabetes mellitus developed increased blood sugar levels. In another patient a slight hyperthyreosis was
discovered after ablation. The thyroid function normalized within one week without any further problems. The patient was treated with microwave ablation because of an indifferent nodule which could not be treated with radioactive iodine therapy due to low uptake in the radioiodine test. All other patients had a euthyroid thyroid function after ablation. In the post therapeutic observation period no other complications were monitored.

**Scintigraphy**

A visual control of the scans was realized by two nuclear medicine specialists with long-time work experience. Pre- and post-ablative images of the ablation area were compared. After the treatment, previously indifferent nodules showed a decreased uptake in the $^{99m}$Tc-pertechnetate-scan in reference to the sonographically defined zone. Previously cold nodules showed a missing uptake in the $^{99m}$Tc-MIBI-scan compared with the preablative image in reference to the sonographically defined area. The CSFIS decreased in all cases after treatment, all ablation areas appeared as cold areas with a CSFIS of 1 or 0 points in $^{99m}$Tc-pertechnetate-scan as well as in $^{99m}$Tc-MIBI-scan.

The mean CSFIS reduction was 1 point ($p < 0.05$). In 66.7% ($n = 12$) of the nodules the CSFIS reduced by 1 point, 27.8% ($n = 5$) by 2 points and 5.6% ($n = 1$) by 3 points. Regarding $^{99m}$Tc-MIBI-scans only, the CSFIS reduced by 1 point in 66.7% ($n = 6$), in 22.2% by 2 points ($n = 2$) and in 11.1% by 3 points ($n = 1$). The mean decrease was 1 point ($p < 0.05$). Regarding $^{99m}$Tc-pertechnetate-scans only, the CFIS reduced by 1 point in 66.7% ($n = 6$) and in 33.3% by 2 points ($n = 3$). The mean reduction was 1 point ($p < 0.05$). The CSFIS did not change in surrounding thyroid tissue.

**Discussion**

The therapy options currently employed for benign thyroid nodules, especially the surgical removal, are mostly successful. However, they involve drawbacks and complications as for example scar formation or nerveal lesions (10, 14, 29).

Minimal invasive alternatives are reasonable. Ethanol sclerotherapy offers a minimally invasive method to treat thyroid nodules and has been tested since 1990 as an alternative to conventional treatment. Kim et al. (19) reported a mean reduction volume of 65% at a 4.4 month follow-up, Guglielmi et al. (15) even reported 82.7% for cystic nodules. Nevertheless, ethanol injection has some drawbacks. First of all, there is the need of multiple sessions until total cure and it is more effective for cysts than large or solid nodules (19). With an increase of the number of sessions there is also an increase of side effects. Even major complications such as vocal cord paresis, haematoma, abscess or dysphagia have been reported by Tarantino et al. (38). Another drawback is the unpredictable leakage of alcohol in surrounding thyroid tissue causing extraglandular fibrosis and pain (38).

Compared to ethanol injection, thermal ablations such as MWA and RFA offer some advantages:

- a well-defined area and
- a regular and homogenous ablation.

Within the group of thermo-ablative techniques RFA has already been established for the treatment of benign and malignant thyroid nodules (26, 29, 35). A significant decrease of the nodule volume and the symptomatology has been shown. Neverthless, this type of ablation holds several drawbacks compared to MWA, for instance dependency on impedance, heat sink effect conditioned by big vessels in the surrounding area as well as the difficult homogeneous heating of well-vascularized nodules (5, 7, 36, 40). The following complications were reported for RFA: pain, haematomas, voice changes, skin burns, hypo- and hyperthyroidism, infections and nodule ruptures (3).

In contrast, MWA is a new technique in the field of thyroid nodules, although it has already been used successfully for the treatment of lung-, liver- and renal tumours (14, 40). MWA is a secure method for thyroid nodules, which has already been described in a few non-European studies (14, 45). Feng et al. (14) described an average reduction of nodule volume of 45.99 ± 29.9% after 12 months and Yue et al. (45) even reported a nodule volume reduction ratio of 65 ± 65% at the 6-month follow-up.

**Tab. 2** Complications

<table>
<thead>
<tr>
<th>complication</th>
<th>number of complications (%)</th>
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<tbody>
<tr>
<td>pain during ablation</td>
<td>11 (100)</td>
</tr>
<tr>
<td>swallowing problems</td>
<td>11 (100)</td>
</tr>
<tr>
<td>hoarseness</td>
<td>0 (0)</td>
</tr>
<tr>
<td>dragging pain in mandibular angle and ear</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>voice changes</td>
<td>0 (0)</td>
</tr>
<tr>
<td>superficial haematomas</td>
<td>11 (100)</td>
</tr>
<tr>
<td>deep haematomas</td>
<td>0 (0)</td>
</tr>
<tr>
<td>first-degress burns</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>infection</td>
<td>0 (0)</td>
</tr>
<tr>
<td>nodule rupture</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
In our study, a volume reduction by MWA of 54.2 ± 19.5% could be shown at 3-month follow-up. This indicates that MWA is an effective procedure to treat benign thyroid nodules.

The exact mechanism of MWA has not yet been detected, but other studies dealing with thermal ablation assume coagulation necrosis and protein denaturizing caused by heat. In this study, temperatures between 60°C and 85°C were applied, showing that MWA with 60°C is supposedly as effective as with 85°C. Presumably, a temperature of only 60°C is too low to cause only thermal but non-thermal effects. Non-thermal effects of microwaves applied to human cells have not been described yet, but were tested in bacteria. Shamis et al. (34) report cell changes in E. coli due to electroporation, pores in the cell membrane open causing free diffusion of molecules. Banik et al. (4) speaks of ion acceleration and collision as well as dipole rotation causing changes in protein structure. The following non-thermal effects caused by MWA are possible to cause cell death in thyroid nodules: changes in
- cell morphology, especially cell membrane and ionic channels,
- protein structures due to dipole moment of molecules
- membrane polarity leading to apoptosis,
- mitochondria.

In previous studies about RFA and MWA ultrasound or Doppler was used to monitor the decrease of blood flow and volume. The follow-up examinations to verify the efficiency took part one to three months after the actual intervention. To our knowledge, there are no publications concerning ultrasound displaying evidences for changes of the ablation area in early post-ablative periods. Of course, ultrasound is still a cost-effective, mostly available and easily applicable method. However, concerning the imaging of the ablation area ultrasonography involves a few disadvantages: First of all, structural changes, as seen in ultrasound, most likely do not develop directly after treatment and are not detectable in early post-ablative phases. Moreover, studies showed that B-mode ultrasound displayed a too low contrast between treated and untreated tissue, the necrotic area could not be clearly defined during ablation (43). Zhou et al. (46) states, that B-mode ultrasound does not reflect the genuine conformation of thermal lesions.

A study on RFA in in vivo porcine liver tissue by Correa-Gallego et al. (9) showed, that ultrasound and elastography, as a technique based on ultrasound, significantly underestimate the size of the ablation area, due to the fact that these methods are “unable to predict the degree of cellular injury” (9). Similar findings have been seen by Pareek et al. (28) in kidney tissues. This increases the risk of incomplete ablation and recurrences.

In conclusion, ultrasound and additionally elastography are not absolutely adequate for early post-ablative measurement of the ablation zone.

Nuclear medical techniques and thereby functional verification of the ablation area has not been used until now but scintigraphy features various advantages over ultrasound.

Scintigraphy does not only picture the decrease of volume, as ultrasound does, but also proves molecular-based changes of the nodular function caused by MWA.

99mTc-pertechnetate is a substrate for the sodium iodine symporter in thyroid tissue (21). After MWA there is no further uptake of 99mTc-pertechnetate in indifferent nodules, thus these molecular-based processes are changed and iodine-storing tissue in the ablation area seems to be destroyed. Regarding cold nodules, 99mTc-MIBI can be used to show changes of the ablation area in pre- and postablative scans. 99mTc-MIBI accumulates in mitochondria and is dependent on sodium influx (2). MIBI-posi-
tive areas show no uptake after MWA, the required mitochondrial membrane potential must be destroyed by necrosis.

In our study the verification by thyroid scans occurred 24 hours after the intervention. More specific and over all earlier statements about the achievements of the thermal ablation are possible. Changes can already be seen shortly after the treatment. In the post-ablative early phases every patient presented a decrease in uptake and storage of the defined areas, a significant change of CSFIS was statistically proven. Moreover, with scintigraphy displaying high resolution imaging, numeric analysis of various diameters are possible. Furthermore, scintigraphy is still the most accurate diagnostic test for detection of thyroid dysgenesis (25), especially considering autonomy (17). Another potential advantage of scintigraphy displays the fact that patients with cold nodules benefit from the high negative predictive value for malignancy of $^{99m}$Tc-MIBI-scans performed with each MWA (24) and the high detection rate of $^{99m}$Tc-MIBI-scans combined with FNAB in comparison to FNAB only (27).

We compared $^{99m}$Tc-MIBI-scans and $^{99m}$Tc-pertechnetate-scans with regard to functional imaging of MWA and change of CSFIS. Both methods seem to be equally applicable; both showed a statistically significant difference in CSFIS and comparable results (Fig. 3).

As far as effectiveness is concerned, the decreased uptake shows a positive impact on the thyroid nodule directly after ablation. In conclusion, this decrease is equivalent to a beginning involution of the nodule. The quick improvement of symptoms, as shown in this and other studies (14, 45), seems to be another demonstration of success, the symptom score was reduced significantly. 3-month follow-up results confirmed these findings.

The surrounding thyroid tissue was not affected by treatment of the nodules; the ablation area is well defined. Various complications emerged; but all vanished without further treatment. Overall, the treatment tolerance was high.

RIT is still a well-established, effective method for treating thyroid diseases, especially autonomous adenomas, multinodular goiter and Graves’ disease (12, 39). MWA could be used as an addition to RIT treating mainly multinodular goiter, most likely offering better prospects. There has already been a first attempt of combining RIT and MWA to treat multinodular goiter (22).

In terms of RIT there are few limitations and contraindications as well; most important are pregnancy and lactation, thyroiditis, pituitary hyperthyroidism, euthyroid hyperthyroxinaemia or a minor uptake in the radioactive iodine uptake test (12, 42). These limitations could display special cases to use MWA as an alternative. Thus, the following indications can be named for the use of MWA:

- non-malignant cold nodules,
- indifferenct nodules with local symptoms,
- relapse of goiter in state after surgery,
- contraindications to surgery or RIT,
- a combination of MWA and RIT for simultaneously appearing cold and hot nodules.

**Limitations**

The present study has limitations such as a small number of patients and nodules, a short follow-up period and no definite exclusion of malignancy without histopathological. Further measurements will show how the ablation area develops and if first promising results for effectivity of MWA are confirmed. Functional imaging shows early-phase and molecular-based changes of the ablation area, which cannot be seen in ultrasound measurements. Still, as radioactive devices should be used reasonably, further studies are needed to approve the benefit of functional imaging.

**Conclusion**

- Microwave ablation is an easily performable and effective technique for an out-patient treatment of benign thyroid nodules. Controls show an early decrease of uptake in scans in the ablated areas, volume is significantly reduced at 3-month follow-up.
- Functional imaging seems a promising technique for post-ablative and early-functional evaluation of microwave ablation efficiency.

Due to the small number of cases further studies and controls of the previously treated patients are required.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**