European Journal of Radiology 85 (2016) 2127–2132

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Cooled microwave ablation of thyroid nodules: Initial experience

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ARTICLE INFO

Article history:
Received 26 July 2016
Received in revised form 2 September 2016
Accepted 22 September 2016

Keywords:
Microwave ablation
Thyroid nodules
Volume reduction
Ultrasound-guidance
Pain scale

ABSTRACT

Objective: To evaluate if internally cooled microwave ablation (cMWA) is a safe and effective method for treatment of benign and malign thyroid nodules.
Methods: 9 patients with 11 symptomatic cold benign thyroid nodules and 1 recurrent thyroid carcinoma ranging in volume from 9.1 to 197 ml (mean size 52 ± 57 ml) were treated with cMWA. The mean age of the patients was 59 years. Pain during the treatment was measured on a 10-point scale. Side effects revealed by ultrasound or patients' complaints were documented. Periablative efficacy was measured 24 h after cMWA as change (Δ) in serum thyreoglobulin (Tg). Nodule elasticity was measured on a 4-point scale, blood circulation and echogenicity on a 3-point scale.
Results: All patients tolerated cMWA well. Median pain intensity averaged 2.1 ± 0.8 (range: 1–3). Postablative hematoma was observed in all cases. In no cases ablation led to hoarseness, superficial burns, nodule ruptures, vagal reactions or dysphagia. cMWA lead to a significant decrease of blood circulation, nodule echogenicity and a significant increase of elasticity (Δ = 1.1 ± 0.33; 0.8 ± 0.4 and 1.1 ± 0.6 points)($p < 0.05$). An average increase of 4495 ng/ml Tg was measured ($p < 0.05$).
Conclusions: cMWA is an effective and secure method for treatment of thyroid nodules.

1. Introduction

Germany is an originally iodine deficient country. A large study including 96278 adults proved that thyroid disorders are still very common in Germany. Thyroid disease like diffuse or nodular disorders are recognizable in about 33% of the adult population. [1].

Thyroid goiters can cause compression of trachea and esophagus and often cause local symptoms, ranging from cosmetic issues, over pain issues to difficulties in swallowing [2]. Large thyroid nodules can even lead into a life-threatening respiratory crisis [3]. Mitigation of patients' suffering and most notably the prevention of malignant reorganization make treatment of symptomatic nodules inevitable.

Standard treatment procedures of thyroid goiters are thyroidectomy and radioiodine therapy. In recent years an improvement of iodine intake caused a decrease of radioiodine therapy and thyroid surgery while thyroid cancer increased moderately, which correlates with the worldwide increasing incidence of this disease [4]. Since 2004 a slight decrease of thyroid surgery and radioiodine therapy could be detected. In spite of the risks about 90.000 (2012) surgical procedures are executed in Germany every year which is whey more frequently than in other countries [5].

As gold standard, surgery is associated with a long list of risks such as injury of the recurrent laryngeal and vagus nerve, damage of the parathyroid glands, wound healing disorders, risk of infections, secondary hemorrhage, long hospitalization, and anesthetic complications [6]. This is particularly a problem for older, multi morbid patients. However, the remaining patient clientele also often refuses treatment, due to surgical complications.

Radioiodine therapy, a frequently performed alternative to surgery, could also be associated with several side effects. RIT should be avoided i.e. in case of large nodules, because unreason-

Abbreviations: MWA, microwave ablation; cMWA, cooled microwave ablation; uMWA, uncooled microwave ablation; RIT, radioiodine therapy; PEIT, percutaneous ethanol injection; RFA, radiofrequency ablation; US, ultrasound.

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http://dx.doi.org/10.1016/j.ejrad.2016.09.019
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Table 1
Side effect rate in n = 9 patients *median pain score on a 10-point scale: 2.1 ± 0.8 (range: 1–3).

Side effects	n (%)
Pain during ablation	9 (100%)
Hematoma	9 (100%)
Hoarseness	0 (0%)
Burns	0 (0%)
Infection	0 (0%)
Nodule rupture	0 (0%)
Dysphagia	0 (0%)
Horner's syndrome	0 (0%)
Vagal reaction	0 (0%)

ably high radiation doses could damage other organs with a high radioiodine-131 uptake like i.e. urinary bladder and kidney.

Thus, various non- and minimal invasive approaches as laser ablation, ethanol injection, and radiofrequency ablation have been attempted and have proven to be an effective alternative approach by a variety of international literature [7]. Percutaneous ethanol injection therapy (PEIT) was the first alternative to surgery offering promising results in long-term experiences [8]. Later on Ultrasound-guided thermal ablation of tumors came to the fore. Goldberg et al. reported optimistic results after Radiofrequency ablation (RFA), Percutaneous Laser ablation (PLA), and Microwave ablation (MWA) used in different types of tumors including treatment of hepatocellular carcinoma (HCC) [9]. A possible advantage of these methods is, that in contrast to PEIT, a defined area of tissue could be ablated exactly. In 1994 Seki et al. were the first to research the efficiency of MWA after treatment of 18 patients suffering from HCC [10]. In 2012 Feng et al. were the first ones to start trials of MWA in benign thyroid nodules offering promising good results [2]. Since then many studies were done researching MWA of thyroid nodules supporting the thesis that MWA is a secure and predictable treatment option to cure thyroid nodules [2,11].

Our study is the first to compare patient comfort and safety during a cMWA procedure with other ablation methods relying on patient pain score during RFA and occurred side effects after uMWA. All patients got ablated in a single treatment session.

The aim of this study is to analyze whether there are any relevant differences between internally cooled shaft or non-internally cooled shaft microwave ablation and Radiofrequency ablation relying on patients safety and if one of the methods should be preferred.

2. Material and methods

2.1. Patients

9 patients (4 male) with an average age of 59 years (range: 41–77 years) and a total of 12 nodules underwent cooled microwave ablation. 11 nodules were classified as cold, complex, benign thyroid nodules, 1 nodule was classified recurrent carcinoma. The nodule volume ranged from 9.1 to 197 ml with a mean volume of 52 ± 57 ml. All patients refused surgery due to possible side effects while suffering symptoms (Table 1) that made treatment inevitable e.g. cosmetic problems or compressive symptoms like foreign body sensation. Exclusion criteria included critical nodule position to adjacent structures such as the recurrent laryngeal nerve, esophagus and the trachea. The same surgeon treated all patients. The local ethics committee approved the study. Each patient had to categorize his individual pain score during the treatment reaching from 0 = no pain to 10 = most imaginable pain, to quantify whether cooled microwave ablation offers a more comfortable treatment option compared to alternative methods. In order to evaluate the treatment success after cooled microwave ablation, nodule elasticity and echogenicity were compared pre- and post-

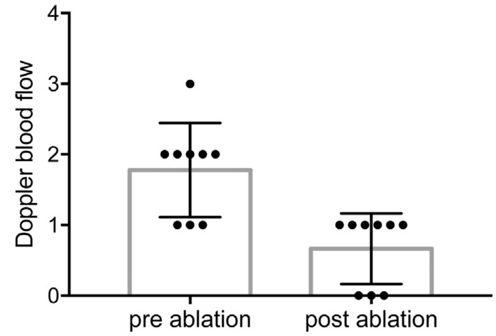

Fig. 1. Doppler blood flow was measured on a 3-point scale (no perfusion = 1; slight perfusion = 2; marked perfusion = 3). Significant ($p < 0.05$) decrease of blood circulation (Δ = 1.1 ± 0.33 points) was measured.

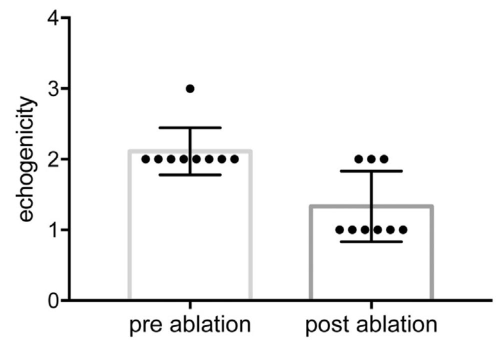

Fig. 2. Echogenicity was measured on a 3-point scale (hypo-echogenic = 1; iso-echogenic = 2; hyper-echogenic = 3). Significant ($p < 0.05$) decrease in echogenicity (Δ = 0.8 ± 0.4 points) was measured.

surgical. Echogenicity, Doppler blood flow and (Fig 1) elasticity were categorized: Doppler blood flow was measured on a 3-point scale (no perfusion = 1; slight perfusion = 2; marked perfusion = 3), elasticity on a 4-point scale (soft = 1, more soft than solid = 2, more solid than soft = 3, solid = 4), and echogenicity on a (Table 2) 3-point scale (hypo-echogenic = 1; iso-echogenic = 2; hyper-echogenic = 3). All ultrasound data was generated by the SonixTOUCH system (Ultrasonix Medical Corporation, Richmond, BD, Canada) [12].

The entry criteria for this study were:

- growing goiters
- symptomatic benign thyroid nodule
- recurrent carcinoma
- cosmetic concerns
- high operative risk
- refusal of surgery

The exclusion criteria for this study were:

- thyroids with retrosternal growth
- critical positions near vessels, nerves, esophagus or trachea

2.2. Pre-ablative assessment

2.2.1. Laboratory evaluation

Each patient underwent B-mode (Fig. 2) ultrasound and a laboratory test including a complete thyroid hormone status consisting of determination of triiodothyronine (T3), thyroxine (T4) thyrotropine (TSH), and thyroglobuline (Tg) prior to ablation. Additionally antibodies against thyroid peroxidase (anti-TPO), thyroglobuline (TgAb), and thyrotropin receptor (TRAb) were mea-

Table 2
Overview of the results.

patient			nodule			Pain Score	time of ablation [s]	Δ Echo-genicity	Δ Elasto-graphy	Δ Vascular-isation	Δ hTg
no.	age	gender	no.	volume [ml]	type						
1	75	f	1	34	cold	2	637	1	2	1	7637
2	41	m	4	9, 12, 21, 15	cold	1	503	0	2	1	1259
3	49	f	1	128	cold	3	622	1	1	1	15276
4	45	m	1	54	cold	1	544	0	1	1	106
5	47	f	1	41	cold	3	660	1	1	1	4800
6	68	m	1	11	cold	2	467	1	1	1	849
7	56	f	1	197	cold	2	612	1	0	1	2266
8	77	m	1	26	recurrent carcinoma	3	325	1	1	1	422
9	74	f	1	79	cold	2	976	1	1	2	7840
								($p < 0.05$)	($p < 0.05$)	($p < 0.05$)	($p < 0.05$)

sured. All tests were determined with commercially available immunoradiometric assey (IMA) or radioimmunoassay (RIA) kits.

2.2.2. Ultrasound evaluation

In this study B-mode ultrasound images were used to evaluate the size, volume und composition of the Thyroid and the Nodules. All images were conducted by the "Sonix Touch Ultrasound system®", by Ultrasonix Medical Corporation, Richmond, Canada.

2.2.3. Microwave ablation instrument (system)

All patients were treated with the HS Amica microwave ablation system. This system has a maximum output of 100 W (60 W recommended) at a frequency of 2450 MHz with a 17-gauge water-cooled applicator [13]. In the current study all ablations were performed with a power of 60 W as recommended by the manufacturer. Frequencies of microwave ablation devices used for medical applications vary between 915 MHz and 2450 MHz.

This system has an internal fluid cooling of the antenna that is necessary to prevent unwanted thermal damage around the proximal antenna shaft. Furthermore it has an internal temperature sensor for measuring the temperature of the applicator probe.

MWA heats tissue to cytotoxic levels through which cell death is caused. Afterwards the created coagulative necrosis is degraded by the patient's own immune system including macrophages, lymphocytes and neutrophils as effector cells [12]. An electromagnetic field around the applicator antenna forces water molecules in the ablated tissue to oscillate during the microwave ablation, causing kinetic heat in the ablation zone. This leads to one of the main side effect of original MWA: skin burn around the ablation area due to the high temperature that is generated in the probe [14].

2.2.4. Procedure

The complete procedure was performed under aseptic conditions and under local anesthesia (Mepivacain Hydrochloride 1%) to reduce the pain during the skin incision. In order to minimalize the preoperative ablation volume and to reduce the possible heat-sink effects, the anesthetic needle was used to drain the nodule fluid in case of a cystic nodule which has already been described by Kim et. al [15].

After making a 1–2 mm wide skin incision, the ablation antenna was put in the right position under sonographic monitoring. If possible a trans-isthmic access was chosen in order to prevent damage to vital structures. A trans-isthmic approach offers several advantages, such as protection of the danger triangle, the area around the recurrental laryngeal nerve, esophagus and trachea, and furthermore a good visualization of the probe during treatment. If this access was not possible a cranio-caudal access was chosen alternatively. To verify if the microwave antenna was in the correct position, the procedure was accompanied by permanent real-time ultrasound. Microbubbles and hypoechogenic areas, visualizing the

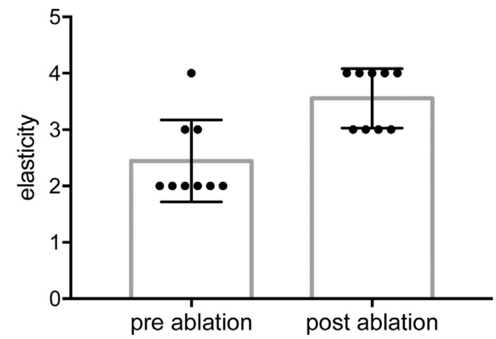

Fig. 3. Nodule elasticity was measured on a 4-point scale (soft = 1; more soft than solid = 2; more solid than soft = 3; solid = 4). Significant ($p < 0.05$) increase in elasticity (Δ = 1.1 ± 0.6 points) was measured.

heat created during MWA were often formed in the ultrasound during the ablation.

2.2.5. Statistical analysis

Statistical analysis was performed using Prism 6 for Mac OS X Version 6.0 f (GraphPad Software, La Jolla, California, USA). Wilcoxon matched-pairs signed rank tests were performed to compare the sonographic scores mentioned above, before and after treatment. Statistical significance was indicated with p-values < 0.05

3. Results

3.1. Assessment of patientís tolerance and safety

During the procedure the patient pain level was measured on a 10-point scale ranging from no pain = 0 to the most imaginable pain = 10. Generated side effects revealed by patients' complaints and by ultrasound were documented. The mean pain score was 2.1 ± 0.8. The treatment was well tolerated by all participants; an interruption during the procedure was not necessary. Each patient suffered superficial hematoma after cMWA. Most likely this is related through vessels around the antennaís shaft and supports the thesis that tissues around the antennaís shaft remain intact. No cases of burns first degree were observed after cMWA which is a frequently appearing side effect after uMWA. In no cases ablation lead to hoarseness, superficial burns, nodule ruptures, vagal reactions or dysphagia.

3.2. Assessment of efficacy

Cooled MWA resulted in a significant ($p < 0.05$) decrease of blood circulation (Δ = 1.1 ± 0.33 points), and echogenicity (Δ = 0.8 ± 0.4 points) with a significant ($p < 0.05$) increase (Fig. 3) in nodule elas-

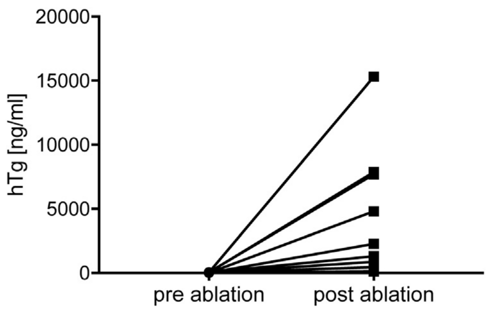

Fig. 4. Significant ($p < 0.05$) increase of serum Thyroglobulin (Tg)-levels (mean Tg 4494.95 ± 5024.47 ng/ml) as evidence that thyroid tissue has been destroyed.

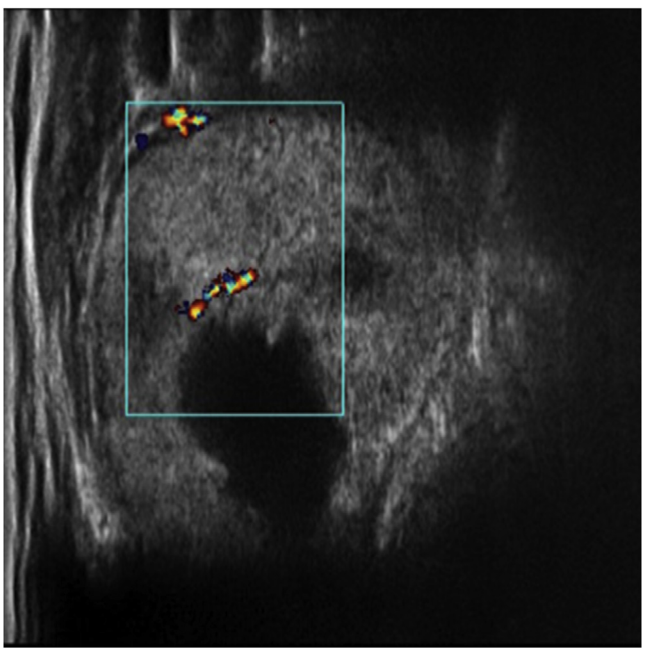

Fig. 5. Color-coded Ultrasound image of the nodule before cooled Microwave ablation treatment showing intranodular blood flow.

ticity (Δ = 1.1 ± 0.6 points) and Tg (median Tg 4495 ± 5024 ng/ml). The increased Tg-concentration after ablation is most likely attributable to thyroid injury and changes in thyroid mass by cMWA. Thermal ablation procedure leads to elevated tissue stiffness (elasticity change) due to protein denaturation and dehydration [16]. Other studies also reported a significant decrease in nodule vascularization after MWA [2].

Still the results of B-mode (Fig. 4) ultrasonography and colour-coded Doppler ultrasound are limited and have to be rated critically because the method is susceptible to artifacts though ultrasound is an easily feasible method to measure nodular changes (Fig. 5) after microwave ablation treatment.

4. Discussion

The common approach of curing benign thyroid nodules is surgery, including long hospitalization, general anesthesia, scar formation, iatrogenic hypothyroidism, and difficulty in reoperation [2]. In order to offer patients an alternative to surgery many studies examined if tumor ablation provides a successful treatment option avoiding the disadvantages of surgery [2,14,17]. Current alternative treatment methods as percutaneous ethanol injections (PEI) [12,18], high-intensity focused ultrasound, radiofrequency abla-

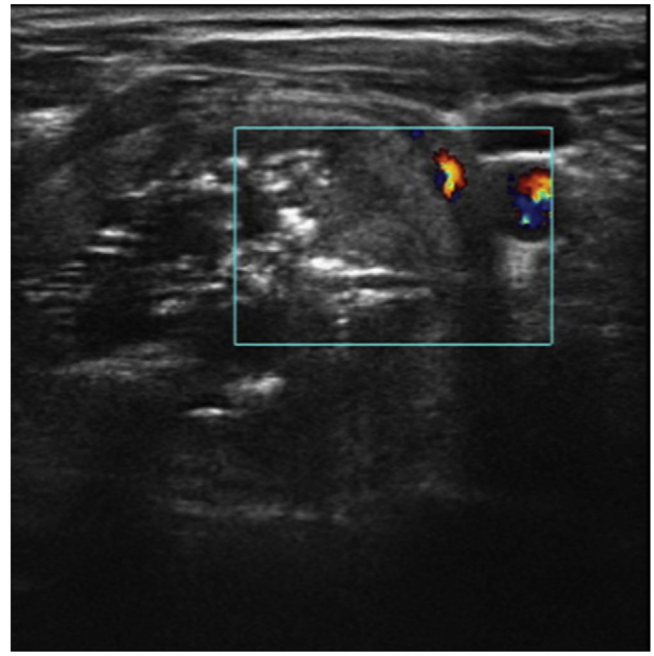

Fig. 6. Color-coded Ultrasound investigation after Microwave ablation does not show any remaining intranodular blood flow.

tion, and (Fig. 6) uncooled microwave ablation have also been examined in multiple studies.

The incidence of thyroid nodules is increased in female gender, with rising age, as well as in people suffering of iodine deficiency, and after radiation exposure [19]. Valcavi et. al reported significant changes of serum thyreoglobulin levels 24 h after treatment which is most likely induced by a high distribution of thyreoglobulin due to thyroid injury [20]. In the current study Tg was significantly elevated 24 h after ablation as well, still thyreoglobulin is a nonspecific finding as it reflects thyroid injury but simultaneously also the change in thyroid mass [20]. Echogenicity was measured on a 3-point score. Hypoechogenic nodules were referred to as US1, isoechogenic nodules as US2 and hyperechogenic nodules as US3. B-mode ultrasonography underlined ablation success due to a decreased echogenicity after ablation. A mean decrease of Δ = 0.8 ± 0.4 points was measured. Furthermore blood flow in the ablated nodules was measured by colour-coded Doppler ultrasonography. Nodules without blood flow were assigned with a Doppler score (DS) of 1, while those with perinodular blood flow were assigned with a DS of 2, and nodules with intranodular and perinodular blood flow were assigned with a DS of 3. The results of B-mode ultrasonography and colour-coded Doppler ultrasound are limited because the method is susceptible to artifacts though ultrasound is an easily feasible method to measure nodular changes after microwave ablation treatment [21].

None of the patients suffered serious (Fig. 7) side effects. Mild pain during the ablation procedure and superficial hematoma around the ablation area were the only inconveniences the patients had to hazard [22]. The mean pain score of 2.1 ± 0.8 provides support for cooled microwave ablation as a more sensitive treatment option than uncooled microwave ablation, which is often associated with skin burn lesions around the ablated tissue. Korkusuz et al. measured patients' pain level during Bipolar Radiofrequency ablation with a mean pain level of 3 including pain intensities reaching from 1 to 7. According to these results cooled microwave ablation is also more convenient for patients than RFA [12].

Compared to radiofrequency ablation, microwave ablation does not rely on the conduction of electricity into the tissue, and is able

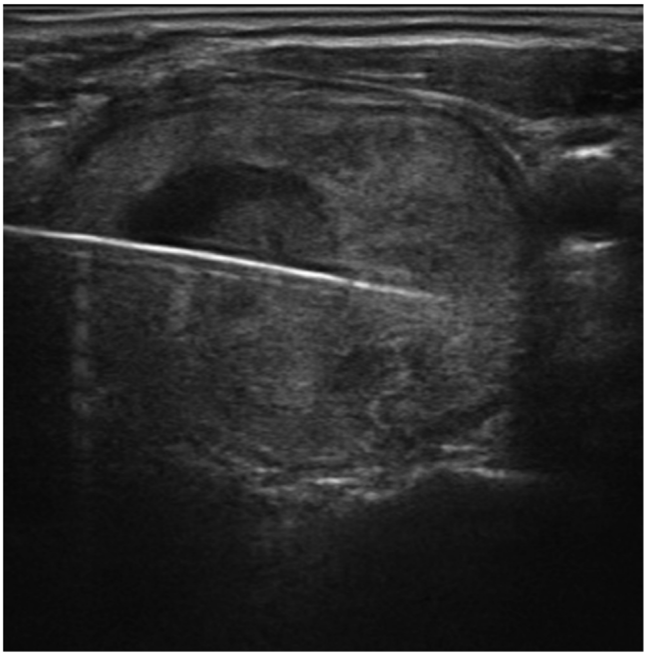

Fig. 7. Ultrasound-guided probe positioning.

to create higher temperatures into the ablation zone which results in a shorter treatment time [23].

Microwaves have the ability to oscillate in all biological tissues, including structures as lung and bone tissue. This enables microwaves to induce heat in a larger ablation volume surrounding the applicator compared to RFA, whereby microwave applicators are able to produce faster, hotter, and larger ablation zones in a bigger diversity of tissue types than RFA [24].

The antenna shaft of non-internally cooled antennas can reach temperatures up to 90 °C, which results in unintended tissue coagulation, whereas the temperatures of internally cooled antenna shafts can only reach a maximum of 20 °C. Unintended tissue necrosis could not be observed in any of the 9 cases above [25]. A reduction of risks for causing local unintended skin burns by using cooled-shaft antenna compared to non-cooled shaft antenna is proved by studies [25].

A study from Liang et al. including a large collective of 1136 patients suffering malignant liver tumor treated with Ultrasound-guided MWA (583 treated with non-cooled shaft antenna, 553 treated with cooled-shaft antenna) underlines the thesis that the use of a cooled-shaft antenna helps minimizing major complications. In their study most cases of skin burn were encountered when uMWA was used [26]. The fact that none of the patients paused the treatment because of pain or discomfort also supports the high potential of cooled microwave ablation. Another advantage of cMWA is the faster ablation procedure due to the higher achievable energy around the probe, which thus allows quicker tissue necrosis than other treatment methods. Compared to non-cooled shaft antennas, cooled shaft antennas seem to be more spherical, additionally they seem to be more effective because they are able to deliver 60 W for a time period of at least 20 min compared to 10 min using a non-cooled shaft [25]. Another advantage of cooled-shaft antennas is the greater percutaneous delivery of microwave energy to treat tumors. When using uncooled-shaft antennas, an elevation of applied energy leads to a rapid temperature increase of the antenna, which goes hand in hand with a less effective ablation, due to greater patient pain level and possible severe damages as skin burn [27]. Due to the aforementioned facts, uncooled-shaft microwave ablation is usually performed in short ablation durations and at low power outputs causing relatively small areas of coagulation necrosis and even incomplete tumor eradication [27–29]. A former study of our institute dealing with initial experiences and occurring complications during and shortly after uncooled antenna microwave ablation shows that patients have to deal with more post- and intraoperative complications than in cases in which cooled antenna microwave ablation systems are used. Korkusuz et al. reported two of 11 patients suffering from first-degree skin burns after treatment with uncooled antenna MWA, while none of the patients in this study suffer from any skin irritations [30].

Although the small patient number of our study represents a limitation, our results are very promising. This study shows the high safety and periablative efficacy of cooled-shaft antenna microwave ablation. Still further studies with a higher number of patients and a longer follow-up time need to be done to allow a clear statement.

5. Conclusion

Microwave ablation with cooled-shaft antenna decreases the risk of skin burn and enables a greater delivery of microwave energy leading to a larger ablation zone which reduces the number of ablation sessions required whereby microwave ablation effectiveness is increased and less risky than uncooled-shaft microwave ablation. In our study only one single treatment session was performed, leading to promising good results referring on raised Tg-concentration post ablation.

Cooled MWA has the potential to be an effective and safe treatment option for thyroid nodules and thus, deserves further refinement.

6. Clinical relevance

- Cooled MWA is a safe and effective treatment for benign and malign thyroid nodules.
- Ultrasound imaging allows guidance during microwave ablation.
- A median pain score of 2 shows that cMWA is a gentle alternative to invasive thyroid surgery.

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