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Value of monopolar and bipolar radiofrequency ablation for the treatment of benign thyroid nodules

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Only a few thyroid nodules are perceived as functional or optically disturbing. If there is a need for action, surgical intervention is the long-term standard by which thermoablative procedures (radiofrequency-, laser-, microwave ablation, high intensity focused ultrasound) must be measured against in terms of safety, effectiveness and patient satisfaction. Prior to intervention assessment of the dignity of the nodule by ultrasound-guided fine needle aspiration is essential for cold and warm nodules, as is the confirmation of an inconspicuous cervical lymph node status. The short-term treatment results of these newer interventions in terms of nodule volume reduction and symptomatic improvement are promising and the general complication rate of the procedures is low. Since functional thyroid parenchyma is preserved, maintaining normal thyroid status is the rule. The procedure is usually performed on an outpatient basis, under local anesthesia and monitoring. The subsequent convalescence is usually very short. Most studies are available on monopolar radiofrequency ablation. Several professional societies have defined indications for radiofrequency ablation (RFA), but these need to be further refined based on practical experience and literature. An acceptable long-term recurrence rate still has to be proven for practically all thermoablative methods, for monopolar RFA limited long-term data are encouraging so far. The recurrence rate as well as patient

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satisfaction will provide the basis for a meaningful overall cost-benefit analysis in the future.

Introduction to thermoablative treatment

Benign thyroid nodules occur with a high prevalence, especially in the elderly population. In Germany, for example, around 40% of the population over 55 years of age show nodules associated with a normal-sized or enlarged thyroid gland [1]. Most of these nodules are not perceived subjectively and are unlikely to grow in the long term. A study carried out prospectively in Italy over 5 years showed a continuous growth in only 11% of the nodules from the time of diagnosis [2]. If about every tenth nodule grows, the high prevalence explains though why symptomatic and/or optically impairing nodules are a relatively common problem. In Austria, thyroid malignancies account for only about 8% of surgically removed nodules, i.e. most nodules are removed to rule out malignancy or because they cause physical or functional discomfort. It is an established fact that in many countries, despite the high diagnostic accuracy of a cytologically benign finding, ultrasound-guided FNPs are still performed far too seldom preoperatively. The positive predictive value (PPV) of a cytological benign finding, however, is 98–99% according to studies by large thyroid centers [3]. Based on a pooled analysis of 12 studies, this figure is still 96.8% [4]. These generally accepted figures make it possible today to think more and more about individual treatment alternatives to thyroid surgery. Since surgical intervention has a long tradition and a wealth of experience, alternative treatment options are naturally only slowly gaining acceptance, especially since there is no single specialist discipline with the necessary training to advance the subject of thermoablation and teach basic skills. It is understandable that with recent developments there is always a time latency of several years until sufficient data on long-term efficacy permit a final cost-benefit analysis. Likewise, for thermoablative methods a more precise indication profile can only be expected over the years.

All thermoablative interventions produce by one way or another “thermonecrosis” via a local, circumscribed damage of tissue when temperatures rise to between 65 and 100 °C. Since at these temperatures cells are irreversibly destroyed, they are subsequently degraded by the body (e.g. by analogy with a bruise), which reduces the volume of the nodules and improves local symptoms. Cell-rich nodules shrink to a greater extent than those having a high proportion of connective tissue. What remains over time is a mostly connective tissue-rich dense nodule with histologically verifiable loose nests of thyroid cells.

All available thermoablative techniques must measure up to the current standard of thyroid surgery in terms of effectiveness, peri- and post-interventional complications, patient satisfaction, and ultimately cost-effectiveness (which includes analyses of several years of prospective follow-up). At the same time, the value of each respective thermoablative technique must still be worked out in carefully planned studies.

Overview of thermoablative techniques

Laser ablation

The first application of laser ablation (LA) in human medicine was mentioned in 2000 in a Russian article by Zubov et al. [5], which described the treatment of 23 patients with cystic nodules with a ND-YAG laser. The first ablation of an autonomous adenoma dates back to 2003 [6]. Numerous other papers on this topic were then published by Italian working groups, which still regularly use this technique today. LA is usually performed under local anesthesia or analgosedation. After planning the procedure, one or more 21G guide needles are placed within the nodule under ultrasound guidance. If several

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needles are used, they are placed at a distance of about 10 mm from each other. Subsequently, a laser fiber is inserted through these needles up to their opening. The guide needle is then retracted slightly so that the fiber lies about 5 mm free in the tissue. By applying a so-called "pull-back technique", the fiber is then pulled through the tissue step by step, with simultaneous retraction of the guide needle. With about 3 W an energy of 1200–1800 J is emitted. Sometimes, the completeness of this process is checked by subsequent application of contrast-enhanced ultrasonography (CEUS), which can very sensitively detect vascularization within a nodule remnant. In a longer, prospective multicenter study by Papini et al. a volume reduction of 60 ± 24% and 57 ± 25% was observed after two and three years, respectively [7]. At the 3-year follow-up visit a "therapeutic success" (usually defined as ≥50% volume reduction) was documented in 67% of the patients. Only 5% showed a partial enlargement of the nodule. In another 3-year observational study of 82 patients treated with LA for "toxic" nodules, a clear association was found between initial nodule size and functional success, i.e. achieved euthyroidism [8]. While normal thyroid function could be restored in 90% of patients with nodule volumes between 5 and 15 ml, this was only the case in 61% and 29% of patients with larger nodules (15–25 ml and >25 ml, respectively). The safety of LA has been investigated in numerous studies. A multicenter, retrospective study of 1837 treatments showed a generally low complication rate of 0.9%. No life-threatening incident occurred [9]. Temporary vocal cord paralysis occurred in 0.5% of cases, other complications were limited to subcapsular or perithyroidal hematoma or skin burns. A retrospective propensity score matching analysis demonstrated a slight superiority of LA over RFA [10]. After 12 months the volume reduction ratio (VRR) was 70 ± 19% for 449 LA treated nodules and 62 ± 22% for 152 RFA treated nodules ($P = 0.001$). In a subgroup of large nodules with volumes >30 ml the result was even more clearly shifted in favor of LA (−73 ± 18%) versus −54 ± 23% in the RFA group ($P = 0.001$). At the same time, the authors of this multicenter study reported that the specific experience of the interventionists played a significant role in modifying the outcome data, which unfortunately limits the overall conclusion of this comparative study (LA versus RFA) by some extent. In addition, an earlier comparative study from 2015 should be mentioned, which was based on "traditional pooling" and "Bayesian network meta-analysis" and found a superiority of RFA over LA [11].

In summary, LA is in most cases a very effective and safe treatment method, which is also accompanied by a corresponding improvement in local pressure symptoms. For larger autonomic adenomas above 15 ml, treatment may have to be repeated or supplemented in many cases by other measures if functional euthyroidism is to be achieved in all cases. As with other ablation techniques, the interventionist's experience seems to influence the final outcome significantly.

Microwave ablation

Approximately 11 years after LA was first used in humans, a study in 2012 also showed treatment potential for microwave ablation (MWA) [12]. This type of ablation technique uses a thicker (16G), usually cooled applicator, which is inserted into the nodule following local anesthesia. In a 12-months prospective comparative study with surgical intervention in a relatively small MWA group of 28 patients (average baseline nodule volume of 17 ± 11 ml) a VRR of 92%, a lower complication rate, better indices of "general" and "mental" health, as well as lower overall costs were reported and MWA seen as an effective alternative to surgery in selected cases [13]. A retrospective, monocentric study with 474 nodules (more than 10% were treated more than once) deserves mention due to its size [14]. Here, with an initial nodule volume of about 13 ml, a VRR of 90% was observed after 12 months and 94% at an unspecified "last" follow up (up to 4 years). Since the MWA applicators have a larger diameter, the report on bleeding complications in only 3.2% of patients in this study is certainly of interest. These bleeding complications were treated either by local MWA with the applicator itself, by compression for 30–60 min, or with hemostyptics if necessary. Temporary recurrent laryngeal nerve paresis occurred in 0.6% and pain in 6.5% of patients.

In a meta-analysis of 9 studies involving 1461 patients treated with either cooled or uncooled MWA, VRR was approximately 88% for both investigated systems at 12 months [15]. In the analysis of "all complications" and "periinterventional pain burden", however, there was a significant advantage for the cooled versus the uncooled MWA (30 versus 98% or 5 versus 100%; both $P < 0.01$). A Chinese retrospective comparative study (based on propensity score matching) between MWA and bipolar RFA

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(bpRFA) of 158 and 102 patients, respectively (with rather small mean baseline nodule volumes of 5 ml) showed a comparable VRR of 81 and 83% after 12 months, respectively, with no significant complications in either group reported [16]. In both groups, as in other studies on MWA, a so-called "hydrodissection technique" was applied, in which a mixture of 2% lidocaine and 0.9% saline solution was infused along the thyroid capsule to shield important structures (such as nerves, carotid artery, trachea or esophagus) from thermal overheating. With the exception of the above-mentioned study by Liu et al. [14] there are no other longer-term data or reports of patients with autonomous adenomas available.

High intensity focused ultrasound

Like MWA, this technology belongs to the newer ablation techniques and differs in some aspects from the above described ones. First treatments with the high intensity focused ultrasound (HIFU) method in humans were published in 2011 [17]. HIFU is based on the principle of bundling ultrasonic waves, which are directed into the interior of the nodule to deliver a corresponding energy deposition which leads to thermonecrosis. It is a non-invasive procedure because the skin above the treated area must be cooled though but remains intact. The nodule is processed and degraded by the device in "voxel volumes" of about 5 × 5 mm (width) and 7 mm (depth). A treatment impulse lasts about 8 s and is followed by a cooling pause of about 20–30 s. The positioning of the patients' head must be kept stable over the treatment period of about 30–45 min (e.g. for a 13 ml nodule), otherwise the device switches off automatically during movements. Larger nodules require two or more treatments. A good analgesia is important, as the ultrasound waves cause irritation of the ventral capsule of the thyroid as well as of structures located further dorsally (dorsal capsule parts, muscle fasciae, brachial plexus). The consequences can be pain radiations into the neck and shoulder region. Among the few working groups that have published worldwide in the field of HIFU, Prof. Lang et al. from the University of Hong Kong has the greatest experience. He frequently uses pericapsular 1% lidocaine infiltration as well as intravenous administration of pethidine and diazepam for analgesia. Despite these measures he reports in a recent study with 128 patients an average burden of pain of 65/100 ("moderate to severe" on an visual analogue scale) in more than 50% and only 12.5% of the patients did not complain of any symptoms [18]. Among the complications worth mentioning are temporary recurrent laryngeal nerve paresis in approx. 1–2%, and skin burns in <1% of cases [19]. Recent developments such as a "low-energy" HIFU in which the pulse energy can be reduced to a minimum [20], or the intravenous administration of so-called "nanodroplets" which can potentiate the effects of the transmitted ultrasound energy, may in future make it possible not only to reduce the duration of treatment time but also accompanying pains. The longest prospective observation period after a single HIFU treatment is 2 years and includes experience with 108 patients [21]. The VRR of medium-sized nodules (13 ± 10 ml) was 68% and 70% after one and 2 years respectively. A "therapeutic success", i.e. a VRR of ≥50% was demonstrated in 67% of patients after 1 year and 70% after 2 years. While in 58% of patients the nodule volume tended to decrease between the first and second year, 20% showed an increase of 13 ± 9% during this period, however, in absolute figures this corresponded to a change of only 0.4 ± 0.6 ml. A medium baseline symptom score (determined with the VAS scale) of 4.1 significantly decreased to 2.5, 1.5 and 1.2 after 6, 12 and 24 months, respectively. Longer-term observations of this cohort as well as the experiences of other working groups are mandatory for a final assessment of HIFU. In patients with autonomous nodules the therapeutic possibilities with HIFU appear to be limited, however, because thorough ablation including nodule periphery is generally important to achieve euthyroidism in such a setting. Despite treatment of very small autonomous nodules averaging 1.7 ml (0.4–6.4) in 15 patients from Switzerland, only 26% showed normalization of their thyroid function after 12 months and 53% a perceptible change in a follow-up thyroid scan [22]. A potential limitation of the publication is that it does not reveal how much experience the authors had with the HIFU application before initiating this study.

Monopolar and bipolar radiofrequency ablation

Monopolar RFA (mpRFA) of thyroid nodules was developed for the treatment of benign and later also malignant indications by Prof. Baek in 2002, who is an interventional radiologist at the Asan

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Medical Center in Seoul and has been continuously working on this method ever since. In 2006, Kim et al. published the first promising treatment results for 35 benign nodules [23]. Among the different thermoablative methods currently in use, mpRFA is the best investigated and established technique. Several Italian experts now offer mpRFA in addition to LA. According to the authors' knowledge, bipolar RFA (bpRFA) is currently used almost exclusively in Germany. In Austria, for example, both mpRFA and bpRFA are offered, so that both variants of RFA will be examined in this article. The bpRFA represents the latest development in thermoablative methods, as the first treatment studies were not published until 2016 [24,25]. The fact that bpRFA already occupies some space in this article is based on positive results on short-term efficacy [16,24,26,27], as well as on the personal experience of one author (HD) that many nodules seem well suited for this method which is especially at the beginning easier to handle than mpRFA. Therefore, bpRFA has the potential to be well received by future interventionists, probably to a greater extent than other technically more demanding methods.

Setting and technical aspects of RFA

The single most important prerequisite before performing an RFA is a thorough ultrasound examination of the thyroid gland and neck region including the cervical lymph nodes by an experienced thyroid specialist. FNA of the nodule must be ultrasound-guided and can be performed once when the sonographic aspect suggests a very low risk for malignancy. In case of conspicuous morphological features, FNA should be performed twice to rule out malignancy and can be waived in case of an unambiguous hot nodule on a thyroid scan in a patient with subclinical or overt hyperthyroidism [3,28]. Regarding latter there is also the opinion of performing a single FNA prior to RFA [29]. In an Austrian position paper on RFA, the general implementation of having a professional vocal cord status performed before and shortly after RFA was defined as a necessary quality assurance measure that has also a long-standing tradition in patients going to surgery. As another part of the mentioned quality measure program the use of a uniform, nationwide consistent, detailed patient information and informed consent is required for RFA interventions in Austria and includes the following statements [28]:

Practice points

- all treatment options have been discussed with the patient
- volume reduction depends on time and nodule structure
- possible interventional risks and complications (pain, laryngeal nerve paresis, bleeding, etc.)
- possibility of nodule recurrence and necessary follow-up treatment (especially in patients with autonomous nodules and hyperthyroidism)
- importance of correctly stating medications before RFA (due to possible risk of bleeding)
- directives for the days following RFA
- requirement of follow-up visits

Ideally, RFA should be performed on the head side of the patient with the monitor in front of the eyes, as this allows an excellent overview and at the same time a relaxed posture for the interventionist (Fig. 1). Usually RFA is performed with two assistants. The patient is continuously monitored during the procedure. After subcutaneous and pericapsular (sometimes also paratracheal) infiltration with a local anesthetic, the RFA applicator is inserted into the nodule from a transisthmic route (rarely laterally). The nodule is then treated systematically “slice by slice” from cranial to caudal and within each treatment plane from medial to lateral. While with mpRFA “club-shaped” heat fields are “pulled” through the nodule (“moving shot technique”), the bpRFA applicator is positioned at a few strategically important locations within the nodule from where a “ball-shaped” ablation area spreads out and finally covers the entire nodule including its periphery (Fig. 2A and B). The figure illustrates the difference in the guidance of the RFA applicator of the two methods as well as the critical anatomic perithyroidal structures. The applicators thickness for mpRFA is usually 18G and for bpRFA 16G. The “active tip” length of the mpRFA applicator is between 5 and 15 mm, and for bpRFA it is 9–40 mm. In case of mpRFA the applicator is cooled with cold water or saline solution, in case of bpRFA with water at room

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Fig. 1. Typical setting during radiofrequency ablation of a benign thyroid nodule.

temperature. Grounding of the current flowing from the probe tip through the nodule, the capsule and the body is necessary with mpRFA and therefore grounding pads must be attached to both thighs. The grounding itself is not accompanied by any discomfort. In male patients, these areas must therefore be shaved before hand. With bpRFA, grounding is not necessary because the electromagnetic field between the cathode and anode is built up within the tip of the applicator.

In Table 1 the application profile of the two RFA systems is compared. In summary, the bpRFA technique is easier to use, but cannot be applied to all nodule geometries to the same extent as is the case with mpRFA. Sharply defined, spherically or ellipsoid shaped nodules are good candidates for bpRFA, as the periphery of the nodules can usually be reached well.

An Italian expert group has recently formulated a proposal for standardization of terms related to RFA as well as uniform outcome data, which will prove to be very helpful for the further development of this area [30].

Outcome with radiofrequency ablation treatment

There are a numerous observational studies on mpRFA, although most of them are retrospective in nature and some describe the effects on comparatively small initial nodule volumes. In the last 3–4 years, however, several studies have been published which already show relatively large numbers of treated cases. In principle, the results of these studies, as in other interventional areas, are relatively difficult to compare because the size of the nodules, the nodule consistency, the experience of the interventionist, the different observation periods and, above all, the number of treatments per patient clearly influence the outcome. For this reason, Table 2 lists exclusively studies in which mpRFA was performed only once. The vast majority of studies have been published by Korean and Italian working groups. Of the twenty studies extracted, eleven presented “last follow-up” data at 6–8 months (mean initial nodule volume: 13 ml, VRR: −74%), five at 12–13 months (20 ml; VRR: −75%), and four at 24–60 months (19 ml; VRR: −76%). The results allow to draw conclusions on a quite homogeneous effect on volume reduction after RFA and at the same time present the sparse data situation for observations that go beyond a 2-year time period (only 85 patients). An interesting and important study with a 5-year follow-up after a single mpRFA was published recently by Deandrea et al. [31]. Initial nodule volume categories of <10 ml, >10 to <20 ml, and >20 ml achieved a VRR of 82, 75, and 65%, respectively, after 5 years. The recurrence rate of nodules showing significant regrowth after RFA was 4.1%. A repeat FNA of these nodules confirmed benign cytology in all cases.

Practically all studies show a very high degree of “therapeutic effectiveness”, which is generally understood as a VRR of >50%, as well as a clear improvement in a visual/haptic (“cosmetic score”) and symptom score measured with a visual analogue scale (“symptom score”).

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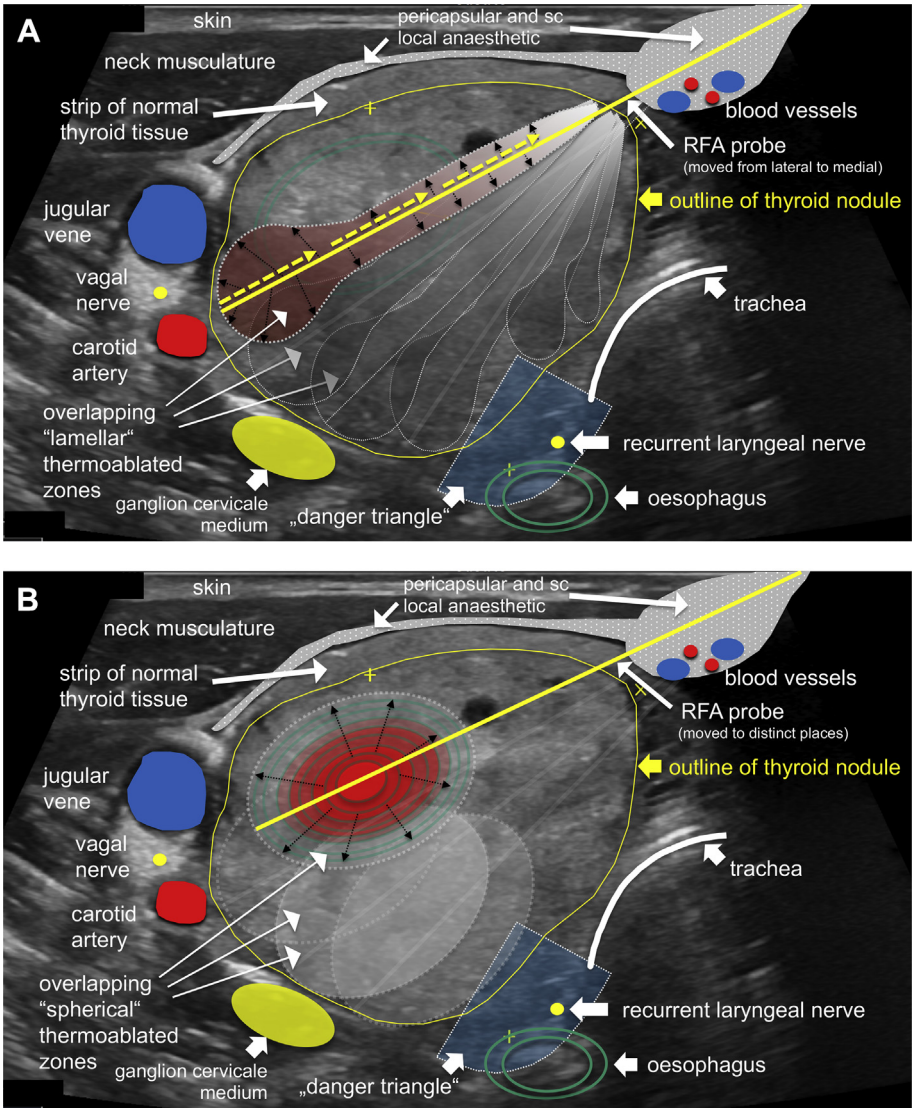

Fig. 2. A) Schematic illustration of the movements of a "monopolar RFA" applicator within a large thyroid nodule ("moving shot technique"). Depicted are also relevant critical anatomic structures in the vicinity of the ablation area. B) Schematic illustration of the movements of a bipolar RFA applicator within a large thyroid nodule ("multiple overlapping shot technique").

Due to the short duration of experience there are only a few studies available with bpRFA. Six months after RFA, Xiao et al. found in 35 patients (mean initial nodule volume 8.8 ml) a VRR of 75–85% depending on the type of nodule consistency [24]. Two studies from Germany report a VRR of 71% (initial nodule volume 21 ml) [26] and 56% (initial nodule volume 8 ml) [27] after three months of observation. The largest and longest observation period to date with bpRFA enrolled 102 patients with a comparatively small mean initial nodule volume of 5.7 ml [16]. After 12 months the average VRR was 84% and a volume reduction of $\geq$50% was observed in virtually all patients.

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Table 1
Differences between monopolar and bipolar radiofrequency ablation technique.

	monopolar RFA	bipolar RFA
Technical difficulty	Rather demanding	More easy
Local anesthesia	Sc and pericapsular	Often only sc, preferably also pericapsular
Guidance of RFA applicator	Transisthmic, rarely lateral "Moving shot"	Transisthmic "Multiple fixed overlapping shot"
Visualization of ablated zone	Very good	Good
Flexibility of applicator guidance to sufficiently reach entire nodule periphery (i.e.when shape of nodule is asymmetric)	High	Low
Flexibility to treat nodules of very different size with one RFA system	High	Low
Treatment of dorsally extending, cone-shaped nodules	Not ideal	Valid option
Palliative volume reduction desired	Not ideal	Valid option
Overall effect on nodule volume reduction with appropriate nodule preselection	Very good	Very good
Treatment time of larger nodule volumes	Longer	Shorter
Grounding pads necessary	Yes	No
Treatment of patients with cardiac pacemakers possible	No	Yes
Treatment during pregnancy possible	No	Yes
Follow-up data of ≤1-year available	Many studies	4 studies (1 with 1-year follow-up)
Follow-up data of >1-year available	Some studies	No studies

Autonomous nodules

Table 3 lists studies for which results of autonomic nodules were given separately in the publications. Overall, the experience here is significantly less than with non-functional benign nodules. With regard to the percentage of patients who achieved euthyroidism following RFA intervention the results are quite heterogeneous. A cut-off of about 12–15 ml volume for autonomous nodules seems to emerge, below which the probability of a successful single intervention is high. For larger nodule volumes, follow-up treatment with a necessary second RFA or low-dose radioiodine treatment for definitive functional cure is much more likely. In such cases, however, the patient would still have been spared the operation, the nodule would have become considerably smaller and hormone replacement therapy would have to be prescribed only rarely.

Indications for radiofrequency ablation

The left column in Table 4 reflects a summary of the principal indications for an RFA treatment that are currently shared by several medical societies [28,29,32–34]. These indications are still relatively broadly defined and thus, in a recent interdisciplinary position statement issued by four Austrian professional societies, a first attempt was made to narrow down these groups based on practical experience as well as the literature [28]. At the same time the paper also attempts to explicitly state limited indications or clear contraindications (Table 5).

Safety of radiofrequency ablation

A systematic review and meta-analysis on the safety of RFA treatment has recently been published. The authors analyzed data from 24 studies on benign treatment indications involving a total of 2245 patients [35]. Temporary vocal cord paralysis occurred in 0.94% of patients, permanent paralysis in 0.04% (1/2245). Among the other "major" complications is the occurrence of a "nodule rupture" (0.17%) 7–50 days after RFA, a case of hypothyroidism and a reversible brachial plexus paresis. In 1.9% of the treatments so-called minor complications occurred, which are listed in the frequency of their occurrence as follows: pain (temporary) during or after RFA; perithyroidal, subcapsular or intranodular hematoma (spontaneously reversible after 1–2 weeks), nausea and vomiting (reversible), skin burns (all reversible within one month), temporary hyperthyroidism. A second in-depth systematic review of 3409 treatments in 32 studies (seven of which were prospective) reports a similar spectrum of complications [36]. In this study, an incidence of recurrent laryngeal nerve paresis of 0.5–4.7% was reported.

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Table 2
Overview of studies with a single monopolar radiofrequency treatment of a cold/warm benign thyroid nodule.

First author (yr)	Journal	Country of study	Number treated nodules	Solidity (%)	Mean baseline nodule volume (ml)	Follow-up (months)	Volume reduction ratio (%)
Kim 2006 [23]	Thyroid	Rep of Corea	35	0–100	6	6	64
Baek 2010 [39]	Am J Roentgenol	Rep of Corea	15	50–100	8	6	80
Lee 2010 [40]	World J Surg	Rep of Corea	27	<50	4	6	92
Huh 2012 [41]	Radiology	Rep of Corea	15	>50	13	6	71
Ha 2013 [42]	Thyroid	Rep of Corea	14	>50	10	43	87
Sung 2013 [43]	Radiology	Rep of Corea	25	<10	9	6	93
Ugurlu 2014 [44]	World J Surg	Turkey	65	NS	7	6	74
Turtulici 2014 [45]	Ultrasound Med Biol	Italy	45	NS	14	6	73
Dobrinja 2015 [46]	Int J Endocrinol	Italy	64	10–100	14	24	67
Deandrea 2015 [47]	Thyroid	Italy, Rep of Corea	40	>70	15	6	72
Valcavi 2015 [48]	Endocr Pract	Italy	40	>80	30	24	80
Cesareo 2015 [49]	JCEM	Italy	42	>70	25	6	69
Aysan 2016 [50]	Langenbecks Arch Surg	Turkey	100	0–100	17	6	85
Mauri 2016 [51]	Int J Hypertherm	Italy	59	NS	33	12	74
Hamidi 2017 [52]	Mayo Clin Proc	US	14	70–100	24	8	44
Cheng 2017[a] [53]	Sci Rep	China	687	NS	7	13	90
Pacella 2017 [10]	Int J Hypertherm	Italy	152	NS	25	12	62
Deandrea 2018 [54]	Eur J Endocrinol	Italy	337	>30-100	21	12	70
Dobnig 2018 [55]	Thyroid	Austria	139	0–100	14	12	80
Deandrea 2019 [31]	JCEM	Italy	71	>70	21	60	70

[a] 3.2% of patients had two sessions of monopolar radiofrequency ablation.

Since most studies are generally retrospective in nature, the incidence of individual complications may be somewhat higher. A systematic examination of the vocal cord status before and after RFA has rarely been performed and would probably result in slightly different numbers for postinterventional recurrent laryngeal nerve paresis. Apart from these limitations, on the basis of the available data, it can nevertheless be stated that RFA as a minimally invasive method is generally a very safe treatment option. None of the studies reported a life-threatening complication and the occurrence of a severe, irreversible side effect is extremely rare.

Follow-up after radiofrequency ablation

In most studies, follow-up visits are performed after 3 or 6 months and then again after 12 months. Subsequently, the success of treatment should be ensured at annual intervals by ultrasound examination and laboratory analysis; in the event of a nodule recurrence, follow-up treatment may be necessary and is likely feasible with a similarly low risk of intervention.

The following issues are important to know for all investigators involved in the follow-up of RFA-treated patients:

Practice points

- The treated nodule is usually clearly hypoechogenic (due to loss of its vesicular structure with RFA treatment), sometimes microcalcifications can also be visualized
- Ideally the nodule remnant is avascular, sometimes hypovascular or rarely shows normal vascularization
- The nodule is usually much smaller than described in a previous examination and there is no need for a repeat work-up
- The treated nodule has undergone an FNA before RFA and was cytologically benign
- The patient should not be unnecessarily frightened because of these characteristics of normal nodule transformation
- In case of doubt, the operator who performed the RFA should be contacted

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Table 3
Overview of studies with monopolar radiofrequency ablation treatment of a toxic/pretoxic thyroid nodule.

	Number of treated nodules	Electrode type	Number of RFA treatments/ patient	Followup (months)	Mean baseline nodule volume (ml)	Volume reduction rate (%)	Patients euthyroid (%)
Deandrea 2008 [56]	23	Starbust (14G)	1	6	27	50	24
Spiezia 2009 [57]	28	Starbust (14G)	1	12 to 24	32	78	Pretoxic nodules: 100 Toxic nodules: 53
Baek 2009 [58]	9	17G/18G	2.2 (1–4)	6 to 14	15	71	67
Faggiano 2012 [59]	18	Starbust (14G)	1	12	18	78	40
Bernardi 2014 [60]	37	18G	1	12	12	70	33
Sung 2015 [61]	44	18G	1 (23%) 2 (61%) 3–6 (16%)	19	19	81	82
Bernardi 2016 [60]	30	18G	1	12	17	75	50
Cesareo 2018 [62]	29	17G	1	24	<12 ml: 15 patients >12 ml: 14 patients	84 68	<12 ml: 86 >12 ml: 45
Dobnig 2018 [55]	32	18G	1	3–12	9	86	84 Subclinical hypothyroidism: 3
Cervelli 2019 [63]	25	18G	1	12	14	76	91 Subclinical hypothyroidism: 9

Teaching aspects/quality control issues

RFA treatment should only be performed by a well-trained interventionist with adequate technical equipment and a well-rehearsed team. An interdisciplinary Austrian position paper has formulated some important issues concerning training and quality assurance measures in an RFA setting [28].

Open questions

Today there is no doubt that most patients with RFA or LA can be offered a safe and effective treatment alternative to surgery or radioiodine therapy provided the indication for the procedure is appropriate and the interventionist is experienced. The most important question concerns possible recurrence of nodule growth and this can only be answered by appropriate long-term prospective observational studies. Data on the frequency of recurrence are sparse in the literature and have to be interpreted carefully. Sometimes the results were obscured due to the performance of more than one RFA treatment per patient or due to incomplete ablation of the nodule (because of pain, bleeding, or large initial nodule volume) [37]. For example, Sim et al. repeated RFA treatment already when an undertreated part of the nodule had grown despite an unchanged total nodule volume, or when the Doppler signal showed an increased blood flow [38]. Whether a repeat treatment was necessary in all these cases is impossible to assess retrospectively.

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Research agenda

- Establishment of reliable figures on the frequency of recurrence of treated nodules
- If subsequent surgery is necessary: what are the consequences for the patient or the surgeon?
- How often do untreated, ipsilateral nodules grow and cause symptoms that warrant later intervention?
- Based on these figures and including the aspect of patient satisfaction, a long-term cost-benefit analysis of RFA treatment should be possible.
- Prospective randomized comparative studies (RFA versus surgery) should be performed (however, such studies are difficult to implement).
- Is there a role for antibody changes following RFA that could possibly have long-term effects on spontaneous thyroid hormone production?

Table 4
Principal indications of radiofrequency ablation of thyroid nodules (left column) and proposal for some subgroup definitions.

Principal indications[a]	Patient or nodule subgroups	Commentary
Benign nodules with symptoms/optically disturbing	Cystic or predominantly cystic nodules	Very good indication for RFA − if puncture and/or alcohol ablation fails or are unlikely effective due to multiple septa within the nodule. After initial successful alcohol ablation around 26 −38% of cystic nodules show early or late recurrence. RFA has a high success rate also in initially very large cystic nodules (i.e. >30 ml)
	Solid/mixed-solid nodules	Single treatment session for nodules up to ca. 30 ml is often feasible. Larger nodules may also be successfully treated but likelihood of second RFA is higher
	Patients with a history of thyroid surgery Elevated risk of general anesthesia Patients with susceptibility to keloid scarring	
	Pregnant patients	When intervention cannot be delayed: bipolar RFA intervention only
	Patients unwilling to have thyroid surgery performed	i.e. Patients who are anxious of general anesthesia, dislike idea of taking hormone replacement therapy, have relevant comorbidities, prefer short convalescence after intervention for various reasons, cannot afford to stay away from home for longer.
Continually growing nodules (>2 cm diameter) with attendant symptoms		Repeat fine needle aspiration or fine needle capillary cytology, consider core needle biopsy if result is not representative; recheck cervical lymph node status
Autonomous nodule, when radioiodine treatment or surgery is contraindicated or undesired	Patient groups where radioiodine treatment is unwanted or contraindicated	i.e. Patients with concerns over radioactive iodine; women who are breast-feeding or have kids; desire to become pregnant within the upcoming year; presence of urinary incontinence
	Solid or cystic autonomous nodule	Single treatment with good functional outcome in nodules with up to 12

(*continued on next page*)

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Table 4 (*continued*)

Principal indications[a]	Patient or nodule subgroups	Commentary
		−15 ml is often feasible. Only sometimes is low-dose radioiodine treatment necessary for satisfactory functional long-term result. Patient should be explicitly informed about a possible additional treatment following first RFA (repeated RFA, radioiodine treatment, medication)
	Large and/or cystic autonomous adenoma	When symptoms due to size or cystic nature of autonomous adenoma are unlikely to be resolved adequately after radioiodine treatment (and surgery is unwanted). Despite often seen marked nodule volume reduction after RFA a low-dose radioiodine treatment or second RFA may be necessary in the long-term
Differentiated, iodine-refractory thyroid carcinoma with local recurrence, high surgical risk		In general understood as a "palliative" approach in such settings
	"low-risk" papillary microcarcinoma (under discussion)	In cases, for which "active surveillance" is currently discussed (favorable topography, cN0, no evidence of multi-focality or invasiveness, contraindication for surgery)

[a] The principal indications refer to published guidelines and statements of various medical associations [28,29,32–34].

Table 5
Overview of relative or absolute contraindications for radiofrequency ablation of benign thyroid nodules or thyroid diseases.

Diagnostic or clinical setting	Commentary
Bethesda classification >II or other form of suspected malignancy	Likelihood of malignancy too high to perform RFA
Diffuse thyroid enlargement with multiple nodules	Despite successful RFA overall result remains unsatisfactory
Large solid/mixed nodules > 30 ml	Symptom improvement following RFA of very large nodules may remain unsatisfactory after a single intervention. This issue should be clearly discussed with the patient
Far caudally extending nodule	Not fully accessible by RFA applicator
Predominant vessels within the plane of treatment	And "lateral" approach is also not possible
Autonomous adenoma (>15 ml)	Euthyroid functional outcome after a single intervention is uncertain. Likelihood of postinterventional treatment (i.e. second RFA, iodine treatment, medication) is generally high and patient should be informed about such a possibility prior to RFA
Multifocal autonomy	Functional outcome may be satisfactory, but will depend on nodule size/number, location of nodules and patient age. A subsequent treatment option may be necessary.
Hashimoto's thyroiditis	
Grave's disease	

Summary

Currently there is a range of different thermoablative treatment modalities available, all of which can demonstrate efficacy in the short term with the addition, that data also suggest positive effects of mpRFA in the medium-term. The treated nodule shrinks considerably in volume and in most cases reduces or eliminates existing symptoms. A transformed residual nodule remnant usually remains, in some cases it may also disappear with time. Ideally, the patient can be spared surgery with general

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anesthesia and a scar in the neck area and the treatment can be carried out on an outpatient basis, usually with minimal pain and subsequent short convalescence. The preservation of spontaneous thyroid function is the rule, exceptions may occur. Life-threatening complications have not yet been described, and the procedure can be performed with a very low risk of adverse side effects. An important open question is the frequency of nodule regrowth, which will also depend very much on the expertise of the interventionist. The overall cost/benefit analysis will decide whether one or more of the thermoablation techniques described will prevail in the long term.

Conflict of interest

The authors declare that they don't have any conflict of interest regarding the content of this review.

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