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Radiofrequency ablation of thyroid nodules: "Good Clinical Practice Recommendations" for Austria

An interdisciplinary statement from the following professional associations: Austrian Thyroid Association (ÖSDG), Austrian Society for Nuclear Medicine and Molecular Imaging (OGNMB), Austrian Society for Endocrinology and Metabolism (ÖGES), Surgical Endocrinology Working Group (ACE) of the Austrian Surgical Society (OEGCH)

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Summary The present "Good Clinical Practice Recommendations" relate to radiofrequency ablation (RFA) training, execution, and quality control, as well as to pre- and postinterventional standards of care. They are aimed at all physicians who intend to learn to perform, or who are already conducting RFA interventions as well as at thyroid specialists providing pre- and postoperative care to RFA patients in Austria. Adoption of these recommendations is strongly encouraged by the afore-listed professional associations.

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All RFA interventionists who adhere to these standards shall be listed on a homepage linked to these professional associations entitled "RFA centers in compliance with the GCP recommendations of the ÖSDG/OGNMB/ÖGES/OEGCH-ACE." This will ensure harmonization of RFA training and quality control in the performance of the treatment in Austria.

Keywords Thermoablation · RFA · Statement · GCP · Monopolar · Bipolar

Introduction[1]

Thermoablative techniques

Monopolar RFA Monopolar radiofrequency ablation (RFA) for the treatment of thyroid nodules was developed in 2002 by Professor Baek, an interventional radiologist at the Asan Medical Centre in Seoul. As of May 2018, PubMed contained more than 130 articles addressing "RFA and thyroid nodules" in both benign and malignant indications. Of these contributions, approximately 40 are treatment studies, 16 report investigations of RFA in comparison with or in combination with other treatment options, 29 are review articles, four are meta-analyses, while the remaining 28 studies deal with basic aspects, safety, and complications.

In the limited number of countries in which it is presently available, the monopolar RFA technique is principally carried out by specialists from a range of disciplines in an outpatient setting. Prerequisites are special training and high-quality equipment. Monopolar RFA is usually performed with a water-cooled 18G probe driven by a high-frequency generator following subcutaneous and pericapsular xylocaine infiltration. Intravenous administration of analgesics, sedatives, or other drugs is, in general, unnecessary, but it is carried out in a few centers. The intervention is, as a rule, almost painless when executed using a good technique. The high-frequency current is dissipated via earthed "pads" attached ventrally to both thighs. Grounding is not associated with any patient discomfort. All patients are monitored throughout the RFA procedure (ECG, blood pressure, pO_2).

Monopolar RFA is a technically relatively demanding procedure. The target nodule must be systematically "degraded" using a freehand ("moving-shot") technique from cranial to caudal and from medial to lateral direction in a comparatively narrow ultrasound window without losing sight of the probe. To make matters worse, nodules can, of course, be located on either side of the thyroid gland, so that the hand guiding the probe is sometimes the left hand, and other times the right hand. This ambidexterity must first be achieved through practice on a phantom. To avoid a need for ambidexterity, the nodule located ipsilaterally to the dominant hand can also be processed transisthmically from the front. This, however, also demands practice. Notwithstanding these technical challenges, the monopolar RFA intervention is, on the other hand, relatively independent of nodule geometry and allows for effective uniform nodule treatment.

At present, virtually all knowledge concerning RFA as a treatment method for thyroid nodules is based on published findings obtained using the "monopolar" technique [1–13].

Bipolar RFA Bipolar RFA—which is, by contrast, a comparatively new RFA technique (first treatment studies published in 2016)—employs a probe containing both positive and negative poles within the tip that directs the flow of current solely through the nodule tissue, thereby removing the requirement for current dissipation. The high-frequency current between these poles creates a relatively spherical heat field within which the tissue is overheated. As the water content of the treated nodule tissue decreases, the electric resistance increases and the power of the device is regulated downward.

Bipolar RFA is, technically speaking, easier to master than monopolar RFA, because the probe tip need only be placed in a few locations within the nodule, although also in a targeted manner ("multiple overlapping shot" technique). While the first results obtained with the bipolar technique are very promising, long-term outcomes and a systematic treatment of larger patient populations with different nodal characteristics are still lacking at present [14–16].

Other thermoablative procedures Other thermoablative procedures are currently subordinate in importance to RFA, either (a) following abandonment in favor of RFA owing to inferior results (laser ablation), or (b) because their efficacy or complication rate remains insufficiently verified (microwave ablation).

High-intensity focused ultrasound High-intensity focused ultrasound (HIFU) is a noninvasive treatment method that uses ultrasound wave bundling to induce thermal coagulation necrosis in targeted nodule tissue. While its complication rate is likely to be lower than for other thermoablative procedures, only comparatively small nodules can be treated within a given reasonable treatment timeframe. Dorsally located nodules are, moreover, topographically unfavorable. Pain associated with HIFU treatment is caused by capsule and brachial plexus irritation and is difficult to avoid. For this reason, HIFU is currently performed under general anesthesia/analgosedation in some treatment centers [17, 18].

[1] To improve its readability this text has been written without gender-specific referencing. Unless stated otherwise, all terms apply to both women and men.

Open questions All thermoablative treatment procedures presently either lack (bipolar RFA, microwave ablation, HIFU) or are associated with sparse (laser ablation, monopolar RFA) long-term documentation of nodule recurrence. It is beyond doubt that, in most patients, nodule shrinkage abates previously existing local symptomatology over a long period and that thyroid function is usually maintained during this time. The frequency with which inadequately treated nodule parts grow in the long term and cause a recurrence of symptoms, or with which new nodules in the same thyroid gland may require intervention, remains unknown. While a (probably smaller) second intervention might be possible in such cases, this will influence the cost–benefit ratio with respect to surgery or radioiodine therapy.

The extent to which a thermoablated thyroid nodule could complicate a subsequently indicated surgical intervention remains unknown. It is, however, foreseeable that adhesions may well occur if the original "heat wave" reaches the thyroid capsule, and possibly the neighborhood of this, to a significant degree.

Given the many years of experience with thyroid surgery alone, every thermoablative method will need to be measured against this, the current gold standard with regard to effectiveness, complications, patient satisfaction, and cost–benefit calculation.

Training

Prerequisites for standardized RFA training

Fig. 1 details a typical setting for a radiofrequency ablation of a thyroid nodule.

- Required: 40 documented "transisthmic" interventions (punctures, core needle biopsies, alcohol ablations), including, ideally, five alcohol ablations.
  Note: This preparatory phase should ensure adequate practice and experience of (1) the positioning of the physician with respect to the neck and the nodules (distal to the patient's head looking directly at the monitor) and (2) transisthmic interventions—both indispensable prerequisites for the performance of RFA. Acquisition of a degree of ambidexterity is also a great advantage, since left- and right-sided nodules can be equivalently treated by the physician from the aforementioned position.
- Desirable: "work shadowing" in an endocrine surgical center (e. g., during two operation mornings) to observe the relevant anatomical structures (in particular nerve and vascular course) in the neck area.

Standardized RFA training

- Attendance of eight to ten RFAs performed by an experienced colleague (who must have carried out at least 100 RFAs).

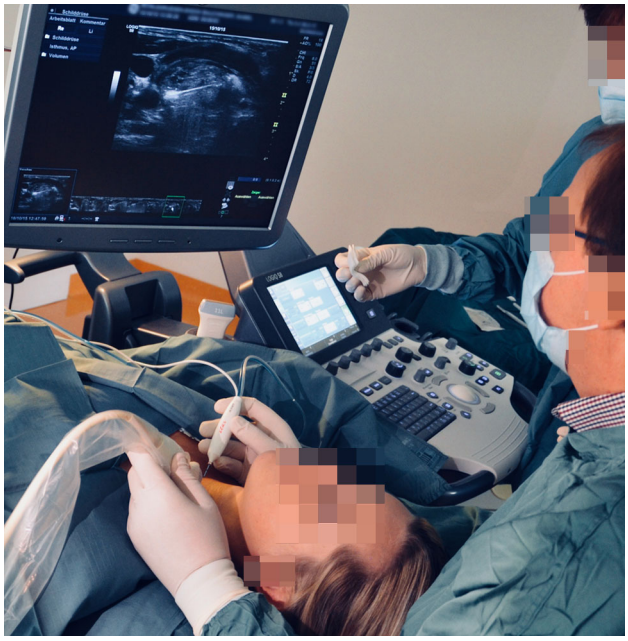

Fig. 1 Typical setting for a radiofrequency ablation of a thyroid nodule. The treating physician sits distal to the patient's head, looking directly into the monitor and ideally ablating nodules on both sides in this position. One assistant monitors the patient and operates the high-frequency generator, while a second directly assists the physician. The ablation procedure typically lasts 30 min and is followed by an observation period

- Accompanied, detailed theoretical training (including demonstration of long-term outcomes, discussion of possible complications and special anatomical features, viewing of video material).
- Practical instruction (with phantom exercises).
- Training of assisting personnel on at least one intervention day.
- Four supervised on-site RFAs in the presence of the trainer.
  Note: Such standardized RFA training allows for maximally individualized and intensive preparation. The teaching of practical content, which is especially important in this case, would never be possible in larger "courses." One-on-one, or maximally one-on-two training should, therefore, ideally take place.
  Courses are, generally speaking, available in South Korea and Italy (monopolar RFA), Germany (bipolar RFA), and in Austria (monopolar and bipolar RFA). The courses in South Korea and Austria are the most time-consuming and span a total of 3 days according to current information.

The Austrian training model comprises "on-site" coaching after training, following which participation in the RFA Working Group quality program is generally expected.

Certification

The RFA Working Group will issue a certificate on behalf of the ÖSDG/OGNMB/ÖGES/OEGCH-ACE to verify completion of the preparatory and/or training phase.

Continuing quality control

- Use of the universal "Patient Information and Consent Form" to ensure a uniform standard (provided to participants by the RFA Working Group).
- Case frequency: Regular performance increases RFA safety and effectiveness (as is generally the case with surgical procedures). The aforementioned participating professional associations consider the threshold of treated patients needed to ensure good treatment quality to be 40 cases per year.
- Case documentation of all RFA interventions using uniform criteria (a corresponding Excel file can be obtained from the RFA Working Group for this purpose).
- Video documentation of all RFA interventions, including recording of a sequence approximately 5 min after completion of the RFA treatment to document final status and absence of bleeding.
- Connection of an RFA center to an endocrine surgery center in order to have a readily available contact person should a complication occur. The cooperating institution, as well as the colleagues involved, must be made known to the RFA Working Group, and shall be published on the homepage.
- Dissemination at the end of the calendar year, of a standardized annual written summary report, detailing results and complications (provided by the RFA Working Group).
- RFA centers, which voluntarily submit to the quality assurance measures, agree to a verification of the transmitted data quality by way of announced audits (every 2–3 years) organized by the RFA Working Group. In order to enable the organization of these (nonprofit) studies, the participating centers are requested (when invoiced) to transfer an annual contribution of 500 € to the ÖSDG RFA Working Group account. These contributions will also cover the costs of homepage creation, data entry, etc.

Confirmation of continuing quality control

Information regarding participating centers, submitted annual quality assurance reports, and the results of the audits will be available on a homepage of the RFA working group, ideally linked to all participating professional associations.

Indications

Published indications

The principal indications are to be found in the guidelines and statements issued by the following entities:

1. Korean Society of Thyroid Radiology (KSThR), 2009, 2011, and 2017 Guideline [19, 20]
2. Italian Expert Opinion Statement 2015 [21]
3. American Association of Clinical Endocrinologists (ACCE) 2016 Guideline
4. American College of Endocrinology (ACE) 2016 Guideline
5. Associazone Medici Endocrinology (AME) 2016 Guideline [22]
6. National Institute for Health and Care Excellence (NICE) 2016 Guideline https://www.nice.org.uk/guidance/ipg562
7. Austrian Thyroid Association 2016 Official statement https://www.kup.at/kup/pdf/13399.pdf

The principal indications are:

- Benign nodule with symptoms and/or which is optically disturbing (for some examples see Fig. 2)
- Continually growing benign nodule (>2 cm diameter) with attendant symptoms
- Autonomous nodule, when radioiodine treatment or surgery is contraindicated or unwanted (for an example see Fig. 3)
- Differentiated, iodine-refractory thyroid carcinoma with local recurrence, high surgical risk (palliative therapy approach)

Under discussion: "low-risk" papillary microcarcinoma—in cases, for which "active surveillance" is currently under discussion (favorable topography, cN0, no evidence of multi-focality or invasiveness, contraindication for surgery [23].

Practical experience regarding indication and restriction[2]

Monopolar RFA

General: Treatment of one to three nodules, including bilateral intervention, is feasible during a single session (although it is dependent on bilateral nodule topography).

Good indications:

- Cystic, or predominantly cystic nodules (including "cystic colloid nodules") are the best indication for an RFA! (volumes >30 ml are also feasible).
  - Should puncturing or alcohol ablation fail to produce the desired outcome, or be inappropriate/impossible.

    Note: "Acute bleeding cysts" should always be fully punctured under ultrasound guidance be-

[2] Compiled by author (HD).

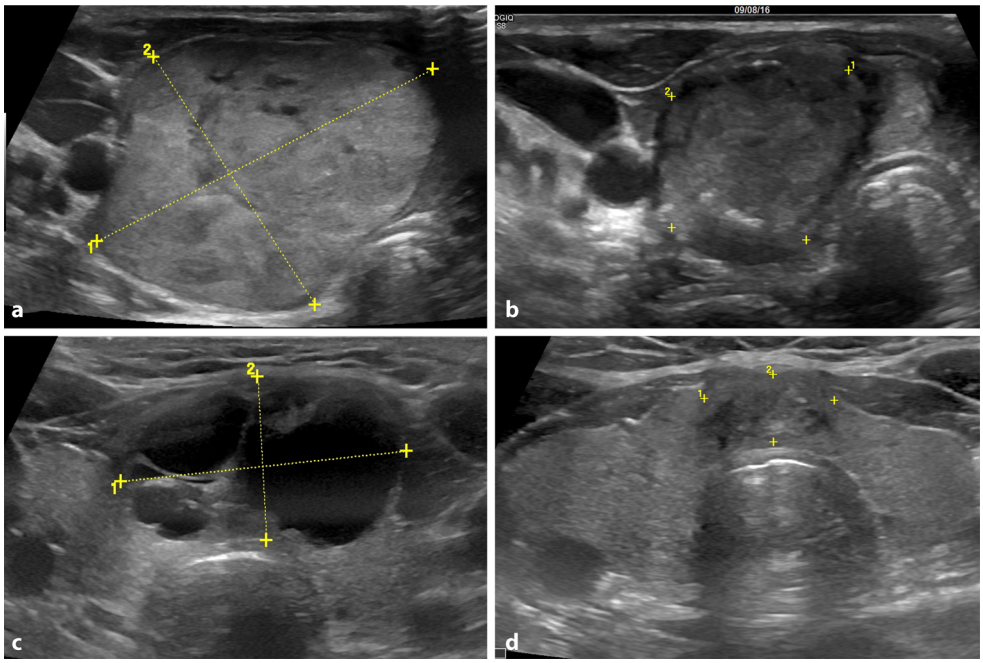

Fig. 2 **a**, **b** Example of a radiofrequency ablation (RFA)-treated solid nodule, prior to and 12 months after ablation. **a** A 50-year-old female patient, fivefold increase in nodule volume over 8 years, multiple recommendations for surgery, nodule clearly perceptible visually, symptom score 4 (out of 10); nodule volume: 40 ml. **b** After 12 months the nodule is only palpable, symptom score 0, nodule volume: 8.2 ml (–80%). This example also demonstrates that a precise setting of the caliper marks along the initially longest transverse axis of the nodule is important to correctly state changes in nodule volume developments afterwards. **c**, **d** Example of RFA of a cystic colloid nodule. **c** Pre-tracheal, cystic autonomous adenoma, highly viscous content, nodule volume: 10.6 ml, thyroid-stimulating hormone (TSH): 0.6 µU/ml, symptom score 4 (out of 10), visual score 3 (out of 3), surgery recommended. **d** Visual and symptom score 0 after 12 months, volume of transformed residual nodule tissue: 1.2 ml (–89%), TSH: 1.0 µU/ml

fore any further measures are taken. So-called benign cysts that exhibit a uniformly smooth border usually respond well to alcohol ablation. Alcohol ablation can, however, only treat the cystic nodule component and not the solid part. Early and late recurrences together occur after about 26–38% of all alcohol ablations.

- Solid and mixed nodules up to around 30 ml (as a single treatment).
- Autonomous adenomas—solid or cystic up to around 12–15 ml (as a single treatment).
- Growing nodules—if causing a beginning symptomatology (always after repeated biopsy using FNA (fine-needle aspiration) or FNCC (fine-needle capillary cytology), or, if necessary, core-needle biopsy!).
- Patients who already had a thyroid surgery.
- Elevated risk of general anesthesia.
- Known susceptibility to keloid scarring.

Limited or no indications:

- Cytological report: Bethesda >II or other form of suspected malignancy.
- Far caudally extending nodules, not fully accessible.
- Rather narrow and cone-shaped nodules extending far dorsally.
- Presence of prominent ventral vessels in the treatment plane.
- Large solid and mixed nodules >30 ml (in a single intervention).
- Diffuse thyroid enlargement comprising multiple nodules (when even a successful RFA is not expected to produce a satisfactory final result).
- Autonomous adenomas >15 ml (in a single procedure). Good results with subsequent low-dose J^{131} therapy are, however, often possible in this case.
- Multifocal autonomy (indication depending on: nodule number/size, patient age).
- Hashimoto thyroiditis.
- Grave's disease.
- Pacemaker wearers (applicable to monopolar RFA).
- Pregnancy (applicable to monopolar RFA).

Bipolar RFA

Good indications:

- Large, solid nodules—those in topographically difficult locations are sometimes easier to treat with bipolar than with monopolar RFA.
- Palliative volume reduction (only in selected cases).
- Pregnancy: no contraindication as with monopolar RFA.
- Pacemaker wearers: no contraindication as with monopolar RFA.

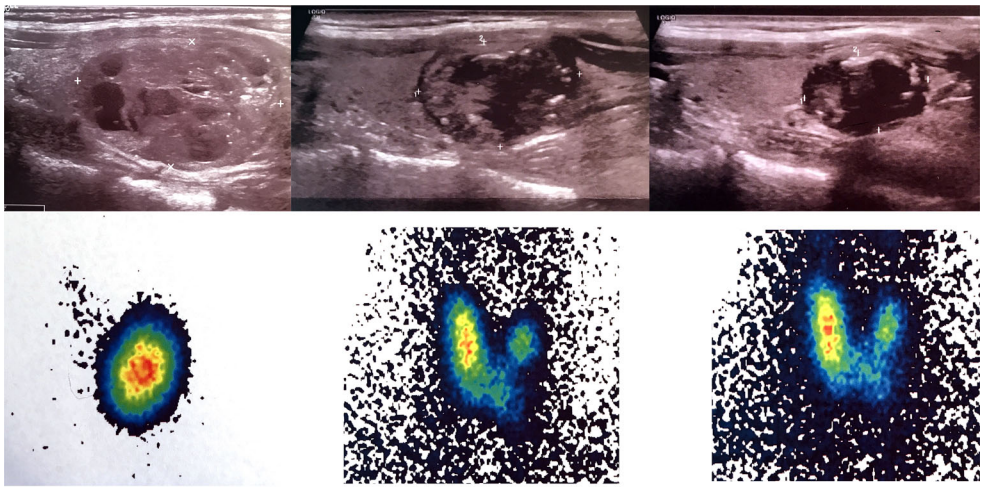

Fig. 3 Example of an RFA of an *autonomous* adenoma. A 48-year-old female patient, with presence of autonomous adenoma known for several years, recent significant growth, and development of subclinical hyperthyroidism. Surgery recommendation. The initial finding is a 13-ml, 40% cystic, autonomous adenoma, which occupies the majority of the left thyroid lobe, functionally decompensated. The ultrasound images show the sagittal section through the left thyroid lobe with morphological changes 3 and 12 months after RFA. Since after RFA the treated autonomous adenoma has been remodeled to form mainly connective tissue, the formally "hot" nodule visualized by technetium-99m scintigraphy becomes a "warm" or, ideally, even a "cold" nodule. *Mon* months, *KV* nodule volume, *LV* lobe volume, *CS* visual nodule (cosmetic-)score (up to grade 3), *SS* symptom score (up to grade 10)

Limited indications:

- Nodules with an elevated bleeding risk (larger probe diameter)
- Variable nodule sizes, if simultaneous treatment of more than one nodule is planned and this cannot be satisfactorily achieved with one probe size alone (increased material costs)
- Smaller autonomous adenomas (higher energy density with monopolar probe)

Patient information

The detailed information provided to patients concerning available treatment options should always be stated in the physician's letter irrespective of the medical specialty of the specialist relating this information.

Surgery is the "standard therapy" for benign symptomatic or troublesome thyroid nodules. That said, suitable patients who do not want an operation, or for whom an operation is associated with a higher than normal risk, can, alternatively, be offered an RFA following detailed explanation of all possible treatment procedures (surgery, radioiodine therapy, alcohol ablation of cystic nodules, RFA) including their advantages and disadvantages. The physician's letter should, ideally, list the reasons for the therapy preference, as well as give a brief explanation of the therapeutic goal.

Should a patient opt to undergo RFA, a signed, uniformly formulated patient information and consent form must be made available (provided to the participants by the RFA Working Group), as is also the case within the framework of a surgical procedure.

Patient selection

The initial selection of a suitable treatment procedure is naturally the responsibility of the treating thyroid specialist, who knows the patient case in its entirety and is best able to assess it, including a weighing of therapy options.

For practical reasons, a pre-evaluation of documents by the RFA interventionist can be very useful for the next step in patient selection. An RFA can often already be excluded following a review of the ultrasound images and the key findings—or a personal introduction recommended as an expedient next step. Experience has shown that when a patient makes enquiries upon his/her own initiative, often with misconceptions about achievable therapy goals, treatment must often be declined.

The RFA interventionist should, therefore, ideally be contacted by the thyroid specialist (e.g., forwarding of significant findings, including laboratory data,

Table 1 Pre-intervention checklist

1. Review of previous findings
2. Laboratory results (TSH, fT4, fT3, TPOAB, TGAB, Tg, facultative: calcitonin, PTH, calcium and total protein, coagulation parameters)
3. Benign status verified by ultrasound-guided FNA or FNCC? Corresponding nodule morphology?
4. Detailed ultrasound results Lymph node status? Prominent vessels in the entrance plane of the probe? Entry site for local anesthesia? Nodule wholly accessible? Number and location of entry sites? Positioning of nodule with respect to the vagus nerve and trachea? Position of nodule with respect to "danger triangle"? Determination of nodule and lobe volumes with documentation of the caliper marks along the horizontal and sagittal plane For cystic nodules: aspiration necessary before RFA? Likelihood of colloid cyst? Bleeding risk?
5. Effects of RFA on spontaneous function and/or medication following the intervention? (sufficient residual tissue present? Likelihood of a low-dose RIT as a follow-up treatment for an autonomous adenoma?)
6. Symptom Score (VAS 1–10). Question posed to patients: "To what extent are you adversely affected by the nodule, in terms of functional, visual, or psychological impact (or a combination of these)?"
7. Visual nodule score (0 = nodule non-palpable, 1 = nodule palpable, 2 = nodule visible upon reclining of the head or during swallowing 3 = nodule readily visible to the naked eye)
8. Existence of major (relative or absolute) contraindications? Tendency to bleed, anticoagulation? Pacemaker wearer? Pregnancy? Is patient breastfeeding? Allergies to local anesthetics? Serious cervical spine problems (due to required overstretching)?
9. Patient information documented in physician's letter?
10. Patient information and consent form issued?
11. ENT findings with vocal cord status requested?
ENT ear, nose, throat specialist, *RFA* radiofrequency ablation, *TSH* thyroid-stimulating hormone, *fT4* free T4, *fT3* free T3, *TPOAB* thyroid peroxidase antibodies, *TGAB* thyroglobulin antibodies, *Tg* thyroglobulin, *PTH* parathyroid hormone, *FNA* fine-needle aspiration, *FNCC* fine-needle capillary cytology, *RIT* radioiodine treatment, *VAS* visual analogue scale

ideally with report of a thyroid scan where necessary and ultrasound images).

Cytological findings

It is important to note that RFA treatment only permits a prior cytological, and not a histological, investigation of the nodule in question. In the case of "cold" or "warm" nodules, a conclusive ultrasound-guided FNA or FNCC with a benign cytological result is therefore necessary prior to RFA, in order to ensure the required certainty of the cytological findings.

The probability that a well-performed, conclusive, ultrasound-guided FNA delivers a false-negative cytological finding is assumed to be 1–2% (see ATA Guidelines). In a large Austrian sample of 4518 US-guided FNAs collected in a high-volume thyroid out-patient clinic a negative predictive value of 98.1% also suggests a high validity of a benign cytological finding in the local population [24].

Since, for a variety of methodological reasons alone, and because Austria can still be considered an endemic goitre area a carcinoma can never be excluded with 100% certainty, the following approach is proposed:

A nodule should, in any event, only be treated with RFA when negative cytology for this particular nodule as well as an unsuspicious cervical lymph node ultrasound status have been established. Nodules that have significantly grown since FNA or FNCC, or that exhibit sonographic abnormalities (e.g., microcalcification, "taller than wide," irregular borders), should undergo a second, ultrasound-guided procedure. According to the ATA guideline, a *confirmed* benign cytology rules out malignancy by practically 100%.

Photo documentation of the needle tip at the moment of puncture is required. An FNA of "hot" nodules exhibiting no other indications of malignancy can be omitted prior to RFA.

It is thus of great importance that the evaluation encompasses the overall sonographic aspects of the nodule, including the obligatory ultrasound status of the adjacent cervical lymph nodes, as well as the cytological findings.

Laryngoscopic evaluation of vocal cord status

There is, as yet, no well-founded scientific literature supporting a routine recommendation that vocal cord status be assessed before and after RFA. A meta-analysis reporting an extremely low risk of permanent vocal cord paralysis (approx. 0.05%) is available, but, owing to a lack of systematic investigations [25], a publication bias cannot be ruled out regarding this sensitive topic.

Since a nervus laryngeus recurrens paresis can be functionally well compensated and not necessarily linguistically apparent, it follows—by analogy to thyroid surgery—that an examination of the laryngoscopic vocal cord status of all patients prior to and as soon as possible after RFA is required. Asking patients to submit the second finding at the latest at the 3-month check-up will close an important gap in the overall assessment of treatment quality.

Checklist for RFA interventionists

Prior to an intervention, thoughtful consideration by the RFA-performing physician of the points listed in Table 1 is important.

Follow-up

As part of a structured follow-up process, ultrasound check-ups should be performed 3 and 12 months after RFA to document the effects of RFA treatment. Patients are asked to bring the postinterventional ear, nose, throat (ENT) findings of vocal cord status to the 3-month follow-up visit. If, however, the patient cannot attend thyroid check-ups (and other recommended check-ups every 1–2 years) conducted by the RFA-performing physician, the aftercare providing thyroid specialist should ideally address the following points in his findings:

- The vocal cord status post RFA intervention.
- The volumetry of treated nodule(s) and of both thyroid lobes.
  The RFA-performing physician should ideally provide the patient with relevant ultrasound images. These contain the *caliper marks* used for volumetry of thyroid lobes and the treated nodule(s) and thus enable the thyroid specialist to perform valid outcome measurements.
  Caution! The RFA-transformed nodule is (due to a loss of vesicular structures and thus of ultrasound-reflecting interfaces) markedly hypoechogenic (!) and often avascular, as well as significantly smaller than described in a previous report. It may also contain microcalcification. Some connective tissue-transformed shrunken nodules can also be vascularized. The nodule, moreover, either has a cytologically "benign past" or was a priori functionally "autonomous" in a thyroid scan (and thus benign).
  It is thus essential that the thyroid specialist "understands" these morphological peculiarities following RFA treatment and interprets them correctly, to avoid causing the patient unnecessarily worry.
- The thyroid-stimulating hormone (TSH), free T4 (fT4) and free T3 (fT3), as well as thyroid peroxidase antibodies (TPOAB) and thyroglobulin antibodies (TGAB) values (the latter at least for the 3-month follow-up) should also be determined. If a toxic nodule has been treated with RFA, an additional thyroid scan is recommended at the 3-month check-up.
- More generally, a 1–2-yearly ultrasound examination of the thyroid gland and cervical lymph node status is recommended following the 3 and 12 months RFA follow-ups.

Conflict of interest H. Dobnig, W. Zechmann, M. Hermann, M. Lehner, D. Heute, S. Mirzaei, A. Gessl, V. Stepan, G. Höfle, P. Riss, and A. Simon declare that they have no competing interests.

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