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LETTER TO THE EDITOR

Radiofrequency ablation for thyroid nodules: which indications? The first Italian opinion statement

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Introduction

Nodular thyroid disease is a very common finding in clinical practice, discovered by ultrasound (US) in about 50 % of the general population, with higher prevalence in women and in the elderly [1–4].

Whereas therapeutic flowchart is quite established and shared for malignant lesions, multiple options are now available for patients presenting with benign thyroid nodules, ranging from simple clinical and US follow-up to thyroid surgery. The majority of thyroid nodules, benign by fine-needle aspiration, are asymptomatic, stable, or slow-growing over time and require no treatment.

Nevertheless, large thyroid nodules may become responsible for pressure symptoms, resulting in neck discomfort, cosmetic complaints, and decreased quality of life. Partial/total thyroid surgery has so far constituted the only therapeutic approach for these. Although surgery is widely available, highly effective, and safe in skilled centers, complications (both temporary and permanent) still occur in 2–10 % of cases [5, 6]. Hypothyroidism is an unavoidable effect after total thyroidectomy, requiring lifelong L-thyroxine replacement therapy. Besides, surgery

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is expensive and may be not recommended for high-risk patients or refused by others.

Radioiodine (^{131}I) therapy has been proven to be effective to treat toxic multinodular goiters and autonomously functioning thyroid nodules (AFTN) [7], although they are usually more radioresistant than toxic diffuse goiters [8]. Radioiodine therapy normalizes thyroid function and significantly reduces thyroid volume. However, hypothyroidism often occurs, in up to 60 % of patients, several years after treatment [9].

Otherwise, radioiodine therapy shows only incomplete, weak effects in nonfunctioning cold thyroid nodules. Pretreatment with recombinant human TSH may improve goiter volume reduction by causing a more homogeneous distribution of radioiodine within the gland, especially increasing the uptake of ^{131}I in scintigraphically relatively cold areas [10].

TSH-suppression therapy with L-thyroxine was widely used to achieve nodule shrinkage and to prevent nodule growth and formation, producing, however, controversial results and exposing patients to heart and bone side effects. Therefore, current guidelines do not recommend its routine use in clinical practice, suggesting its usefulness in some cases only [3, 4].

Over the last two decades, nonsurgical, minimally invasive, US-guided techniques have been proposed for the treatment of thyroid nodules [11–16]. Percutaneous ethanol injection (PEI) is recommended for the treatment of relapsing cysts and dominantly cystic thyroid nodules [17]. Because of the limitations of PEI in the management of solid thyroid nodules, hyperthermic methods (laser ablation and radiofrequency ablation) have been introduced afterward for the treatment of solid, benign thyroid lesions [18], achieving marked nodule size reduction and clinical improvement in nodule-related symptoms, in several series from skilled centers, especially in Korea and Italy.

Other nonsurgical therapies, such as high-intensity focused-ultrasound (HIFU), microwaves, cryotherapy, and electroporation, are presently under investigation.

Radiofrequency ablation in thyroid pathology

Radiofrequency (RF) induces thermal injury into the target lesion by means of an alternating electric field, produced by an electrode needle connected to an external radiofrequency generator. Tissue necrosis is achieved around the needle tip, through the heating induced by rapid ion movement, in a controlled fashion.

First RF ablation studies on thyroid nodules were performed with a 17-gauge internally cooled electrode needle [19–21] or with a 14-gauge device, equipped with expandable hooks to obtain a more extended ablation area [22–24]. After local anesthesia, the needle is inserted into the target nodule through a small incision. The application of RF energy requires several minutes to produce tissue necrosis, without moving the needle ("fixed-electrode procedure"). When the ablation area is obtained, the needle can be removed or relocated in a different part of the lesion, if necessary, to complete the ablation treatment.

Afterward, thinner (18-gauge or 19-gauge) internally cooled electrode needles were developed, specifically designed for thyroid lesions, to make it easier to control the needle, minimizing normal tissue injury [25]. With a percutaneous (no skin incision) transisthmic approach, the electrode is introduced within the nodule. A few seconds of RF application are needed to induce thermal necrosis of the tissue around the needle tip. The efficacy of induced necrosis can be evaluated by monitoring tissue impedance that progressively increases during the shot, as shown by the monitor of the RF generator and by transient hyperechoic changes in the treated tissue. Initially, the active electrode tip is positioned in the deepest portion of the

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nodule and then moved backward in the central area and in superficial directions. Using this "moving shot technique", multiple conceptual areas of the nodule are destroyed unit-by-unit by moving the electrode tip under US surveillance, tailoring the extent of the treatment according to nodule shape and features.

Published data about the RF treatment of benign thyroid nodules are summarized in Table 1. Using both approaches, the fixed-electrode procedure and the moving shot technique, a significant nodule shrinkage is obtained in nonfunctioning thyroid nodules, coupled with a marked clinical improvement in nodule-related symptoms. In all series [19, 20, 22–24, 26–32], volume shrinkage gradually occurs during the first months after treatment, when necrotic tissue within nodule is reabsorbed. Following one or more RF sessions, a significant, sometimes impressive, nodule size reduction (46–93 % in different studies) is reached after 6 months and seems to be stable during a four-year follow-up [29]. Remarkably, thyroid function is not affected by RF treatment, and this is an important advantage as compared with surgery or radioiodine therapy.

Ultrasound and clinical outcomes appear to be faster and more pronounced in cystic and mixed nodules than in solid ones. However, in cystic lesions, a similar therapeutic success is obtained using PEI, which is an easier and less expensive technique [33, 34]. When after PEI symptoms persist, together with a residual solid portion in the treated nodule, one or more RF sessions can be useful to complete the ablation process [35, 36].

Hyperthyroidism caused by AFTN can be completely or at least partially cured by RF treatment. A significant improvement in thyroid function, as well as in nodule shrinkage and related symptoms, is obtained in several series [21, 23–25, 28, 30, 37] using both techniques. Nevertheless, incomplete ablation of peripheral tissue can be followed by partial nodule regrowth and relapse of hyperthyroidism. Therefore, several RF sessions are usually required to achieve a satisfactory result. On the other hand, radioiodine therapy is considered to be the main therapeutic approach for hot nodules, although its effectiveness is sometimes reduced for very large nodules, when surgery is usually preferred. The possible usefulness of a combined treatment, using thermal ablation and radioiodine therapy, has been recently proposed for large hyperfunctioning nodular goiters [38].

Several studies [39–42] investigated the usefulness of RF ablation to treat metastatic lymph nodes from recurrent thyroid cancer, in patients at high surgical risk, when radioiodine is not effective. Results showed a marked shrinkage of treated lesions, coupled with serum thyroglobulin reduction, suggesting that RF treatment, such as laser ablation or PEI, may be effective in selected cases.

In a recent large multicenter study [43], the overall complication rate for RF treatment was 3.3 %, and the major complication rate was 1.4 %. Pain, usually transient and mild, is the most frequent side effect during procedure. Voice change due to laryngeal dysfunction is reported, although very rare, and may be prevented paying special attention when the treatment is performed in nodular tissue close to laryngeal nerve. Hemorrhage, vagal symptoms, skin burns, and nodule rupture may also infrequently occur, as well as in other thermal ablation techniques. A learning curve is required to prevent complications or properly manage in case they occur.

Consensus statement from the Korean Society of Thyroid Radiology

In 2009, the Korean Society of Thyroid Radiology (KSThR) proposed a first set of recommendations for the RF ablation of thyroid nodules (published in the KSThR website only). In 2011, a task force committee of KSThR revised these earlier recommendations, through a comprehensive analysis of scientific evidence and a consensus of expert opinion in Korea, about the indications and management of the RF ablation of thyroid lesions in clinical practice [44].

Indications include patients presenting with

- benign thyroid nodules with nodule-related symptoms (neck pain, dysphagia, foreign body sensation, discomfort, and cough);
- benign thyroid nodules responsible for cosmetic complaints;
- autonomously functioning thyroid nodules (AFTN); and
- recurrent thyroid cancers, in the operation bed and lymph nodes, in patients at high surgical risk.

In this consensus statement, nodule size is not considered a specific criterion for RF treatment, although authors declare that "patients with nodules with a maximum diameter >2 cm that continue to grow, may be considered for thyroid RF ablation, based on symptoms and clinical concerns." Indeed, large thyroid nodules may frequently cause local symptoms or cosmetic complaints and are therefore addressed through surgery or RF ablation more often than smaller ones. Nevertheless, small nodules may elicit symptoms or cosmetic discomfort too, depending on their location and on a patient's feeling.

Moreover, in Korean and Asian culture, the subjective perception of neck disorders may significantly differ from those reported in Europe and the United States, emphasizing cosmetic concern and allowing to treat thyroid nodules with pretreatment volume smaller than reported in our clinical practice.

Table 1 Published data about RF treatment of benign thyroid nodules

References	Journal	Treated nodules	Control group	US pattern (% of fluid component)	Scintiscan	Nodule volume at baseline (ml)	RF electrode type	RF session no.	Follow-up months	Volume reduction (%)
Kim [19]	*Thyroid*	35	No	Solid, mixed, cystic	Cold	6.3	17G c–e	1	6.4	73
Spiezia [22]	*J Am Geriatr Soc*	39	No			24	14G m–e	1–3	6	74
Jeong [20]	*Eur Radiol*	302	No	Solid, mixed, cystic		6.1	17G c–e	1–6	6	85
Baek [21]	*Thyroid*	1	No	Mixed	Hot	5.1	17G c–e		19	97
Deandrea [23]	*Ultrasound Med Biol*	33	No	Solid or mixed (<30 %)	23 Hot–10 cold	22.6–39.3	14G m–e	1	6	52–46
Spiezia [24]	*Thyroid*	94	No	Solid or mixed (<30 %)	28 Hot–66 cold	32.7–21.1	14G m–e	1–3	12	78
Spiezia [24]	*Thyroid*	Of whom 52	No	Solid or mixed (<30 %)			14G m–e	1–3	24	79
Baek [25]	*World J Surg*	9	No	Solid, mixed, cystic	Hot	15	17-18G c–e	1–4	6	71
Baek [26]	*Am J Roentgenol*	15	Follow-up	Solid or mixed	Cold	7.5	18G c–e	1	6	80
Lee [35]	*World J Surg*	27	No	Cystic or mixed (>50 %)		14	18G c–e	1–4	6	92 PEI + RF
Sung [33]	*Am J Roentgenol*	21	RF vs PEI	Cystic		10.2	17-18G c–e	1–3	6	92
Jang [36]	*Eur J Radiol*	20	No	Cystic or mixed (>50 %)		11.3	18G c–e	1–2	6	91 PEI + RF
Huh [27]	*Radiology*	15 vs 15	1 vs 2 RF sessions	Solid or mixed (<50 %)	Cold	13.3 vs 13.0	18G c–e	1 vs 2	6	70 vs 78 (ns)
Faggiano [28]	*J Clin Endocrinol Metab*	20	Follow-up	Solid or mixed (<30 %)	10 Hot–10 cold	13.3	14G m–e	1	9	85
Lim [29]	*Eur Radiol*	126	No	Solid, mixed, cystic		9.8	17-18G c–e	1–7	49	93
Sung [34]	*Radiology*	25	RF vs PEI	Cystic		9.3	18G c–e	1	6	93
Turtulici [32]	*Ultrasound Med Biol*	45	No		Cold	13.5	18G c–e	1	6	72
Sung [37]	*Thyroid*	44	No	Solid or mixed (<90 %)	Hot	18.5	18G c–e	1–6	19.9	81
Cesareo [31]	*J Clin Endocrinol Metab*	42	Follow-up	Solid or mixed (<30 %)	Cold	24.5	17G c–e	1	6	68
Bernardi [30]	*Int J Endocrinol*	37	Surgery	Solid or mixed	12 Hot–25 cold	12.4	18G c–e	1–2	12	70

c–e Cooled electrode, m–e multitined electrode

Nevertheless, these recommendations do not compare and define specific indications for RF ablation, surgery, or radioiodine therapy. All the above-mentioned thyroid lesions are indeed eligible for surgery, and RF ablation can be proposed when surgery is contraindicated or declined by patients. Physician's attitude for surgical or nonsurgical approach, together with the availability of skilled centers in US-guided interventional techniques, may certainly condition the therapeutic choice.

In agreement with the above-cited data, authors recommend that "patients with cystic thyroid nodules that regrow after simple aspiration should be treated first with PEI rather than RF ablation."

About thyroid malignant disease, authors state that "surgery is a standard treatment for recurrent thyroid cancers, followed by radioactive iodine and thyroid hormone therapy. RF ablation, however, can be used in patients at high surgical risk and in patients who refuse to undergo repeated surgery." Moreover, "RF ablation for follicular neoplasms or primary thyroid cancers is not recommended."

Italian opinion statement

Moving from published data, Korean recommendations, and personal experiences and opinions, Italian physicians skilled in the management of nodular thyroid disease and in thyroid interventional ultrasound met in Turin, on May 11, 2012, to discuss and clarify which are the current, appropriate, and shared indications for thermal ablation therapy by radiofrequency in thyroid pathology.

This meeting was organized by the University of Turin as a public satellite symposium at the *master on diagnostic and interventional neck ultrasound.*

The schedule of the meeting was planned according to the current methodological guidelines about consensus conference organization [45–47].

The organizing committee designated a group of physicians expert in thyroid pathology and interventional ultrasound, including endocrinologists, surgeons, radiologists, and specialists in nuclear medicine, coming from the main centers for thyroid disease in Italy and several Italian scientific societies [Società Italiana di Ultrasonologia in Medicina e Biologia (SIUMB), Società Italiana di Endocrinologia (SIE), Associazione Medici Endocrinologi (AME), Società Italiana di Radiologia Medica (SIRM), Club delle Unità di Endocrinochirurgia Italiane (Club delle UEC), Società Italiana di Chirurgia (SIC), Associazione Italiana di Medicina Nucleare (AIMN)].

Also, patients' delegates, agents from biomedical and pharmaceutical companies, and a delegate of public health management took part in the panel.

During the first part of the symposium, experts described to the audience the current knowledge about nonsurgical US-guided therapy for nodular thyroid disease, such as percutaneous ethanol injection, laser thermal ablation, and radiofrequency thermal ablation, highlighting effectiveness, limits, and side effects for each technique, in different clinical conditions. Experts' reports were concise and exhaustive, including technical information and summary of published data, together with personal experience and considerations. Moreover, to evaluate the pros and cons of US-guided therapies for nodular thyroid disease as compared with surgery and radioiodine therapy, reports by invited thyroid surgeons and specialists in nuclear medicine were made. Finally, a brief cost evaluation was carried out by a delegate of public health management, showing that radiofrequency and other current US-guided therapies are less expensive than surgery.

In the second part of the symposium, a broad discussion was made among members of the panel, focusing on safety, limits, and effectiveness of RF ablation for nodular thyroid disease.

Indications for RF ablation in thyroid pathology

After the reports by experts and the comprehensive discussion, the panel agreed on the following indications for RF ablation in nodular thyroid disease:

- Large (volume $>$ 20 ml), nonfunctioning, benign thyroid nodules in patients presenting with local symptoms or cosmetic complaints when surgery is contraindicated or declined (***) (Table 2)
- Autonomously functioning thyroid nodules (AFTN), hot/warm at scintiscan, either toxic or pretoxic, when surgery and radioiodine are contraindicated or declined (***) (Table 2)
- Palliative therapy for recurrent thyroid cancers in the neck when surgery is contraindicated and radioiodine is ineffective (***) (Table 2).

The above-mentioned indications are intended for solid or dominantly solid thyroid nodules. All these indications were accepted with complete agreement by experts' panel.

The following indications were accepted instead with partial disagreement:

- Nonfunctioning, benign thyroid nodules (even with volume $<$ 20 ml) coupled with early local discomfort that significantly grow over time (**) (Table 2).

In this case, RF may be useful to strongly reduce nodule size to prevent its future growth, together with progressive increase in symptoms and cosmetic concerns, and to avoid future thyroid surgery. Besides, RF treatment could have

Table 2 Strength of experts' agreement

(***)	Accepted indication, strong: complete agreement supporting indication
(**)	Accepted indication, intermediate: partial agreement (weak disagreement)
(*)	Accepted indication, weak: partial agreement (strong disagreement)
(-)	Rejected indication: complete agreement against indication

easier, faster, more tolerable, and more effective results if pretreatment nodule volume is not too large. The agreement for this indication was not complete among experts because someone suggested that surgery is more advisable if thyroid nodules seem to be fast-growing. Although nodule growth speed is not considered to be a significant marker for malignancy, the panel concluded that special caution is needed in fast-growing nodules, for which FNA repeat is recommended to rule out the risk of malignancy, before RF treatment can be proposed.

- Large (volume > 20 ml) AFTN, for whom combined treatment RF + radioiodine could induce faster and greater improvement in local symptoms, allows a reduction in radioiodine-administered activity, if compared with radioiodine alone (*) (Table 2).

The usefulness of a combined treatment, using thermal ablation and radioactive iodine, is not yet fully established in scientific literature such as in clinical practice. However, it has been recently proposed for large hyperfunctioning nodular goiters [38], producing a faster and more marked nodule shrinkage, coupled with a lower-radioiodine-administered activity, if compared with radioiodine therapy alone. These data, similar to those obtained from previous studies using PEI + radioiodine for the treatment of large toxic thyroid nodules [48], seem to be promising, suggesting that combined nonsurgical treatment could be effective and safe in selected cases. Nevertheless, the agreement for this indication was incomplete among experts, meeting disagreement especially from specialists in nuclear medicine.

The following discussed indications for RF ablation were not accepted:

- Thyroid cysts and dominantly cystic thyroid nodules (−) (Table 2): PEI is first-line treatment.
- Primary thyroid cancers or follicular neoplasms (−) (Table 2): surgery is standard therapy.

Conclusion and future perspectives

Radiofrequency ablation and other nonsurgical, minimally invasive, US-guided techniques may play an important role in the management of nodular thyroid disease today and in future clinical practice. This statement was made to clarify this role and to make it consistent in Italian centers for thyroid disease.

Focusing on radiofrequency thermal ablation after a comprehensive evaluation of pieces of scientific evidence and experts' opinions and suggestions, the panel approved several indications for this technique in thyroid pathology, with complete or partial agreement among experts, trying to define the most appropriate treatment in different clinical conditions.

Looking at the future outlook, we can speculate about other possible fields of application of these techniques in benign and malignant diseases. For example, if cost-effectiveness evaluation will be favorable, slow-growing benign thyroid nodules might be treated with RF even at an early stage before they become responsible for local symptoms and cosmetic complaints, making RF treatment even more tolerable, easy, and effective.

Finally, some authors are highlighting worldwide that papillary thyroid microcarcinoma (PTMC) often represents a very low-risk lesion of indolent course, for which total thyroidectomy might be a very aggressive therapeutic choice [49–51]. Although current pieces of scientific evidence and experts' opinions do not allow us to treat these lesions in a nonsurgical, conservative fashion [52, 53], we can suppose that in the near future, US-guided techniques might play a role also in primary PTMC, when no multifocality or nodal metastasis was found, offering patients a less aggressive therapeutic option without reducing the clinical outcomes and the very high rate of disease-free survival.

Conflict of interest The authors (Roberto Garberoglio, Camillo Aliberti, Marialuisa Appetecchia, Marco Attard, Giuseppe Boccuzzi, Flavio Boraso, Giorgio Borretta, Giuseppe Caruso, Maurilio Deandrea, Milena Freddi, Gabriella Gallone, Giovanni Gandini, Guido Gasparri, Carlo Gazzera, Ezio Ghigo, Maurizio Grosso, Paolo Limone, Mauro Maccario, Luigi Mansi, Alberto Mormile, Pier Giorgio Nasi, Fabio Orlandi, Donatella Pacchioni, Claudio Maurizio Pacella, Nicola Palestini, Enrico Papini, Maria Rosa Pelizzo, Andrea Piotto, Teresa Rago, Fabrizio Riganti, Lodovico Rosato, Ruth Rossetto, Antonio Scarmozzino, Stefano Spiezia, Ornella Testori, Roberto Valcavi, Andrea Veltri, Paolo Vitti, Matteo Zingrillo) have no conflict of interest to disclose.

Ethical statement The study described in this article does not contain studies with human or animal subjects performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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