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REVIEW ARTICLE

Image-guided thermal ablation of benign thyroid nodules

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Abstract Benign thyroid nodules are a common disease in the general population. Most often, they are completely asymptomatic and discovered occasionally during routine ultrasound examinations, and do not require any treatment. When thyroid nodules become symptomatic, surgical excision is still considered standard treatment. In the last few years, several experiences in the treatment of benign thyroid nodules through image-guided percutaneous thermal ablation have been reported with encouraging results, so that currently, these treatments are often proposed as first-choice options for patients with symptomatic benign thyroid nodules. In this paper, we discuss the present literature on the topic, focusing on different techniques available for image-guided percutaneous ablation, particularly radiofrequency (RFA), laser (LA), microwave (MWA), and high-intensity-focus ultrasound (HIFU). Little evidence about the efficacy of MWA and HIFU is now available. According to the literature, good results have been obtained with RFA and LA. Regarding RFA, volume reduction after ablative treatment has been found to range from 47 to 84 % at 3–6 months, and from 62 to 93 % at 1 year; LA also seems to be effective in achieving shrinkage of thyroid nodules, with volume reduction from 37 to 81 % at 3–6 months, and from 13 to 82 % at 1-year follow-up. Moreover, applications of advanced image-guidance modality, such as contrast-enhanced ultrasound and virtual navigation with fusion imaging, are discussed.

Keywords Laser · Radiofrequency · Microwave · High-intensity focused ultrasound · Thyroid nodule

SOMMARIO I noduli benigni della tiroide sono una evenienza comune nella popolazione generale. Più spesso vengono scoperti occasionalmente durante un esame ecografico fatto per altri motivi, sono asintomatici e non richiedono alcun trattamento. Qualora i noduli diventino sintomatici, l'escissione chirurgica è ancora considerato il trattamento standard. Tuttavia, negli ultimi anni, è cresciuta l'esperienza circa il trattamento di tali noduli tramite ablazione percutanea sotto guida ecografica tanto che, attualmente, questo viene spesso proposto come trattamento di scelta. Lo scopo del nostro lavoro è fare una revisione della letteratura riguardante l'argomento, con un particolare focus sulle differenti tecniche attualmente a disposizione, in particolare radiofrequenza (RFA), laser (LA), microonde (MWA) e high-intensity-focus ultrasound (HIFU). Al momento ci sono ancora poche evidenze sull'efficacia di MWA e HIFU. Secondo quanto riportato in letteratura, buoni risultati sono stati ottenuti con RFA e LA. Riguardo la radiofrequenza, la riduzione volumetrica dopo la procedura ablativa va da 47 a 84 % a 3–6 mesi e da 62 a 93 % a 1 anno; anche il laser sembra essere efficace nel causare la riduzione del nodulo, con percentuali che vanno da 37 a 81 % a 3–6-mesi a da 13 a 82 % a 1 anno di follow-up Abbiamo poi discusso brevemente le

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applicazioni di tecniche di imaging più avanzate, come l'ecografia con mezzo di contrasto e la navigazione virtuale.

Introduction

Thyroid nodules are a common occurrence, with a palpable thyroid nodule prevalence of approximately 5 % in women and 1 % in men living in iodine-sufficient parts of the world [1, 2]. They are discovered through ultrasounds (US) in 20–70 % of the general population [3–8]. The risk of nodular disease increases with age, exposure to ionizing radiation and iodine deficiency, and is more prevalent in women than in men [7, 9, 10]. Most thyroid nodules are benign, with cancer occurring in approximately 7–15 % of cases [4, 7, 10–12]. Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (>90 %) of all thyroid malignancies [13].

When asymptomatic, benign nodules generally do not require treatment and are only monitored with clinical visits and US examinations. However, some nodules require treatment for cosmetic reasons or symptoms due to compression of surrounding structures (esophagus, trachea) [12, 14]. According to American Thyroid Association thyroid nodule guidelines, routine thyroid stimulating hormone (TSH) suppression therapy in iodine-sufficient populations is not recommended. Though modest responses to therapy can be detected, the potential harm outweighs the benefit for most patients [15].

When nodules are cystic or predominantly cystic, percutaneous ethanol injection (PEI) represents a valuable minimally invasive treatment strategy [15–19], with a reported success rate of 82–85 % (volume reduction >85 % from baseline) after an average of two sessions [19–22]. However, there are several limitations to the use of this technique for solid nodules; these are related to the difficulty in predicting the diffusion of the ethanol within the nodule, the leakage-induced pain, and the possibility of extra-glandular fibrosis making subsequent surgery more complex [23, 24].

The mainstay treatment for solid benign thyroid nodules remains surgery, though radioiodine therapy is also feasible for hyperfunctioning ones. Whereas thyroid surgery is widely available and safe in many centers, it still carries a 2–10 % risk of complications, such as neck scarring, hypothyroidism, postoperative hypoparathyroidism, recurrent laryngeal nerve injury, and the risks associated with general anesthesia. Surgery is also expensive, and may not be appropriate for a surgically high-risk individual [10, 25–30]. Over the last decade, thermal ablation techniques, such as laser ablation (LA), radiofrequency ablation (RFA), high-intensity-focus ultrasound (HIFU), and microwave ablation (MWA), have been proposed for the treatment of benign solid thyroid nodules, with encouraging results.

The goal of this paper is to perform a review of thermal ablation techniques for the treatment of benign solid nodules, analyzing the indications, efficacy, and side effects of each method. Patient assessment US-guided minimally invasive techniques have been proposed for the treatment of benign solid nodules in patients with symptoms or cosmetic problems. Symptom scores can usually be self-measured by patients using a 10-cm visual analogue scale (grade 0–10). Cosmetic scores can be measured by a physician as follows: 1 = no palpable mass; 2 = no cosmetic problem but palpable mass; 3 = cosmetic problem on swallowing only; and 4 = readily detected cosmetic problem. Performing an ultrasound examination before the procedure is important to characterize the nodule and to evaluate the critical anatomic structures surrounding it. To further exclude malignancy, fine-needle aspiration cytology and/or core needle biopsy must be performed prior to any ablation procedure. Laboratory tests are usually performed before thermal ablation techniques and during the follow-up, and include a complete blood count, blood coagulation, measurements of thyrotrophin, thyroid hormones, thyroid auto-antibodies, and calcitonin concentrations.

RFA

Devices and procedures

RF refers to an alternating electric current with frequencies of fewer than 900 kHz (most frequently 375–500 kHz), produced by an electrode needle connected to an external radiofrequency generator [31]. Application of energy causes the agitation of tissue ions, generating an increase of local temperature with subsequent controlled tissue necrosis. Tumor tissue farther from the electrode is heated slowly by the thermal current conducted from the hot region around the electrode [32].

The first RFA studies on thyroid nodules were performed with a 17-G straight internally cooled electrode needle with a 1-cm active tip [33–37] or with 14-gauge multi-tined expandable electrodes to obtain a more extended ablation area [38–40]. Thinner (18-G or 19-G) internally cooled multi-tined (0.5–1–1.5 cm) electrode needles were later developed specifically for thyroid lesions, to make control of the needle easier, minimizing normal tissue injury [41–49].

The patient is usually positioned in the supine position with mild neck extension. Most procedures are performed with local anesthesia [33–38, 40–49].

Two different approaches have been developed to perform RF ablation of thyroid nodules: the cranium-caudal approach along the greatest axis and the trans-isthmic approach along the shortest axis of the nodule. In the cranium-caudal approach, the electrode tip is inserted along the long axis of the nodule. The tip is kept at least 15 mm away from surrounding cervical structures. Conversely, in the trans-isthmic approach, the electrode is inserted from the medial to the lateral part of the nodule with transverse US image.

The trans-isthmic approach is preferable to the cranium-caudal one for various reasons. First, the entire length of the electrode can be visualized on the transverse US view. Second, the "danger triangle", which includes the laryngeal recurrent nerve and the esophagus, is less exposed with this approach. Finally, the electrode passes through an adequate volume of thyroid parenchyma to prevent electrode movement [32].

Two techniques have been used to perform RF ablation: the ''moving shot technique,'' proposed by Baek et al. [37] and actually more frequently used than the "fixed electrode technique." In the ''moving shot technique," the thyroid nodule is divided into multiple small conceptual ablation units and the ablation procedure is performed unit by unit, moving the electrode continuously. This ideal area is smaller in the periphery of the nodule and larger in the safe center. Initially, the electrode tip is positioned in the deepest part of the nodule. Thus, it is easier to control the position of the tip, with no disturbance caused by generation of micro bubbles. Ablation starts with 30 W (1-cm active tip) or 50 W (1.5 cm active tip) of RF power.

During the procedure, the tip reaches a maximum of 95–105 °C for 5–8 min. When a transient hyperechoic zone appears in the treated area, the RF power is decreased and the electrode is moved to a different area. If the transient hyperechoic area does not appear within 5–10 s, RF power is increased in 10 W increments to a maximum of 100–110 W. If the patient feels pain, the power is also reduced for several seconds. The RF ablation is concluded when the whole nodule has become hyperechoic. Operators monitor adverse events that may occur during and immediately after the procedure. If the patient feels severe neck pain or discomfort, a painkiller is usually administered.

Complications

Major and minor complications have been defined by the Society of Interventional Radiology [50, 51]. A major complication is defined as one that, if left untreated, might threaten the patient's life or result in a lengthened hospital stay. All other complications are considered minor.

Reported major complications of thyroid RF ablation include voice change, nodule rupture, hypothyroidism, and brachial plexus injury; minor complications include hematoma, vomiting, skin burn, pain, edema, fever, or coughing. In most articles, pain is considered as a minor complication only when it persists for more than 2 or 3 days after ablation; otherwise, it is considered as side effect. Pain during the procedure was considered as a complication, not simply as a side effect [42], in only one article.

In a multicentric study of 1459 patients, the overall complication rate was 3.3 %, with a major complication rate of 1.4 % [52]. The most common complication in all studies was pain [33, 34, 38, 45–52] (Table 1). In the order of frequency, authors also reported hematomas [33, 47, 52], vomiting [47, 52], skin burn [33, 52], fever [38], and thyrotoxicosis [46]. Hematomas can be controlled by neck compression and usually disappear within 2 weeks. There was only one case of thyrotoxicosis, which spontaneously resolved within 30 days [46]. Major complications were, in the order of frequency, permanent voice change [33, 34, 44, 46, 47, 52], rupture of the nodule [44, 52], permanent hypothyroidism [41, 52], and brachial plexus injury [47, 52]. None of the patients experienced any life-threatening complications related to RFA. Baek et al. showed that the major complication rate was lower for patients treated by experienced operators than for those treated by less-experienced operators, indicating that RFA is a safe procedure when performed by well-trained operators [52]. Voice change may be caused by the involvement of the recurrent laryngeal or vagus nerve [34, 37]. Voice changes are usually transient, with most patients recovering within 3 months [34, 44, 46, 47, 52].

To prevent injury to the recurrent laryngeal nerve, RFA should be performed using the moving shot technique, and

Table 1 Comparison of thermal ablation techniques for the treatment of solid benign nodules

Thermal ablation methods	Energy delivery through skin	Number of studies	Number of patients	Nodule volume reduction at last follow-up (%)	Minor complications (%)	Major complications (%)
Radiofrequency	Percutaneous	16	2435	62–93	4.6	1.2
Laser ablation	Percutaneous	17	584	47–82	38.3	3
Microwave ablation	Percutaneous	2	233	45–65	3	3.9
HIFU ablation	Transcutaneous	5	65	48	10.8	0

by undertreating the ideal ablation units adjacent to the nerve [34, 36, 37, 41]. The vagus nerve is usually located between the common carotid artery and internal jugular vein, but may also be located adjacent to the thyroid gland [53, 54]. Therefore, before performing RFA, operators should check the location of the vagus nerve.

Four patients experienced nodule rupture [44, 52]. They presented with sudden neck bulging and pain during follow-up. Two of these four patients recovered without treatment. One patient was admitted to the hospital and treated with antibiotics and analgesics. The other one underwent surgery, resulting in nodule rupture followed by abscess formation.

Two patients developed permanent hypothyroidism 6 months after RFA [41]. These patients showed persistent elevation of serum anti thyroid peroxidase antibodies (TPO-Ab) before and after RFA.

Although the risk of hypothyroidism is very low and its cause is unclear, patients with elevated anti-TPO-Ab before ablation should be informed about the risk of hypothyroidism after RFA. As the brachial plexus is located deep in the neck, thermal injury is unusual, but this complication has been reported during RFA [47, 52]. Two patients experienced a brachial plexus injury just after RFA. They gradually recovered during the next two months. Continuous moving of the electrode without tracing the electrode tip, and echogenic microbubbles that prevent the electrode tip from being clearly visualized, may result in penetration of the RF electrode beyond the thyroid capsule and in damage to the brachial plexus nerves. Therefore, operators should monitor the entire length of the electrode continuously on real-time US images.

Clinical results

Radiofrequency ablation of benign thyroid nodules has been proposed for patients with symptoms and cosmetic problems and for patients with AFTN. Three orthogonal nodule diameters, including the largest diameter, are measured by US to assess nodule volume using the following equation: $V = \pi abc/6$, where V is the volume, a is the maximum diameter, and b and c are the other two perpendicular diameters [33, 34, 37, 41, 43, 45–49]. Laboratory tests usually include a complete blood count, a blood coagulation battery, measurements of thyrotrophin, thyroid hormones, thyroid auto-antibodies, and calcitonin concentrations.

If hyperthyroidism or AFTNs is suggested, a technetium 99mTc pertechnetate or a 123I thyroid scan may be helpful for diagnosis [35, 41, 42]. The results of RFA are evaluated by change in nodule volume and improvement of clinical problems, including symptoms and cosmetic issues. Some studies consider the efficacy of RFA only in hyperfunctioning thyroid nodules [35, 41, 42], others only in cold nodules [33, 37, 47] and others in both hyperfunctioning and cold nodules [38–40, 44–46]. Follow-up US examinations are usually performed at 1, 3, 6, and 12 months and every 6–12 months after that. Most articles consider a 3–6-month and a 1-year follow-up. The mean volume reduction has been found to range from 47 to 84 % at 3–6 months, and from 62 to 93 % at 1 year [34, 37–48] (Table 2). Most of the volume reduction was observed within 3–6 months, and then, the volume size decreased more gradually up to 1 year. Improvement of symptoms and cosmetic problems was demonstrated in all studies.

Table 2 RF ablation: volume reduction in patients with solid benign thyroid volume

Author	Year	Number of patients	Mean volume reduction at 3–6 months	Volume reduction at 1 year
Sung YS	2015	44	62 %	NR
Hong MJ	2015	18	54 %	76 %
Che Y	2015	200	78 %	62 %
Ugurlu MU	2015	33	84 %	93 %
Bernardi S	2014	37	63 %	NR
Lim HK	2013	111	NR	69 %
Faggiano A	2012	20	76 %	NR
Hu JY (a)	2012	15	71 %	86 %
Hu JY (b)	2012	15	77 %	NR
Baek JH	2010	15	83 %	NR
Baek JH	2009	9	70 %	NR
Spiezia S	2009	94	64 %	NR
Jeong WK	2008	302	76 %	69 %
Deandrea M	2007	32	47 %	82 %

NR not reported

Regarding hyperfunctioning nodules, RFA has been shown effective in reducing nodule volume. At 6-month follow-ups, nodule volume was reduced from 52.1 to 74.5 % [39, 41, 42]. Baek et al. [41] and Sung et al. [42] showed a greater volume reduction than Deandrea et al. [39], probably because RFA was performed using different techniques in each study. Deandrea et al. used the fixed-needle technique and a straight type of internally cooled electrode, not the "moving shot" technique [39]. Hyperthyroidism due to hyperfunctioning nodules improved in all patients [39, 41, 42]. Sung et al. demonstrated that hyperthyroidism completely normalized in 81.8 % of patients [42].

Comparing RFA to hemithyroidectomy, Bernardi et al. showed that RFA significantly reduces thyroid nodule volume and improves nodule-related clinical problems, such as local symptoms and cosmetic concern, as effectively as surgery, with a lower rate of complications [46]. Italian indications for RF ablation in benign thyroid nodular disease, elaborated during a meeting on diagnostic and interventional neck ultrasound, were published in 2015. RF ablation was strongly recommended for solid or predominantly solid nonfunctioning nodules with volume >20 ml in patients with local symptoms or cosmetic complaints when surgery is contraindicated or declined, and in autonomously functioning thyroid nodules (AFTN) which are hot or warm at scintiscan, or toxic or pre-toxic when surgery and radioiodine are contraindicated or declined. RF ablation was considered as a treatment option with partial disagreement among the experts for nonfunctioning thyroid nodules (even with volume <20 ml) when those nodules were coupled with the early local discomfort growing significantly over time [55]. The Korean Society of Thyroid Radiology (KSThR) also proposed RF ablation as a treatment option for benign thyroid nodules if those nodules were responsible for cosmetic complaints and for autonomously functioning thyroid nodules (AFTN). In this consensus statement, nodule size was not considered a specific criterion for RF treatment [14].

LA devices and procedures

LA is based on the emission of photons by excited atoms within target tissue [56–58]. Tissue is destroyed by energy absorption. The patient is placed in a supine position with neck hyperextended. The procedure is performed under ultrasound system guidance [59–74]. In most studies, a 21-G needle is inserted into the lesion along its longest axis. In some studies, an 18- or 22-G needle is used [61, 66, 68, 69, 71, 72, 74]. For small nodules, usually, only one needle is used, while for larger nodules, two-to-three needles are applied. If more than one needle is used, care should be taken to maintain a distance of 1 cm between the needles [34]. A 300-μm-diameter plane-cut quartz optical fibers are subsequently introduced and advanced up to the needle tip. The introducer needle is withdrawn to expose the fiber tip by at last 5 mm [57, 59, 63–65, 67, 69, 70], 20 mm according to Dossing et al. [61, 66, 68, 71, 72, 74].

Care should be taken to place the needle tip in the deepest part of the nodule, with a distance of at least 15 mm (10 mm according to Gambelunghe et al. [60, 65]. from the inferior margin of the lesion [59, 62, 74], and to maintain the same distance between the needle tip and surrounding cervical structures [57, 58, 61, 62, 66, 69, 70, 72–74]. A laser source, a continuous-wave Nd-YAG laser operating at 1.064 μm, is used with an optical beam-splitting device with as many as four separate fibers that can be illuminated separately or concurrently [12]. The total energy applied is usually between 1.200 and 1.800 Joules [57, 59, 63, 67, 73], with a continuous output power of 1.5 and 3.5 W [57, 59–61, 64–72, 74].

In two studies, the power increases more than 3.5 W [64, 73]. The number of fibers, number of pullbacks, and total energy delivered are tailored to nodule volume and shape. The duration of laser illumination ranges from 6 to 30 min, depending on nodule size. Light irradiation is continuous, being suspended only in the case of severe pain, cough, or appearance of other side effects [32]. During LA, the necrosis of the tissue is visible as an irregular echogenic area, enlarging during the procedure. The treatment stops when this area is stationary in size [61]. Each treatment is performed under conscious sedation or local anesthesia with lidocaine.

Complications

Major complications are uncommon (Table 1). Five patients experienced dysphonia within 24–48 h of LA ablation, with cord palsy at direct laryngoscopy [57, 59, 63]. Corticosteroids were administered and the patients recovered completely after 6–10 weeks. Nerve compression because of perinodular edema is probably the cause of dysphonia [57, 59, 63]. Spiezia et al. also reported transient dysphonia, lasting 24 h, which spontaneously resolved [73]. Thyroid dysfunctions occurred in approximately 2 % of patients; most of them experienced transient hyperthyroidism, with a normalization of Ft3, Ft4, and TSH within 6 weeks.

The rate of permanent hypothyroidism was low (only three patients) [63, 65]. Valcavi et al. have found that thyroid pericapsular bleeding developed in almost 2 % of patients, but this disappeared in 3–4 weeks. They also reported pseudocystic transformation in 5 % of patients, exemplified by rapid development of painful neck swelling 2–4 weeks after LA; such patients underwent

drainage. Then, in 3 % of patients, fluid leakage into the neck muscle fascia was observed, but such subfascial effusion disappeared within 3–4 months without any consequences. No patient required surgical drainage [63]. Minor side effects included pain and fever. A burning cervical pain during the procedure was common and stopped after the end of the procedure. Moderate pain could persist for a few days after LA ablation, but it disappeared after analgesic use. Fever was usually self-limiting, returning to normality in 24–48 h [57, 59–68, 70–74].

None of the patients experienced any life-threatening complications related to LA ablation. In a retrospective multicenter study that considered 1534 nodules in 1531 patients, an overall rate of complications of 0.9 % was registered. Only 0.5 % of the patients experienced transitory voice changes that completely resolved within 2–84 days. Minor complications were 0.5 %. No changes in thyroid function or autoimmunity were observed [75].

Clinical results

The efficacy of LA ablation has been evaluated considering the change in nodule volume and improvement of clinical problems, including symptoms and cosmetic issues. Some studies also analyze these outcomes in patients with hyperfunctioning nodules [57, 62, 66, 71, 73]. For the evaluation of symptoms and cosmetic scores, different methods are used, making the comparison between various studies difficult.

Most articles consider a 3–6 month and a 1-year follow-up. The follow-up lasts 3 years in only one case [63]. LA ablation seems to be effective in achieving shrinkage of cold, solid, and benign thyroid nodules, with volume reduction from 37 to 81 % at 3–6 months and from 13 to 82 % at 1-year follow-up (Table 3).

Achille et al. demonstrated that there is no correlation between the initial size of the nodule and the degree of volume reduction after the procedure [59], as some authors have previously reported [61, 63]. Some studies that analyze volume reduction of hyperfunctioning nodules treated with LA have reported normalization of thyroid function [71, 73]. However, other studies showed that LA seems not to be effective in the control of autonomously hyperfunctioning nodules [57]. A randomized trial that compared LA with 131-I therapy demonstrated that the two procedures are similar in reducing nodule volume, with reductions of almost 44 %; serum TSH was normalized in 7 of the 14 patients treated with LA, and in all patients treated with 131-I therapy [66]; only 50 % of the patients treated with LA achieved normal serum levels of TSH. Conversely, the reduction of nodular volume was associated with progressive normalization of thyroid function in another study. After three cycles of LA, 87 % of the hyperthyroid patients achieved normal serum levels of TSH [62].

MWA

Devices and procedures

The MW unit consists of a microwave generator, a flexible low-loss coaxial cable and a cooled shaft antenna. The generator is capable of producing 1–100 W of power at 2450 MHz, in the form of pulse or continuous energy. The internally cooled needle antenna (16-G) has a diameter of 1.6 or 1.9 mm and a length of 3–5 mm and is coated with polytetrafluoroethylene to prevent tissue adhesion. The large diameter of the MW antenna makes the ablation of thyroid lesion near critical spaces of the neck difficult. The patient is placed in the supine position with neck hyperextended. Electrocardiogram, oxygen tension, breath rate, and blood pressure are continuously monitored. Local anesthesia with lidocaine is given, and then, an incision is made in the skin. The internally cooled antenna is placed into the thyroid nodule along its longest axis under ultrasound guidance. After the antenna is placed, an endovenous unconscious anesthesia is administered. According to Yue et al., a mixture of 0.9 % of lidocaine and saline should be infused into the surrounding thyroid capsule to achieve a "liquid isolating region," protecting the vital structure of the neck [76]. Energy ranging from 20 to 50 W is usually used. The therapy continues until the whole nodule becomes hyperechoic. At the end of the treatment, the patient remains under observation for 30 min, with compression of the neck to prevent hematoma formation [76, 77].

Complications

The MW procedure was reported to be well tolerated (Table 1). A mild sensation of heat in the neck was experienced by most of the patients, but no one stopped the treatment. Slight fever was found in three patients, but lasted only one day [77]. 3–9 % of patients complained of voice changes, all recovering spontaneously within 3 months; in one case, treatment with corticosteroid was necessary [76, 77]. Hemorrhage was reported in nearly 40 % of cases [77].

Clinical results

MWA is a minimally invasive technique that has been already used to treat benign and malignant tumors [78–80]. Nevertheless, only a few studies considering MWA efficacy in the treatment of benign solid thyroid nodules are

Table 3 LA ablation: volume reduction in patients with solid benign thyroid volume

Author	Year	Patients	Volume reduction at 3–6 months	Volume reduction at 1 year
Achille G	2016	45	NR	81 %
Døssing H	2013	22	79 %	NR
Gambelunghe G (a)	2012	20	37 %	13 %
Gambelunghe G (b)	2012	20	57 %	57 %
Amabile G (a)	2011	51	81 %	NR
Amabile G (b)	2011	26	81 %	NR
Døssing H	2011	78	NR	57 %
Valcavi R	2010	122	45 %	49 %
Døssing H	2007	14	57 %	NR
Papini E	2007	21	NR	47 %
Gambelunghe G	2006	13	44 %	NR
Døssing H (a)	2006	15	44 %	NR
Døssing H (b)	2006	15	57 %	NR
Cakir B	2006	12	NR	82 %
Amabile G	2006	23	37 %	NR
Døssing H	2005	15	41 %	NR
Pacella CM (a)	2004	8	66 %	NR
Pacella CM (b)	2004	16	59 %	NR
Papini E	2004	20	60 %	NR
Spiezia S (a)	2003	7	NR	74 %
Spiezia S (b)	2003	5	NR	67 %
Døssing H	2002	16	46 %	NR

NR not reported

available. In these studies, at the post-treatment follow-up (from 1 to 12 months), nodule volume reduction ranged from 45 to 65 % [76, 77, 81, 82]. Feng et al. reported an improvement of symptoms and cosmetic score [77]. In a recent study, 30 patients with a total of 34 benign thyroid nodules underwent MWA. Serum levels of triiodothyronine (T3), thyroxine (T4), thyrotropin (TSH), and thyroglobuline (Tg) were measured at enrollment and during the follow-up. They observed that serum TSH, T4, T3, and Tg levels did not change significantly during the follow-up; this fact showed that thyroid function seemed not to be affected by MWA [81]. In the last years, the use of scintigraphy has been proposed for the follow-up after MWA procedures, with good results. Scintigraphic imaging is performed using two different types of tracers, 99 mTc pertechnetate and 99 mTc MIBI. All patients should undergo 99 mTc-pertechnetate imaging prior to the procedure to classify nodules as "cold" (reduced tracer uptake), "indifferent" (neutral tracer uptake), and "hot" (increased tracer uptake). A 99 mTc-MIBI imaging should be performed for cold nodules to detect malignant ones; 99 mTc pertechnetate imaging should be used for hot and indifferent nodules. It has been shown that tracer uptake after MWA ablation and during the follow-up was significantly reduced in the ablated tissue. Further research is necessary to establish the real role of scintigraphic imaging in follow-ups after MWA is used in the treatment of benign thyroid nodules [83, 84].

HIFU ablation

Devices and procedures

HIFU induces thermal tissue destruction (coagulative necrosis) within a few seconds by focusing a high-energy US beam onto a target, without skin penetration by any device. Since very small ablation areas are obtained with each sonication, several subsequent ablations have to be performed to cover the whole tumor volume, and the treatment may take quite a long time. The patient is placed in a supine position with neck hyperextended. A conscious sedation is given. HIFU is produced by arrays of piezoelectric elements driven by a high-frequency amplifier. The planned treatment volume and the vulnerable structures (carotid artery, trachea, and skin) are outlined on the touch screen interface of an US-guided HIFU system. On the basis of this information, the device software defines the treatment unit and safety margins. Multiple HIFU impulses are needed to induce a clinically significant ablation volume.

Complications

No major complications, such as vocal cord palsy, tracheal, vagal, or esophageal injuries, infections, or nodule rupture, were observed [85–88] (Table 1). The most frequent adverse events were local pain, mild skin burns, cough, and hematoma. In Esnault et al.'s study, 7 patients out of 25 developed skin blisters [86].

Clinical results

HIFU has been proposed for the treatment of various medical conditions, such as uterine fibroids and prostate, breast, pancreatic, and liver tumors [89–93]. Good results have also been obtained in patients with primary or secondary hyperparathyroidism [94]. Two preliminary studies were conducted on ewe thyroids, confirming the safety and reproducibility of this technique for localized thyroid disease [95, 96]. Little evidence about the efficacy of HIFU for the treatment of thyroid nodular disease in humans is still available. It should also be noticed that studies focused on the efficacy of HIFU in thyroid nodular disease were performed using different outcomes, making the comparison between different analyses impossible.

The efficacy of HIFU was established using different outcomes. Two studies analyzed the nodule volume reduction after HIFU procedure. In these studies, thyroid nodule volume and US structure were assessed at the baseline and during follow-ups at 3–6 months [87, 88]. Kovatcheva et al. showed a nodule volume reduction of 48.7 % at 6-month follow-ups after a single HIFU procedure. In this study, isoechoic nodules had greater volume reduction than hypoechoic ones, and highly vascularized nodules had a smaller reduction [87]. Thus, the assessment of nodule vascularization and the initial echogenity of the nodule seem to be important as predictors of the efficacy of this procedure [87]. Korkusuz et al. found a median volume reduction of 48.8 % after 3 months [88].

In another study, the uptake values of 99mTc-pertechnetate or 99mTc-MIBI pre- and post-treatment were analyzed. A decrease of total thyroidal uptake after one session of HIFU was discovered in all cases. Median 99mTc-MIBI uptake reduction was 35.5 % (ranging from 11 to 57 %), while 99mTc-pertechnetate scintigraphy showed a median uptake reduction of 27 % (range 10–44 %) [97].

In a monocentric, non-randomized, non-controlled trial, Esnault et al. considered the histology of nodules that were treated with HIFU two weeks before surgery. Histological examination revealed that the damage was limited to the treated lesions with a nodule necrosis that ranged from 2 to 80 % [86]. A pilot study of a single hyperfunctioning nodule demonstrated that the nodule developed into a predominantly cystic lesion 2 weeks after treatment and that hyperthyroidism normalized after 3 months was maintained at 18 months [85]. The location of the nodule is important in determining the efficacy of HIFU. Deep nodules require higher energy to overcome absorption by tissue between the skin and the nodule and more time to achieve an effective ablation.

Future directions in thyroid ablation: contrast-enhanced ultrasound (CEUS), virtual navigation with fusion imaging, and applications in malignant disease

In the last years, two important innovations have been introduced to improve the efficacy of minimally invasive percutaneous interventional procedures, including biopsy and tumor ablation: CEUS and virtual navigation. CEUS is extremely helpful in different phases of the treatment of patients with thyroid nodules, from planning of the treatment to follow-up. CEUS allows for a better identification and definition of the target lesion, and is important in the procedure planning, because it helps define the volume of the nodule correctly. Targeting of the nodule might also be enhanced by the intraoperative use of CEUS.

Moreover, CEUS is particularly helpful immediately after ablation, to better depict the completeness of the treatment, and to guide an eventual subsequent ablation of residual viable tissue, as reported in liver ablation and even in brain surgery [98–101]. Use of CEUS during follow-up might help predict the future reduction of the treated nodules, as CEUS is able to show the exact amount of devascularized nodule treatment, as compared to the whole volume shown at the standard US.

Another interesting method recently applied in thyroid disease is US elastography, which today is mainly used for better characterization of thyroid nodules, but which could be used in the follow-ups to minimally invasive treatment [102–104] in the future.

Virtual navigation and fusion imaging might also be extremely helpful when performing ablations in the neck [105]. With the fusion of different imaging modalities and the possibility of virtually navigating into a pre = acquired volume, the operator might be more confident during the ablation procedure, particularly when gas develops from the ablation, limiting the real-time US visualization [105, 106]. Virtual navigation and fusion imaging may be particularly important in complex and delicate anatomical regions, such as the neck, allowing a better identification of the target tumor or nodule and a clearer visualization of surrounding anatomical structures [105].

Turtulici et al. applied virtual navigation and fusion imaging to ultrasound-guided percutaneous RFA of benign thyroid nodules, using a real-time virtual needle tracking system to track the RF electrode tip when the tip is

obscured by the bubbles produced by RFA [106]. This technique, which is already described during use in the abdomen [107–110], is still under investigation in neck applications, but appears possibly one of the most relevant recent technical advancements for increasing the success rate and reducing the complications of image-guided ablations in the neck.

As ablations are widely applied to malignant tumors in other regions, such as the liver, the kidneys, or even the lungs, and good results have been reported in the treatment of benign thyroid disease, a few authors have started investigating the feasibility and effectiveness of image-guided thermal ablations in malignant diseases in the neck [111–115]. LA and RFA, in particular, seem to offer a possible curative treatment in the case of recurrent thyroid nodules and in metachronous lymph-node metastases from papillary thyroid carcinoma [111–115]. Such techniques, if further validated, may offer patients with difficult surgical approaches novel, minimally invasive therapeutic options. Thus, with the wider application of CEUS and virtual navigation with fusion imaging, and increased evidence of efficacy in the treatment of malignant diseases, image-guided ablation will easily see a larger and larger application in the treatment of thyroid diseases.

Conclusions

Image-guided percutaneous ablations appear to be effective in obtaining volume reduction of benign solid nodules and in providing significant improvement in cosmetic and pressure symptoms. Moreover, these techniques allow for the treatment of hyperfunctioning nodules, often providing a complete treatment without the subsequent need of radioiodine administration. Finally, thanks also to the wider application of advanced techniques, such as CEUS and virtual navigation, with fusion imaging, image-guided thermal ablation might easily become the first-choice treatment for patients with benign thyroid nodules in the near future. Hopefully, it will also become a recognized option for the treatment of malignant diseases which are not suitable for surgical resection.

Compliance with ethical standards

Conflict of interest Dr. Anna Pisani Mainini has nothing to disclose; Dr. Cristina Monaco has nothing to disclose; Dr. Lorenzo Carlo Pescatori has nothing to disclose; Dr. Chiara De Angelis has nothing to disclose; Prof. Francesco Sardanelli has nothing to disclose; Prof. Luca Maria Sconfienza has nothing to disclose; and Dr. Giovanni Mauri has nothing to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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