DIAGNOSIS OF ENDOCRINE DISEASE

Thyroid ultrasound (US) and US-assisted procedures: from the shadows into an array of applications

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Abstract

In patients with thyroid nodules, ultrasound (US) imaging represents an indispensable tool for assessment of the risk of malignancy. Over approximately four decades, innovative technology and successive improvements have facilitated its entry into the routine management and greatly improved its predictive value. When US features cannot reliably rule out thyroid cancer, US guidance allows a correct and safe sampling also of small or deeply located thyroid lesions. Obtained in this way, cytological or microhistological specimens may reliably define the nature of most thyroid nodules, and the information from histochemical or molecular markers shows promise in the classification of the remaining indeterminate cases. While a prompt surgical treatment can be offered in the minority of suspicious or definitely malignant cases, most individuals warrant only a follow-up. However, at initial evaluation, or over the years, a fraction of these benign lesions may grow and/or become symptomatic. Such cases may benefit from US-guided minimally invasive procedures as an alternative to surgery. Image-guided percutaneous treatments most often achieve relief of neck complaints, are inexpensive, and can be performed on an outpatient basis. The risk of major complications, after adequate training, is very low. Importantly, thyroid function is preserved. Currently, percutaneous ethanol injection for cystic lesions and thermal ablation, with laser or radiofrequency, for solid nodules are increasingly used and disseminated beyond the initial core facilities. In centres with expertise and high patient volume, their use should be considered as first-line treatment alternatives to surgery for selected patients with benign enlarging or symptomatic thyroid lesions.

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Invited Author's profile

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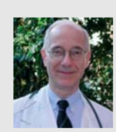

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Introduction

The incidence of thyroid nodules, and that of nodular goitre, has steadily increased over the last decades (1). In most cases, these lesions are harmless and asymptomatic and therefore warrant no treatment. However, a reliable diagnosis is mandatory for correct planning of their management and timely treatment of the minority that cause local symptoms or are at risk of harbouring cancer (2).

History and physical findings are still cornerstones in the clinical management of thyroid disease (3), but ultrasound (US) imaging represents an indispensable tool in the initial categorisation of malignancy risk in thyroid nodules, even if sonography cannot with absolute certainty rule out thyroid cancer in any individual case. Additionally, US imaging provides accurate guidance for biopsy procedures when US features cannot reliably exclude thyroid malignancy. Moreover, it is increasingly, and with wide dissemination, employed for minimally invasive treatments of benign symptomatic lesions (3, 4). In this study, we aim at, with a short historical and technological background, giving an overview of current evidence concerning the diagnostic and therapeutic use of US for thyroid nodular disease. Our ambition is to provide the endocrinologists, and other caretakers, with an updated approach to this frequent clinical situation.

Thyroid US: technological advances over four decades

US evaluation for thyroid imaging was introduced in the late 1960s and early 1970s (5, 6, 7, 8, 9, 10, 11). The A-mode (amplitude mode) thyroid scan allows distinction between solid and cystic lesions and the measurement, with reasonable accuracy, of the dimensions of the thyroid gland and of medium-sized thyroid nodules (9, 12). In 1967, Fugimoto *et al.* (6) first described the B-mode (brightness mode) imaging technique and the US patterns generated by nodular areas within the thyroid gland. Thyroid tissue was defined either as ‘cystic’, ‘sparsely spotted’ or ‘malignant’ on the basis of the quantity and degree of attenuation of the echoes produced by the lesions crossed by the US beam (6). In 1974, the advent of the ‘gray-scale’ display offered a real-time creation of easy-to-read images, enabling a more accurate differentiation between benign and malignant nodules and a precise measurement of thyroid volumes (13, 14, 15). Gray-scale is based on the differences in reflectivity of tissues. That is, on the screen the more reflective structures appear brighter than the less reflective ones. No information, however, can be obtained about the movement of small structures (like red blood cells) within the target area. In 1988, the Doppler mode was introduced for the study of the vascularity of the thyroid gland (16). Movements towards the receiver cause a positive frequency shift, while movements away from the transducer produce a negative frequency change. Thus, in clinical practice, Colour Doppler (CD) has permitted the assessment of blood flow, its direction and velocity, and of the possible changes in flow patterns (17). Power Doppler, a more recent technique, integrates the total amount of motion detected, irrespective of its direction and velocity, and encodes the flow in colour signals. The high sensitivity for the slow intra-parenchymal flow, scarcely imaged by CD, and the detailing of the course of small vessels within the tissues reveal the presence of both physiologic and pathologic vascularity, and its imaging in inflammatory, malignant or ischaemic areas of the thyroid (18, 19).

Presently under development and refinement, contrast-enhanced US (20) and sonoelastography (21) provide technological advances of diagnostic value (22). Although contrast agents provide only ancillary data for the diagnosis of thyroid malignancy, they are useful for the definition of the areas of tissue ablation induced by thermal ablation procedures (23). Sonoelastography was introduced in 2005 and seems promising for improving the diagnostic accuracy. Sonoelastography, in analogy with manual palpation, reveals the stiffness of a lesion in response to an external force not provided by B-mode US. The deformation of the nodule under evaluation is compared, by software, with that of the adjacent thyroid parenchyma and the relative hardness of the lesion is showed by a quantitative measure (strain index) or a qualitative colour picture superimposed on the B-mode image. The demonstration of an elevated hardness should prompt a fine-needle biopsy (FNA) even in lesions without suspicious US findings (22).

Reliability of US criteria for malignancy

The presence of a considerable overlap of the US features between benign and malignant nodules still hampers the diagnosis of thyroid carcinoma by US examination. However, as evidenced by several large-scale studies (24, 25, 26, 27, 28, 29, 30, 31, 32, 33), certain US features appear reliably associated with a higher risk for malignancy in thyroid nodules (2). A taller-than-wide shape and centrifugal growth across the tissue planes are indicators of malignancy. But, and importantly, their sensitivity is low because small papillary carcinomas frequently present with a well-defined round shape. The presence of irregularly microlobulated or spiculated margins, suggestive of an infiltrative neoplastic growth into the surrounding parenchyma, may be clearly depicted by current US equipment. Most slightly hypoechoic nodules are benign, but a marked hypoechogenicity (similar to cervical muscles) represents a suspicious feature. Finally, intranodular microcalcifications, albeit occasionally difficult to distinguish from comet-tail colloid interfaces, strongly indicates papillary carcinoma. The demonstration of aggressive growth (extension of the lesion beyond the thyroid capsule, invasion of the strap muscles or infiltration of the tracheal cartilage) or that of pathologic adenopathy (absence of hilum, cystic changes and/or microcalcifications) are obvious signs of thyroid neoplasia. Finally, even a chaotic intranodular neovascularisation may be indicative of malignancy (34).

In contrast, a spongiform or isoechoic US appearance and the presence of well-defined smooth margins are US findings suggestive of a benign thyroid lesion. Also, purely cystic lesions are, with few exceptions, benign. These nodules, in the absence of local symptoms or clinical suspicion, usually do not prompt a fine-needle-aspiration evaluation.

Taken together (Table 1), the above hallmarks permit appropriate risk stratification for malignancy (35), selection of lesions to biopsy and thereby also, ultimately, allow selection of nodules eligible for non-surgical intervention (4). The latter is the focus from here on.

US-assisted thyroid biopsy: from certainty to perspectives

FNA, either with or without aspiration, is the most important technique for the malignancy risk stratification of thyroid nodules. The major limitations of FNA are the non-negligible number of non-diagnostic samples, and the risk of an incorrect sampling site in small or cystic lesions and for nodules located deep in the neck. In 1977, Walfish *et al*. (36) proposed the combined use of the FNA procedure with US guidance in order to improve the accuracy of biopsy sampling. Since then, several reports have confirmed the improved diagnostic accuracy provided by US-guided and US-assisted biopsy. There is wide acceptance of the need of US-guidance for FNA of non-palpable nodules and of lesions in regions difficult to access. In our opinion, US-guided FNA should also be routinely used in palpable thyroid nodules as well, based on the lower risk of complications and the improved diagnostic accuracy (37, 38). In these cases the recommended sampling sites are as follows (39):

i) *Large nodules*. The peripheral part of the lesion rather than the central area, to avoid degenerative changes and fluid which may hamper the adequacy of sampled material.
ii) *Cystic or complex lesions*. After the drainage of the fluid component, a targeted sampling should be performed from the solid wall of complex lesions or from the pedicles protruding into the cyst cavity. The vascularised peripheral areas and the basis of the hubs should be preferentially sampled because the pedicle extremities and the inner layers of the wall represent mostly necrotic debris and degenerative changes (3).

The major limitations of FNA are the occurrence of repeat unsatisfactory specimens and of cytologically indeterminate cases. In solid nodules which are repetitively non-diagnostic at FNA, the use of US-guided core-needle biopsy should be considered (40). A small bore (20–21G) cutting needle device usually provides a micro-histological sample even from densely fibrotic lesions and permits the evaluation of both cytological and architectural features of the nodule (41).

Table 1 US features associated with risk of thyroid cancer. Sensitivity, specificity, positive- and negative-predictive value are expressed as the range of the values reported in the quoted trials (see references).

US feature	**Sensitivity** (%)	**Specificity** (%)	**Positive-predictive value** (%)	**Negative-predictive value** (%)
Marked hypoechogenicity (24, 25, 28, 30, 32)	26.5–87.2	43.4–94.3	11.4–68.4	73.5–93.8
Spiculated margins (24, 25, 28, 30, 32)	17.4–77.5	38.9–91.8	9.3–81.3	38.9–97.8
Microcalcifications (24, 25, 26, 28, 30, 32)	26.1–59.1	85.8–95.0	24.3–77.9	41.8–94.2
Solid structure (28, 29, 30)	69.0–75.0	52.5–55.9	15.6–27.0	88.0–92.1
Intranodular vascularity (24, 30)	54.3–74.2	78.6–80.0	24.0–41.9	85.7–97.4
More tall than wide (25, 32)	32.7–40.0	91.4–92.5	66.7–77.4	67.4–74.8
Macrocalcifications (32)	9.7	96.1	64.8	59.1

When correctly performed, the procedure is safe and rapid, and prevents the need for diagnostic surgery for those solid lesions for which a cytological diagnosis cannot reliably be obtained. In the near future, immunochemical and molecular markers with elevated negative predictive value for malignancy will become more widely accessible in clinical practice for the assessment of the nature of cytologically indeterminate thyroid nodules (42).

Minimally invasive treatment options of benign thyroid nodules

Most thyroid nodules are benign and remain asymptomatic, but some grow progressively and may cause local symptoms or elicit anxiety. Surgery is a much used therapeutic approach for thyroid lesions that, even if benign at FNA, are steadily growing over time (1, 3). However, surgery is expensive, may necessitate life-long thyroid hormone substitution therapy and may be followed, even if infrequently, by permanent complications (43). There is also increasing focus on the side-effects, including the effect on quality of life, not traditionally considered in this context (44, 45). Over the last two decades non-surgical, minimally invasive techniques have been proposed for the treatment of benign thyroid nodules when surgery is contraindicated or declined (37). In 1983, Sugiura *et al*. (46) achieved destruction of a small hepatocellular carcinoma (HCC) with percutaneous injection of ethanol. During the following years encouraging results were obtained in small series of HCC treated with percutaneous ethanol injection therapy (PEIT) (47, 48). In 1983, Bown (49) proposed the use of laser as a thermal source for the ablation of liver tumours and during the 1990s the first clinical applications were reported. Since then, new minimally invasive techniques, such as radiofrequency, proposed by Rossi *et al*. (50) and McGahan *et al*. (51), or microwave (52) and cryotherapy (53), have been suggested for the non-surgical treatment of liver tumours.

Technological improvements in imaging methods and guiding devices have made the reliable use of minimally invasive procedures for thyroid gland lesions possible. PEIT was the first therapeutic procedure proposed in 1990 for hyperfunctioning nodules (54). Owing to the limitations of PEIT, in the management of solid thyroid lesions, various hyperthermic methods have, over the past 10–15 years, been introduced for the treatment of benign thyroid lesions. During this period, laser ablation therapy (LAT), the first method proposed in 2000 for size reduction of benign solid thyroid nodules (55), and radiofrequency ablation (RFA) (56), introduced in 2007, have achieved increasing acceptance for use in selected patients. Additional therapeutic modalities, such as focused US (57) and microwaves (58), are presently under evaluation and have yet to gain wider acceptance.

Percutaneous ethanol injection

The injection of 95% ethanol into thyroid tissue induces thrombosis of small vessels and an irregular area of coagulative necrosis surrounded by interstitial oedema and granulomatous inflammation. Over time, these histological changes are followed by fibrosis, progressive shrinkage and reduction of the volume of the treated lesion (59, 60, 61).

Non-functioning benign thyroid nodules ▸ PEIT may effectively reduce the size of solid thyroid nodules. Several non-randomised trials, heterogeneous as for nodule size, ethanol volume and length of follow-up, demonstrate a significant decrease in nodule volume after PEIT (62, 63, 64).

In a 12-month randomised study, a single PEIT session induced a nearly 50% volume reduction, while thyroid-stimulating hormone (TSH)-suppression with levothyroxine had no significant effect on nodule reduction (63). Repeat treatment seemed only to increase the efficacy of PEIT marginally (65). These observations were confirmed in a randomised study that demonstrated a reduction just over 50% after three PEIT sessions (64). The major limitations of this otherwise rapid and inexpensive procedure are the non-predictable diffusion of ethanol within solid lesions and the leakage of ethanol into neck tissues. Owing to alcohol seepage, the majority of patients experience moderate to severe cervical pain lasting from minutes to hours (66). In our experience, a possible complication is the development of local fibrosis that may make less manageable a subsequent thyroid surgery if needed (60, 61, 66). Major side-effects, fortunately not common, are recurrent laryngeal nerve palsy with mostly transient dysphonia and, rarely, Graves' disease, Horner's syndrome, and necrosis of the larynx and the skin (62, 66). In most cases, no change in thyroid function or thyroid autoimmunity has been reported (62, 63, 64). Currently, and in accordance with relevant guidelines, PEIT is not the procedure of choice for non-surgical treatment of solid thyroid nodules. It should be restricted to highly selected patients.

Cystic nodules ▸ This covers thyroid nodules that are purely cystic (the minority) or predominantly cystic (the majority) (2). US-guided percutaneous drainage is the treatment of choice, but most cystic lesions (about 80%) refill and enlarge over time (62). Several non-randomised studies (62, 67, 68), in both colloid and haemorrhagic lesions, have reported good efficacy, a favourable side-effect profile and the preservation of thyroid function. A randomised study in recurrent thyroid cysts compared percutaneous cyst drainage followed by ethanol flushing and subsequent aspiration with cyst drainage followed by flushing with isotonic saline (69). After a single session, a significant volume reduction was obtained in 82% of cases in the PEIT group, while the cure rate in the saline group was only 18%. The success rate was inversely correlated with the baseline cyst volume and number of previous aspirations. Pain, if any, is usually mild and rapidly self-resolving and the risk of dysphonia is very low. In a follow-up study of thyroid lesions treated with PEIT, the volume reduction of the cysts was fairly stable after 5 years (70). The major endocrine society guidelines (3, 71) state that treatment of recurrent benign thyroid cysts with ethanol is a clinically effective non-surgical option for thyroid cysts that recur after repeat aspirations.

Functioning thyroid nodules ▸ Hyperfunctioning lesions account for 5–10% of all thyroid nodules (2). Malignancy is extremely rare and radioiodine ^{131}I is considered as the first-line therapy in the majority of patients (2, 3, 72, 73) because normalisation of thyroid function is attained in most cases and the reduction of nodule volume is about 30–45% within 1–2 years (2, 72, 74). PEIT appeared promising in the initial studies (54, 75), but no prospective randomised trials are available. One study in 132 patients treated with multiple sessions demonstrated normalisation of serum TSH in all pretoxic adenomas and in 71% of toxic adenomas (76). Nodule volume reduction was similar to that reported for cold thyroid nodules. Moderate to severe cervical pain was frequently encountered (77). Subsequent trials have confirmed that several PEIT-sessions are necessary for a complete treatment and that the recurrence of hyperthyroidism and the regrowth of the treated nodules are common (77). Based on these considerations, with the exception of the infrequent conditions in which ^{131}I is contraindicated or ineffective, efficacy and side effects are in favour of ^{131}I when compared with PEIT.

Laser ablation

Laser light is coherent and monochromatic, can be highly collimated or focused and may transmit considerable amounts of energy over long distances with minimal dispersion. Laser light is transmitted from the source to the targeted lesion in a thin (300–400-μm) 'optical fibre', which consists of a silica-based core with a surrounding cladding made of silica or hard polymer material. The photons transmitted from the tip of the optic fibre scatter within the targeted tissue, generate heat and coagulate the surrounding parenchyma. Further out in the tissue, heating is affected by heat conduction and tissue carbonisation (78). Currently, the majority of laser procedures use either Neodimium:Yttrium Aluminium Garnet (Nd:YAG) with a wavelength of 1064 nm or diode lasers with a wavelength of 800–980 nm, because penetration of light is optimal in the near-infrared spectrum. Laser technology induces a fairly predictable and reproducible area of tissue damage while inducing only minimal damage outside the targeted ablation zone (55, 79). Laser ablation is usually performed on conscious patients after local anaesthesia at the entry site and thyroid capsule. A minority refrain from local anaesthesia (80). After information and reassurance, the patient is placed in the supine position with appropriate extension of the neck. Subsequently, one or more optical fibres are inserted into the targeted lesion through spinal needles with variable diameter from 18 to 22G (81, 82, 83). LA sessions may be performed either under US guidance or assistance, using a commercially available US system equipped with a high-frequency linear transducer (7.5–15 MHz).

Treatment algorithm and laser equipment differ among centres. Most frequently, the laser source is either a continuous diode laser of varying power and wavelength (81, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96) or a continuous wave Nd:YAG laser (80, 82, 97, 98, 99, 100, 101, 102, 103, 104). Operators may insert the applicator(s) in the appropriate area of the targeted lesion and terminate the procedure when the area of echogenicity (identifiable by 'white spots' and typically decreasing hypoechogenicity caused by evaporation) generated by energy delivery is stationary in size (81, 84, 85, 86, 87, 88, 89, 90). Alternatively, the energy may be delivered continuously while retracting the applicators (83, 91, 96, 99, 102, 103) or by pull back technique (80, 82, 98, 101, 104).

Cold nodules ▸ After an initial *ex-vivo* feasibility study (55), several non-randomised (81, 82, 92, 97, 98, 102, 103) trials have demonstrated the efficacy of LAT in thyroid lesions. Cytological and histological samples obtained after LAT have demonstrated necrosis, degenerative changes and inflammatory reaction in the treated lesions without signs of extrathyroidal damage or cervical fibrosis

(92). Two randomised studies have compared the clinical and the US changes inflicted by LAT with those obtained by levothyroxine suppressive therapy or plain follow-up (85, 101). These trials were performed with an Nd:YAG or with a diode laser source respectively. Both studies confirmed that a single LAT session results in a significant volume decrease (around 45%) at the 6- and 12-month US controls, while no changes were observed in either the levothyroxine therapy or the control groups. Volume decrease was stable up to 5 years after treatment, and most LAT-treated patients report amelioration of local symptoms (89). A recent multicentre randomised trial confirmed a nodule volume reduction of 45–55% 24 months after a single LAT, and without major regional variation among the participating centres (105).

Autonomously functioning thyroid nodules ▸ Studies in small series of autonomously functioning thyroid nodules (AFTNs) treated with LAT have reported normalisation of thyroid function and destruction of the previously hyperfunctioning area at post-treatment radioisotope scan (84, 93, 97). Subsequent studies have demonstrated that LAT has an inconsistent efficacy in that multiple LAT sessions were needed to normalise serum TSH levels (82, 100). A randomised trial in solitary hot nodules with suppression of extranodular thyroid tissue demonstrated that LAT and ^{131}I therapy had a similar effect on nodule volume reduction. However, LAT was followed by normalisation of serum TSH in only 50% of patients, which is much lower than that obtained with radioactive iodine (88). Taken together, these results demonstrate acceptable efficacy of LAT when treating small, solitary and mildly hyperfunctioning nodules (102). At variance, in large AFTNs the cure rate is unsatisfactory and normalisation of thyroid function usually requires multiple (median 1–3) laser sessions (82, 100).

Cystic lesions ▸ In a recent study, recurrent predominantly cystic nodules were randomised to aspiration with or without subsequent LAT (90). After 6 months, remission of the cystic component was seen in 68% of LAT patients as opposed to 18% in the aspiration-alone group. Local symptoms improved in the LAT group only and thyroid function remained unaffected in all. Clinical results of LAT for the treatment of thyroid nodules are summarised in Table 2.

Tolerability and safety ▸ Moderate pain or low-grade fever can occur after LAT, but infrequently, and can be controlled by acetaminophen or ketoprophene. Subcapsular haematoma (94), dizziness, skin burn and cervical swelling have been reported, but are rare (103). Transient hyperthyroidism and late hypothyroidism are likewise rare (103). No pathological changes have been found in tissue adjacent to the ablated area in patients who subsequently underwent surgery (95, 106). The low risk of major complications (about 1%) and the high tolerability of LAT have been confirmed in a recent multicentre study (105).

Radiofrequency ablation

RFA is achieved by means of an alternating electric field created within the target lesion by an electrode needle coupled to an external radiofrequency generator (107). The rapid movement of the ions adjacent to the electrode-needle induces a speedily increasing heating of the tissue and thereby thermal necrosis (108). After initial feasibility studies performed either with internally cooled (17-gauge) (56, 109, 110) or with multitined large (14-gauge) (111) electrodes in patients under conscious sedation, thinner (18-gauge) internally cooled electrodes have been recently developed and employed (112). With the presently used ‘moving shot technique’, an electrode-needle is introduced into the targeted nodule and multiple areas of the lesion are destroyed by moving the electrode tip. Initially, the electrode is positioned in the deepest part of the nodule whereafter it is moved into the central and finally the superficial areas of the lesion (113, 114).

Solid non-functioning thyroid nodules ▸ Several series of patients, in non-randomised studies, have been treated with the fixed electrode technique, using a 14-gauge device with multitined expandable electrodes. On average, nodule size has been reduced by 50% after 6 months and by nearly 80% 1 year after therapy, and accompanied by amelioration of anterior neck symptoms (111, 115, 116). The efficacy using the ‘moving shot’ technique in a selected series of non-randomised patients with solid and cystic nodules has been reported (56, 109, 112). Two recent non-randomised controlled studies have compared the clinical and the US changes obtained with RFA in patients with nodules with a solid component $>50\%$ with a control group. These trials were performed with the ‘moving shot’ or the fixed electrode techniques respectively. Both studies confirmed that in complex lesions a single RFA session results in a significant volume decrease (around 80–84%) at the 6- and 9-month US controls, while no changes were observed in the control subjects (113, 117). Repeated RFA sessions (range 1–6; mean 1.4)

Table 2 Clinical outcomes of patients with symptomatic benign thyroid nodules treated with laser ablation.

Author	Pts/nodules no.	RCT	US pattern[a] Solid-cystic	Baseline (vol ml mean)	Nodule function hot/cold no.	Laser source	Energy load (J/ml mean)	Number of sessions (mean)	FU mo	Volume reduction (% mean)
Dossing *et al.* (2002) (81)	16		Solid	10.0	Cold	820 diode	761 (median)	1	6	46
Dossing *et al.* (2003) (84)	1		Solid	8.2	Hot	820 diode		1	9	40 (median)
Spiezia *et al.* (2003) (97)	12		Solid	3.2/11.1	7/5	Nd:YAG		1/2.2	12	74/61
Pacella *et al.* (2004) (82)	24		Solid	8.0/22.7	16/8	Nd:YAG	816/788	2.7/4.1	6	62/63
Papini *et al.* (2004) (98)	20		Solid	24.1	Cold	Nd:YAG	300	2.2	6	64
Dossing *et al.* (2005) (85)	15 vs 15	Yes	Solid	8.2	Cold	820 diode	224 (median)	1	6	44 (median)
Dossing *et al.* (2006) (87)	10		Cystic-solid	9.6	Cold	820 diode	254 (median)	1	12	57 (median)
Amabile *et al.* (2006) (83)	23		Solid	15.0	Cold	980 diode	33	1.2	3	36
Dossing *et al.* (2006) (86)[b]	15 vs 15	Yes	Solid	10.1/10.7	Cold	820 diode	262 vs 412	1	6	45 vs 58 (median)
Gambelunghe *et al.* (2006) (99)	13 vs 13	Yes	Solid	8.2	7[c]/13 vs 6[c]/3	Nd:YAG	1900 (median)	1	30 weeks	44
Cakir *et al.* (2006) (92)	12/15		Solid	11.9	Cold	810 diode	2726	1.5	12	82
Barbaro *et al.* (2007) (100)	18		Solid	21.1	Hot	Nd:YAG		3	12	59
Dossing *et al.* (2007) (88)[d]	14 vs 15	Yes	Solid	10.6/11.2	Hot	820 diode	217	1	6	44 (median)
Papini *et al.* (2007) (101)[e]	21 vs 21 vs 20	Yes	Solid	11.7/13.6/12.1	Cold	Nd:YAG	1221	1	12	>40
Valcavi *et al.* (2008) (102)	119		Solid	24.8	Cold	Nd:YAG		1	12	56
Valcavi *et al.* (2008) (102)	1		Solid	2.5	Hot	Nd:YAG		1		CR
Rotondi *et al.* (2009) (96)	1		Solid	55.0	Hot	980 diode		4	10	91
Valcavi *et al.* (2010) (103)[f]	122		Solid	23.1	Cold	Nd:YAG	484 (median per nodule)	1	36	48
Dossing *et al.* (2011) (89)	78	Yes	Solid	8.2	Cold	820 diode	242 (median)	1	67	51 (median)
Amabile *et al.* (2011) (91)[g]	78		Solid	55.3/55.3	51/26	980 diode	391/379	3.2 cycle	12	81.3/81.9
Gambelunghe *et al.* (2013) (80)[h]	20/20		Solid	15/14	Cold	Nd:YAG	71/579 (median)	1	36	+11/57
Gambelunghe *et al.* (2013) (104)[i]	50/50		Solid	21/21	Cold	Nd:YAG	502/499	1	6	55/56 (median)
Dossing *et al.* (2013) (90)[i]	22 vs 22	Yes	Mixed	10.0/11.8	Cold	820 diode	83 (median)	1	6	26 vs 73 (median)

Pts, patients; CR, complete response.
[a]Uniformly solid or predominantly solid with not more than 20% fluid component.
[b]One laser session vs three laser sessions.
[c]Retrospective comparison between patients treated with local anesthetic and patients treated without local anesthetic.
[d]RCT comparing single LAT session vs single radioiodine dose.
[e]Patients treated with laser energy vs patients treated with L-T_4 or not treated.
[f]The energy was delivered continuously while retracting the applicators in a single session.
[g]The energy was delivered continuously while extracting the needle. All patients were addressd to one to three cycles of LAT. Each cycle consisted of three LAT sessions at an interval of 1 month.
[h]Retrospective comparison between a group treated with low amount of energy and the group treated with a high amount of energy.
[i]RCT comparing aspiration alone vs aspiration with subsequent LAT in recurrent predominanlty cystic thyroid nodules.

induced a nodule shrinkage of about 85% (109) after 6 months. Nodule shrinkage appears to persist since multiple RFA treatment sessions (range 1–7; mean 2.2) resulted in a 93.5% mean volume reduction after 4 years. Volume reduction seems faster and more pronounced in cystic than in solid nodules (118). Complication rate is deemed reasonable at about 3.3% in large multicentre series of patients (119). Careful training and centralised therapy are recommended because recurrent nerve damage, perithyroidal haemorrhage, nodule rupture and skin burns have been occasionally reported, and are not just theoretical concerns (119).

Hyperfunctioning thyroid nodules ▸ Hyperfunctioning nodules have been treated with either the fixed-electrode procedure (111, 115, 116, 117) or the moving shot technique (110, 112). A significant improvement in thyroid hyperfunction, as well as nodule volume reduction, has been reported in non-controlled series of patients (111, 112, 115, 116). A major limitation, in unison with the other thermal ablation procedures, is the risk of incomplete and insufficient ablation of the external border of the hyperfunctioning lesion, followed by regrowth of the AFTN and relapse of hyperthyroidism (112).

Cystic thyroid nodules ▸ RFA has been used in the treatment of cystic lesions in a few uncontrolled studies (56, 109, 118). Similar therapeutic success (volume reduction >50%) with fewer treatment sessions with PEIT compared with RFA (1.19 vs 1.67) has been reported (120). A head-to-head study of a single session of either RFA or PEIT demonstrated a similar efficacy of both techniques (121) with a considerable volume reduction at 6 months (93.3 vs 96.9%). Owing to higher cost and longer treatment duration with RFA, PEIT or laser should remain the treatment of choice for recurrent cystic lesions (90, 121). Clinical results of RFA for the treatment of thyroid nodules are summarised in Table 3.

Translating all the aforementioned into clinical practice

Currently available US-guided minimally invasive procedures can induce a rapid, clinically significant long-term size reduction of benign thyroid nodules with minimal risk of causing thyroid dysfunction. PEIT should preferentially be considered as the first-line treatment for relapsing thyroid cysts. In solid non-functioning thyroid nodules LAT and RFA can, in a single session, achieve a 50% volume decrease. In comparison with radioactive iodine, these procedures seem less cost-effective for treating AFTN.

Minimally invasive procedures appear appealing because they most often achieve relief of anterior neck complaints, are relatively inexpensive and can be performed on an outpatient basis. As these techniques are increasingly disseminated and used, it is important to remember that the vast majority of thyroid nodules, once malignancy has been ruled out, are asymptomatic, slowly growing and do not warrant treatment (1). Nevertheless, a minority of the vast number of patients with thyroid nodules may benefit from one or the other of these ablation procedures to address pressure symptoms, local pain or cosmetic issues. Progressively growing benign thyroid lesions that reach to a volume over 12 ml seem to be especially suited for minimally invasive procedures. Less appropriate indications are large nodular goitres, multinodular thyroid disease or deeply positioned lesions. It is noteworthy that pre-treatment nodule size is not significantly correlated with the degree of nodule volume reduction after thermal ablation (89). Technically, easily treated lesions are medium- or large-size nodules that are centrally located in the thyroid lobe. In contrast, nodules situated in the isthmus and para-isthmus region, those at the apex of the thyroid lobes and nodules that are located behind the jugulum are characterised as difficult to treat.

Even if the cost- and risk-effectiveness of minimally invasive techniques vs surgical treatment have not yet been established with head-to-head studies, image-guided ablation techniques are office-based procedures that carry no risk of cosmetic damage and are more rapid and less expensive than thyroidectomy. In European centres, the price of a disposable RFA device is about 1300 euros, and the cost of a laser kit including a guidance device and a fibreoptic is about 300 euros. The costs of disposable materials are nearly negligible and the duration of the procedure is about 30 min.

An advantage of minimally invasive procedures is the nearly complete sparing of thyroid function with a very low risk of subsequent hypothyroidism. The risk of overlooking thyroid malignancy should always be considered before planning percutaneous treatments and should be carefully ruled out with dedicated US neck examination and a repeated FNA of the targeted lesion.

Additional, but still inadequately investigated non-surgical treatment options such as High Intensity Focused Ultrasound (HIFU) (57, 122) and microwaves (58, 123) are currently under evaluation. Although results are promising, they are too preliminary and sparse to allow any recommendations. Advances in technology are rapidly

Table 3 Clinical outcomes of patients with symptomatic benign thyroid nodules treated with radiofrequency ablation.

Author	Pts/ nodule no	RCT	US pattern cystic-solid	Fluid component (%)	Baseline (vol. ml mean) hot/cold	Nodule function hot/cold no	Electrode type	Energy load (J/ml mean)	Number of session (mean)	FU m_o	Volume reduction (% mean) hot/cold
Kim *et al.* (2006) (56)[a]	30/35		Cystic-solid	>80	6.3	Cold	17G cooled elctrode		1	6.4 (median)	88
Spiezia *et al.* (2007) (111)	39/39		Solid			Cold	14G multitined electrodes		1.4	6	74
Jeong *et al.* (2008) (109)[b]	236/302		Cystic-solid	>80	6.1	Cold	17G cooled electrode		1.4	6	85
Baek *et al.* (2008) (110)	1		Mixed		5.1	Hot	17G cooled electrode			19	97
Deandrea *et al.* (2008) (115)[c]	33/33		Cystic-solid	<30	22.6/39.3	23/10	14G multitined electrodes		1	6	52 vs 46
Spiezia *et al.* (2009) (116)[c]	94/94		Cystic-solid	<30	32.7/21.1	28/66	14G multitined electrodes		1 (median)	12	78
Baek *et al.* (2009) (112)	9/9		Cystic-solid	>80	14.9	Hot	17–18G cooled electrode	10 818	2.2	6	71
Baek *et al.* (2010) (113)	15 vs 15		Cystic-solid	>50	6.9/7.5	Cold	18G cooled electrode	4966	1	6	80
Sung *et al.* (2011) (120)[d]	21		Cystic	>90	10.2	Cold	18G cooled electrode		1.7	6	>50
Huh *et al.* (2012) (114)[e]	15 vs 15	Yes	Cystic-solid	>50	13.3/13.0	Cold	18G cooled electrode	4377 vs 6157	1	6	70 vs 78
Faggiano *et al.* (2012) (117)[c]	20/20		Cystic-solid	<30	11.2/13.3	10/10	14G multitined electrodes		1	9	85
Lim *et al.* (2013) (118)[f]	111/126		Cystic-solid	65	9.8	Cold	17/18G cooled electrode	2936	2.2	49	93
Sung *et al.* (2013) (121)[g]	25 vs 25	Yes	Cystic	>90	9.3	Cold	18G cooled electrode		1	6	93

Pts, patients.
[a]Sixteen of 35 (45.7%) nodules were mainly cystic with cystic portion >80%.
[b]Fifty-four percent with solid portion >80%, 16% with cystic component >80%, and remaining 30% with mixed structure.
[c]Uniformly solid (100% solid) or predominantly solid with not more than 30% fluid component.
[d]Therapeutic success defined as volume reduction >50 was achieved with RFA in 20/21 (95%) nodules.
[e]One RF session vs two RF sessions.
[f]Forty-five nodules with solid component ≤50% and 81 nodules with solid component >50%.
[g]RCT: RFA vs PEIT.

improving commercially available guiding systems and ablation devices. Equally important, a large number of individuals have now been trained and master these ablation techniques. Minimally invasive procedures may, in a number of centres with expertise and adequate patient volume, already be offered to selected patients in an attempt to achieve a higher degree of individualised management of benign symptomatic thyroid lesion.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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Author contribution statement

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References

1 Gharib H & Papini E. Thyroid nodules: clinical importance, assessment, and treatment. *Endocrinology and Metabolism Clinics of North America* 2007 **36** 707–735 vi. (doi:10.1016/j.ecl.2007.04.009)

2 Hegedus L, Bonnema SJ & Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. *Endocrine Reviews* 2003 **24** 102–132. (doi:10.1210/er.2002-0016)

3 Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedus L & Vitti P. American Association of Clinical Endocrinologist, Associazione Medici Endocrinologi, and European Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. *Endocrine Practice* 2010 **16** (Suppl 1) 1–43. (doi:10.4158/10024.GL)

4 Gharib H, Hegedus L, Pacella CM, Baek JH & Papini E. Nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3949–3957. (doi:10.1210/jc.2013-1806)

5 Yamakawa M & Naito S. In *Diagnostic Ultrasound*, vol 966, pp 27–41. Eds CH Grossman, JH Holmes, CL Joyner & EW Purnell. Plenum Press and Plenum Publishing Corporation, New York Proceeding of the First International Congress, University of Pittsburgh.

6 Fugimoto Y, Oka A, Omoto R & Hirose M. Ultrasound scanning of the thyroid gland as a new diagnostic approach. *Ultrasonics* 1967 **5** 177–180. (doi:10.1016/S0041-624X(67)80065-9)

7 Damascelli B, Cascinelli N, Livraghi T & Veronesi U. Preoperative approach to thyroid tumours by a two-dimensional pulsed echo technique. *Ultrasonics* 1968 **6** 242–243. (doi:10.1016/0041-624X(68)90135-2)

8 Rasmussen SN, Christiansen NJ, Jorgensen JS & Holm HH. Differentiation between cystic and solid thyroid nodules by ultrasonic examination. An estimation of the value of ultrasonic examination as a supplement to isotope scanning. A preliminary communication. *Acta Chirurgica Scandinavica* 1971 **137** 331–333.

9 Thijs LG. Diagnostic ultrasound in clinical thyroid investigation. *Journal of Clinical Endocrinology and Metabolism* 1971 **32** 709–716. (doi:10.1210/jcem-32-6-709)

10 Blum M, Weiss B & Hernberg J. Evaluation of thyroid nodules by A-mode echography. *Radiology* 1971 **101** 651–656.

11 Miskin M, Rosen IB & Walfish PG. B-mode ultrasonography in assessment of thyroid gland lesions. *Annals of Internal Medicine* 1973 **79** 505–510. (doi:10.7326/0003-4819-79-4-505)

12 Rosen IB, Walfish PG & Miskin M. The ultrasound of thyroid masses. *Surgical Clinics of North America* 1979 **59** 19–33.

13 Crocker EF, McLaughlin AF, Kossoff G & Jellins J. The gray scale echographic appearance of thyroid malignancy. *Journal of Clinical Ultrasound* 1974 **2** 305–306. (doi:10.1002/jcu.1870020411)

14 Scheible W, Leopold GR, Woo VL & Gosink BB. High-resolution real-time ultrasonography of thyroid nodules. *Radiology* 1979 **133** 413–417.

15 Hegedus L, Perrild H, Poulsen LR, Andersen JR, Holm B, Schnohr P, Jensen G & Hansen JM. The determination of thyroid volume by ultrasound and its relationship to body weight, age, and sex in normal subjects. *Journal of Clinical Endocrinology and Metabolism* 1983 **56** 260–263. (doi:10.1210/jcem-56-2-260)

16 Rails PW, Mayekawa DS, Lee KP, Colletti PM, Radin DR, Boswell WD & Halls JM. Color-flow Doppler sonography in Graves' disease: "thyroid inferno". *AJNR. American Journal of Neuroradiology* 1988 **150** 781–784.

17 Burns PN. The physical principles of Doppler and spectral analysis. *Journal of Clinical Ultrasound* 1987 **15** 567–590. (doi:10.1002/jcu.1870150903)

18 Rubin JM, Bude RO, Carson PL, Bree RL & Adler RS. Power Doppler US: a potentially useful alternative to mean frequency-based color Doppler US. *Radiology* 1994 **190** 853–856.

19 Bude RO & Rubin JM. Power Doppler sonography. *Radiology* 1996 **200** 21–23.

20 Grant EG. Sonographic contrast agents in vascular imaging. *Seminars in Ultrasound, CT, and MR* 2001 **22** 25–41. (doi:10.1016/S0887-2171(01)90016-2)

21 Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, Mai JJ, Pellot-Barakat C, Insana MF, Brill AB, Saga T *et al*. Thyroid gland tumor diagnosis at US elastography. *Radiology* 2005 **237** 202–211. (doi:10.1148/radiol.2363041248)

22 Trimboli P, Guglielmi R, Monti S, Misischi I, Graziano F, Nasrollah N, Amendola S, Morgante SN, Deiana MG, Valabrega S *et al*. Ultrasound sensitivity for thyroid malignancy is increased by real-time elastography: a prospective multicenter study. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 4524–4530. (doi:10.1210/jc.2012-2951)

23 Papini E, Bizzarri G, Bianchini A, Guglielmi R, Graziano F, Lonero F, Pacella S & Pacella CM. Contrast-enhanced ultrasound in the management of thyroid nodules. In *Thyroid Ultrasound and Ultrasound-Guided FNA*, pp 151–171. Eds HJ Baskin, DS Duick & RA Levine. New York, NY: Springer, 2008.

24 Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, Panunzi C, Rinaldi R, Toscano V & Pacella CM. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 1941–1946. (doi:10.1210/jcem.87.5.8504)

25 Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT & Yoo HS. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. *AJR. American Journal of Roentgenology* 2002 **178** 687–691. (doi:10.2214/ajr.178.3.1780687)

26 Khoo ML, Asa SL, Witterick IJ & Freeman JL. Thyroid calcification and its association with thyroid carcinoma. *Head & Neck* 2002 **24** 651–655. (doi:10.1002/hed.10115)

27 Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ, Kim WB & Shong YK. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with pathological findings. *Clinical Endocrinology* 2004 **60** 21–28. (doi:10.1046/j.1365-2265.2003.01912.x)

28 Peccin S, de Castsro JA, Furlanetto TW, Furtado AP, Brasil BA & Czepielewski MA. Ultrasonography: is it useful in the diagnosis of cancer in thyroid nodules? *Journal of Endocrinological Investigation* 2002 **25** 39–43.
29 Alexander EK, Marqusee E, Orcutt J, Benson CB, Frates MC, Doubilet PM, Cibas ES & Atri A. Thyroid nodule shape and prediction of malignancy. *Thyroid* 2004 **14** 953–958. (doi:10.1089/thy.2004.14.953)
30 Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, Cronan JJ, Doubilet PM, Evans DB, Goellner JR *et al*. Management of thyroid nodules detected at US: society of radiologists in ultrasound consensus conference statement. *Radiology* 2005 **237** 794–800. (doi:10.1148/radiol.2373050220)
31 Wienke JR, Chong WK, Fielding JR, Zou KH & Mittelstaedt CA. Sonographic features of benign thyroid nodules: interobserver reliability and overlap with malignancy. *Journal of Ultrasound in Medicine* 2003 **22** 1027–1031.
32 Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, Kim J, Kim HS, Byun JS & Lee DH. Benign and malignant thyroid nodules: US differentiation – multicenter retrospective study. *Radiology* 2008 **247** 762–770. (doi:10.1148/radiol.2473070944)
33 Lee YH, Kim DW, In HS, Park JS, Kim SH, Eom JW, Kim B, Lee EJ & Rho MH. Differentiation between benign and malignant solid thyroid nodules using an US classification system. *Korean Journal of Radiology* 2011 **12** 559–567. (doi:10.3348/kjr.2011.12.5.559)
34 Leenhardt L, Hejblum G, Franc B, Fediaevsky LD, Delbot T, Le Guillouzic D, Menegaux F, Guillausseau C, Hoang C, Turpin G *et al*. Indications and limits of ultrasound-guided cytology in the management of nonpalpable thyroid nodules. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 24–28. (doi:10.1210/jcem.84.1.5418)
35 Russ G, Royer B, Bigorgne C, Rouxel A, Bienvenu-Perrard M & Leenhardt L. Prospective evaluation of thyroid imaging reporting and data system on 4550 nodules with and without elastography. *European Journal of Endocrinology* 2013 **168** 649–655. (doi:10.1530/EJE-12-0936)
36 Walfish PG, Hazani E, Strawbridge HT, Miskin M & Rosen IB. A prospective study of combined ultrasonography and needle aspiration biopsy in the assessment of the hypofunctioning thyroid nodule. *Surgery* 1977 **82** 474–482.
37 Hegedus L. Therapy: a new nonsurgical therapy option for benign thyroid nodules? *Nature Reviews. Endocrinology* 2009 **5** 476–478. (doi:10.1038/nrendo.2009.152)
38 Can AS. Cost-effectiveness comparison between palpation- and ultrasound-guided thyroid fine-needle aspiration biopsies. *BMC Endocrine Disorders* 2009 **9** 14. (doi:10.1186/1472-6823-9-14)
39 Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedus L & Vitti P. Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. *Journal of Clinical Investigation* 2010 **33** 51–56.
40 Samir AE, Vij A, Seale MK, Desai G, Halpern E, Faquin WC, Parangi S, Hahn PF & Daniels GH. Ultrasound-guided percutaneous thyroid nodule core biopsy: clinical utility in patients with prior nondiagnostic fine-needle aspirate. *Thyroid* 2012 **22** 461–467. (doi:10.1089/thy.2011.0061)
41 Nasrollah N, Trimboli P, Guidobaldi L, Cicciarella Modica DD, Ventura C, Ramacciato G, Taccogna S, Romanelli F, Valabrega S & Crescenzi A. Thin core biopsy should help to discriminate thyroid nodules cytologically classified as indeterminate. A new sampling technique. *Endocrine* 2013 **43** 659–665. (doi:10.1007/s12020-012-9811-z)
42 Faquin WC. Can a gene-expression classifier with high negative predictive value solve the indeterminate thyroid fine-needle aspiration dilemma? *Cancer Cytopathology* 2013 **121** 116–119. (doi:10.1002/cncy.21277)
43 Bergenfelz A, Jansson S, Kristoffersson A, Martensson H, Reihner E, Wallin G & Lausen I. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. *Langenbeck's Archives of Surgery* 2008 **393** 667–673. (doi:10.1007/s00423-008-0366-7)
44 Watt T, Groenvold M, Rasmussen AK, Bonnema SJ, Hegedus L, Bjorner JB & Feldt-Rasmussen U. Quality of life in patients with benign thyroid disorders. A review. *European Journal of Endocrinology* 2006 **154** 501–510. (doi:10.1530/eje.1.02124)
45 Chandrasekhar SS, Randolph GW, Seidman MD, Rosenfeld RM, Angelos P, Barkmeier-Kraemer J, Benninger MS, Blumin JH, Dennis G, Hanks J *et al*. Clinical practice guideline: improving voice outcomes after thyroid surgery. *Otolaryngology – Head and Neck Surgery* 2013 **148** S1–S37. (doi:10.1177/0194599813487301)
46 Sugiura N, Takara K, Ohto M, Okuda K & Hirooka N. Percutaneous intratumoral injection of ethanol under ultrasound imaging for treatment of small heptocellular carcinoma. *Acta Hepatologica* 1983 **24** 1920.
47 Livraghi T, Festi D, Monti F, Salmi A & Vettori C. US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. *Radiology* 1986 **161** 309–312.
48 Sheu JC, Huang GT, Chen DS, Sung JL, Yang PM, Wei TC, Lai MY, Su CT, Tsang YM, Hsu HC *et al*. Small hepatocellular carcinoma: intratumor ethanol treatment using new needle and guidance systems. *Radiology* 1987 **163** 43–48.
49 Bown SG. Phototherapy in tumors. *World Journal of Surgery* 1983 **7** 700–709. (doi:10.1007/BF01655209)
50 Rossi S, Di Stasi M, Buscarini E, Cavanna L, Quaretti P, Squassante E, Garbagnati F & Buscarini L. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer Journal from Scientific American* 1995 **1** 73–81.
51 McGahan JP, Browning PD, Brock JM & Tesluk H. Hepatic ablation using radiofrequency electrocautery. *Investigative Radiology* 1990 **25** 267–270. (doi:10.1097/00004424-199003000-00011)
52 Seki T, Wakabayashi M, Nakagawa T, Imamura M, Tamai T, Nishimura A, Yamashiki N, Okamura A & Inoue K. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. *Cancer* 1999 **85** 1694–1702. (doi:10.1002/(SICI)1097-0142(19990415)85:8<1694::AID-CNCR8>3.0.CO;2-3)
53 Seifert JK, Cozzi PJ & Morris DL. Cryotherapy for neuroendocrine liver metastases. *Seminars in Surgical Oncology* 1998 **14** 175–183. (doi:10.1002/(SICI)1098-2388(199803)14:2<175::AID-SSU10>3.0.CO;2-2)
54 Livraghi T, Paracchi A, Ferrari C, Bergonzi M, Garavaglia G, Raineri P & Vettori C. Treatment of autonomous thyroid nodules with percutaneous ethanol injection: preliminary results. Work in progress. *Radiology* 1990 **175** 827–829.
55 Pacella CM, Bizzarri G, Guglielmi R, Anelli V, Bianchini A, Crescenzi A, Pacella S & Papini E. Thyroid tissue: US-guided percutaneous interstitial laser ablation – a feasibility study. *Radiology* 2000 **217** 673–677. (doi:10.1148/radiology.217.3.r00dc09673)
56 Kim YS, Rhim H, Tae K, Park DW & Kim ST. Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. *Thyroid* 2006 **16** 361–367. (doi:10.1089/thy.2006.16.361)
57 Esnault O, Rouxel A, Le Nestour E, Gheron G & Leenhardt L. Minimally invasive ablation of a toxic thyroid nodule by high-intensity focused ultrasound. *AJNR. American Journal of Neuroradiology* 2010 **31** 1967–1968. (doi:10.3174/ajnr.A1979)
58 Feng B, Liang P, Cheng Z, Yu X, Yu J, Han Z & Liu F. Ultrasound-guided percutaneous microwave ablation of benign thyroid nodules: experimental and clinical studies. *European Journal of Endocrinology* 2012 **166** 1031–1037. (doi:10.1530/EJE-11-0966)
59 Crescenzi A, Papini E, Pacella CM, Rinaldi R, Panunzi C, Petrucci L, Fabbrini R, Bizzarri GC, Anelli V, Nardi F *et al*. Morphological changes in a hyperfunctioning thyroid adenoma after percutaneous ethanol

injection: histological, enzymatic and sub-microscopical alterations. *Journal of Endocrinological Investigation* 1996 **19** 371–376.

60 Monzani F, Caraccio N, Basolo F, Iacconi P, LiVolsi V & Miccoli P. Surgical and pathological changes after percutaneous ethanol injection therapy of thyroid nodules. *Thyroid* 2000 **10** 1087–1092. (doi:10.1089/thy.2000.10.1087)

61 Pomorski L & Bartos M. Histologic changes in thyroid nodules after percutaneous ethanol injection in patients subsequently operated on due to new focal thyroid lesions. *APMIS: Acta Pathologica, Microbiologica, et Immunologica Scandinavica* 2002 **110** 172–176. (doi:10.1034/j.1600-0463.2002.100208.x)

62 Bennedbaek FN, Karstrup S & Hegedus L. Percutaneous ethanol injection therapy in the treatment of thyroid and parathyroid diseases. *European Journal of Endocrinology* 1997 **136** 240–250. (doi:10.1530/eje.0.1360240)

63 Bennedbaek FN, Nielsen LK & Hegedus L. Effect of percutaneous ethanol injection therapy versus suppressive doses of L-thyroxine on benign solitary solid cold thyroid nodules: a randomized trial. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 830–835. (doi:10.1210/jcem.83.3.4673)

64 Bennedbaek FN & Hegedus L. Percutaneous ethanol injection therapy in benign solitary solid cold thyroid nodules: a randomized trial comparing one injection with three injections. *Thyroid* 1999 **9** 225–233. (doi:10.1089/thy.1999.9.225)

65 Bennedbaek FN & Hegedus L. Alcohol sclerotherapy for benign solitary solid cold thyroid nodules. *Lancet* 1995 **346** 1227. (doi:10.1016/S0140-6736(95)92930-4)

66 Guglielmi R, Pacella CM, Bianchini A, Bizzarri G, Rinaldi R, Graziano FM, Petrucci L, Toscano V, Palma E, Poggi M *et al*. Percutaneous ethanol injection treatment in benign thyroid lesions: role and efficacy. *Thyroid* 2004 **14** 125–131. (doi:10.1089/105072504322880364)

67 Verde G, Papini E, Pacella CM, Gallotti C, Delpiano S, Strada S, Fabbrini R, Bizzarri G, Rinaldi R, Panunzi C *et al*. Ultrasound guided percutaneous ethanol injection in the treatment of cystic thyroid nodules. *Clinical Endocrinology* 1994 **41** 719–724. (doi:10.1111/j.1365-2265.1994.tb02785.x)

68 Zingrillo M, Torlontano M, Chiarella R, Ghiggi MR, Nirchio V, Bisceglia M & Trischitta V. Percutaneous ethanol injection may be a definitive treatment for symptomatic thyroid cystic nodules not treatable by surgery: five-year follow-up study. *Thyroid* 1999 **9** 763–767. (doi:10.1089/thy.1999.9.763)

69 Bennedbaek FN & Hegedus L. Treatment of recurrent thyroid cysts with ethanol: a randomized double-blind controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5773–5777. (doi:10.1210/jc.2003-031000)

70 Watt T, Hegedus L, Groenvold M, Bjorner JB, Rasmussen AK, Bonnema SJ & Feldt-Rasmussen U. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. *European Journal of Endocrinology* 2010 **162** 161–167. (doi:10.1530/EJE-09-0521)

71 Paschke R, Hegedus L, Alexander E, Valcavi R, Papini E & Gharib H. Thyroid nodule guidelines: agreement, disagreement and need for future research. *Nature Reviews. Endocrinology* 2011 **7** 354–361. (doi:10.1038/nrendo.2011.1)

72 Bonnema SJ & Hegedus L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. *Endocrine Reviews* 2012 **33** 920–980. (doi:10.1210/er.2012-1030)

73 Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA *et al*. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocrine Practice* 2011 **17** 456–520. (doi:10.4158/EP.17.3.456)

74 Nygaard B, Hegedus L, Nielsen KG, Ulriksen P & Hansen JM. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. *Clinical Endocrinology* 1999 **50** 197–202. (doi:10.1046/j.1365-2265.1999.00635.x)

75 Lippi F, Ferrari C, Manetti L, Rago T, Santini F, Monzani F, Bellitti P, Papini E, Busnardo B, Angelini F *et al*. Treatment of solitary autonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 3261–3264.

76 Monzani F, Caraccio N, Goletti O, Casolaro A, Lippolis PV, Cavina E & Miccoli P. Treatment of hyperfunctioning thyroid nodules with percutaneous ethanol injection: eight years' experience. *Experimental and Clinical Endocrinology & Diabetes* 1998 **106** (Suppl 4) S54–S58. (doi:10.1055/s-0029-1212058)

77 Yano Y, Sugino K, Akaishi J, Uruno T, Okuwa K, Shibuya H, Kitagawa W, Nagahama M, Ito K & Ito K. Treatment of autonomously functioning thyroid nodules at a single institution: radioiodine therapy, surgery, and ethanol injection therapy. *Annals of Nuclear Medicine* 2011 **25** 749–754. (doi:10.1007/s12149-011-0526-7)

78 Jacques SL. Laser-tissue interactions. Photochemical, photothermal, and photomechanical. *Surgical Clinics of North America* 1992 **72** 531–558.

79 Prapavat V, Roggan A, Walter J, Beuthan J, Klingbeil U & Muller G. *In vitro* studies and computer simulations to assess the use of a diode laser (850 nm) for laser-induced thermotherapy (LITT). *Lasers in Surgery and Medicine* 1996 **18** 22–33. (doi:10.1002/(SICI)1096-9101(1996)18:1<22::AID-LSM3>3.0.CO;2-T)

80 Gambelunghe G, Bini V, Monacelli M, Avenia N, D'Ajello M, Colella R & De Feo P. The administration of anesthetic in the thyroid pericapsular region increase the possibility of side effects during percutaneous laser ablation of thyroid nodules. *Lasers in Surgery and Medicine* 2013 **45** 34–37. (doi:10.1002/lsm.22110)

81 Dossing H, Bennedbaek FN, Karstrup S & Hegedus L. Benign solitary solid cold thyroid nodules: US-guided interstitial laser photocoagulation – initial experience. *Radiology* 2002 **225** 53–57. (doi:10.1148/radiol.2251011042)

82 Pacella CM, Bizzarri G, Spiezia S, Bianchini A, Guglielmi R, Crescenzi A, Pacella S, Toscano V & Papini E. Thyroid tissue: US-guided percutaneous laser thermal ablation. *Radiology* 2004 **232** 272–280. (doi:10.1148/radiol.2321021368)

83 Amabile G, Rotondi M, De Chiara G, Silvestri A, Di Filippo B, Bellastella A & Chiovato L. Low-energy interstitial laser photocoagulation for treatment of nonfunctioning thyroid nodules: therapeutic outcome in relation to pretreatment and treatment parameters. *Thyroid* 2006 **16** 749–755. (doi:10.1089/thy.2006.16.749)

84 Dossing H, Bennedbaek FN & Hegedus L. Ultrasound-guided interstitial laser photocoagulation of an autonomous thyroid nodule: the introduction of a novel alternative. *Thyroid* 2003 **13** 885–888. (doi:10.1089/105072503322401104)

85 Dossing H, Bennedbaek FN & Hegedus L. Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules – a randomised study. *European Journal of Endocrinology* 2005 **152** 341–345. (doi:10.1530/eje.1.01865)

86 Dossing H, Bennedbaek FN & Hegedus L. Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules: one versus three treatments. *Thyroid* 2006 **16** 763–768. (doi:10.1089/thy.2006.16.763)

87 Dossing H, Bennedbaek FN & Hegedus L. Beneficial effect of combined aspiration and interstitial laser therapy in patients with benign cystic thyroid nodules: a pilot study. *British Journal of Radiology* 2006 **79** 943–947. (doi:10.1259/bjr/40698061)

88 Dossing H, Bennedbaek FN, Bonnema SJ, Grupe P & Hegedus L. Randomized prospective study comparing a single radioiodine dose and a single laser therapy session in autonomously functioning thyroid nodules. *European Journal of Endocrinology* 2007 **157** 95–100. (doi:10.1530/EJE-07-0094)

89 Dossing H, Bennedbaek FN & Hegedus L. Long-term outcome following interstitial laser photocoagulation of benign cold thyroid

nodules. *European Journal of Endocrinology* 2011 **165** 123–128. (doi:10.1530/EJE-11-0220)

90 Dossing H, Bennedbaek FN & Hegedus L. Interstitial laser photocoagulation (ILP) of benign cystic thyroid nodules – a prospective randomized trial. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** E1213–E1217. (doi:10.1210/jc.2013-1503)

91 Amabile G, Rotondi M, Pirali B, Dionisio R, Agozzino L, Lanza M, Buonanno L, Di Filippo B, Fonte R & Chiovato L. Interstitial laser photocoagulation for benign thyroid nodules: time to treat large nodules. *Lasers in Surgery and Medicine* 2011 **43** 797–803. (doi:10.1002/lsm.21114)

92 Cakir B, Topaloglu O, Gul K, Agac T, Aydin C, Dirikoc A, Gumus M, Yazicioglu K, Ersoy RU & Ugras S. Effects of percutaneous laser ablation treatment in benign solitary thyroid nodules on nodule volume, thyroglobulin and anti-thyroglobulin levels, and cytopathology of nodule in 1 yr follow-up. *Journal of Endocrinological Investigation* 2006 **29** 876–884.

93 Cakir B, Gul K, Ugras S, Ersoy R, Topaloglu O, Agac T, Aydin C, Dirikoc A, Gumus M, Korukluoglu B *et al*. Percutaneous laser ablation of an autonomous thyroid nodule: effects on nodule size and histopathology of the nodule 2 years after the procedure. *Thyroid* 2008 **18** 803–805. (doi:10.1089/thy.2007.0316)

94 Cakir B, Gul K, Ersoy R, Topaloglu O & Korukluoglu B. Subcapsular hematoma complication during percutaneous laser ablation to a hypoactive benign solitary thyroid nodule. *Thyroid* 2008 **18** 917–918. (doi:10.1089/thy.2007.0338)

95 Cakir B, Ugras NS, Gul K, Ersoy R & Korukluoglu B. Initial report of the results of percutaneous laser ablation of benign cold thyroid nodules: evaluation of histopathological changes after 2 years. *Endocrine Pathology* 2009 **20** 170–176. (doi:10.1007/s12022-009-9081-3)

96 Rotondi M, Amabile G, Leporati P, Di Filippo B & Chiovato L. Repeated laser thermal ablation of a large functioning thyroid nodule restores euthyroidism and ameliorates constrictive symptoms. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 382–383. (doi:10.1210/jc.2008-1782)

97 Spiezia S, Vitale G, Di Somma C, Pio Assanti A, Ciccarelli A, Lombardi G & Colao A. Ultrasound-guided laser thermal ablation in the treatment of autonomous hyperfunctioning thyroid nodules and compressive nontoxic nodular goiter. *Thyroid* 2003 **13** 941–947. (doi:10.1089/105072503322511346)

98 Papini E, Guglielmi R, Bizzarri G & Pacella CM. Ultrasound-guided laser thermal ablation for treatment of benign thyroid nodules. *Endocrine Practice* 2004 **10** 276–283. (doi:10.4158/EP.10.3.276)

99 Gambelunghe G, Fatone C, Ranchelli A, Fanelli C, Lucidi P, Cavaliere A, Avenia N, d'Ajello M, Santeusanio F & De Feo P. A randomized controlled trial to evaluate the efficacy of ultrasound-guided laser photocoagulation for treatment of benign thyroid nodules. *Journal of Endocrinological Investigation* 2006 **29** RC23–RC26.

100 Barbaro D, Orsini P, Lapi P, Pasquini C, Tuco A, Righini A & Lemmi P. Percutaneous laser ablation in the treatment of toxic and pretoxic nodular goiter. *Endocrine Practice* 2007 **13** 30–36. (doi:10.4158/EP.13.1.30)

101 Papini E, Guglielmi R, Bizzarri G, Graziano F, Bianchini A, Brufani C, Pacella S, Valle D & Pacella CM. Treatment of benign cold thyroid nodules: a randomized clinical trial of percutaneous laser ablation versus levothyroxine therapy or follow-up. *Thyroid* 2007 **17** 229–235. (doi:10.1089/thy.2006.0204)

102 Valcavi R, Bertani A, Pesenti M, Al Jandali Rifa'Y LR, Frasoldati A & Pacella CM. Laser and radiofrequency ablation procedures. In *Thyroid Ultrasound and Ultrasound-Guided FNA*, 2nd edn, pp 198–208. Eds BJ Baskin, DS Duick & RA Levine RA. New York: Springer, 2008.

103 Valcavi R, Riganti F, Bertani A, Formisano D & Pacella CM. Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. *Thyroid* 2010 **20** 1253–1261. (doi:10.1089/thy.2010.0189)

104 Gambelunghe G, Fede R, Bini V, Monacelli M, Avenia N, D'Ajello M, Colella R, Nasini G & De Feo P. Ultrasound-guided interstitial laser ablation for thyroid nodules is effective only at high total amounts of energy: results from a three-year pilot study. *Surgical Innovation* 2013 **20** 345–350. (doi:10.1177/1553350612459276)

105 Rago T, Papini E, Vitti P, De Feo P, Gambelunghe G, Valcavi R, Bizzarri G & Pacella CM. A multicenter randomized prospective trial of laser ablation versus follow-up for the treatment of cold thyroid nodules – twelve-month results. In *36th Annual Meeting of the European Thyroid Association (ETA)*, Abstract No. A-485-0124-00180; 8th–12th September, Pisa, 2012.

106 Piana S, Frasoldati A, Ferrari M, Valcavi R, Froio E, Barbieri V, Pedroni C & Gardini G. Is a five-category reporting scheme for thyroid fine needle aspiration cytology accurate? Experience of over 18,000 FNAs reported at the same institution during 1998–2007. *Cytopathology* 2011 **22** 164–173. (doi:10.1111/j.1365-2303.2010.00777.x)

107 Siperstein AE & Gitomirsky A. History and technological aspects of radiofrequency termoablation. *Cancer Journal from Scientific American* 2000 **6** 5293–5305.

108 Scudamore C. Volumetric radiofrequency ablation: technical considerations. *Cancer Journal from Scientific American* 2000 **6** S316–S318.

109 Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ & Lee D. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. *European Radiology* 2008 **18** 1244–1250. (doi:10.1007/s00330-008-0880-6)

110 Baek JH, Jeong HJ, Kim YS, Kwak MS & Lee D. Radiofrequency ablation for an autonomously functioning thyroid nodule. *Thyroid* 2008 **18** 675–676. (doi:10.1089/thy.2007.0274)

111 Spiezia S, Garberoglio R, Di Somma C, Deandrea M, Basso E, Limone PP, Milone F, Ramundo V, Macchia PE, Biondi B *et al*. Efficacy and safety of radiofrequency thermal ablation in the treatment of thyroid nodules with pressure symptoms in elderly patients. *Journal of the American Geriatrics Society* 2007 **55** 1478–1479. (doi:10.1111/j.1532-5415.2007.01306.x)

112 Baek JH, Moon WJ, Kim YS, Lee JH & Lee D. Radiofrequency ablation for the treatment of autonomously functioning thyroid nodules. *World Journal of Surgery* 2009 **33** 1971–1977. (doi:10.1007/s00268-009-0130-3)

113 Baek JH, Kim YS, Lee D, Huh JY & Lee JH. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. *AJR. American Journal of Roentgenology* 2010 **194** 1137–1142. (doi:10.2214/AJR.09.3372)

114 Huh JY, Baek JH, Choi H, Kim JK & Lee JH. Symptomatic benign thyroid nodules: efficacy of additional radiofrequency ablation treatment session – prospective randomized study. *Radiology* 2012 **263** 909–916. (doi:10.1148/radiol.12111300)

115 Deandrea M, Limone P, Basso E, Mormile A, Ragazzoni F, Gamarra E, Spiezia S, Faggiano A, Colao A, Molinari F *et al*. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. *Ultrasound in Medicine & Biology* 2008 **34** 784–791. (doi:10.1016/j.ultrasmedbio.2007.10.018)

116 Spiezia S, Garberoglio R, Milone F, Ramundo V, Caiazzo C, Assanti AP, Deandrea M, Limone PP, Macchia PE, Lombardi G *et al*. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. *Thyroid* 2009 **19** 219–225. (doi:10.1089/thy.2008.0202)

117 Faggiano A, Ramundo V, Assanti AP, Fonderico F, Macchia PE, Misso C, Marciello F, Marotta V, Del Prete M, Papini E *et al*. Thyroid nodules treated with percutaneous radiofrequency thermal ablation: a comparative study. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 4439–4445. (doi:10.1210/jc.2012-2251)

118 Lim HK, Lee JH, Ha EJ, Sung JY, Kim JK & Baek JH. Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up

results for 111 patients. *European Radiology* 2013 **23** 1044–1049. (doi:10.1007/s00330-012-2671-3)

119 Baek JH, Lee JH, Sung JY, Bae JI, Kim KT, Sim J, Baek SM, Kim YS, Shin JH, Park JS *et al*. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. *Radiology* 2012 **262** 335–342. (doi:10.1148/radiol.11110416)

120 Sung JY, Kim YS, Choi H, Lee JH & Baek JH. Optimum first-line treatment technique for benign cystic thyroid nodules: ethanol ablation or radiofrequency ablation? *AJR. American Journal of Roentgenology* 2011 **196** W210–W214. (doi:10.2214/AJR.10.5172)

121 Sung JY, Baek JH, Kim KS, Lee D, Yoo H, Kim JK & Park SH. Single-session treatment of benign cystic thyroid nodules with ethanol versus radiofrequency ablation: a prospective randomized study. *Radiology* 2013 **269** 293–300. (doi:10.1148/radiol.13122134)

122 Esnault O, Franc B, Menegaux F, Rouxel A, De Kerviler E, Bourrier P, Lacoste F, Chapelon JY & Leenhardt L. High-intensity focused ultrasound ablation of thyroid nodules: first human feasibility study. *Thyroid* 2011 **21** 965–973. (doi:10.1089/thy.2011.0141)

123 Yue W, Wang S, Wang B, Xu Q, Yu S, Yonglin Z & Wang X. Ultrasound guided percutaneous microwave ablation of benign thyroid nodules: safety and imaging follow-up in 222 patients. *European Journal of Radiology* 2013 **82** e11–e16. (doi:10.1016/j.ejrad.2012.07.020)

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