Nodular thyroid disease is very common in clinical practice, discovered by palpation in 3 to 7% and by ultrasound (US) in about 50% of the general population (1). Most nodules are asymptomatic and benign and are usually managed by observation only and follow-up. The recently published guidelines by neither the American Association of Clinical Endocrinologists (2) nor the American Thyroid Association (3) recommend TSH suppressive therapy with levothyroxine (LT4) for benign nodules. However, some nodules do grow, cause symptoms, and require treatment. Surgical therapy has so far constituted the mainstay of therapy for these.

The problem is that whereas thyroid surgery is widely available and safe in many centers, it still carries a 2 to 10% risk of complications, it is costly, and it may not be appropriate for a surgically high-risk individual or for someone refusing surgery (4). The last two decades have witnessed the development of several nonsurgical, image-guided, minimally invasive approaches that appear safe and effective and can be used to treat symptomatic or enlarging thyroid masses. (J Clin Endocrinol Metab 98: 3949–3957, 2013)
guided, minimally invasive approaches for treatment of thyroid nodules. No one center or group has accumulated enough experience with all techniques. Therefore, this report describes our collective experience as well as a brief literature review on these techniques, describing indications, efficacy, safety, and cost considerations for each procedure. It should be noted that the focus of our literature search has been on large-scale, preferably randomized, studies.

**Percutaneous Ethanol Injection Therapy (PEIT)**

Small vessel thrombosis and coagulative necrosis, as is the case with the other US-guided interventional techniques, forms the basis of achieving shrinkage of solid thyroid tumors with PEIT, whether functioning or nonfunctioning (5). There is abundant literature (around 150 papers since the early 1990s) on the effect on thyroid function and/or size. The use in benign solid thyroid tumors is on the wane due to availability of alternatives with a better ratio between efficacy and side effects (6). The same is true for the use in benign parathyroid tumors (5, 6). Most expert centers, those introducing it in the first place, have abandoned this technique during the last decade for solid thyroid as well as parathyroid tumors. The exception is benign cysts and predominantly cystic thyroid nodules, where it has become the recommended standard therapy (7). Interestingly, the use in locoregional recurrence of papillary thyroid cancer, whether in the thyroid bed or in the regional lymph nodes, although heavily debated, is increasingly employed (8–10).

**Clinical results**

**Solid nonfunctioning (cold) benign thyroid nodules**

On average, such nodules have a slight growth potential, which is unpredictable in the individual patient. In a randomized study, TSH suppression with thyroid hormone did not halt spontaneous growth, whereas one session of PEIT (20% of pretreatment nodule volume) decreased nodule volume by 47% in a year (11). In another randomized study, three PEIT sessions marginally increased the reduction to 51% (12). A number of studies, depending on nodule size, ethanol amount, and length of follow-up, report reductions of up to 80% in nodule size (5, 11, 12). Although many do not report side effects at all, there is agreement on most patients having mild to severe transient pain lasting for minutes, and many have low-grade fever. Serious side effects are rare, but recurrent nerve palsy with transient dysphonia, Graves’ disease, Graves’ orbitopathy, Horner’s syndrome, facial dysesthesia with increased tear flow, necrosis of the larynx and skin, as well as impairment of post-PEIT surgery due to local fibrosis, have been reported (5). These and other side effects are most likely linked to seepage of alcohol along the needle tract and are not only due to insufficient training. Thyroid function has been preserved in all patients in several large series (5, 11, 12). There are no follow-up studies of whether nodule volume reduction and decrease in pressure symptoms are maintained in the long run or studies of quality of life using disease-specific instruments (13).

**Cysts or dominantly cystic benign thyroid nodules**

Fifteen to 25% of solitary thyroid nodules are cystic or predominantly cystic, and most are benign (14). Simple aspiration is the treatment of choice for diagnostic and therapeutic purposes in symptomatic patients. However, the recurrence rate is up to 80%, depending on the number of aspirations and the cyst volume (5, 11). Tetracycline, as a sclerosing agent, has been tried, but the remission rate was no better than with isotonic saline in a randomized study (15). In a prospective double-blinded study, 66 consecutive patients with recurrent and benign thyroid cysts were randomized either to subtotal cyst aspiration, flushing with 99% ethanol, and subsequent complete fluid aspiration or to subtotal cyst aspiration, flushing with isotonic saline, and subsequent complete fluid aspiration (16). In the ethanol group, cure (6-mo follow-up) was obtained in 21 of 33 (64%) patients with just one session (27 of 33 [82%] after three sessions), compared with 6 of 33 (18%) in the saline group (16 of 33 [48%], after three sessions) (P = .002). The chance of success decreased with the number of previous aspirations and with increasing cyst volume. Seven patients (21%) treated with ethanol had moderate to severe pain (median duration, 5 min), and one had transient dysphonia with normal indirect laryngoscopy. A high number of observational studies, both before (5) and after (17) the above randomized study (16), offer supportive data for efficacy as well as for the favorable side effect profile and preservation of normal thyroid function. We, along with major specialist societies (2, 7), conclude that treatment of recurrent thyroid cysts with ethanol is superior to simple aspiration and flushing with saline, devoid of serious side effects, and that flushing with ethanol is a clinically significant nonsurgical alternative for thyroid cysts that recur despite repeat aspirations.

**Solid functioning (warm/hot) benign thyroid nodules**

These nodules, which are more prevalent in iodine-deficient than iodine-sufficient regions, constitute around 5–10% of all solitary thyroid nodules (14). Malignancy is extremely rare, surgery is rarely necessary, and radioio-
Radiofrequency ablation (RFA)

RFA induces thermal injury to thyroid nodules through the deposition of electromagnetic energy. An alternating electric field is created within the target lesion by an electrode needle connected to a radiofrequency generator. The agitation of the ions surrounding the electrode results in frictional heat and subsequent tissue necrosis. The first results were obtained with a 17-gauge internally cooled electrode, followed by 14-gauge devices equipped with expandable prongs (23, 24). Treatments were mostly performed under conscious sedation and on large-size lesions due to the large bore of the employed needles.

Dedicated 18-gauge, straight-type, internally cooled electrodes have recently been developed for thyroid lesions. After local anesthesia, with a transisthmic approach, the electrode is inserted from the isthmus into the targeted nodule. With a “moving shot technique,” multiple conceptual areas of the nodule are ablated unit-by-unit by moving the electrode tip. Initially, the electrode tip is positioned in the deepest area of the nodule and then moved backward in the central area and in superficial directions. Ablation is started with 30–50 W of radiofrequency power and is followed by 10-W increments if an echogenic zone does not appear at the electrode tip (25, 26).

Clinical results

**Solid nonfunctioning (cold) benign thyroid nodules**

Two studies on 97 patients overall who were not eligible for surgery or radioiodine therapy were performed with a 14-gauge device and a fixed electrode technique (23, 24). The mean nodule volume reduction was 50 and 78% at 6 and 12 months, respectively. After treatment, all patients remained euthyroid, and no major complications were observed. Improvement in compressive symptoms was reported by the patients. A recent prospective, controlled, nonrandomized study confirmed these results. Twenty patients with cold or autonomously functioning thyroid nodules (AFTNs) were treated with RFA, and 20 similar cases did not receive any treatment (27). Nodule volume significantly decreased in the RFA group (1.8 ± 0.3 mL at 12 mo vs 13.3 ± 1.8 mL at baseline; \(P < .0001\)), whereas it remained stable in the control group. At the end of the follow-up, pressure symptoms were improved in all patients in the RFA group but remained unchanged in the control group.

The “moving shot” technique has been proposed in a few prospective nonrandomized studies. RFA was performed with 18-gauge electrode needles on solid or complex nodules with various thyroid function levels. A variable number of treatments induced a reduction of the nodule volume that ranged from 33–58% at 1 month and 51–85% at 6 months (25, 26). Recently, a 4-year follow-up study demonstrated that repeated RFA treatments resulted in a 93.5% volume reduction and the improvement of symptomatology. Subgroup analysis showed that larger nodules required more treatment sessions than smaller nodules to achieve a similar volume reduction. Volume reduction was significantly more rapid and greater in cystic than in solid nodules (28).
Solid functioning (warm/hot) benign thyroid nodules

RFA was performed using a hook-umbrella 14-gauge needle on 28 toxic or pretoxic nodules (24). Two years after RFA, a nearly 80% decrease of thyroid nodule size was observed. Compressive symptoms disappeared in 88% of the patients, and hyperthyroidism resolved in 100% of patients with autonomously functioning nodules and in about 50% of those with toxic nodules who previously required methimazole therapy. No major complications were observed.

RFA was reported as effective in AFTNs with the moving shot technique as well. Nodule volume, local problems, and thyroid hyperfunction showed a significant improvement in a few noncontrolled series of patients. It is noteworthy that the incomplete ablation of the margin of the hyperfunctioning nodule is followed by the partial regrowth of the AFTN. Hence, a complete ablation of the nodule margins is required to prevent the regrowth of the toxic nodule, thus preventing the relapse of hyperthyroidism at long-term follow-up (29, 30).

Cysts or dominantly cystic benign thyroid nodules

RFA has been proposed for the treatment of dominantly cystic nodules in a few small studies. Fifty-seven patients with benign cystic nodules causing pressure symptoms were treated with either PEIT or RFA (31). Both PEIT and RFA resulted in a significant decrease of nodule volume, with no significant differences between the two groups in other parameters. However, these similar outcomes were obtained with fewer treatments and at a much lower cost in the PEIT series than in the RFA group. Hence, for symptomatic cystic (fluid portion > 90%) nodules, PEIT should be the first-line treatment because of its similar safety and efficacy compared to RFA, the fewer number of treatment sessions, and its cost effectiveness.

Complications

In a recent multicenter study of 1459 patients, the overall complication rate was 3.3%, and the major complication rate was 1.4% (32). Pain is the most common complaint during the RFA procedure, but in most cases the pain decreases rapidly when the radiofrequency generator is turned off. Only a few patients complain of protracted or intractable pain (29, 32). Voice changes due to injury of the recurrent laryngeal or vagus nerves are the major risk. This complication may be prevented by undertreating the conceptual ablation areas adjacent to the nerves (26). Perithyroidal hemorrhage may be prevented by examining the perithyroidal vessels before inserting the electrode and with the use of small-bore electrodes. Hematomas can be controlled by neck compression and usually disappear within 2 weeks. Skin burn at the electrode puncture site is possible, especially in large thyroid nodules. Nodule rupture presents with sudden neck bulging and pain during the follow-up period (32). This complication is due to the acute volume expansion of a nodule due to hemorrhage and should be managed conservatively with antibiotics and/or analgesics.

Cost, time consumption, and indications

The cost of a radiofrequency generator is approximately $25,000, and the cost of an electrode is about $750 per session. Treatment may be performed on outpatients by an operator and a sonographer with a time expenditure of about 30 minutes.

Recent recommendations for thyroid RFA by the Korean Society of Thyroid Radiology (33) suggested indications as follows: 1) patients with nodule-related symptoms; 2) patients with cosmetic problems; and 3) patients with AFTNs causing thyrotoxicosis. RFA is currently not recommended for follicular neoplasms or primary thyroid cancers. Caution should be taken in pregnant women, patients with serious heart problems, and patients with contralateral vocal cord palsy.

Laser ablation therapy (LAT)

Laser ablation is based on the emission of photons by excited atoms within a target tissue (34–36). Laser light is transmitted from the source to the patient in flexible and small-diameter silica optical fibers that are inserted into the lesion through a 21-gauge spinal needle. Most laser procedures are currently performed either with Nd:YAG (neodimium:yttrium aluminum garnet) laser medium operating at 1064 nm or with diode lasers (λ = 800–980 nm) operating in the range of 2 to 40 W. A nearly spherical volume of coagulative necrosis, up to 2 cm in diameter, is produced from a single bare 300- to 400-μm fiber. To produce larger volumes of necrosis, multiple fibers may be arrayed at 1.0- to 1.8-cm spacing throughout a target lesion or may be used by cooled-tip diffuser fibers (34). The procedure is performed on conscious patients after careful local anesthesia.

Clinical results

After the initial feasibility studies (35, 36), several case reports (37, 38) and single-center, nonrandomized (39–45) and randomized cohort studies (46–48) have been published on laser ablation. Overall, results confirmed the clinical efficacy of laser thermal ablation, despite the fact that treatment plans and equipment were not identical in different centers.

Cold nodules

Two prospective randomized studies on patients with benign cold thyroid nodules compared the clinical effect...
Cysts and predominantly cystic lesions

ally requires repeated treatment sessions. In toxic nodular goiters or large AFTNs, the favorable results are inconsistent, and the normalization of thyroid function usually requires repeated treatment sessions. A single LAT session in both studies resulted in a similar, significant nodule reduction at 6 and 12 months (Δ volume, −44% and −43%, respectively). No significant changes were observed in either the LT4 or control group. Most LAT-treated patients reported an improvement in local symptoms (47, 48). Cytological and histological samples obtained in 15 cold thyroid nodules 12 months after multiple LAT procedures demonstrated necrosis, degenerative changes, and signs of inflammatory reaction in the treated areas (42).

The results of laser ablation are fairly stable over time. An uncontrolled study on a series of 122 patients showed persistence of a 47.8% mean nodule volume decrease 3 years after LAT. In only 9% of patients could a slight regrowth of the nodules be demonstrated. It should be noted that smaller nodules (up to 15 mL) showed a better response than larger nodules (44). These findings were confirmed in another study in which, after a median of 38 months, the volume decrease was about 51% and correlated with a persistent decrease in local symptoms (49). Offering confirmation, a recent multicenter prospective randomized trial demonstrated a nodule volume reduction of 45–55% 12 months after a single LAT (50).

Autonomously functioning thyroid nodules

Studies on a small series of AFTNs treated with LAT have reported normalization of thyroid function and destruction of the previously hyperfunctioning area at posttreatment radioisotope scan (37, 40, 51). On the other hand, two studies demonstrated that LAT was not invariably effective and that multiple LAT sessions were required to normalize TSH levels (41, 52). Finally, a randomized trial on 30 solitary hot nodules with extraglandular suppression, treated with either a single LAT session or one radioiodine dose, demonstrated that LAT and 131-I therapy had a similar effect on nodule volume reduction. At variance with radioiodine ablation, LAT was followed by normalization of serum TSH in only 50% of patients (53). Overall, these results demonstrate the efficacy of LAT when treating small, solitary, and mildly hyperfunctioning nodules (43). In toxic nodular goiters or large AFTNs, the favorable results are inconsistent, and the normalization of thyroid function usually requires repeated treatment sessions.

Cysts and predominantly cystic lesions

In a recent report, 44 patients with recurrent predominantly cystic nodules were randomized to complete fluid drainage, with or without subsequent LAT, and were followed for 6 months (54). A successful outcome was seen in 15 of 22 patients in the LAT group, significantly higher numbers than the 4 of 22 patients in the aspiration group. In the LAT group, the solid part of the nodule was significantly reduced from 1.8 to 1.0 mL, whereas in the aspiration-alone group neither the median cyst volume nor the solid component was reduced. Correspondingly, pressure symptoms were significantly reduced in the LAT group. No serious side effects were seen, and thyroid function was unaffected.

Side effects and risks

Major complications are definitely uncommon. One case of damage to the trachea wall, caused by erroneous positioning of the fiber tip and surgically repaired after 4 weeks, was reported by a nontrained operator (55). In a series of 122 patients, vocal cord paresis was reported in 1.6% of patients (44). A recent study carried out by four trained centers confirmed the very low risk of major complications (1 of 101 patients presented a self-resolving vocal cord paresis) and the excellent tolerability of the procedure (analgesics were needed in just 5% of cases) (50). The risk of recurrent nerve damage is higher during the training period and for lesions close to the trachea. Minor side effects include a cervical burning pain that develops during the procedure and ceases after the ending of laser firing. In the rare cases of pain that radiates to the ear, lower jaw, or back, repositioning of the fibers in a more central area of the nodule is recommended (44). Moderate pain or low-grade fever persisting for a few days after LAT are uncommon and can be easily controlled by acetaminophen. Subcapsular hematoma during aspirin therapy (56), faintness, skin burn, cervical swelling due to edema, bruise, and cystic transformation have been occasionally reported (44). Transient hyperthyroidism and late hypothyroidism are rare (44). No significant pathologic changes have been found in tissues adjacent to the ablated area in patients who subsequently, and successfully, have undergone surgery (57, 58).

Costs

The cost of state-of-the-art US equipment with a built-in laser source is about $120 000, whereas a separate diode or Nd:YAG laser source is much less expensive (about $15 000 to $20 000). The price of disposables is about $400 per session. Treatment may be performed on outpatients or in day-hospital by an operator and a sonographer with a time expenditure of about 30 minutes. The cost of utensils, including local anesthetics and painkillers, is very low.
Microwave ablation (MWA)

The passage of microwaves into a tissue is followed by a fast rotation of the molecules, an increase of local kinetic energy, and the rapid increase of the tissue temperature in the targeted lesion. Microwave energy is radiated from the active portion of an antenna and does not require the use of ground pads. The large diameter of microwave antennas makes a safe ablation of thyroid lesions located in the critical space of the neck difficult. The procedure is performed under conscious sedation.

Clinical efficacy

After an ex vivo feasibility study on pig liver, a single clinical trial has been performed. Eleven benign solid or complex thyroid nodules were treated with an internally cooled 16-gauge needle antenna. In cystic lesions, the fluid component was drained before the MWA treatment. MWA was performed under general anesthesia. At the post-treatment control (from 1 to 9 mo), nodule volume decreased slightly less than 50%. The symptom grading score improved accordingly (59).

Side effects and risks

One of the patients (9%) had ipsilateral vocal cord palsy, and subcapsular hemorrhage was reported in nearly 40% of cases. Over 70% of patients complained of pain at the ablation site, and a slight fever was registered in 30% of cases (59).

Costs

The cost of microwave antennae for the treatment of cervical structures is still to be defined in Europe. The active treatment period lasted from 5 to 16 minutes, but patients needed a skin incision and unconscious sedation with the assistance of an anesthesiologist (59). Due to the need for an inpatient treatment, total costs are higher than those of the other currently available percutaneous procedures.

High-intensity focused US (HIFU) ablation

HIFU induces thermal destruction without any skin penetration (36). US are produced by arrays of piezoelectric elements driven by a high-frequency amplifier. The US beam is focused by means of a curved or phase-array transducer to reach an energy concentration that is followed by local hyperthermia and tissue coagulation. The US focus within the tissue is highly collimated, and multiple impulses are needed to induce an ablation volume of clinical significance. The data received from an imaging device are used to focus the US energy into the target lesion. The procedure is usually performed under conscious sedation and requires from 1 hour to a few hours to achieve an effective volume ablation (60–62).

Clinical efficacy

Clinical data on the thyroid gland are limited and from a single research center (60–62). A pilot study on a single 9 × 8-mm hyperfunctioning nodule demonstrated that 2 weeks after treatment, the nodule developed into a predominantly cystic lesion (61). Hyperthyroidism normalized after 3 months and was maintained at 18 months. At US examination, the treated nodule appeared as a hypoechoic scar devoid of vascular signals, and thyroid scintiscan demonstrated the functional recovery of the surrounding thyroid tissue. In an open feasibility study, 25 patients were treated with HIFU 2 weeks before surgery for nodular goiter. Histological examination revealed that the damage was limited to the treated lesions with a nodule necrosis that ranged from 2–80% (62).

Side effects and risks

No major complications have been reported, but in three patients (12%), HIFU ablation was stopped because of neck pain and/or the appearance of skin blisters (62).

Conclusion and Future Directions

A large body of data is now available on the use of minimally invasive techniques for benign thyroid nodules. These techniques appear effective, reasonably safe in experienced hands, and with low cost when applied to nodular thyroid disease. However, several points need attention. Most thyroid nodules are benign and small, remain stable and asymptomatic, and can be followed by observation alone (1). Only a minority of patients may need treatment because of cosmetic reasons, local pain or pressure, or systemic symptoms of hyperthyroidism. Currently, only a small number of randomized controlled trials are available, and most are with limited follow-up. The actual cost and risk effectiveness of minimally invasive techniques, moreover, have not yet been established with head-to-head studies vs the traditional surgical treatment. Clearly, the minimally invasive treatments are associated with less morbidity and cost compared to surgical thyroidectomy. For example, the charge for partial thyroidectomy is $24 000 to $30 000, whereas the charge for PEIT is $4200 (courtesy of the Mayo Clinic Business Office, June 2013). However, a more detailed cost analysis cannot be provided because these procedures are not in routine use in the United States. Additionally, where these are offered on a routine basis, such as Denmark, Italy, or South Korea, there is much institutional or regional variability in charges and reimbursements to make a cost evalu-

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uation meaningful. For example, patients are not charged for the procedure in public hospitals in Denmark.

Although surgery remains the standard of care, nonsurgical treatment may be an acceptable option for some cases. Minimally invasive therapy offers an effective, rapid, and less expensive alternative to surgery. US-guided PEIT is the treatment of choice for recurrent, benign thyroid cysts. LAT and RFA should be reserved for symptomatic, fine-needle aspiration-benign, solid nodules and typically result in an almost 50% reduction in nodule size. Nodule shrinkage as well as the frequency of adverse effects seems to be about equal with both techniques. Nodule size reduction results in complete or partial relief of symptoms in most cases. In the case of AFTNs, improvement in thyroid function or nodule size decrease is more likely with smaller nodules. LAT of large AFTNs may require additional treatment sessions and seems not to be cost-effective when compared with radioiodine treatment. Minimally invasive techniques should hence be considered only in patients not eligible for radioiodine treatment, as in case of iodine interference or pregnancy. Although RFA and LAT are done in the outpatient and require only local anesthesia, they must be performed by experienced teams in specialized clinics. This point needs to be emphasized because good results and infrequent side effects are reported from centers with expertise in thermal ablation techniques. In contrast, PEIT may be confidently used for the treatment of benign thyroid cysts by operators with sufficient expertise in fine-needle aspiration biopsy.

The risk of overlooking thyroid malignancy, including papillary and follicular microadenomas, in those treated with minimally invasive techniques exists but must be very small. During long-term follow-up (>5 y), no patient operated on due to growth and/or pressure symptoms has been diagnosed with thyroid malignancy after PEIT (11, 12, 16), tetracycline (15), or LAT (49, 53). We are aware of only one report that documented a single case of thyroid cancer in a nodule previously submitted to PEIT. However, treatment appeared not to hinder histological diagnosis (63).

HIFU appears as the potentially less invasive procedure due to the absence of skin penetration. At the moment, however, the high cost of the equipment, its limited availability, the protracted time of treatment, and very limited data preclude its use in clinical practice. We still consider MWA an experimental procedure for the treatment of thyroid lesions.

Only a few reports have been published on the use of minimally invasive procedures for patients with recurrent thyroid cancer who may not be surgical candidates, because of either high surgical risk or refusal of repeated surgery. PEIT (8–10, 64), RFA (64–68), and laser ablation (68, 69) have each been reported as effective for locoregional control of cancer or for improving tumor-related symptoms in selected patients. Prospective randomized trials with a large number of patients and adequate follow-up information are needed to assess the indications for and the limitations of these procedures for cervical recurrences of thyroid tumors.

Acknowledgments

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