



Nodular Thyroid Disease in the Era of Precision Medicine

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Management of thyroid nodules in the era of precision medicine is continuously changing. Neck ultrasound plays a pivotal role in the diagnosis and several ultrasound stratification systems have been proposed in order to predict malignancy and help clinicians in therapeutic and follow-up decision. Ultrasound elastosonography is another powerful diagnostic technique and can be an added value to stratify the risk of malignancy of thyroid nodules. Moreover, the development of new techniques in the era of “Deep Learning,” has led to a creation of machine-learning algorithms based on ultrasound examinations that showed similar accuracy to that obtained by expert radiologists. Despite new technologies in thyroid imaging, diagnostic surgery in 50–70% of patients with indeterminate cytology is still performed. Molecular tests can increase accuracy in diagnosis when performed on “indeterminate” nodules. However, the more updated tools that can be used to this purpose in order to “rule out” (Afirma GSC) or “rule in” (Thyroseq v3) malignancy, have a main limitation: the high costs. In the last years various image-guided procedures have been proposed as alternative and less invasive approaches to surgery for symptomatic thyroid nodules. These minimally invasive techniques (laser and radio-frequency ablation, high intensity focused ultrasound and percutaneous microwave ablation) results in nodule shrinkage and improvement of local symptoms, with a lower risk of complications and minor costs compared to surgery. Finally, ultrasound-guided ablation therapy was introduced with promising results as a feasible treatment for low-risk papillary thyroid microcarcinoma or cervical lymph node metastases.

Keywords: microcarcinoma, thyroid nodule, ultrasound, mini invasive treatment, molecular testing

INTRODUCTION

One of the main clinical challenge in endocrine clinical practice is certainly the management of thyroid nodules disease. During the last years, new technologies have been developed and new diagnostic and therapeutic approaches have been introduced to guide clinician through the diagnosis, follow-up and therapeutic decision. This review will provide an evidence-based summary of the optimal approach to the management of thyroid nodules.

THE KEY ROLE OF ULTRASOUND

The prevalence of nodular thyroid disease in the general population is high, reaching 60% according to ultrasound and autopsy findings (1–3), though the incidence of malignancy is relatively low, ranging 1.6% and 12% (4, 5). Thyroid ultrasonography (US) is the primary tool used for the diagnosis and the initial cancer risk stratification of thyroid nodules. Currently, it guides decision making for fine-needle aspiration biopsy (FNA), the timing of subsequent clinical evaluations during long-term follow-up (6), and the eligibility for active surveillance of suspicious nodules (7). A complete report should include a description of the whole thyroid parenchyma, nodule location, size, and sonographic features, and assessment of the lymph nodes in the neck (8–10). The US features that should be evaluated for each nodule are: echogenicity, composition (solid, cystic, mixed), margins, calcifications or other hyperechoic foci, shape, and relations with the thyroid capsule (11, 12). Ultrasound patterns associated with malignancy include: hypoechogenicity, infiltrative, irregular, or lobulated margins, micro-calcifications, taller-than-wide shape, absence of a halo. However, none of these single US pattern have sensitivity, specificity and accuracy high enough to be considered predictive for malignancy (11, 13, 14). The combination of US patterns leads to a higher specificity, but it associates to a lower sensitivity (15). Finally, it is worth to mention that the evaluation of these US features is characterized by a high interobserver variability (16, 17). In the last decade, to improve standardization of thyroid ultrasound reporting, the guidelines of the American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi (AACE/ACE/AME) (3), the 2015 guidelines of the American Thyroid Association (ATA) (18), the guidelines of the European Thyroid Association (ETA; EU-TIRADS, European Thyroid Imaging Reporting and Data System) (8), the American College of Radiology (ACR) TIRADS (9), and the Korean Society of Thyroid Radiology's K-TIRADS system, have proposed risk stratification systems with the goal of detecting nodule at greatest risk for malignancy and then to recommend graduated size cut-offs for FNA cytology (19) (Table 1). All these risk-stratification systems are similar, but there are some differences: the endocrinological societies' systems are based on recognition of patterns, while ACR TIRADS is score-based, considering 5 US features and their sum to obtain the final classification of the nodule. Furthermore, the weight of each sonographic feature varies across various systems (e.g., echogenicity being the most important one for EU-TIRADS, and composition for K-TIRADS), and the size threshold to recommend FNA is different, too. Some of the systems have been validated in multicenter studies (20–22). Independent comparison studies (usually involving 2–3 of the systems) were mostly retrospective (23–28). Two prospective Italian studies compared the systems developed by the British Thyroid Association, the ATA, and the AACE/ACE/AME (29), or the ATA and the ETA (30) and found no significant differences between overall diagnostic accuracy. A recent study comparing the main five systems endorsed by international societies, found that four of the five

(AACE/ACE/AME, ATA, ACR-, and EU-TIRADS) showed a significant diagnostic value (31). The ACR TIRADS, which classified over half of the requested biopsies as unnecessary, with a negative predictive value of 97.8%, showed the best overall performance (31). To reproduce these results in the real clinical practice, an essential prerequisite is the adoption of a uniform language and definition of suspicious features (10). Classification of thyroid nodules using any of the five classification systems results in higher interobserver agreement than evaluation of single suspicious features, and identification of nodules needing biopsy has an almost perfect agreement (32). However, a specific “training by consensus” involving joint evaluation of images can improve the reproducibility for all classifications (with significant improvements for ATA, K-TIRADS, and EU-TIRADS systems), even for trained clinicians with similar experience (32). In recent years, the useful of ultrasound patterns to stratify the risk of malignancy of indeterminate thyroid nodules, has also been evaluated (33–35). Sonographic patterns were associated with different rate of malignancy suggesting that these systems are also able to stratify the risk of malignancy in the subgroup of cytologically indeterminate thyroid. These preliminary data suggest that sonographic patterns would be useful not only to guide FNAC, but also to personalize management after an indeterminate cytological results. Recently, software applications performing automated image analysis were also proposed to extract quantitative parameters using a variety of mathematical methods. These approaches may be the basis for computer-aided diagnosis (CAD) systems to yield an automated “second opinion” (36). According to some evidence, thyroid CADs based on artificial intelligence may further improve diagnostic performance and reliability (37). The use of thyroid CAD to differentiate malignant from benign nodules showed accuracy similar to that obtained by an expert radiologist (38, 39) and may reduce intra- and inter-observer variability, that however, still remains (38). Ultrasound elastography (USE) has emerged as an additional tool in combination with B-Mode Ultrasound (US) for thyroid nodules work-up. It is a non-invasive, cost-effective, dynamic diagnostic method for the measurement of tissues elasticity (40, 41). Malignant lesions tend to be harder and firmer than the normal thyroid parenchyma or benign lesions, related to fibrosis and higher expression of Galectin-3 and Fibronectin-1 (41–43), suggesting that elastography can be useful to distinguish between benign and malignant thyroid nodule (43, 44). There are two main elastography techniques to quantify thyroid nodules stiffness currently in clinical use: strain elastography (SE), which evaluates the degree of tissue deformation induced by manual compression or acoustic forces, and in which tissue deformation is parallel to the direction of the force; and shear wave elastography (SWE), in which a push beam is created and tissue displacement is perpendicular to the direction of the force (45, 46). Many studies and meta-analyses have identified for USE some limitations and confounding factors, including nodule features (calcifications, cystic components, size, position), the operator expertise, artifacts such as carotid artery pulsation, coexistent systemic, or thyroid diseases (Hashimoto's thyroiditis, acromegaly, previous thermal ablation

TABLE 1 | An overview of the standardized thyroid nodule US scoring systems proposed or endorsed by international practice guidelines.

Risk score	AACE/AME/ACE	ATA	EU-TIRADS	K-TIRADS
Suspicious US features	<ul style="list-style-type: none"> Marked hypoechogenicity Spiculated or lobulated margins Microcalcifications Taller-than-wide shape Extrathyroidal growth Pathologic adenopathy 	<ul style="list-style-type: none"> Irregular margins (infiltrative, microlobulated) Microcalcifications Taller-than-wide shape Rim calcifications with small extrusive soft-tissue component Evidence of extrathyroidal extension 	<ul style="list-style-type: none"> Non-oval shape Irregular margins Microcalcifications Marked hypoechogenicity 	<ul style="list-style-type: none"> Microcalcification Taller-than-wide shape Spiculated/microlobulated margins
Category	<p>Low-risk: Cysts (fluid component >80%)</p> <p>Mostly cystic nodules with reverberating artifacts and not associated with suspicious US signs</p> <p>Isoechoic spongiform nodules, either confluent or with regular halo.</p> <p><i>Risk of malignancy: 1% FNA >20 mm (selective)^a</i></p>	<p>Benign: Purely cystic nodules (no solid component)</p> <p><i>Risk of malignancy: <1% FNA is not indicated</i></p> <p>Very low suspicion: Spongiform or partially cystic nodules without any of the US features defining low-, intermediate-, or high-suspicion patterns</p> <p><i>Risk of malignancy: <3% FNA ≥20 mm or observation</i></p> <p>Low suspicion: Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid area without: microcalcifications, irregular margin, extrathyroidal extension, taller than wide shape</p> <p><i>Risk of malignancy: 5–10% FNA ≥15 mm</i></p>	<p>Benign (EU-TIRADS 2): Pure/anechoic cysts; entirely spongiform nodules</p> <p><i>Risk of malignancy: ≈ 0% FNA is not indicated</i></p> <p>Low-Risk (EU-TIRADS 3): Oval shape, smooth margins, isoechoic, or hyperechoic, without any feature of high risk</p> <p><i>Risk of malignancy: 2–4% FNA >20 mm</i></p>	<p>Benign: Spongiform Partially cystic nodule with comet-tail artifact Pure cyst</p> <p><i>Risk of malignancy: <1–3% FNA ≥20 mm</i></p> <p>Low suspicion: Partially cystic or isohyperechoic nodule without any of 3 suspicious US features*</p> <p><i>Risk of malignancy: 3–15% FNA ≥15 mm</i></p>
	<p>Intermediate-risk: Slightly hypoechoic (vs. thyroid tissue) or isoechoic nodules, with ovoid-to-round shape, smooth or ill-defined margins</p> <p>May be present: Intranodular vascularization</p> <p>Elevated stiffness at elastography,</p> <p>Macro or continuous rim calcifications</p> <p>Indeterminate hyperechoic spots</p> <p><i>Risk of malignancy: 5–15% FNA: >20 mm</i></p>	<p>Intermediate suspicion: Hypoechoic solid nodule with smooth margins without: microcalcifications, extrathyroidal extension or taller than wide shape</p> <p><i>Risk of malignancy: 10–20% FNA ≥10 mm</i></p>	<p>Intermediate-Risk (EU-TIRADS 4): Oval shape, smooth margins, mildly hypoechoic, without any feature of high risk</p> <p><i>Risk of malignancy: 6–17% FNA >15 mm</i></p>	<p>Intermediate suspicion: Solid hypoechoic nodule without any suspicious US feature or partially cystic or isohyperechoic nodule with any of the following: microcalcification, non-parallel orientation (taller-than-wide), spiculated/microlobulated margin</p> <p><i>Risk of malignancy: 15–50% FNA ≥10 mm</i></p>

(Continued)

TABLE 1 | Continued

Risk score	AACE/AME/ACE	ATA	EU-TIRADS	K-TIRADS
	High-risk: Nodules with ≥ 1 of the following: Marked hypoechoogenicity (vs. prethyroid muscles) Spiculated or lobulated margins Microcalcifications Taller-than-wide shape (AP>TR) Extrathyroidal growth Pathologic adenopathy Risk of malignancy: 50–90% ^b FNA ≥ 10 mm (5 mm, selective) ^c	High suspicion: Solid hypoechoic nodule or solid hypoechoic component of partially cystic nodule with ≥ 1 of the following: Irregular margins (infiltrative, microlobulated) Microcalcifications Taller than wide shape Rim calcifications with small extrusive soft tissue Extrathyroidal extension Risk of malignancy: >70–90% FNA ≥ 10 mm	High-Risk (EU-TIRADS 5): Nodules with ≥ 1 of the following: Non-oval shape Irregular margins Microcalcifications Marked hypoechoogenicity Risk of malignancy: 26–87% FNA >10 mm	High suspicion: Solid hypoechoic nodule with any of the following: Microcalcification Nonparallel orientation (taller-than-wide) Spiculated/microlobulated margin Risk of malignancy: >60 FNA ≥ 10 mm (>5 mm selective)

^aGrowing nodule, high-risk history, before surgery, or local therapies.

^bIn accordance with the presence of 1 or more suspicious findings.

^cFNA is recommended for the following nodules: Subcapsular or paratracheal lesions; Suspicious lymph nodes or extrathyroid spread; Positive personal or family history of thyroid cancer; History of head and neck irradiation, coexistent suspicious clinical findings (e.g., dysphonia).

or radiofrequency on thyroid nodule) and pathological type of thyroid cancer (40, 41, 47–71). Therefore, USE should be performed in selected thyroid nodules by qualified operators using objective criteria provided by elastographic machines. Two clinical practice guidelines include recommendation on thyroid USE. The 2015 ATA guidelines (18) reported that USE may be a helpful tool for preoperative risk assessment in patients, although it cannot be universally recommended. The 2016 AACE/ACE/AME guidelines (3) reported that USE data are complementary to gray-scale findings, especially in nodules with indeterminate US or cytological findings. Moreover, other specialized guidelines specific for USE [European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) (72) and World Federation of Societies for Ultrasound in Medicine and Biology (WFSUMB) guidelines (50)], provide an adequate description of the technique and its reproducibility, results and limitations. Although many reports have demonstrated that USE performed the same or better than the gray-scale US (40, 41), its diagnostic efficacy is still controversial (73). In clinical practice USE is usually performed as a complementary tool to conventional US, as the combination of the two techniques proved to have higher sensitivity (74). Recently, some studies evaluated the potential role of elastography in non-diagnostic or indeterminate nodules (43, 75), even if conventional US also has been shown to display good diagnostic results (37, 76). Utility of USE has also been explored in many studies (40, 54, 77, 78) but therefore, other authors failed to demonstrate the diagnostic utility in indeterminate nodules (75, 79) and a meta-analysis of eight studies demonstrated there was a great variability of both sensitivity and specificity in USE, with pooled estimates of 69 and 75%, respectively (77). Further studies are required concerning the supplementary role of elastography in the risk stratification of thyroid nodules.

HAVE MOLECULAR ANALYSIS AN ADDED VALUE?

When thyroid nodules are evaluated with fine-needle aspiration biopsy (FNAB), in ~5–20% of cases it is not possible to discriminate between benign and malignant nodules because of an indeterminate cytology (78). According to The Bethesda System for Reporting Thyroid Cytopathology (79, 80) indeterminate cytology includes two different categories: atypical or follicular lesion (Bethesda III) and follicular neoplasm/suspicious for follicular (or Hürthle cell) neoplasm (Bethesda IV). The observed rates of cancer in these categories vary widely ranging from 6 to 48% for Bethesda III and 14 to 34% for Bethesda IV (81). This wide range of cancer risk, involves that diagnostic hemithyroidectomies are still performed in order to discriminate between benign and malignant nodules. Unfortunately, in 50–70% of patients with indeterminate cytology a diagnostic surgery is performed. Moreover, surgery exposes patients to surgical risks and in the event of malignant lesions, a second-stage surgery is often indicated with additional costs and risks for patients (82–85). Molecular tests using gene expression and/or mutational analysis, have been developed to reduce the need for diagnostic surgery for indeterminate (Bethesda III/IV) thyroid nodules (86). Several molecular tests have been proposed over the years, since different gene-mutation panels has been introduced (86), with reported NPV and PPV ranging from 56 to 100% and from 19 to 100%, respectively, and the most successful are the Thyroseq and the AFIRMA Gene Expression Classifier (GEC). The first version of Thyroseq included the 7 gene panel (BRAF, H-K-N-RAS, RET/PTC1-3, PAX8/PPAR γ) (87) with a reported sensitivity of about 65% (87–89). Following versions migrated to the next generation sequencing platforms (NGS) and included a 13-gene panel

(ThyroSeq v1) (90) and a 56-gene panel (ThyroSeq v2) with a significant increase in sensitivity and negative predictive value (NPV) (91, 92). The last version of Thyroseq, v3, Nikiforov and Baloch (92) is a targeted NGS test that evaluates point mutations, gene fusions, copy number alterations and abnormal gene expression in 112 thyroid cancer related genes. Using the last version of Thyroseq, a recent prospective and multicenter validation study (93) on 286 cytological indeterminate nodules submitted to surgery reported a 94% of sensitivity and 82% of specificity with a NPV of 97% and a positive predictive value (PPV) of 66%. These data may obviate diagnostic surgery in up to 61% of patients with indeterminate nodules. The AFIRMA GEC is a microarray based test with a proprietary algorithm able to differentiate benign from malignant nodules based on messenger RNA expression pattern. The sensitivity is approximately of 90%, but the specificity is lower (88, 94). Moreover, a significant site to site variability in the benign call rate (range 27–53%) and in the malignancy rate (range 15.6–70%) was reported in a follow-up multicenter study (95). Very recently, the AFIRMA Genomic Sequencing Classifier (GSC) replaced the original GEC. It is a RNA sequencing based test, including 12 classifiers composed of 10,196 genes and 7 additional components in order to exclude parathyroid lesions and medullary thyroid cancer, and includes the analysis of BRAFV600E mutations, RET/PTC1 or RET/PTC3 and of specific alterations typical of Hürthle cell lesions. Compared to GEC, the GSC has a better specificity and reduces the number of histological benign samples classified as suspicious. An initial validation study showed a 36% increase in specificity compared with the GEC with a reported sensitivity of about 91% (96). Harrell et al. (97) demonstrated that GSC is able to identify less indeterminate cytology nodules as suspicious when compared to GEC, suggesting that GSC further reduces surgery by improving in specificity. In a recent independent study, Endo et al. (98) compared GEC with GSC and demonstrated that GSC had a significant higher benign call rate (76.2 vs. 48.1%), PPV (60.0 vs. 33.3%), and specificity (94.3 vs. 61.4%) than GEC in both Bethesda III and Bethesda IV categories. In particular, benign call rate of GSC was significantly higher in nodules with Hürthle cell changes (88.8 vs. 25.7%). In summary, both ThyroSeq and AFIRMA have reached a high sensitivity and enough specificity to function as rule in and rule out tests. The main problem is the limited number of validation studies and the high costs that remain a limit in their worldwide utilization. Currently, there are no data to prefer a molecular test rather than another one, and long term outcome data are needed.

MINI INVASIVE TREATMENTS

Most benign thyroid nodules are asymptomatic, stable and do not require treatment, while large thyroid nodules may become responsible for pressure symptom, neck discomfort or cosmetic complaints thus resulting in decreased quality of life (99). Over the last two decades, non-surgical, minimally invasive US-guided techniques have been proposed for the treatment of symptomatic nodules. Minimally invasive procedures include

percutaneous ethanol injection (PEI), laser thermal ablation (LTA), radiofrequency ablation (RFA), high intensity focused ultrasound (HIFU), and percutaneous microwave ablation (PMWA) (Table 2). PEI represents the first-line treatment for thyroid cysts and nodules with a predominant fluid component (100), while in solid nodules, LTA and RFA have proven to be very effective and safe in producing significant and stable reduction of nodule volume (101). Radiofrequency thermoablation consists in thermal ablation of the nodular tissue by exploiting the heat released by an energy source with consequent coagulation necrosis. The purpose of the treatment is to determine a volumetric reduction of the thyroid nodule, a condition that usually occurs in the weeks and months following the procedure as a consequence of the gradual replacement of the thyroid tissue with fibro-scar tissue and the procedure can be repeated after some time (102). Overall complication rate is low, about 3.5% (103). Some authors reported an higher difficulty of surgery after treatments, and exists the rare possibility of cancer spreading while treating patients with supposedly benign nodules (104). Radiofrequency thermoablation can be used for the treatment of benign nodular masses on cytological evaluation, which cause aesthetic alteration or compressive symptoms which cannot be treated surgically, for comorbidities or patient's preference. It is also recommended for the treatment of both pre-toxic and toxic nodules, when surgery or radioiodine are contraindicated or refused by the patient (3, 102, 105). Radiofrequency thermoablation has been proposed for papillary thyroid microcarcinoma and in cases of recurrence or loco-regional persistence of thyroid carcinoma when surgery is contraindicated or radiometabolic therapy has proved ineffective (18, 106). Some limitations still remain, such as the difficult to determine if cancer cells are fully eliminated even if ablation zones completely disappear on US and long-term outcomes (107). Another procedure based on the principles of hyperthermia is LTA that significantly reduce thyroid nodule volume as well as symptoms and cosmetic problems, due to coagulative necrosis into the target tissue (108, 109). A 3-year multicenter prospective randomized trial with LTA showed persistent volume reduction and local symptom improvement at 36 months after treatment (110). A systematic meta-analysis, comparing the efficacy of RFA and LTA for the treatment of benign thyroid nodules, concluded that both LTA and RFA are able to significantly decrease nodule volume, though RFA has a superior efficacy to LTA in nodule shrinkage despite minor number of treatment sessions (111). Only one study reported minor complications, as transient thyrotoxicosis and fever, after LTA (112) while no studies reported major complications such as voice change or hypothyroidism after either RFA or LA. It remains unclear if the different results are linked to the different energy delivered per ml of thyroid tissue, to the treatment time or technique. Finally, HIFU and PMWA are other promising forms of thermal ablation technique, but need further clinical testing. High intensity focused ultrasound (HIFU) have some advantages over other ablation techniques such as the ability to induce a focused thermal tissue destruction without needle puncture and seems to be less dependent on the skill of the operator. However, it produces thermal coagulation within a

TABLE 2 | An overview of the non-surgical, Image-Guided, Minimally Invasive Therapy for thyroid nodules or recurrent thyroid cancer.

Clinical Indication	Treatment	
	First line	Second Line
Cysts or predominantly cystic benign thyroid nodules	<ul style="list-style-type: none"> • Cystic nodules (>90% of fluid composition) • Predominantly cystic nodules (51–90% of fluid component) 	<ul style="list-style-type: none"> • Us-guided percutaneous ethanol ablation (PEI) • Us-guided thermal ablation <p><i>RFA can be recommended as the next step in cases with incomplete resolved symptoms due to the residual solid component or recurrence following PEI</i></p>
Solid non-functioning (cold) benign thyroid nodules	<ul style="list-style-type: none"> • Benign, non-functioning solid nodules with symptoms or cosmetic problems • Benign, non-functioning solid nodules that progressively enlarge • Benign multinodular goiter in patient who refuse or cannot undergo surgery 	<ul style="list-style-type: none"> • Thermal ablation (Radiofrequency ablation, laser ablation) • Surgery
Autonomously functioning thyroid nodules (AFTN)	<ul style="list-style-type: none"> • Radioactive iodine (RAI) • Surgery 	<ul style="list-style-type: none"> • Thermal ablation (Radiofrequency ablation, laser ablation)
Primary Thyroid Cancer Follicular neoplasm	<ul style="list-style-type: none"> • Surgery 	<ul style="list-style-type: none"> • Thermal ablation <p><i>Who refuse surgery or who cannot undergo an operation, thermal ablations can be considered as an alternative. Radiofrequency ablation, laser ablation, and microwave ablation have been attempted for patients with papillary thyroid microcarcinoma (PTMC).</i></p>
DTC patients with metastatic disease	<ul style="list-style-type: none"> • Surgery • TSH-suppressive thyroid hormone therapy for patients with stable or slowly progressive asymptomatic disease • 131-I therapy for RAI-responsive disease 	<ul style="list-style-type: none"> • External beam radiation therapy • Thermal ablation • Systemic therapy with kinase inhibitors

small volume and the ablation of a larger tissue volume may take an excessive period of time (113). The treatment efficacy (i.e., extent of nodule shrinkage at 6-month) in larger-sized benign thyroid nodules has been evaluated by Lang et al. in 63 nodules with a noticeably less efficacy for larger-sized nodules (114). HIFU is a safe treatment although transient side effects have been reported, such as pain, skin redness, mild subcutaneous swelling and transient vocal cord paralysis (115, 116). Percutaneous microwave ablation (PMWA) is a new technique that produce a rapid increase of the target tissue temperature through the rotation of molecules produced from microwave energy. Few studies analyzed the effectiveness of PMWA in the treatment of benign solid thyroid nodules. Liu et al. evaluated 474 benign thyroid nodules in 435 patients treated with PMWA showing a mean 90% decrease in volume at 1-year, with no major complications described (70). Another study by Yue et al. reported, in 110 patients treated with PMWA, a significant reduction at 1 year (ranging from 12.6 ± 15.1 to 3.2 ± 5.7 mL) (117). A retrospective, observational trial at a single institution compared the efficacy and safety of

RFA in 40 patients, PMWA in 40 patients and HIFU in 14 patients with small nodules at 3 months after ablation. RFA showed a slightly better mean volume reduction of nodules (50%) than MWA (44%) and HIFU (48%). The study limitation is the short period of time (118). In conclusion, non-surgical minimally invasive approaches can be used to treat symptomatic or enlarging thyroid nodule and appear safe and effective. Currently, percutaneous ethanol injection (PEI) is recommended for symptomatic cystic or relapsing cystic lesions. Either laser thermal ablation (LTA) or radiofrequency ablation (RFA) can be used for symptomatic solid nodules. Microwave ablation (PMWA) or high intensity focused ultrasound (HIFU) are newer techniques with promising results that await further clinical evaluation.

DISCUSSION

In the era of precision medicine, the most important landmark remains the correct identification of malignant thyroid nodules. Newer and promising imaging techniques

combined with the more accurate molecular examination will be able to reduce diagnostic uncertainty. Moreover, newer therapeutic options will be able to reduce, when possible, avoidable thyroidectomy. These approaches will allow the clinician to set up a tailored management, from diagnosis to treatment, of thyroid nodule disease, according to the patient's needs.

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AUTHOR CONTRIBUTIONS

LF and MC contributed to conception and design of the review. DT, GG, MDS, MDM, MS, TR, and FM wrote the first draft of the manuscript. All authors wrote sections of the manuscript, contributed to manuscript revision and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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