

A 2016 Italian Survey about Guidelines and Clinical Management of Thyroid Nodules

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Abstract

Background: While thyroid nodules are frequent in endocrine clinical practice, patients are often asymptomatic and euthyroid, and death is rare in cases of malignancy. **Objectives:** To evaluate the perception of current international guidelines regarding thyroid nodule management among Italian endocrinologists, and to compare daily clinical practice with suggested recommendations. **Methods:** Italian Association of Clinical Endocrinologists (AME) members were invited to participate in a Web-based survey. **Results:** A total of 566 physicians responded. About 50% had read the full text of the guidelines. Over half appreciated the suggested ultrasound (US) risk categories. Fine-needle aspiration (FNA) was obtained more frequently than recommended. Follow-up of a cytologically benign nodule was largely performed

according to the guidelines. Molecular testing would be most commonly requested when cytology reports showed atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) (TIR3A for Italian System). Iodine and/or levothyroxine were largely prescribed for cytologically benign asymptomatic nodules. Laser/radiofrequency ablation and percutaneous ethanol injection were commonly considered as alternatives to surgery (46.2 and 71.4%, respectively). **Conclusions:** Efforts are needed to make the guidelines more user-friendly and to encourage the use of codified risk categories in thyroid US reports. FNA indications remain a matter of debate as FNA is obtained in clinical practice more often than is recommended. Current US follow-up modalities for a benign nodule are correct, but probably could be performed less frequently without any harm. Molecular testing, if accessible, would be helpful in guiding clinicians' strategies in cases of AUS/FLUS-TIR3A cytologic results. Nonsurgical procedures are favorably embraced.

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Introduction

Thyroid nodules are the most frequent endocrine disease. Palpable thyroid nodules occur with a prevalence of approximately 5% in women and 1% in men, but thyroid nodules are detectable by ultrasound (US) in up to 70% of randomly selected individuals, with higher frequencies in women and the elderly [1, 2]. Most nodules are asymptomatic, are not associated with thyroid dysfunction, and do not cause compressive symptoms or cosmetic concerns. However, widespread use of imaging techniques reveals an epidemic of nonpalpable thyroid nodules that necessitate a complete workup, including US, testing for thyroid-stimulating hormone, and fine-needle aspiration (FNA) [3].

The first objective in thyroid nodule evaluation is to exclude malignancy. Therefore, detected nonpalpable nodules undergo FNA, massively increasing the performance of surgical procedures for indeterminate lesions or small papillary cancer [4–6]. This situation has prompted scientific societies to publish updated guidelines incorporating technical advancements in this field [7, 8].

With our present questionnaire-based survey, we aimed to investigate how current international guidelines (American Thyroid Association [ATA] and American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi [AACE/AME]) are perceived by Italian endocrinologists. We further compared daily clinical practice with the suggested recommendations.

Methods

We employed a Web-based survey constructed using LimeSurvey, an open-access platform providing various question templates. Our questionnaire included 37 questions, divided into 3 sections. The first section comprised 18 questions pertaining to the respondents' demographic data and perceptions of the 2015 ATA and the 2016 AACE/AME guidelines regarding thyroid nodules and differentiated thyroid cancer. The second section included 10 questions about clinical management of thyroid nodules. The third section comprised 9 questions about clinical management of thyroid cancer. An initial e-mail including an electronic link to the questionnaire was sent to 1,911 AME members. This was followed by weekly reminders from the AME secretary from June to July of 2016. Survey responses were anonymously collected and electronically stored by the survey service, where they were accessible by password. The survey service automatically blocked contradictory answers and repeated submissions from the same IP address.

This analysis presents the results from the first 2 sections of the questionnaire: demographic data and thyroid nodule clinical management.

Statistical Analysis

Summary statistics were prepared for the responses to each question. Not every participant answered every question. Thus, the percentage of respondents providing a given answer was calculated individually for each question. Questionnaire response rates were analyzed using the χ^2 test. Data were analyzed using IBM SPSS Statistics version 19 software (SPSS, Chicago, IL, USA).

Results

Response Rate and Respondents' Demographics

A total of 566 AME members (29.6%) participated in the survey, of whom 448 (79.2%) answered every question. For statistical evaluation, we included respondents who answered $\geq 51\%$ of the questions (472/566; 83.4%). Of these respondents, 50.8% were female. The age distribution was as follows: 3%, <30 years; 21%, 31–40 years; 19.9%, 41–50 years; 36.6%, 51–60 years; and 19.5%, >60 years. Most respondents (91.5%) specialized in endocrinology, while 4% specialized in internal medicine, 1.3% nuclear medicine, 1.1% surgery, 0.6% pediatric endocrinology, and 1.5% other specialties. The main fields of interest were “thyroid and endocrine disease” (52.3%), “thyroid and diabetes” (41.3%), and “diabetes and metabolism” (6.4%). Places of employment included referral hospitals (44.9%), private practice (30.7%), district hospitals (17.2%), and university hospitals (7.2%). Among the physicians, 40.9% performed thyroid US and 33.9% performed FNA in their practice. Distributions of sex, age, specialty, workplace, and region did not significantly differ between respondents and the whole cohort of AME members.

2015 ATA and 2016 AACE/AME Guidelines

The survey questions aimed to examine the perception of international guidelines regarding thyroid nodules and differentiated thyroid cancer. The overwhelming majority was aware of the 2015 ATA or 2016 AACE/AME guidelines ($p = ns$) (Fig. 1, 2). Only 50–60% of respondents had extensively read the guidelines. The majority of those who had not extensively read the guidelines had read only the recommendations (more common with the ATA guidelines than the AACE/AME guidelines) ($p < 0.05$). Some respondents found the guidelines difficult to read and understand, significantly more so for the ATA guidelines than the AACE/AME guidelines ($p < 0.01$).

US Risk Categories

When asked about providing clinical data or US risk categories in US reports, 63.8% of respondents provided descriptive clinical information, 9% provided no infor-

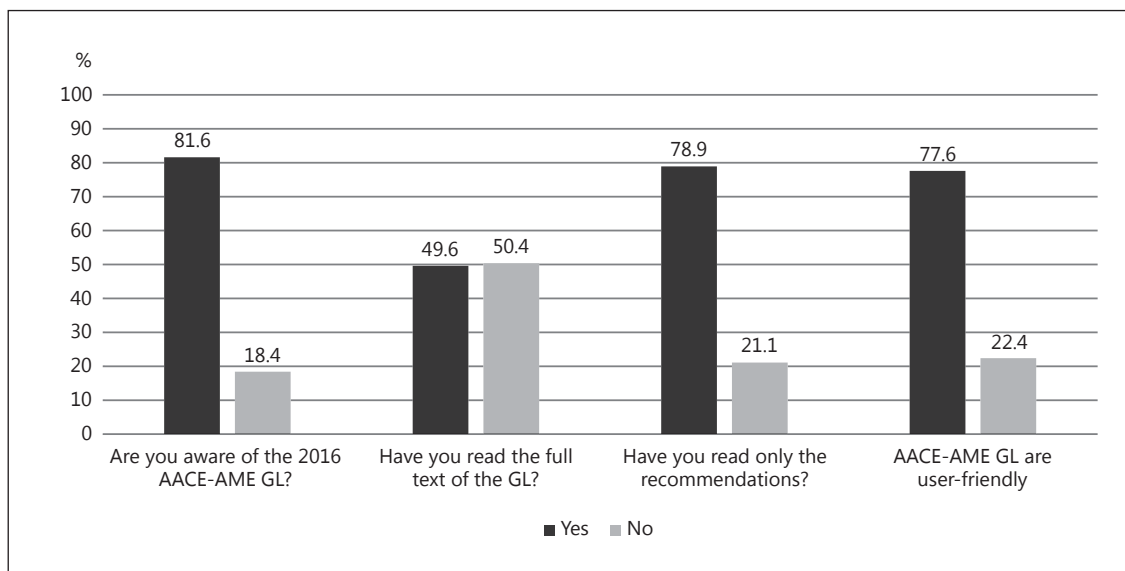


Fig. 1. Level of acceptance of the 2016 American Association of Clinical Endocrinologists (AACE)-Associazione Medici Endocrinologi (AME) guidelines (GL).

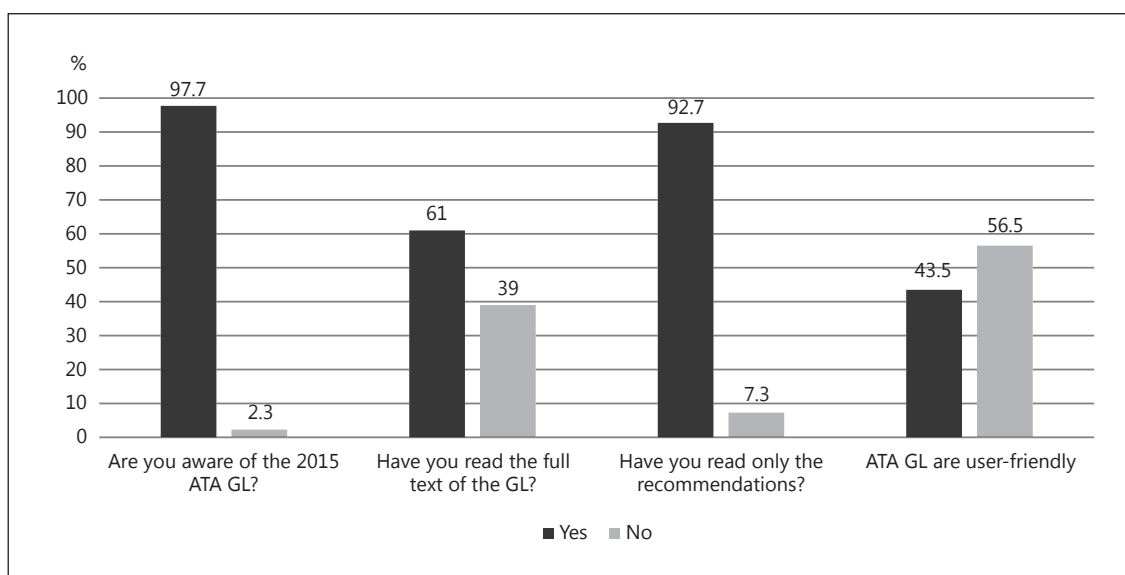


Fig. 2. Level of acceptance of the 2015 American Thyroid Association (ATA) guidelines (GL).

mation nor used any categorical system, and the remaining 27.2% equally used the Thyroid Imaging Reporting and Data System (TIRADS) or British Thyroid Association (BTA) system (clinical information vs. other systems, $p < 0.01$). About half of the respondents would consider using the suggested ATA or AACE/AME US risk categories for thyroid nodules (52.7% for ATA, 59.7% for AACE/AME) ($p = ns$).

Fine-Needle Aspiration

In a case with a high-suspicion nodule measuring 5–10 mm in diameter, 83.9% would suggest FNA, whereas the remaining respondents would opt for US monitoring ($p < 0.01$). For a low-suspicion nodule with a diameter of 15–20 mm, 11.4% do not suggest FNA, 33.3% suggest FNA, and 52.3% would choose FNA only in the presence of risk factors (FNA + risk factors vs. other options, $p < 0.01$).

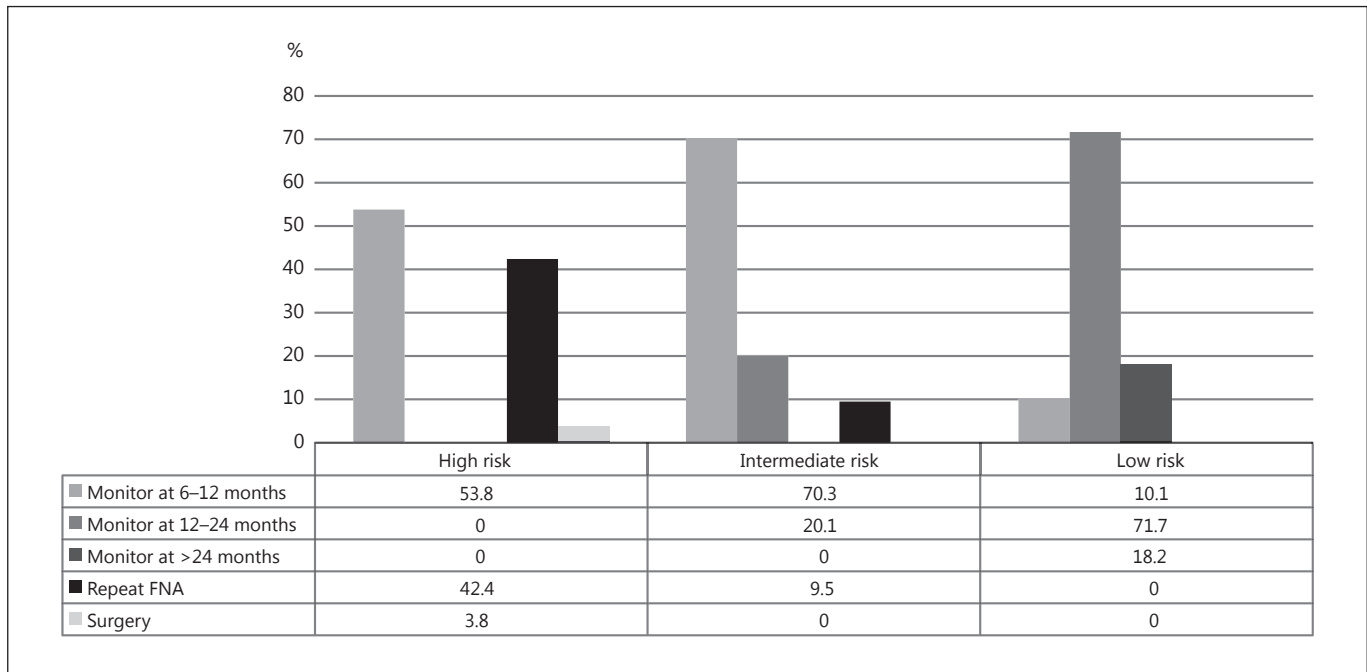


Fig. 3. Follow-up of cytologically benign nodules with different ultrasound risk categories.

Follow-Up of a Cytologically Benign Nodule

For a cytologically benign nodule, about 70% monitor at 12–24 months if low risk ($p < 0.01$). If intermediate risk, about 70% opt for follow-up at 6–12 months ($p < 0.01$). If high risk, about 40% repeat FNA, about half repeat US at 6–12 months ($p = ns$), and a minority suggests surgery (Fig. 3).

Molecular Testing

In the case of a cytology report showing atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) (TIR3A for Italian System), 46% would request molecular testing and suggest surgery if the results are positive, 43.6% would prefer US follow-up due to the low malignancy risk ($p = ns$), and 9.3% prefer surgery without additional information. For a cytology report showing follicular neoplasm/suspected follicular neoplasm (FN/SFN) (TIR3B for Italian System), 71.4% would suggest surgery, while 27.1% would request molecular testing and suggest surgery if the results are positive ($p < 0.01$).

Management of Different Cases with a Benign Nodule

For a 25-year-old patient with a nodular goiter, benign FNA, and no compressive symptoms, 54.7% suggest iodized salt, 24.4% levothyroxine treatment aiming at a low-normal thyroid-stimulating hormone, and 18.6%

advise avoidance of iodine supplementation (iodized salt vs. other options, $p < 0.01$). Endocrinologists older than 60 years more frequently prescribe levothyroxine than iodine (28.7 vs. 15.9%, $p < 0.05$), while those younger than 40 years more frequently suggest iodine than levothyroxine (27.1 vs. 11%, $p < 0.01$).

For a patient with a 3.5-cm cystic nodule and compressive symptoms, two-thirds opt for aspiration followed by percutaneous ethanol injection (PEI), while one-third recommend surgery ($p < 0.01$). For a 70-year-old patient with a 4.0-cm spongiform nodule and compressive symptoms, ~46% each would choose surgery or laser/radiofrequency ablation, while <4% would choose US monitoring.

Discussion

This is the first survey developed after publication of the 2015 ATA and 2016 AACE/AME guidelines regarding thyroid nodules and differentiated thyroid cancer [7, 8]. It was designed to evaluate how current guidelines are perceived by Italian endocrinologists and to compare daily clinical practice with recommendations. Over half of the respondents were primarily involved in thyroid disease management, and most of the other respondents were mainly interested in diabetes and thyroid disease. Thus,

the investigated sample of physicians managed thyroid disease on a daily basis, as reflected by the large proportion who performed thyroid US and FNA in their practice.

2015 ATA and 2016 AACE/AME Guidelines

The overwhelming majority of endocrinologists were aware of the recent guidelines. However, only 50–60% of respondents had extensively read the guidelines, ~30% had read only the recommendations, and a small proportion had not read them at all. Some respondents found the guidelines difficult to read and understand, more so for the ATA guidelines than the AACE/AME guidelines. This is likely because the ATA guidelines deal with both nodules and cancer, and are longer and more complex (about 70,000 words, 1,078 references, and 101 recommendations), potentially making them difficult to read, especially for endocrinologists not strictly focused on thyroid disease. On the other hand, the AACE/AME guidelines deal only with nodules and are shorter (about 20,000 words, 367 references, and 151 recommendations), which is apparently more acceptable to the reader.

US Risk Categories

The use of codified US risk categories apparently does not appeal to Italian endocrinologists, as many stated that they prefer reporting descriptive clinical information. The classifications (TIRADS or BTA) were largely not used. However, over half of the respondents declared their willingness to adopt the ATA or AACE/AME classification system, suggesting that the AME may have success in implementing a category system, at least in Italy.

Fine-Needle Aspiration

Given the high prevalence of thyroid nodules, which are predominantly benign, a major aim of the guidelines is to limit FNA performance without missing cancer diagnoses. The AACE/AME guidelines suggest FNA only for intermediate- and low-risk nodules ≥ 20 mm, while the ATA guidelines suggest avoiding FNA for small high-risk nodules. Our respondents clearly use FNA more frequently than recommended, including for high-risk nodules < 10 mm (against ATA guidelines) and for low-risk nodules of 15–20 mm (against AACE/AME guidelines). Although the disease is rarely fatal, it appears that Italian physicians are reluctant to limit FNA performance.

This attitude is also described in a 2015 American survey about thyroid nodule management among members of The Endocrine Society, ATA, and AACE [9]. In that survey, two-thirds of the respondents would biopsy high-suspicion nodules < 10 mm, ~40% would biopsy low-sus-

picion nodules < 15 mm, and ~40% would biopsy very-low suspicion nodules < 20 mm. These results highlight a generally prudent approach shared by different endocrine communities, which probably fear missing a diagnosis of malignancy.

Follow-Up of a Cytologically Benign Nodule

A prospective multicenter observational study, including 992 consecutive patients with asymptomatic and sonographically or cytologically benign thyroid nodules, reported that the majority of nodules did not significantly increase in size during a 5-year follow-up, and that thyroid cancer was rare (0.3%) [10]. In a retrospective study evaluating 249 euthyroid patients with benign uni-multinodular goiters, one-fourth of the patients experienced a significant event, such as new nodule appearance, a nodule diameter increase of $> 50\%$, appearance of compressive symptoms, thyroidectomy, FNA repetition on the same nodule, or FNA on a new nodule. Among these events, 71.9% occurred at the 24- or 36-month follow-up visit, suggesting that a patient can be safely followed up at an interval of 2–3 years [11].

For patients with initially benign cytologic results, the ATA guidelines suggest US monitoring for > 24 months for very-low-suspicion nodules and 12–24 months for low-intermediate-suspicion nodules, and US monitoring and/or FNA within 12 months for high-suspicion nodules. The AACE/AME guidelines suggest monitoring benign nodules every 12–24 months, with an increase to > 24 months if the size remains stable. Our present results showed that most respondents followed the guidelines of either the ATA or AACE/AME, with nodule monitoring dependent on US features. Italian physicians generally chose the shortest recommended interval time between the initial diagnosis and the successive follow-up US. The American survey revealed a similar attitude, with 60% of the respondents following an intermediate-suspicion nodule at a 12-month interval [9].

Molecular Testing

Up to 30% of FNA results show cytologically “indeterminate” lesions, which carry a cancer risk of 5–30% [12]. This “indeterminate” category is subdivided into 2 categories based on risk: AUS/FLUS (TIR3A) or FN/SFN (TIR3B) [13, 14]. Molecular testing presents another opportunity to identify thyroid cancer. Detection of *BRAF*, *NRAS*, *HRAS*, and *KRAS* point mutations and *PAX8/PPARG* and *RET/PTC* rearrangements (rule in) carries a positive predictive value of approximately 90% for cancer [15–17]. The gene expression classifier is a proposed

method based on excluding malignancy. A negative gene expression classifier result (i.e., benign gene expression profile) has a negative predictive value of ~95% for cytologically AUS/FLUS and FN/SFN lesions (90% sensitivity, 53% specificity) [18]. Although molecular testing provides an additional tool for thyroid cancer prediction, it cannot guarantee a correct diagnosis [19].

Molecular testing is not currently commercially available in Italy, but may be helpful in some cases given the variable risk of malignancy in “indeterminate” lesions. Our present respondents would use molecular testing for AUS/FLUS-TIR3A cases, whereas the majority would perform surgery in FN/SFN-TIR3B cases. Similarly, in the American survey, more physicians (38.8%) would request molecular testing in AUS/FLUS-TIR3A cases, whereas surgery was preferred for FN/SFN-TIR3B cases (61.2%) [9]. These findings suggest that clinicians in both the USA and Italy would request molecular testing in cases where decision-making is difficult given the variable risk of malignancy in an “indeterminate” lesion, but not in FN/SFN-TIR3B cases where they are already planning surgery. In this view, the use of US risk categories may be helpful and should never be disregarded. In a recent retrospective study from Korea, AUS and FLUS nodules were compared in terms of US features (composition, echogenicity, margin, shape, and calcifications), US diagnosis (probably benign, malignant), malignancy rate, and final malignant histology. Results showed that the AUS group more frequently had US suspicion features, US diagnosis suggestive for malignancy, mutated BRAF, and final malignant histology [20].

Management of Different Cases with a Benign Nodule

For young patients bearing asymptomatic benign nodules, the ATA and AACE/AME guidelines do not recommend routine levothyroxine treatment, except for patients living in areas characterized by mild iodine deficiency. In Italy, where mild iodine deficiency is common, and the use of iodized salt in foods is not compulsory by law, >80% of physicians followed strategies involving iodine or levothyroxine. Notably, <20% suggested avoiding any iodine-containing supplement, including iodized salt, perhaps due to concerns of autonomous function development. We also found that while levothyroxine is commonly prescribed by older endocrinologists, this tendency is reduced among younger endocrinologists. This is probably due to evidence that levothyroxine side effects (aimed at a low-normal thyroid-stimulating hormone value) are not satisfactorily counterbalanced by benefits in nodule reduction [21–23].

Prospective randomized trials and long-term studies show that PEI is significantly superior to aspiration alone for volume reduction of cysts and complex nodules with a dominant fluid component [24–26]. PEI was preferred by two-thirds of the respondents for a 3.5-cm cystic nodule complicated by compressive symptoms. This long-standing treatment is effective, safe, and feasible in an outpatient setting, and cheaper than surgery [27, 28]. Our results confirmed PEI as a standard of care for cystic nodules in clinical practice.

Laser/radiofrequency ablation appears to be an effective and safe outpatient treatment for volume reduction of solid cold thyroid nodules [29, 30], offering infrequent side effects, lower cost than surgery, and persistent nodule size reduction, especially for spongiform nodules [31]. Our respondents would equally choose surgery or radiofrequency ablation (~46% each) to treat a 70-year-old patient with a 4.0-cm spongiform nodule and compressive symptoms. Notably, nearly half of the respondents would consider laser/radiofrequency as an alternative to surgery. Such minimally invasive procedures are a welcome novelty, allowing individualized treatment for not only thyroid nodules, but also cystic, “hot” nodules, small papillary cancer, and neck recurrences of papillary thyroid cancer [32, 33].

Conclusions

Scientific societies should make guidelines easier to use and more readily transferable to clinical practice. Efforts should be made to introduce the use of codified US risk categories in thyroid US reports in Italy. FNA indications remain debatable, as FNA is performed more often in clinical practice than guidelines suggest (the clinical risk of small-size carcinomas remains incompletely understood). For benign nodules, current US follow-up modalities are correct, but can likely be performed less frequently without harm. Molecular testing, if accessible, would be predominantly requested for AUS/FLUS-TIR3A nodules. Nonsurgical procedures, mainly PEI and laser/radiofrequency ablation, are frequently considered as alternatives to surgery due to their favorable cost- and risk-effectiveness. Overall, North American and Italian endocrinologists show substantial similarities regarding thyroid nodule management.

Disclosure Statement

The authors have nothing to disclose.

References

- 1 Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA: The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf)* 1977;7:481–493.
- 2 Guth S, Theune U, Aberle J, Galach A, Bamberger CM: Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest* 2009;39:699–706.
- 3 Russ G, Leboulleux S, Leenhardt L, Hegedüs L: Thyroid incidentalomas: epidemiology, risk stratification with ultrasound and work-up. *Eur Thyroid J* 2014;3:154–63.
- 4 Leenhardt L, Grosclaude P, Cherie-Challine L; Thyroid Cancer Committee: Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. *Thyroid* 2004;14:1056–1060.
- 5 Davies L, Welch HG: Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 2006;295:2164–2167.
- 6 Rossing M, Nygaard B, Nielsen FC, Bennedbaek FN: High prevalence of papillary thyroid microcarcinoma in Danish patients: a prospective study of 854 consecutive patients with a cold thyroid nodule undergoing fine-needle aspiration. *Eur Thyroid J* 2012;1:110–117.
- 7 Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P; AACE/ACE/AME Task Force on Thyroid Nodules: American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract* 2016;22:622–639.
- 8 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1–133.
- 9 Burch HB, Burman KD, Cooper DS, Hennessey JV, Vietor NO: A 2015 survey of clinical practice patterns in the management of thyroid nodules. *J Clin Endocrinol Metab* 2016;101:2853–2862.
- 10 Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciaroni A, Puxeddu E, Tortolano M, Tumino S, Attard M, Lamartina L, Nicolucci A, Filetti S: The natural history of benign thyroid nodules. *JAMA* 2015;313:926–935.
- 11 Negro R: What happens in a 5-year follow-up of benign thyroid nodules. *J Thyroid Res* 2014;2014:459791.
- 12 Ali SZ, Cibas ES (eds): *The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria and Explanatory Notes*. New York, Springer, 2010.
- 13 Baloch ZW, LiVolsi VA, Asa SL, et al: Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. *Diagn Cytopathol* 2008;36:425–437.
- 14 Nardi F, Basolo F, Crescenzi A, et al: Italian consensus for the classification and reporting of thyroid cytology. *J Endocrinol Invest* 2014;37:593–599.
- 15 Nikiforov YE, Ohori NP, Hodak SP, et al: Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. *J Clin Endocrinol Metab* 2011;96:3390–3397.
- 16 Nikiforov YE, Steward DL, Robinson-Smith TM, et al: Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. *J Clin Endocrinol Metab* 2009;94:2092–2098.
- 17 Cantara S, Capezone M, Marchisotta S, et al: Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. *J Clin Endocrinol Metab* 2010;95:1365–1369.
- 18 Alexander EK, Kennedy GC, Baloch ZW, et al: Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med* 2012;367:705–715.
- 19 Eszlinger M, Hegedüs L, Paschke R: Ruling in or ruling out thyroid malignancy by molecular diagnostics of thyroid nodules. *Best Pract Res Clin Endocrinol Metab* 2014;28:545–557.
- 20 Lee S, Shin JH, Oh YL, Hahn SY: Subcategorization of Bethesda System Category III by ultrasonography. *Thyroid* 2016;26:836–842.
- 21 Bandeira-Echtler E, Bergerhoff K, Richter B: Levothyroxine or minimally invasive therapies for benign thyroid nodules. *Cochrane Database Syst Rev* 2014;6:CD004098.
- 22 Klein Hesselink EN, Lefrandt JD, Schuurmans EP, Burgerhof JG, Groen B, Gansevoort RT, van der Horst-Schrivers AN, Dullaart RP, Van Gelder IC, Brouwers AH, Rienstra M, Links TP: Increased risk of atrial fibrillation after treatment for differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2015;100:4563–4569.
- 23 Wang LY, Smith AW, Palmer FL, Tuttle RM, Mahrous A, Nixon IJ, Patel SG, Ganly I, Fagin JA, Boucai L: Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. *Thyroid* 2015;25:300–307.
- 24 Bennedbaek FN, Hegedüs L: Treatment of recurrent thyroid cysts with ethanol: a randomized double-blind controlled trial. *J Clin Endocrinol Metab* 2003;88:5773–5777.
- 25 Valcavi R, Frasoldati A: Ultrasound-guided percutaneous ethanol injection therapy in thyroid cystic nodules. *Endocr Pract* 2004;10:269–275.
- 26 Raggiunti B, Fiore G, Mongia A, Balducci G, Ballone E, Capone F: A 7-year follow-up of patients with thyroid cysts and pseudocysts treated with percutaneous ethanol injection: volume change and cost analysis. *J Ultrasound* 2009;12:107–111.
- 27 Reverter JL, Alonso N, Avila M, Lucas A, Mauricio D, Puig-Domingo M: Evaluation of efficacy, safety, pain perception and health-related quality of life of percutaneous ethanol injection as first-line treatment in symptomatic thyroid cysts. *BMC Endocr Disord* 2015;15:73.
- 28 Guglielmi R, Pacella CM, Bianchini A, Bizzarri G, Rinaldi R, Graziano FM, Petrucci L, Toscano V, Palma E, Poggi M, Papini E: Percutaneous ethanol injection treatment in benign thyroid lesions: role and efficacy. *Thyroid* 2004;14:125–131.
- 29 Papini E, Rago T, Gambelunghe G, Valcavi R, Bizzarri G, Vitti P, De Feo P, Riganti F, Misischi I, Di Stasio E, Pacella CM: Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial. *J Clin Endocrinol Metab* 2014;99:3653–3659.
- 30 Deandrea M, Sung JY, Limone P, Mormile A, Garino F, Ragazzoni F, Kim KS, Lee D, Baek JH: Efficacy and safety of radiofrequency ablation versus observation for nonfunctioning benign thyroid nodules: a randomized controlled international collaborative trial. *Thyroid* 2015;25:890–896.
- 31 Negro R, Salem TM, Greco G: Laser ablation is more effective for spongiform than solid thyroid nodules. a four-year retrospective follow up study. *Int J Hyperthermia* 2016;12:1–18.
- 32 Papini E, Pacella CM, Misischi I, Guglielmi R, Bizzarri G, Dossing H, Hegedüs L: The advent of ultrasound-guided ablation techniques in nodular thyroid disease: towards a patient-tailored approach. *Best Pract Res Clin Endocrinol Metab* 2014;28:601–618.
- 33 Gharib H, Hegedüs L, Pacella CM, Baek JH, Papini E: Clinical review: nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. *J Clin Endocrinol Metab* 2013;98:3949–3957.