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Original Article

Redefining Thyroid Nodule Evaluation: Demographics, Misleading Symptoms, and Diagnostic Challenges. Insights From a Multicenter Study

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ABSTRACT

Objective: Thyroid ultrasound (US) is the cornerstone for diagnosing nodular thyroid disease, yet many US examinations are prompted by nonspecific local symptoms (LS) like dysphagia or a palpable neck mass (NM). The clinical utility of such referrals remains debated.
Methods: This multicenter retrospective study analyzed 614 patients diagnosed with thyroid nodules (TNs) via US from 2 endocrinology centers in Italy between December 2021 and October 2022. Patients were grouped based on referral reason: symptomatic TNs, further subdivided into NM and LS, versus nonsymptomatic TNs. Clinical, ultrasonographic, and management data were compared.
Results: Symptomatic TNs accounted for 28.7% of cases (19.2% NM, 9.5% LS). NM patients were younger, more often female, and had larger, often cystic or isthmic-located nodules than nonsymptomatic TN patients. Conversely, LS patients had no significant differences in thyroid volume or nodule size but showed a higher prevalence of gastroesophageal reflux disease. Fine-needle aspiration was more common in the NM group because of larger nodules, but malignancy rates did not differ across groups. Surgical rates were similar, whereas thermal ablation was more frequent in the NM group.
Conclusions: A third of TNs are diagnosed during US prompted by LS, yet only NMs are associated with distinct nodule characteristics. Dysphagia and dysphonia were nonspecific and more related to gastroesophageal reflux disease than TNs. These findings support caution against overuse of US. Demographics, nodule features, and location should guide clinical suspicion and imaging decisions to avoid unnecessary imaging and interventions.

Introduction

Thyroid ultrasound (US) is the main tool for the diagnosis and characterization of thyroid nodular disease because of its efficacy, low cost, and lack of radiation exposure for patients. Recent guidelines recommend that diagnostic thyroid and neck US should be performed in all patients "clinically suspected" of having

Abbreviations: FNA, fine-needle aspiration; GERD, gastroesophageal reflux disease; LS, local symptom(s); NM, neck mass; nSTN, nonsymptomatic thyroid nodule; STN, symptomatic thyroid nodule; TN, thyroid nodule; US, ultrasound.

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nodular thyroid disease.[1] In patients with normal thyroid function, the clinical signs and symptoms potentially related to the presence of thyroid nodules (TNs) include the presence of a self-palpable lump in the neck, and the presence of local compressive symptoms (such as dysphagia and dysphonia). These signs and symptoms have been reported to be more prevalent in subjects with particularly large TNs or multinodular goiters[2-5], or in those with aggressive thyroid cancer due to local invasiveness.[6] Nevertheless, recent evidence suggests that these symptoms may be very nonspecific and they are often not related to the gland. Indeed, a recent meta-analysis reported that nearly 30% of patients with benign thyroid diseases complain of local symptoms (LS), especially when assessed through a questionnaire, but the same symptoms are also reported in patients without nodular disease.[7] Indeed, symptoms like dysphagia and globus sensation are frequently reported by patients with gastroesophageal reflux disease (GERD).[8] Moreover, a recent study by Kennedy et al,[9] showed that, among patients undergoing a thyroid US for compressive symptoms, less than half had a TN, and only 6% of these were warranted of a fine-needle aspiration (FNA). Even among patients with a palpable neck mass (NM), only 55% reached a diagnosis of TN. Unfortunately, the study lacked information regarding TN characteristics and thyroid volume.[9]

The routine use of thyroid US has lead in the last 20 years to an "epidemic" of small, nonpalpable TN. Overdiagnosis of clinically insignificant TNs can have an impact on health care costs, as well as on the psychological well-being of patients.[10] Locally symptomatic TNs (STNs) have become less frequent by comparison, but they still represent the reason leading to the performance of thyroid US in 30% to 40% of patients.

The aim of the present multicenter retrospective study was to compare patients performing thyroid US specifically for LS (ie, a NM or dysphagia/dysphonia) with patients in whom US was performed for another reason (including screening, thyroid dysfunction, and incidental detection of TN through other imaging) in terms of (1) patient characteristics, with a specific focus on gender, age, and comorbidity with GERD; (2) ultrasonographic characteristics; (3) clinical course (ie, performance of FNA, radiofrequency ablation, thyroidectomy), (4) rate of detection of malignancy.

Highlights

- Almost one third of thyroid nodules are diagnosed following ultrasound prompted by local symptoms, yet only neck masses are associated with specific sonographic and demographic features
- Patients presenting with a palpable neck mass tend to be younger, predominantly female, and more likely to have larger, cystic, and isthmic/paraisthmic nodules
- Local symptoms such as dysphagia or dysphonia are frequently unrelated to nodule size or thyroid volume and are more commonly associated with gastroesophageal reflux disease
- Fine-needle aspiration and thermal ablation are more commonly performed in patients presenting with a neck mass; however, malignancy detection rates are similar across all groups
- These findings support a more selective use of thyroid ultrasound, favoring clinical evaluation based on demographics and nodule characteristics rather than nonspecific symptoms alone

Clinical Relevance

Thyroid ultrasound should not be routinely used for evaluating nonspecific symptoms such as dysphagia or dysphonia, as they are often unrelated to thyroid pathology. A more targeted approach could reduce unnecessary imaging and interventions.

Methods

The outpatient Data Bases of the Unit of Endocrinology of ICS Maugeri (Pavia, Italy) and of the Unit of Endocrinology of Messina were retrospectively searched for consecutive patients who received a diagnosis of nodular thyroid disease between December 2021 and October 2022. The 2 geographic areas are quite similar concerning iodine nutrition.[11,12]

The inclusion criteria were as follows: (1) a thyroid US performed in an endocrinology clinic confirming the presence of TN; (2) the availability of information regarding the reason leading to the performance of a thyroid US.

Patients were then stratified according to the reason leading to the performance of thyroid ultrasound in 2 broad categories: (1) those who were addressed to thyroid ultrasound for the presence of local signs/symptoms (STN), (2) those who were addressed for other reasons (nonsymptomatic thyroid nodule [nSTN]). For the purpose of this study, STN patients were further stratified into 2 groups: those having US for a self-reported NM (NM group) and those performing US for the presence of LS, including dysphagia, dysphonia, dyspnea, and globus sensation (LS group).

The nSTN group included patients undergoing a thyroid US for one or more of the following conditions: (1) any type of thyroid function abnormality (subclinical or overt hypohyperthyroidism); (2) positive tests for thyroid auto-antibodies even in the presence of normal thyroid function parameters; (3) screening procedures for family history of thyroid disease or any thyroid function-related symptom; (4) incidental detection of a TN by imaging performed for another purpose.

In any case, the diagnosis of TN was confirmed by a thyroid US performed by skilled endocrinologists. At each center, thyroid US scans were performed by the same experienced operator using a real-time US device equipped with a linear transducer operating at 7.5 MHz.

At the time of diagnosis, the following data were recorded: patient's age (years), sex (male vs female), body mass index (kg/m^2), and a full medical history specifically focusing on the presence of GERD. Ultrasonographic data, including thyroid volume, number of nodules, longest diameter of the biggest nodule, location (isthmic or lobar), and ultranosonographic structure (ie, solid, mixed, or cystic) of the biggest nodule were also collected.

Data regarding postdiagnosis follow-up, including FNA results (classified according to the Italian Cytological Classification)[13] and performance of thyroidectomy or minimally invasive thermal ablation, were collected. In case of thyroidectomized patients, histologic diagnosis was collected.

All patients have signed an informed consent concerning the future use of their clinical-pathologic data for research purposes. The present study was approved by the Ethical Committee of ICS Maugeri, Pavia (Protocol N. 2742 CE).

Statistical Analysis

Statistical analysis was performed using the SPSS Software (SPSS, Inc.). Between-group comparisons were performed using

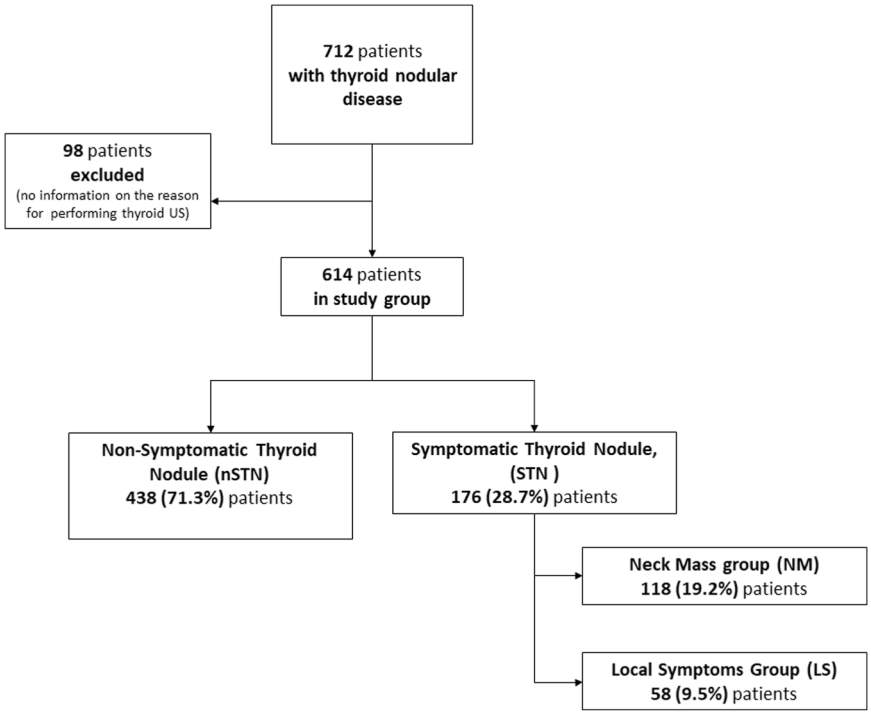

Fig. 1. Flowchart of the study.

the *t* test for unpaired data and the Mann-Whitney *U* test according to a normal or a nonparametric distribution. Within-group comparisons were performed using the *t* test for paired data and the Wilcoxon test according to a normal or a nonparametric distribution. Frequencies among groups were performed using the χ^2 test with Fisher's correction when appropriate. A logistic regression model was designed including being part of the NM group as a dependent variable and age, sex, thyroid volume, nodule size, nodule structure, and location as independent covariates.

Results

Study Participants

As illustrated in the flow diagram in Figure 1, the final study group encompassed 614 patients. The STN group included 176 patients (28.7%), among which 118 (19.2%) patients had undergone a thyroid US specifically for a suspected thyroid mass (NM group), whereas 58 (9.5%) patients were referred for LS (LS group).

Comparison of Clinical and Ultrasonographic Characteristic Patients in the nSTN and NM Groups

As summarized in Table 1, when compared with the nSTN group patients in the NM group had a significantly higher percentage of females ($P = .024$) and were significantly younger ($P < .001$), whereas body mass index and prevalence of GERD was similar. On the other hand, patients in the LS group had a significantly higher prevalence of GERD compared with the nSTN group ($P = .002$), without any significant differences in terms of age, gender, and body mass index. The main significant differences between groups are illustrated in Figure 2. When evaluating US

Table 1
Comparison Between Patients Undergoing Ultrasound for the Suspicion of a Neck Mass or Local Symptoms and Patients Without Local Signs or Symptoms of a Neck Mass (nSTN)

Clinical characteristics	nSTN group	STN group		*P* value
		NM group	LS group	
N	438 (71.3%)	118 (19.2%)	58 (9.5%)	
Age (y)	56 (44-66)	49 (37-56)[a]	53 (43-66)	**<.001**
Sex M/F (% of males)	134/304 (30.6%)	96/22 (18.6%)[a]	45/13 (22.4%)	**.024**
BMI (kg/m^2)	27.0 (23.5-30.5)	26.1 (23.8-30.1)	27.1 (24.3-30.7)	.587
GERD (N, %)	40 (9.1%)	5 (4.2%)	12 (20.7%)[a]	**.002**
Thyroid volume (mL)	14 (10-22)	19 (12-26)[a]	15 (10-20)	**<.001**
Number of nodules (N [IQR])	3 (1-5)	3 (2-5)	3 (2-5)	.351
Multinodular goiter (N, %)	324 (74.0%)	91 (77.1%)	47 (81.0%)	.439
Nodule maximum size (mm)	14 (9-22)	25 (14-37)[a]	17 (10-25)	**<.001**
Cystic US structure (N, %)	30 (6.8%)	19 (16.1%)[a]	4 (6.9%)	**.006**
Isthmic/paraisthmic nodule location (N, %)	30 (6.8%)	18 (15.3%)[a]	7 (12.1%)	**.012**

Abbreviations: BMI = body mass index; GERD = gastroesophageal reflux disease; LS = local symptom; NM = neck mass; nSTN = nonsymptomatic thyroid nodule; STN = symptomatic thyroid nodule; US = ultrasound.
Bold values indicate statistically significant comparisons ($P < .05$).
[a] Post hoc $P < .05$ vs nSTN.

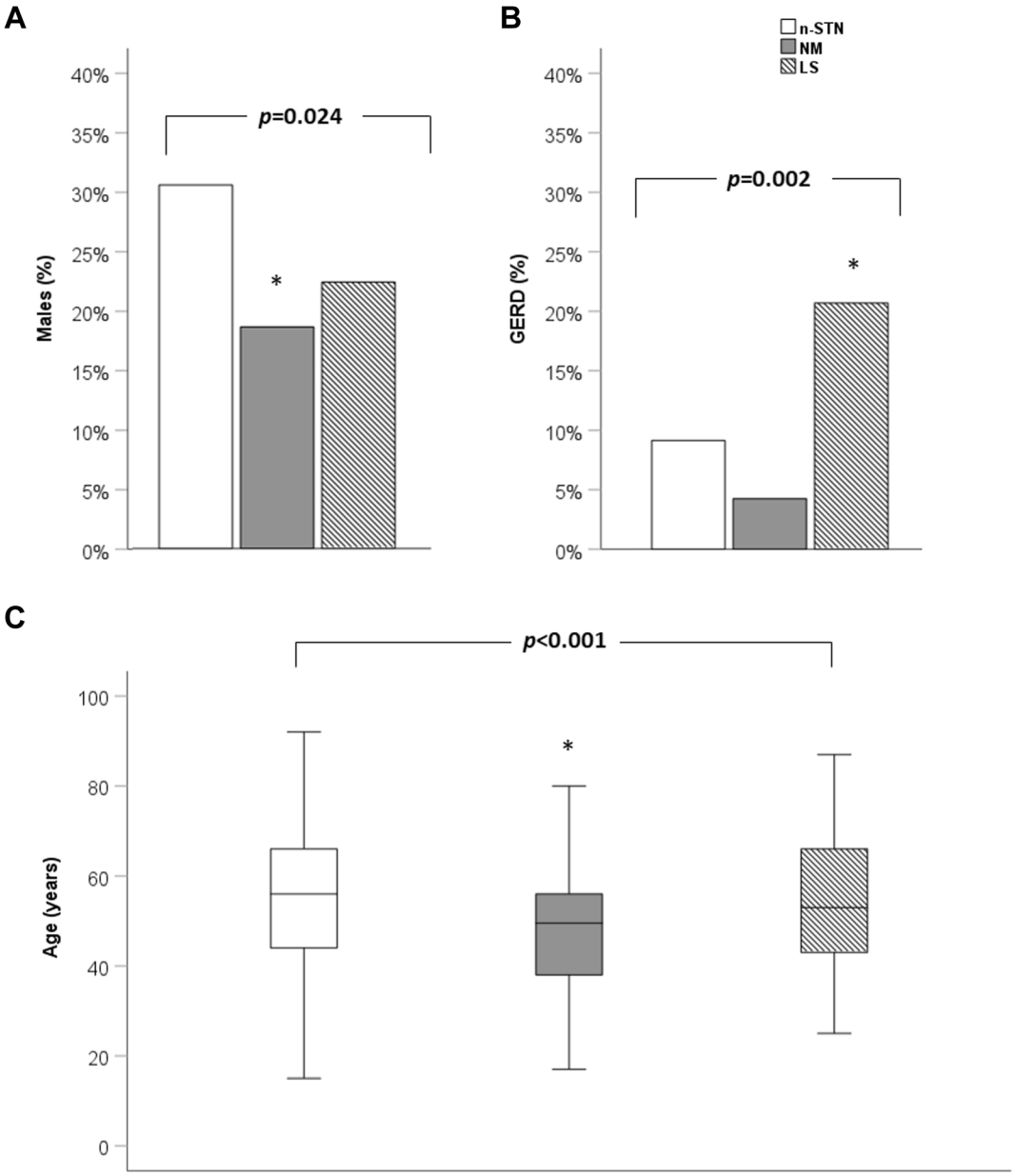

Fig. 2. Main significant differences in clinical characteristics between patients without local signs or symptoms of a neck mass (nSTN) and those with a neck mass (NM) or local symptoms (LS). *A*, Histogram representing the percentage of males in each group. *B*, Histogram representing the prevalence of gastroesophageal reflux disease (GERD) in each group. *C*, Box plot representing age distribution in each group. *Post hoc comparison vs nonsymptomatic group ($P < .05$).

features, patients in the NM group had a larger nodule size ($P < .001$), and thyroid volume ($P < .001$) than those in the nSTN group, as shown in Figure 3. Moreover, a significant difference in terms of US structure of nodules was observed, with a higher rate of cystic nodules in the NM group ($P = .006$). Also the isthmic/paraisthmic location of nodules was more frequent in the NM group as compared with the nSTN group ($P = .012$). The number of nodules and the rate of multinodular goiter were similar between the NM and nSTN groups. No significant differences in the US characteristic of nodules could be observed between the LS and the nSTN group.

A logistic regression model was designed including being part of NM versus the nSTN group as dependent variable and age, gender, thyroid volume, nodule size, US structure, and location as covariates. The regression analysis showed that age, gender, nodule size, cystic structure, and isthmic location, but not thyroid volume, were significantly and independently related with the risk of being part of the NM group (Table 2), that is to have a visible/palpable NM.

FNA Results, Thermal Ablation, and Surgical Treatment

As shown in Table 3, FNA was performed more frequently among nodules in the NM group when compared with the nSTN and LS group ($P < .001$). Nevertheless, among patients who underwent FNA, cytologic results did not significantly differ between the 3 groups. Thermal ablation procedures were more frequently performed in patients in the NM group when compared with the nSTN group and the LS group ($P = .006$). A similar percentage of patients underwent thyroidectomy in the 3 groups. The rate of histologic detection of malignant thyroid cancer among those who underwent thyroidectomy was similar in the 3 groups.

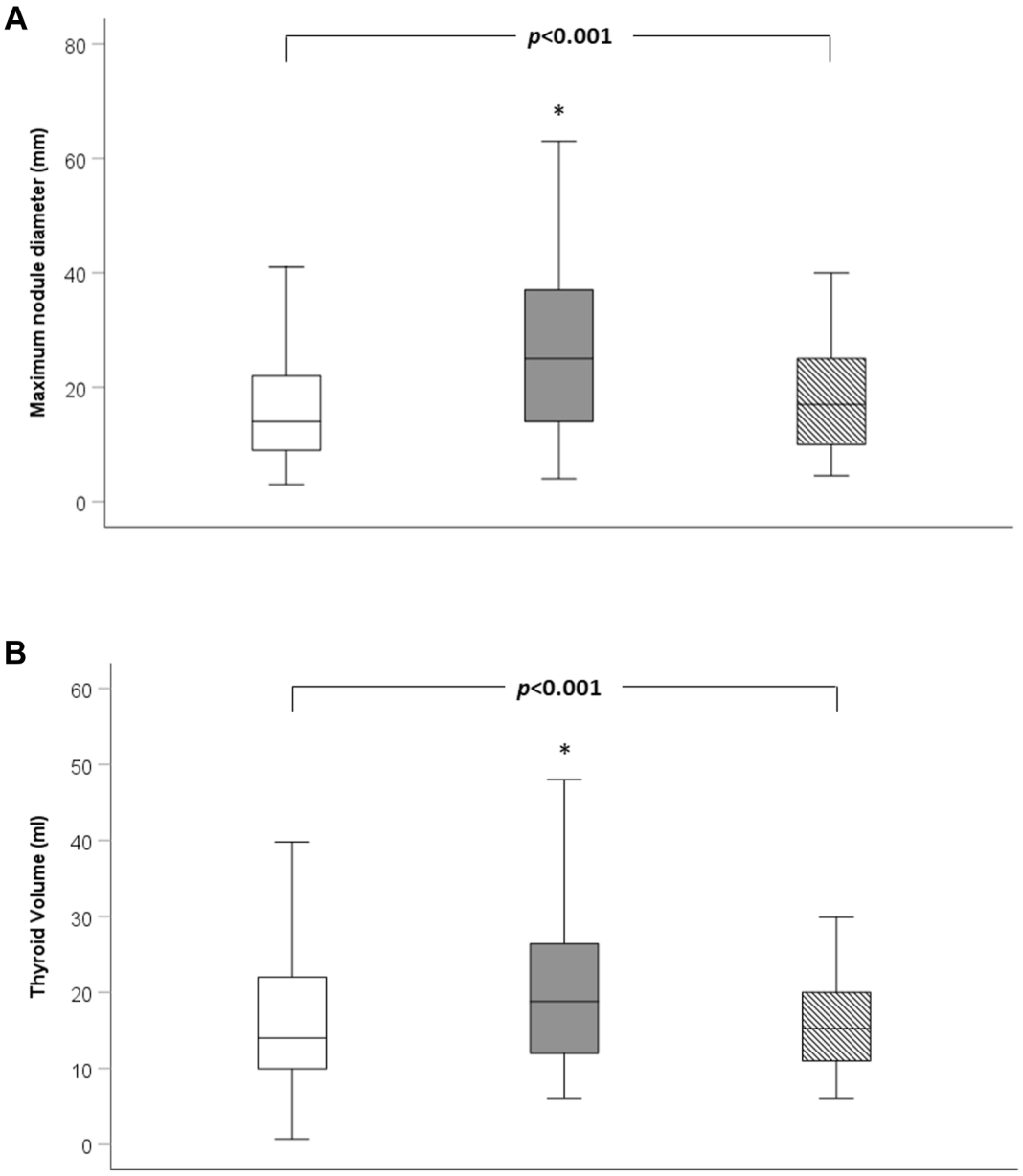

Fig. 3. Box plot representing the comparison of nodule maximum size (*A*) and thyroid volume (*B*) between patients without local signs or symptoms of a neck mass (nSTN) and those with a neck mass (NM) or local symptoms (LS). *Post hoc comparison vs nonsymptomatic group ($P < .05$).

Table 2
Results of the Logistic Regression Model Including Being Part of the Neck Mass Group Versus the Nonsymptomatic (nSTN) Group as Dependent Variable and Age (Years), Sex (Males vs Females), Thyroid Volume (mL), Nodule Maximum Size (mm), Ultrasonographic Structure of the Nodule (Cystic vs Mixed-Solid), and Nodule Location (Isthmic/Paraisthmic vs Lobar) as Covariates

Covariates	OR	95% CI for OR		*P* value
		Lower	Upper	
Age (y)	0.969	0.954	0.984	**<.001**
Sex (F vs M)	1.894	1.065	3.369	**.030**
Thyroid volume (mL)	1.001	0.989	1.014	.830
Nodule maximum size (mm)	1.063	1.043	1.083	**<.001**
US structure (cystic vs mixed-solid)	2.739	1.379	5.439	**.004**
Location (isthmic/paraisthmic vs lobar)	2.482	1.251	4.926	**.009**

Abbreviations: NM = neck mass; nSTN = nonsymptomatic thyroid nodule; STN = symptomatic thyroid nodule; OR = odds ratio; US = ultrasound.
Bold values indicate statistically significant comparisons ($P < .05$).

Table 3
Comparison of Fine-Needle Aspiration Results, Rates of Thermal Ablation, Rates of Thyroidectomy, and Histologic Diagnosis Between Performing Ultrasound for the Suspicion of a Neck Mass or Local Symptoms and Patients Without Local Signs or Symptoms of a Neck Mass (nSTN)

No of patients (%)	nSTN group	STN group		*P* value
		NM group	LS group	
FNA performed	197 (45.0%)	78 (66.1%)[a]	30 (51.7%)	**<.001**
FNA result[b]				.088
TIR1	34 (17.3)	12 (15.4%)	6 (20.0%)	
TIR2	112 (64.4%)	41 (52.6%)	21 (70.0%)	
TIR3A	23 (11.7%)	18 (23.1%)	1 (3.3%)	
TIR3B	13 (6.6%)	5 (6.4%)	2 (6.7%)	
TIR4/5	15 (7.6%)	2 (2.6%)	0 (0.0%)	
Thermal ablation (N, %)	7 (1.6%)	8 (6.8%)[a]	4 (6.9%)[a]	**.003**
Thyroidectomy	71 (16.2%)	27 (22.9%)	9 (15.5%)	.223
Thyroid cancer at histology	28 (6.8%)	8 (6.8%)	2 (3.4%)	.653

Abbreviations: FNA = fine-needle aspiration; LS = local symptom; NM = neck mass; nSTN = nonsymptomatic thyroid nodule; STN = symptomatic thyroid nodule.
Bold values indicate statistically significant comparisons ($P < .05$).
[a] Post hoc $P < .05$ vs nSTN.
[b] FNA results are classified according to The Italian Thyroid Cytology Classification (ICCRTC) as recommended by the SIAPEC-AIT (Italian Society of Anatomic Pathology and Cytology–Italian Thyroid Association) as follows: TIR1 (nondiagnostic): Insufficient or inadequate for interpretation; TIR2 (benign): Indicates a low probability of malignancy. TIR3A (low-risk indeterminate): Increased cellularity with microfollicular structures, but not enough for a diagnosis of follicular neoplasm; TIR3B (high-risk indeterminate): High cellularity with scant or absent colloid, and may show mild or focal nuclear atypia; TIR4 (suspicious): Suggests a high probability of malignancy; TIR5 (malignant): Definite evidence of malignancy.

Discussion

The results of the present multicenter study show that only one third of patients with nodular thyroid disease receive a diagnosis of a TN after an US performed for signs and symptoms ascribed to a thyroid mass. As expected, patients seeking medical attention for a NM had larger nodules and a larger thyroid volume. Patients in this group were also younger, with a higher percentage of women, and more frequently had cystic nodules and nodules located at the isthmus. On the other hand, patients who underwent a thyroid US for LS, such as dysphagia or dysphonia, were similar in terms of clinical and US characteristics to the nSTN patients, the only significant difference being a more than double prevalence of GERD (20.7% vs 9.1%). FNA was performed more frequently in patients in the NM group, mainly because nodule size was larger than in the other 2 groups. On the other hand, comparing FNA results the rates of detection of malignancy were similar in the 3 groups. Although the rate of thyroidectomies was similar in the 3 groups, the rate of thermal ablation treatment was slightly higher in patients in the NM group.

Our results show that, although nodule size is an important predictor of the detection of a TN through its mass effect, other factors play a significant role. First, independent of thyroid volume or nodule size, younger patients and women were more likely to seek medical attention for a NM. This observation in part contradicts the commonly reported notion that an overdetection of TN in women stems mainly form an excess of screening in asymptomatic patients. Indeed, the diagnosis of TN and thyroid cancer in men occurs more frequently incidentally through nonthyroid related imaging, even when TNs are very large.[14,15] Indeed, this could be in part due to the general and widely reported tendency in men for a delayed access to health care,[16,17] but it could also be due to a lower suspicion of thyroid diseases in men compared with women. This finding highlights how TNs are frequently overlooked in males, and it warrants further investigation and awareness in clinical practice.

When evaluating the US characteristics of nodules, independent of nodule size, patients with cystic nodules were more represented in the NM group. It can be hypothesized that these patients may seek medical attention more frequently for a NM, probably because of the rapid enlargement that typically characterizes cystic nodules. The rapid enlargement of a hemorrhagic cyst can also cause neck pain that leads to rapid medical care seeking.[18] Also isthmic and paraisthmic nodules tend to be more noticed by patients, likely due to their anatomical position.[19] Conversely, multinodular goiters, despite their size, often go undetected by patients, either due to their slowly progressive enlargement or to limited detectability on physical examination when extending substernally.

An unexpected observation was that patients receiving a thyroid US for LS, such as dysphagia or dysphonia, did not have larger nodular size or thyroid volume when compared with the nSTN group. These complaints did not correlate with larger nodules or increased thyroid volume, and were more frequently associated with GERD. Previous studies suggested that the presence of LS was associated with larger nodules.[5,19] On the other hand, recent evidence supports the notion that dysphagia and dysphonia are very nonspecific symptoms, and probably in most cases these are due to nonthyroid related conditions.[8] This is demonstrated also by a recent study showing that, in almost half of the patients receiving a thyroid US for LS, no TN was detected.[9] This reinforces recommendations to prioritize otolaryngologic or gastroenterologic evaluation before pursuing thyroid imaging in these cases.[20]

The proportion of patients who underwent FNA differed significantly between groups, with a higher frequency observed among symptomatic individuals, particularly those presenting with a cervical mass. Nevertheless, no significant differences were identified in cytologic outcomes, including the prevalence of malignant or suspicious findings. These results indicate that the presence of symptoms, including cervical mass, was not predictive of a positive fine-needle aspiration biopsy result and was not associated with an increased risk of malignant or indeterminate cytology. As a result, the definitive therapeutic approach was consistent between groups, with a similar percentage of patients undergoing surgical thyroidectomy. A slightly higher rate of thermal ablation procedures was performed in symptomatic patients. This finding appears in line with the fact that these techniques are specifically indicated for benign lesions that cause local pressure symptoms or cosmetic concerns, independently from nodule size.[21]

In conclusion, this multicenter study reveals that a significant proportion of TNs are diagnosed during US examinations prompted by nonspecific signs and symptoms. Although nodule size remains a key factor in prompting medical evaluation, our findings emphasize

the additional roles of demographic and ultrasonographic characteristics—particularly patient age, sex, nodule composition, and location—in influencing clinical presentation and diagnostic procedures.

Further studies should aim to clarify gender differences in TN detection, improve understanding of symptom perception across nodule types and locations, evaluate the impact of nonthyroid conditions like GERD on referrals and imaging, and assess the cost-effectiveness of US in patients with nonspecific symptoms. These insights could help optimize diagnostic strategies, and reduce unnecessary imaging, ultimately improving patient care. In details, the findings of the present study support a more cautious use of neck US on patients with dysphagia/dysphonia, prioritizing an gastroenterological or ear-neck and throat evaluation on these symptoms. Moreover, these findings suggest that patients presenting with a palpable NM are not characterized in general by a higher risk of thyroid malignancy, supporting the use of noninvasive techniques, such as thermal ablation, if necessary.

Disclosure

The authors have no conflicts of interest to disclose.

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