Ultrasoundelastography: Can it provide valid information for differentiation of benign and malignant thyroid nodules?

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KEYWORDS

Thyroid;
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FNAC.

Abstract Ultrasoundelastography (USE) is a new imaging technique that is performed with a normal ultrasound transducer. It provides improved characterization of a tissue or nodule based on the latter's elasticity and stiffness. The aim of the present, prospective study was to assess the validity of USE in characterizing thyroid nodules. USE patterns were analyzed in light of nodule cytology (*British Thyroid Association* classification) to determine whether these patterns can be used to decide whether or not fine-needle aspiration cytology (FNAC) is indicated. We examined a consecutive series of 617 thyroid nodules in patients referred for the first time to the Endocrinology Unit of Atri Hospital (Atri, [TE]). Patients underwent ultrasonographic and USE examinations of their thyroid nodules, which were then subjected to FNAC. All nodules with Thy 1 cytology were excluded, leaving 567 nodules for analysis. USE findings were classified on the basis of the degree and distribution of elasticity within the lesion: four patterns were identified (1, 2, 3a, 3b, or 4).

None of the nodules with Thy 4 cytology (malignant) had USE pattern 1 or 2; patterns 3 and 4 were associated with higher cytologic grades. In conclusion, USE provides additional information on thyroid nodules, which can be used with ultrasound features of the nodules, to decide whether FNAC is indicated. In fact, patterns 1 and 2 do not seem to be associated with Thy 4 cytology.

Sommario L'Elastosonografia (ESG) è una nuova tecnica d'immagine che, utilizzando una normale sonda ecografica, consente una migliore caratterizzazione tissutale, fornendo informazioni su elasticità e durezza di un tessuto o di un nodulo.

L'obiettivo di questo studio prospettico è quello di valutare l'effettiva validità della ESG nel caratterizzare i noduli tiroidei, associando il pattern elastosonografico al grading citologico e,

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quindi, valutare se eseguire o meno l'agoaspirazione del nodulo tiroideo, in base al pattern ESG. Sono stati studiati, in serie successiva, 617 noduli tiroidei di pazienti afferiti per la prima volta presso la nostra UO di Endocrinologia del P.O. di Atri (TE), sottoposti ad esame ecografico, elastosonografico e ad agoaspirato con ago sottile (FNAC), per lo studio citologico. Tutti i noduli che al referto citologico presentavano un grado Thy 1 sono stati esclusi dallo studio, pertanto sono stati esaminati 567 noduli. Lo score elastosonografico utilizzato prevede 5 patterns cromatografici (1; 2; 3a; 3b e 4) a seconda della distribuzione di tessuto più o meno elastico all'interno del nodulo.

I risultati dell'ESG hanno evidenziato che nessun nodulo con citologico Thy 4 presenta un grado elastosonografico 1 o 2; passando ai patterns elastosonografici 3 e 4 si assiste ad una crescita concomitante del grading citologico. In conclusione l'ESG può essere considerata un ulteriore parametro, in associazione alle caratteristiche ecografiche del nodulo, per decidere se eseguire o meno lo studio citologico. Infatti i patterns elastosonografici 1 e 2 sembrerebbero non associarsi a citologici Thy 4.

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Introduction

Palpation has always been the simplest, quickest, and most economical way to detect thyroid nodules. It reveals nodules in 5%–10% of the adult population residing in moderately goitrogenic areas like Italy. The use of ultrasoundography with high-resolution probes—which has revolutionized the diagnosis of thyroid nodules—increases this figure appreciably to 50% of the adults over the age of 50 years [1–3]. In the foothills of the Abruzzo region of Italy, sonographic screening of the over-50 population has disclosed thyroid nodules in over 60% [4]. With high-frequency ultrasound, even nodules that are nonpalpable and clinically silent are now being detected although only 5.0–6.5% of these lesions present features that are compatible with neoplastic disease [5].

Sonography with a high-frequency probe can identify nodular thyroid lesions with a high degree of accuracy, but it is of limited use in distinguishing benign nodules from those that are malignant [6]. Sonography allows us to select the nodules for fine-needle aspiration cytology (FNAC) that have suspicious features, regardless of their size (larger or smaller than 1 cm in diameter). Therefore, despite its limited value in differentiating malignant and benign nodules, the sonographic examination is fundamental for the diagnosis, treatment, and follow-up of thyroid nodules—so much so that it is recommended in the most recent guidelines issued by the AME-ETA-AACE [7]. At present, the most effective method for diagnosing thyroid tumors is FNAC. Although it is only a minimally invasive procedure, it is by no means devoid of sampling errors and analysis errors. For this reason, clinicians are constantly searching for a method that will facilitate differentiation of malignant and benign nodules.

Ultrasoundelastography (USE) is a technique that allows improved characterization of tissues/nodules, based on their elasticity and firmness [8,9]. USE was first used to characterize breast lumps and later thyroid nodules [10]. The aim of the present prospective study was to evaluate the use of USE in characterizing thyroid nodules. USE patterns were analyzed in light of nodule cytology (British Thyroid Association classification) to determine whether these patterns can be used to decide whether or not FNAC is indicated.

Materials and methods

Sonoelastography is simple to perform. Using a dual transducer method, real-time sonographic and USE images can be viewed simultaneously on the monitor. During the USE examination, the operator compresses the tissues beneath the transducer. The pressure must be applied (and released) with a continuous movement, exerted at a right angle to the proximal plane of the lesion, and care should be taken to avoid lateral displacement of the probe. A numerical rating (from 1 to 5) displayed on the scanner panel shows the quality of the pressure being exerted by the operator. Appropriate compression is indicated by a rating of 3 or higher that is maintained for at least 5 s. The system provides color-coded mapping of tissue elasticity: blue represents the stiffest tissues, red is used for those that are most compressible, and green indicates intermediate stiffness. Ueno was the first to correlate the color code with the elasticity of tissues. Their classification included 4 patterns [10]. Today, however, the classification of thyroid nodule USE includes 5 color-coded patterns [1, 2, 3a, 3b, 4] (Fig. 1), each characterized by a specific degree of elasticity or distribution of elasticity within the nodule (3a,3b). Pattern 1 [P1] (Fig. 2A) describes a nodule that is diffusely elastic, with respect to surrounding tissues, producing a pattern that is predominantly red and green. Nodules exhibiting Pattern 2 [P2] (Fig. 2B) are predominantly elastic, with a green background and scattered islands of blue, representing the initial onset of tissue stiffness. In lesions with Pattern 3a [P3a] (Fig. 3A), a substantial portion of the tissue, located in the peripheral regions of the nodule, is stiff, and the color map shows a predominance of green and blue. Pattern 3b [P3b] (Fig. 3B) reflects the same degree of elasticity seen in pattern 3a, but the stiff areas are located at the center of the lesion, which appears blue, while the periphery is green. As for pattern 4 [P4] (Fig. 4), it is associated with nodules with uniformly low elasticity compared with the surrounding thyroid tissues. On the monitor, these lesions appear uniformly blue (Table 1) [12].

The USE examination was done with a free-hand technique with an Esaote Logos sonoelastographer and a 10-MHz transducer. The sonoelastographic image was viewed in real-time on the left side of the screen, side by side with the real-time sonographic image on the right, so that the

Fig. 1 Ultrasound elastography patterns reflect the degree of elasticity or the differential distribution of elasticity within the nodule.

Fig. 2 (A) Pattern 1: Ultrasound elastography shows a nodule that is diffusely elastic with respect to the surrounding tissue. (B) Pattern 2: Ultrasound elastography shows a nodule that is predominantly elastic.

operator could continuously monitor both examinations. Fine-needle aspiration was performed with a 22-gauge needle that was 70 mm long with rigid coupling of 25-mm, connected to a 30-cc syringe. The USE examinations considered in our analyses were validated by the concordance of two independent examiners. The US-guided aspirate was subjected to cytological analysis and classified as follows: Thy 1 – inadequate material for diagnosis; Thy 2 – within normal limits; Thy 3 – indeterminate: adenoma vs. follicular carcinoma; Thy 4 – suspicious: cannot exclude carcinoma; Thy 5 – malignant: unequivocal evidence of carcinoma. The patient underwent thyroid ultrasonography to evaluate the sonographic parameters and USE to define the elasticity/stiffness of the nodules and FNAC to obtain cytological data that could be correlated with USE data.

Results

In this study, we examined 617 patients seen for the first time in the Endocrinology Unit of Atri Hospital between October 2009 and May 2010. All nodules with Thy 1 cytology (inadequate material for diagnosis) were excluded, leaving 567 nodules for our analysis. None of these nodules were cytologically classified as Thy 5. Frequency, percentages, mean indexes and indexes of variability were calculated, when appropriate, for the variables sex, age, and nodule type. The USE results were then analyzed in light of the cytological findings (Thy). The degree of concordance between the two examinations was statistically analyzed with the chi-squared test or Fisher's exact test. The diagnostic accuracy of USE, compared with Thy-grade cytology, was assessed with ROC analysis. We calculated the sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive values (NPV) for different USE cut-offs. All statistical analyses were carried out with the SPSS® Advanced Statistical™ 13 (SPSS Inc., Chicago, IL, USA) software package.

Fig. 3 (A) Pattern 3a: Ultrasoundelastography shows a nodule with large areas of stiffness located at the periphery of the lesion. (B) Pattern 3b: Ultrasoundelastography shows the same degree of elasticity typical of pattern 3a, but the stiff areas are located at the center of the lesion (which appears blue) instead of the periphery (which appears green).

Table 2 summarizes the main characteristics of the patient subgroups defined by Thy cytology. There was a clear prevalence of women (83%), and the mean age of the total population was 53.1 years (SD 15.7 years). Most of the nodules were solid (58%) or mixed (28%); 8% were calcified, and 6% were cystic. Analysis of the USE patterns showed that none of the Thy 4 nodules had USE pattern 1 or 2; Thy 3 (indeterminate) cytology was reported for a low percentage of patients with cystic lesions (10%) and 24% of the calcified nodules. In essence, USE patterns 3 (a and b) and 4 were associated with higher Thy cytology grades. There was also a statistically significant association (chi-squared = 24.13, Fisher's exact test = 19.82, $p < 0.001$) between the USE pattern subgroup (patterns 1-2-3a vs. pattern 3b vs. pattern 4) and Thy cytology subgroup (normal vs. indeterminate vs. suspicious) (Table 3). Nodules were then classified as potentially pathological (Thy 3 or Thy 4) vs. non-pathological (Thy 2). Table 4 shows the SE, SP, PPV and NPV for the different SEG patterns, considered in increasing order of severity from 1 to 4 with 3a < 3b.

On the basis of the results reported in Table 2 and those of the ROC analysis, we identified USE pattern 3b as the optimal cut-off (SE = 38%, SP = 72%). It is important to note that this cut-off was associated with a good NPV (84%), which suggests that the USE patterns 1, 2, and 3a tend to predict Thy cytology that is neither indeterminate nor suspicious for malignancy. However, contingency table analysis of USE patterns and cytological findings for each type of nodule (Table 5) indicate that greater caution is needed when deciding whether patients need FNAC or surgery. In patients with cystic or mixed nodules, indeterminate cytology (Thy 3) is relatively infrequent (6.7%), and suspicious cytology (Thy 4) was not observed for any of the nodules with USE pattern 1 or 2. As for calcified nodules, indeterminate cytology is also fairly infrequent in patients with USE pattern 1, 2, or 3a (14.4%), and none of these nodules was classified as Thy 4. In contrast, the frequency of indeterminate or suspicious cytology in patients with solid nodules was by no means negligible (23%), and the diagnostic value of the USE patterns seems to be relatively limited.

Fig. 4 Pattern 4: Ultrasoundelastography shows a nodule with limited elasticity that is decidedly stiff compared with the surrounding thyroid tissue.

Table 1 Summary of ultrasound elastography patterns.

Patterns	Characteristics	Colors
P1	The entire nodule is diffusely elastic as compared with the surrounding tissue	Red, green
P2	Largely elastic nodule	Mostly green with small islands of blue
P3a	Elastic nodules with peripheral areas of stiffness	Green center with blue rim
P3b	Elastic nodules with central stiffness	Blue center with green rim
P4	The entire nodule is stiff with respect to the surrounding tissue	Diffusely blue, sometimes with tiny areas of green

Table 2 Clinical characteristics and USE patterns associated with the three categories of thyroid nodule cytology.

Variable	Thyroid nodule cytology		
	Normal <i>n</i> = 464	Indeterminate <i>n</i> = 96	Suspicious <i>n</i> = 7
Age, media (SD)	55.3 (14.0)	55.0 (13.5)	49.0 (19.6)
Women, <i>n</i> (%)	387 (83.0)	81 (84.0)	4 (57.0)
Nodule type, <i>n</i> (%)			
Cystic	27 (90.0)	3 (10.0)	—
Mixed	147 (91.3)	13 (8.1)	1 (0.6)
Solid	255 (77.3)	69 (20.9)	6 (1.8)
Calcified	35 (76.1)	11 (23.9)	—
USE pattern, <i>n</i> (%)			
1	10 (83.3)	2 (16.7)	—
2	122 (84.1)	23 (15.9)	—
3a	201 (83.8)	38 (15.8)	1 (0.4)
3b	111 (78.8)	28 (19.8)	2 (1.4)
4	20 (69.0)	5 (17.2)	4 (13.8)

Table 3 Association between cytology findings and ultrasound elastography patterns.

USE pattern	Thyroid nodule cytology			Total
	Normal	Indeterminate	Suspicious	
1-2-3a	333	63	1	397
3b	111	28	2	141
4	20	5	4	29
Total	464	96	7	567

Chi-squared = 24.13; Fisher's test = 19.82; $p < 0.001$.

Table 4 SE, SP, PPV and NPV of USE patterns for nodules that were potentially pathological (Thy 3 e 4) vs. non-pathological (Thy 2).

USE pattern	Sensitivity %	Specificity %	PPV %	NPV %
≥1	100.0	0.0	18.2	—
≥2	98.1	2.2	18.2	83.3
≥3a	75.7	28.5	19.0	84.1
≥3b	37.9	71.8	22.9	83.9
≥4	8.7	95.7	31.0	82.5

Discussion

High-resolution ultrasound is one of the most important examinations in patients with thyroid nodules. In fact, it can reveal small nodules measuring a few millimeters in diameter, which would be missed by palpation alone. Sonography is a simple, rapid imaging study that has no contraindications. It provides data on the presence, size, structural characteristics and echogenicity of the nodule. It can also reveal the presence of risk factors that are currently considered the most reliable predictors of thyroid malignancy. These include nodule hypoechoogenicity, microcalcifications, irregular margins, an anteroposterior diameter that exceeds the longitudinal diameter, and chaotic intranodular vascularization. The strongest predictor of malignancy—aside from hypoechoogenicity—is the absence of the halo, according to some authors [13], or the presence of microcalcifications, according to others [14]. Our experience indicates that, despite its fundamental role in the study of thyroid nodules, sonography is not capable of clearly and definitively distinguishing between benign and malignant nodules. The same can be said of Doppler ultrasound and the use of last-generation acoustic contrast medium [15].

For this reason, clinicians are looking for a method that allows them to differentiate between benign and malignant lesions. Thyroid nodule SEG is one of the methods that have been considered. The results we have obtained differ from those published in the literature, where the specificity, sensitivity, PPV, and NPV are more significant. However, it is important to consider the inclusion criteria used in the studies. In one, the investigators enrolled patients who had already undergone FNAC and been referred to a surgeon [16]; in the other, sonoelastography was done after the ultrasound examination, and in any case all the patients had already undergone FNAC [11].

We performed USE and FNAC on a series of patients referred to our unit for the first time. Ultrasonography and USE were done in real time and immediately thereafter the nodule was subjected to FNAC. We feel that our experience needs to be extended so that the results of USE can be compared not only with those of cytology but also with histological findings in patients that have undergone surgery. At the present, however, we can conclude that in the presence of a cystic lesion, cytological examination is not necessary if the nodule presents SEG pattern 1, 2 or 3a; for other patterns, periodic re-evaluation is appropriate. For calcified or mixed nodules, cytology can be deferred when the SEG pattern is 1, 2 or 3a, but FNAC is always necessary if the pattern is 3b or higher. As for solid nodules,

Table 5 Contingency table analysis of USE patterns and cytological findings for each type of nodule. USE patterns 1 and 2 do not appear to be associated with Thy 3 or Thy 4 cytology.

USE pattern	Cystic		Calcified		Mixed			Solid		
	Thy 2	Thy 3	Thy 2	Thy 3	Thy 2	Thy 3	Thy 4	Thy 2	Thy 3	Thy 4
1	5	—	—	1	2	—	—	3	1	—
2	—	—	8	1	35	3	—	79	19	—
3a	7	2	10	1	61	6	1	123	29	—
3b	10	—	13	6	43	4	—	45	18	2
4	5	1	4	2	6	—	—	5	2	4
Total	27	3	35	11	147	13	1	255	69	6

the frequency of indeterminate or suspicious cases in non-negligible (23%), and for this reason, cytology should be considered even when the USE pattern is 1 or 2, with due consideration for the ultrasound findings as well.

Conclusions

USE is simple and rapid, and it seems to be a promising technique for structural characterization of thyroid nodules. Our study shows that the USE examination can provide additional data on the nodule, which—combined with sonographic findings—can aid the endocrinologist in deciding whether FNAC is necessary. In fact, our findings indicate that SEG patterns 1 and 2 are not associated with “indeterminate” or “suspicious” cytology. Therefore, in these cases, the physician can opt for morphofunctional follow-up of the nodular lesion. As far as cysts are concerned, it is important to consider the internal tension. Indeed, those with higher tension tend to have higher USE patterns, which often correspond to higher cytologic grades. Larger, prospective studies are needed to confirm our results and provide a more precise definition of the diagnostic accuracy of this approach.

Conflict of interest statement

The authors have no conflict of interest.

Appendix Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.jus.2011.06.008.

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