Evaluation of the Diagnostic Accuracy and Interobserver Agreement of Elastoscan

Cantisani V, Di Rocco G, Lodise P, Grazhdani H, Giannotti D, Patrizi G, Medvedeyeva E, Olive M, Giacomelli L, Ricci P, Redler A

ABSTRACT

Purpose: To assess the most useful technique and the efficacy of Elastoscan in differentiating thyroid nodules. Inter-observer agreement was also evaluated

Material and Methods: In order to define the best cut off value of different examination techniques, a preliminary study on 50 patients with 54 thyroid nodules was carried out with a dedicated quantitative software (Elastoscan). All the patients underwent total thyroidectomy and histology was used as gold standard. Thereafter, 154 nodules in 137 consecutive patients were prospectively evaluated by three operators with different experience. Standard of reference was cytology (FNAB-fine needle aspiration biopsy) or histopatology (post surgical). ROC curves and K values were calculated.

Results: According to ROC curves, Elastoscan presented 91% sensitivity, 90% specificity (AUC=0.961, $p<0.01$, 95% CI: 0.000-1.000) when using a cut-off value 3.00 elasticity contrast index (ECI) and axial peri-intranodular measurement. Elastoscan was more sensitive (91%) and more specific (90%) than Color-doppler ultrasound (70 and 59%) in predicting malignancy of nodules ($p<0.05$). Interobserver agreement between operator 1 and operator 2 was k=0.794 ($p<0.05$, 95% CI: 0.684-0.904) and was considered substantial; also substantial agreement was found between operator 1 and operator 3 (k=0.731, $p<0.05$, 95% CI: 0.607-0.854) and between operator 2 and operator 3 (k=0.710, $p<0.05$, 95% CI: 0.584-0.835).

Conclusion: Elastoscan seems to have the potential to be an effective and valuable tool as it provides quantitative evaluation of thyroid nodule with low inter-observer variability. Elastoscan can be used for guiding fine-needle aspiration biopsy to a thyroid nodule with a high probability of cancer, by a preliminary noninvasive differentiation.

INTRODUCTION

Thyroid nodules are a common clinical problem with a prevalence of 2-6% at palpation, 19-35% at ultrasound, and 8-65% at autopsy (1). Although most thyroid nodules are benign, differentiated thyroid cancer is becoming increasingly prevalent due to the improvements in routine high-resolution ultrasonography (US) and fine-needle aspiration biopsy (2). US has been widely used to differentiate between malignant and benign nodules considering some distinctive features such as irregular margins, microcalcifications, marked hypoechogenicity, intranodular vascularization greater than perinodular vascularization, interval growth of diameter > 20% and deeper than wide shape. Several studies demonstrated a correlation between these characteristics and malignancy even if they cannot be considered highly predictive. In fact sensitivity, specificity, NPV and PPV data show a variability depending on the study taken into account (3). Actually fine-needle aspiration biopsy (FNAB) is considered the best preoperative method for the assessment of the nature of thyroid nodules. FNAB contributes to a better selection of surgical patients, as the procedure can accurately define 65% to 80% of diagnoses (4).

FNAB is a preoperative diagnostic method with the highest specificity (60%– 98%) but with varying sensitivity (54%–90%) (5-8). Still in 15–25% of cases FNAB findings can be suspicious and in 5–15% of cases inconclusive; moreover, it is invasive, even minimally. Recently US elastosonography, has been utilized for the diagnostic management of thyroid nodules by assessing the elasticity of tissues in vivo. The first application of elastosonography provided a freehand external compression by using a US probe applied to the thyroid gland with a periodic force. The operator acquired two ultrasonographic images before and after tissue compression and a dedicated software performed an accurate measurement of tissue distortion. The US elastogram was displayed over the B-mode image in a color scale that ranged from red that indicated tissues with high elastic strain (softer components), to blue for those without strain (harder components). All the images are matched with an elasticity color scale and then classified by the Ueno elasticity score (9). Literature data have suggested a great potential of this newly developed US technique in the definition of benign and malignant nodular disease. Rago et al. reported a sensitivity of 97% and a specificity of 100% in detecting malignant thyroid nodules with a PPV of 100%, emphasizing the role of this new tool especially in nodules with indeterminate cytology (10).

However, Parks et al. (11) performed a prospective study to investigate interobserver agreement for the diagnosis of malignant thyroid nodules using conventional B-mode ultrasound and real-time freehand ultrasound elastography. Observers determined Ueno classification and area ratio for each nodule using ultrasound elastography and the data recorded by different operators (Spearman's correlation) did not show a reliable interobserver agreement. Variability in data acquisition and scoring are identified by the Authors as the main limitations of US elastography. More recently, Bae et al. proposed a different technique using the carotid artery pulsation as an in vivo compression source, located adjacent to the thyroid, to reduce the variability of different compression levels applied by the operators (12,13). The out-of-plane motion, which could degrade the quality of elastosonography images during external compression, is minimized by using in vivo compression as the trasducer is fixed during data acquisition. On the other hand a newly developed quantitative scoring method called ECI (elasticity contrast index) can avoid the bias due to external compression elastography. The ECI index is based on the Elastoscan method, which is a Steady-State Quasi-static physiological excitation technique with the use of the carotid pulsation as strain inductor, for obtaining a quantitative stiffness evaluation more accurate than that of the freehand method. Lim et al. using this technique evaluated interobserver agreement and intraobserver reproducibility in thyroid ultrasound elastography (14).
We performed a prospective study to assess feasibility, accuracy, interobserver of ECI (Elastography Core Index) and to define the most sensitive technique in the differentiation of thyroid lesions provided by a new equipment (Accuvix A30).

MATERIAL AND METHODS

Patients

A first series of 50 consecutive patients, undergoing thyroid surgery, with 54 thyroid nodules (46 females, 4 males; age range 38-78 years, mean: 58 years) were examined with ACCUVIX A30 with dedicated quantitative software Elastoscan (Samsung Medison) by the most expert Radiologist (VC). This was done in order to fully investigated the relation between the performance and ECI threshold value. As a result an ECI cut off value was defined. For this first group of patients, post-surgical histopatological results were used as standard of reference for correlation with the ECI values.

Subsequently other 154 nodules (28 papillary cancers, 1 follicular cancer, 1 medullary cancer, 118 hyperplasia and 6 adenomas) in 137 consecutive patients (121 females and 16 males, mean age 45 years, range 20-70 years) were prospectively evaluated by three operators with different experience using peri-intranodular ECI (VC, ME, MO).

Informed consent was obtained from all patients and the study was performed in accordance with the ethical guidelines of the Helsinki Declaration and approved by the local ethics committee. All cohort consisted of patients presented at our Institution between October 2011 and February 2012. Inclusion criteria were the presence of a suspicious thyroid nodule, and FNAB and/or surgery planned at the time of ultrasound examination and finally performed within the study period.

The exclusion criteria were: cystic nodules; cystic nodules with solid portions of insufficient size to be sampled; spongiform nodule (microcystic portion >50% - a well established benign feature) (15); the presence of a coarse calcification inside a nodule; pregnancy; heart failure; severe pulmonary hypertension. The isthmic nodules were also excluded from this study as the carotid pulsation is scarcely transmitted in this site.

All patients underwent ultrasound examination of the thyroid gland, including Doppler ultrasound, followed by elastography with dedicated quantitative software (Elastoscan, Samsung Medison). Cytology or post-surgical histological results were used as standard of reference.

Each lesion was characterized according to US parameters on the bases of the statement criteria of the "Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules" (16). In order to obtain statistical elaboration, we processed the categorical data of US features in a synthesis, as if they were numerical data, by employing the subsequent simplified dichotomous score criteria (0/1): hyperechogenicity or isoechogenicity was scored 0 whereas marked hypoechogenicity (more hypoechoic than the strap muscles) as sign of malignancy was scored 1; symmetric halo or regular margins as signs of a benign lesion was scored 0 whereas margin irregularity (spiculations or microlobulations), asymmetric irregular halo or microcalcific halo as signs of malignancy was scored 1; blood flow pattern at CDUS: absent (pattern I) - peripheral (pattern II) - as signs of benign lesion were scored 0, whereas peri-intralesional with intranodular flow greater than perinodular flow (pattern III) as sign of malignancy was scored 1; absent microcalcifications as sign of benign lesion scored 0, whereas if present as sign of malignancy scored 1 (not considering microcalcifications the hyperechoic spots with a reverberation artifact, a finding indicative of inspissated colloid); shape round or wider than deep as sign of benign lesion scored 0, whereas the deeper than wide shape, as sign of malignancy scored 1.

The sum of the scores assigned to the factors led to a parameter as an expression of a quantitative analysis, easily comparable with the elastography results of deformability, allowing statistical evaluation.

For nodules with two, or less than 2 suspicious features, according to the above classification, an echo-score equal to 0 was assigned, and for those with at least three elements of suspected malignancy, an echo-score equal to 1 was assigned.

FNAB / histology

All patients were tested either with cytology using FNAB and/or histology from thyroidectomy. FNAB was performed with a 23-25-gauge needle attached to a 20 ml syringe. Adequacy of aspirates was defined according to the guidelines of the Papanicolaou society

Elastoscan

In vivo elastography with the Elastoscan method using the equipment ACCUVIX A30 (Medison Co. Ltd., Seoul, Korea) was performed. No external compression with transducer was applied since pulsation from the carotid artery was used (in vivo compression) and ECI calculation was assessed.

The thyroid expands and compresses because of carotid artery pulsation. During systole, higher blood pressure in the lumen of the carotid artery compresses the thyroid against the trachea in the

mediolateral direction and compression in one direction causes expansion in the other directions. Thus, thyroid expansion and retraction can be observed in the anteroposterior direction and measured by the ECI index elastography. The score of Elastoscan, ECI index, assesses quantitatively the nodule stiffness.

To compute an ECI score for a nodule, the strain distribution within the nodule was first calculated, visually depicted in a strain oscillation map (SOM). Example SOMs are shown in Fig. 2 and 3. Red indicates higher strain (i.e., softer tissue) while blue indicates less strain (i.e., harder tissue). A distinct difference feature is the local contrast. In a malignant nodule (Fig. 2), the differences between low and high strain areas are large, and the transitions from high to low (or low to high) strain happen over a short distance, leading to a high local contrast. On the other hand, as the stiffness difference between a benign nodule and normal thyroid tissue is relatively small, a high local contrast cannot be seen in Fig.3. An ECI score was calculated from the SOM to quantify the local stiffness contrast within a nodule (17).

In the preliminary study, Three different techniques of in vivo elastography measurements were evaluated: axial intranodular ECI; axial periintranodular ECI; and longitudinal intranodular ECI, as shown in Fig.1. , executed by the expert radiologist. The largest diameter of the thyroid nodule was included in the image. The operator asked the patient to hold breath and acquired the US data for 3-4 seconds without applying any external compression with the transducer. The strain frames were generated using the acquired data. After the nodule boundary was delineated by the operator, the SOM of a nodule and its ECI value were computed and displayed on the screen (Fig. 2 and 3). A large ECI value indicates an increased probability of the nodule being malignant, as shown in Fig.2 (14). After defining the technique with best performance, in the preliminary study, the evaluation of consecutive patients by three observers was carried out. The observers were the expert radiologist and two radiologist-in-training with two and three years of experience respectively, in CDUS. During a one-month period prior to this study, the three radiologists practiced thyroid elastography on more than 30 nodules to get familiar with data acquisition and ECI scoring. The three radiologists individually performed both elastography data acquisition and nodule delineation for scoring, in order to obtain data for evaluation of the technique as a whole and not its single steps.

Statistical analysis

Data were collected prospectively and recorded by each radiologist in a computerized spreadsheet (Excel, Microsoft). Sensitivity and specificity of CDUS and elastoscan by means for the different techniques used were compared using Fisher's exact test and ROC curves. The best elastosonographic measurement method with its cut-off value were defined and data were compared to histopathological findings to evaluate effective sensitivity, specificity, positive predictive value, negative predictive value and accuracy, that were analyzed for statistical significance according to the $\chi 2$ test. Interobserver variability for the ECI measurements (considering it qualitatively as categorical data: benign or malignant), was calculated and interpreted according to Landis and Koch’s paper (18), with a k value of 0.20 or less indicating poor agreement; 0.21–0.40 indicating fair agreement; 0.41–0.60 indicating moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00 indicating excellent agreement. In order to further evaluate the interobserver variability for the ECI index alone, considering this time the ECI value as numerical data (quantitative variable), estimation with the Pearson product-moment correlation coefficient was performed. For the interpretation of the Pearson correlation coefficient the agreement was considered to be: poor when Pearson's R 0,00-0,20; weak: 0,21-0,39; fair to good: 0,40-0,75; excellent: >0,75. $p<0.05$ was considered as statistically significant.

RESULTS

A preliminary study on 54 nodules in order to define the best technique together with an ECI cut off value with best performance, was carried out by the expert operator (Fig. 1). All patients of the preliminary study, subsequently underwent thyroidectomy and hystopathologic findings were used as gold standard (54 nodules, 34 hyperplastic nodules 17 papillary carcinoma, and 2 adenomas and 1 medullary carcinoma).

The median ECI value of malignant nodules 3,99, was significantly different from those of the other lesions 1,99 (P <0.0028).

According to ROC curves (Tab.1), the most sensitive technique was the axial peri-intranodular, measurement which showed 91% of sensitivity, 90% of specificity (AUC=0.961, p<0.01, 95% CI: 0.000-1.000) when using a 3.00 ECI value as cut-off; axial intranodular measures showed 90% of sensitivity, 93.2% of specificity (AUC=0.889, p<0.01, 95% CI:0.000-1.0000) when using a 3.07 ECI value as cut-off; longitudinal ECI measures showed 80% of sensitivity, 80.5% of specificity when using a 3.03 ECI value as cut-off (AUC=0.834, p<0.01, 95% CI 0.61-1.000).

By applying the cut-off of 3.00 for the Elastoscan (ECI index) value using axial peri-intranodular measurements, was more sensitive (91%) and more specific (90%) than Echo-score (70 and 59%) in predicting malignancy of the thyroid nodules (p<0.05) (Fig. 2). Therefore an ECI>3.00 in an axial peri-intranodular measurement, may be suggestive for malignancy and this criterion was subsequently adopted in our study.

Further 154 nodules in 137 patients (121 females and 16 males, age 45 years, with mean range 20-70 years) were prospectively evaluated by three operators with different experience for CDUS and peri-intranodular ECI. Final diagnosis was based on the cytologic and histopathologic findings: FNAB was used as the reference standard for the diagnosis of benign nodules if the patients did not have thyroid surgery and histopathology was used if the patients had thyroid surgery.

The final diagnosis of the 154 nodules was: 124 were benign and 30 were malignant. Among the malignant nodules, 28 were papillary cancers, 1 was follicular carcinoma and 1 was medullary carcinoma. Among the benign nodules: 118 were hyperplastic nodules and 6 were adenomas.
The size of the benign nodules ranged between 5 and 30 mm (mean 15,1 mm, SD:7,48 mm) in the transverse view (the scan of ECI measurement). Whereas the size of the malignant nodules ranged between 9 and 31 mm (mean 16,4 mm, SD:7,47 mm) in the transverse view (the scan of ECI measurement).
84 of the 154 nodules were located in the right lobe of the gland; 70 nodules in the left lobe; no nodules were sited at the isthmus of the thyroid gland (as isthmic nodules were excluded from this study).
The mean age of patients with malignant nodules was younger than that of patients with benign nodules ($P < 0,001$).
There was no association between sex of patients and malignancy of nodules ($P = 0.079$).
The statistical analysis yielded for operator 1: 90% of sensitivity, 92.7% of specificity, 75% of positive predictive value, 95% of negative predictive value and 92.2% of accuracy ($p<0.05$, $\chi2$: 92.237); for operator 2, 86.7% of sensitivity, 87.1% of specificity, 61.9% of positive predictive value, 96.4% of negative predictive value, 91% of accuracy ($p<0.05$, $\chi2$: 66.264); for operator 3, 80% sensitivity, 83.9% specificity, 54.5% positive predictive value, 83.1% negative predictive value, 83.1% accuracy ($p<0.05$, $\chi2=48.286$) as shown in Tab.2.
Interobserver agreement calculated with the Landis and Koch's k value, between operator 1 and operator 2 was $k=0.794$ ($p<0.05$, 95% CI: 0.684-0.904) considered substantial; also substantial agreement was found between operator 1 and operator 3 ($k=0.731$, $p<0.05$, 95% CI: 0.607-0.854) and between operator 2 and operator 3 ($k=0.710$, $p<0.05$, 95% CI: 0.584-0.835), as shown in Tab.3.
When we assessed the interobserver agreement with Pearson's correlation coefficient, it resulted the values of: between operator 1 and operator 2: Pearson's $R=0.799$ (Assymp. Std. Error: 0.055); between operator 1 and operator 3: $R=0.737$ (Assymp. Std. Error: 0,060) and between operator 2 and operator 3: $R=0.710$ (Assymp. Std. Error: 0,064) which were all in the range considered either as excellent: >0.75 or as good: 0.40-0.75. In all $p<0,01$.

DISCUSSION

Imaging of the viscoelastic properties of tissue has gained popularity over the last decade because it provides noninvasive and new diagnostic information about nodular lesions. Elastosonography is based upon the principle that malignancies have stiffer tissues than benign lesion and that, under compression, the softer parts of tissues deform easier than the harder parts (9). This technique assesses the elasticity of tissues in vivo by exploiting the potential offered by the ultrasonic waves. Thyroid gland is an interesting target for elastography because its external deformation is easy to detect using the ultrasound transducer. Different technique are at present available, providing operators with either qualitative, semiquantitative or quantitative information and a number of studies report promising results.

A recent meta-analysis by Bojunga et al. summarizes the results of eight studies (a total of 639 thyroid nodules) on Real-time Elastography in the diagnosis of malignant thyroid nodules reporting a global sensitivity and specificity of 92% and 90% respectively (19). However, in this paper a significant heterogeneity was found for specificity in the different studies and maybe this was due to the fact that 6 (out of 8) of the analyzed studies used qualitative elastography with a subjective evaluation of elastograms. Further developments have brought about a trend towards the standardization of elastography with semiquantitative and quantitative methods (9). Xing et al. performed a study to compare semiquantitative elastosonography (strain ratio), to conventional qualitative elastosonography for thyroid nodule characterization (20). The authors found that the strain ratio measurement had 97.8% sensitivity and 85.7% specificity. More recently Q-elastosonography technique (a semiquantitative method) compared with multiparametric ultrasound in differentiating the nature of thyroid nodules, showed promising results (21,22). In spite of very good sensitivity and specificity values reported in the literature about thyroid US elastography, this modality has not yet spread in clinical practice. The main reason is the low interobserver and intraobserver agreement owing to the variability in collecting data and scoring. Park et al. (11) evaluated interobserver agreement both in data acquisition and scoring for thyroid US elastography. In their study, three radiologists independently performed elastography data acquisition and scoring analyzing 52 malignant thyroid nodules with external compression technique; no interobserver agreement was found among three radiologists and this aspect was attributed mainly to the fact that the extent of compression influences both the elastography image and, consequently, elasticity score. Their results showed a larger variability in elastography data acquisition than in scoring. Both the qualitative and semiquantitative evaluation of strain images with the free hand compression method, have shown limitations. The strain image (elastogram) is an image of the relative stiffness that depends on the dynamics of the particular compression (strain changes with the applied compression) which makes the free hand method limited in its accuracy.

However, on the other hand, there are authors that have reported good results with this method. Merino et al. (23), employing a qualitative system that scored the nodules according to strain homogeneity, found an excellent agreement between operators with a k=0.82 (0.74-0.89). The recent study of Ragazzoni et al. (24), which adopted the qualitative elastosonography, found good accuracy (84%, OR 29) and interobserver concordance (k test 0,643).

During our 5 year experience with Elastography in our Institution, we have found that, its reliability with external free-hand compression suffers since the color pattern elastogram could vary depending on: the imaging plane selected, the amount of externally-applied compression, the subjective selection of an elastography image in addition to the variability in score assignment.

In our previous studies (21,22) and in our long experience with various techniques and equipment, we have observed that the quality of strain images and the resulting diagnostic performance were significantly affected not only by undesirable motion during external freehand compression but also by the pulsation of the carotid artery that is right next to the thyroid.

The new method with the use of the in vivo natural compression of the carotid artery, combined with a quantitative evaluation of stiffnes, seems to be a viable technique and it was studied by some authors:

Lim et al performed a study with in vivo compression elastography which showed significant interobserver and intraobserver agreement (14). Because carotid artery pulsation is used, the variability due to different compression levels used by operator could be substantially reduced. The out-of-plane motion, which could degrade the quality of elastography images during external compression, could be minimized by using in vivo compression as the transducer is fixed during data acquisition. In our study we achieved similar results with carotid pulsation ECI measurements, in a larger population.

Evidentely, more reliance on nodule stiffness quantification could bring about improved performance and reproducibility. Lim et al. used for the study ACCUVIX V20 (Medison Co. Ltd., Seoul, South Korea), while we performed our study using the evolution of that US machine (ACCUVIX A30). Another aspect that differentiates our study from Lim's is that we analyzed both benign and malignant nodules; we evaluated the feasibility, the best technique, the interobserver variability and the diagnostic performance of the technique on a more typical clinical scenario. Whereas one of the limits of the previous study was represented by the limited surgery-bound patients population with predominantly malignant nodules, it was our aim to avoid a spectrum composition bias, thus our patient inclusion criteria were not restricted to cases previously selected for FNAB or surgery. Therefore, the cohort of our study is representative of the general population that may receive elastosonography for the evaluation of thyroid nodules.

The results of our study showed the validity of the quantitative, carotid artery compression elastography: the Elastoscan technique had a good performance (91% sensitivity, 90% specificity) using an ECI cut-off value of 3.00. Elastoscan was more sensitive (91%) and more specific (90%) than CDUS (70 and 59%) in predicting malignancy of nodules ($p<0.05$). In this study, the three radiologist individually performed all steps of the Elastoscan technique, in order to obtain data for evaluation of the inter-observer variability of the method as a whole and not its single steps. We found that the interobserver agreement between all operators was in the substantial range (operator 1 and 2: $k=0.794$; operator 1 and operator 3: $k=0.731$ and between operator 2 and 3: $k=0.710$, $p<0.05$ in all). Substantial agreements were also found with the Pearson method.

Thus reproducibility is improved with in vivo compression elastography, but interobserver variability still exists. This could be due to the variability in selecting the scanning image for measurement with Elastoscan and therefore sampling different portions of the same nodule with different stiffness. We used for acquisition a transverse plane in the maximum diameter of the nodule, but two of the observers were radiologists-in-training and with limited US experience. They could have sampled the nodules somehow differently, delineating the area for the measurement differently. In spite of this fact, the substantial inter-observer agreement of this study, suggests that the reproducibility with in vivo compression elastography may be less dependent on an operator's prior experience. However, we believe that training and experience is likely to improve the reproducibility further. With in vivo compression elastography, not as much training is required as that needed with the free hand compression techniques.

In the problematic situation of a multinodular thyroid, in 6 patients we were able to distinguish a papillary carcinoma nodule and a benign nodular goiter located in the same thyroid lobe based on the ECI > 3 information obtained from Elastoscan, showing the potential use of this technique.
In our study the 4 lesions which were incorrectly classified as malignant by sonoelastography were characterized by areas of cystic degeneration and with gross calcifications.
A major limitation of in vivo elastography is the impossibility to analyze nodules in the isthmus as there is no valid compression induced by the carotid pulsation in this site. Therefore examination with the free hand elastography is to be used in the isthmus.
ECI may be slightly different according to the strength of the pulsation from carotid artery dependeding on age, atherosclerotic changes and hypertension.
In order to obtain the most accurate results, we found in our study that the best plane for the measurement is the axial plane with carotid artery non included in the elastoscan box combined with peri-intranodular evaluation and apnea of the patient for 3~4 seconds.

CONCLUSIONS

In vivo elastography with the Elastoscan method, is a valuable tool since it allows a quantitative stiffness evaluation of thyroid nodules and in our study it was more accurate than color-Doppler ultrasound. The Elastoscan technique showed good reproducibility as demonstrated in this study by the low inter-observer variability. Its application in current clinical practice may help to limit unnecessary FNAB. Larger studies, preferentially multicentric, are needed for the validation of this methodology.

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FIGURES

Fig.1

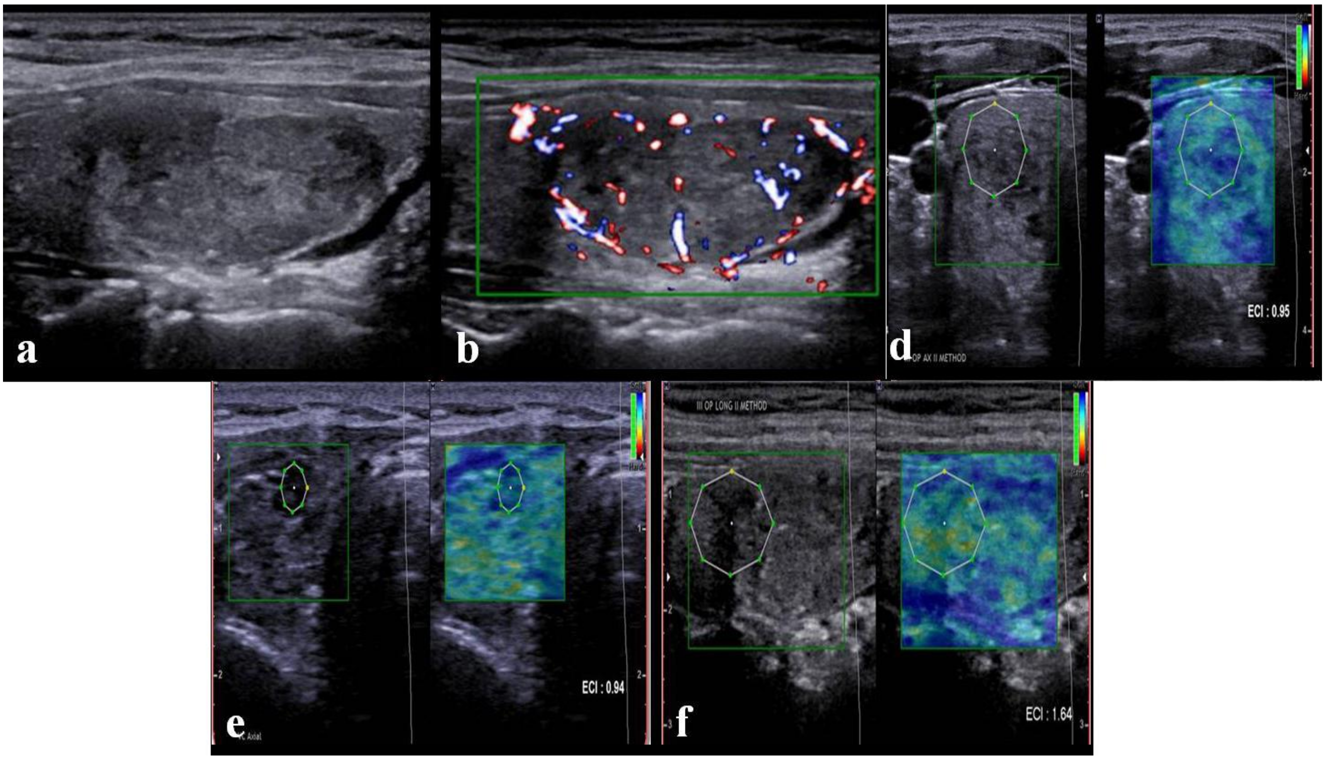

Fig.1 = The image shows a case of an iso-hyperechoic nodule with well defined margins and oval shape, localized in the right middle lobe (a) of the thyroid gland, characterized by a vascular pattern of type III (b). The axial perintranodular ECI was 0.95 (fig c); the axial intranodular measure amount on 0.94 (d); the longitudinal intranodular measure amount on 1.64 (e). These values were lower than the cut-off (3.00) value chosen by operators to discriminate the malignancy of a lesion with ECI (d). Histology confirmed the diagnosis of benign nodular hyperplasia.

Fig.2

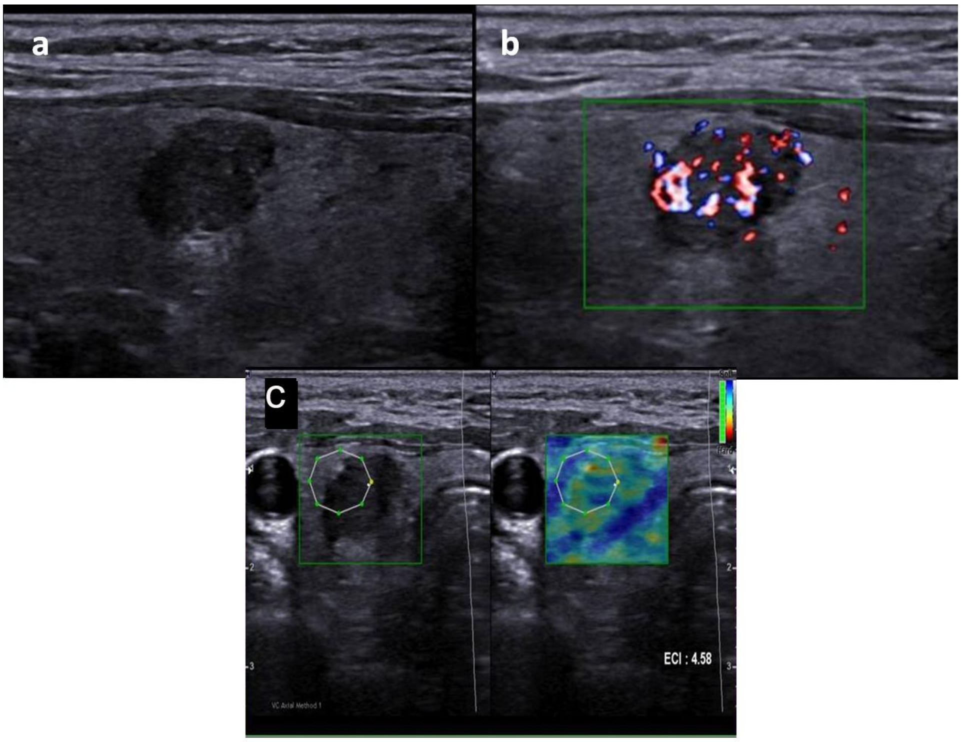

Fig.2 = The image shows a case of an hypoechoic nodule with irregular margins localized in the right middle lobe (a) of the thyroid gland characterized by a vascular pattern of type III (b) The axial perintranodular ECI measures 4.58 (c). Histopatology confirmed the diagnosis of medullary carcinoma.

Tab.1

Measures	Cut-off	Sensitivity	Specificity	AUC	Significance	95% CI
Axial Peri-intranodular	3.00	91%	90%	0.961	0.000	0.000-1.000
Axial intranodular	3.07	90%	93.2%	0.889	0.000	0.000-1.000

Longitudinal periintranodular	3.03	80%	80.5%	0.834	0.000	0.000-1.000

Tab.1= ROC features for operator1 in the preliminary study.

Tab.2

Operator	Sensitivity	Specificity	PPV	NPV	Acc	Significance	x2
Op1	90%	92.7%	75%	95%	92.2 %	0.000	92.237
Op2	86.7%	87.1%	61.9%	96.4%	91%	0.000	66.264
Op3	80%	83.9%	54.5%	94.5%	83.1%	0.000	48.286

Tab.2= Operator's diagnostic performance at elastography WITH peri-intranodular measures AND 3.00 ECI value as a cut-off on 154 nodule.

Tab.3

comparison	k value	std err	ULV	LLV	significance
op1-op2	0.794	0.056	0.90376	0.68424	0.000
op1-op3	0.731	0.063	0.85448	0.60752	0.000
op2-op3	0.71	0.064	0.83544	0.58456	0.000

Tab.3= Interobserver agreements in the second part of the study. ULV = upper limit value; LLV = lower limit value.