



The Role of Elastography in the Management of Thyroid Nodules

Hervé Monpeyssen and Jean Tramalloni

The discovery in a soft tissue area of a stiffer area has always been subject to suspicion. Nodules that are stiff at palpation often suggest malignancy. An increase in tissue stiffness is related to a loss of elasticity, meaning its ability to recover its initial shape after deformation.

Malignant neoplasms are often characterized by the desmoplastic transformation of their stroma which is responsible for the presence of collagen and myofibroblasts. This tumor stroma promotes the proliferation of malignant cells (and could even initiate them) [1]. However, some benign fibrous tumors such as fibrous histiocytomas can nevertheless be very stiff.

By studying the deformability/stiffness couple, elastography reproduces the palpable feeling of stiffness.

The concept of stiffness measurement was first reported in 1980 by a French researcher named Eisencher. The TM mode was the first modality, and he named his technique “echo-sis-mography,” also designated “rhythmed ultrasonic palpation” (speech in Congress) [2].

Two years later, Dickinson published a paper on the measurement of soft tissue motion using a combination with A-Scan [3].

In 1987, Krouskop used a pulsed Doppler ultrasonic system to carry out noninvasive

measurements of the mechanical properties of soft tissues in order to adjust a prosthesis for the management of amputation stump rigidity [4].

However, the term “elastography” was first introduced by Johnathan Ophir et al. in 1991 [5] to describe a quantitative method for the assessment of the elasticity of biological tissues. In 1993, his team published the preliminary results of in vivo elasticity imaging: “Elasticity imaging using ultrasound with application to muscle and breast” [6].

Elastography: Technical Approach

Numerous ultrasound elastographic methods are currently available, all of them measuring tissue displacement. The deformation may be represented in an elasticity image (elastogram) or as a local measurement using three techniques: [7]

- Direct measurement (acoustic radiation force impulse—ARFI)
- Calculation of the tissue strain
- Record of the propagation of the shear waves

Quasi-static Elastography (QSE): Strain Imaging

The first technique developed uses external compression, i.e., decompression cycles applied by

H. Monpeyssen (✉) · J. Tramalloni
American Hospital of Paris,
Neuilly-sur-Seine, France

the transducer, and is called quasi-static elastography (or strain elastography—SE). It is mostly a qualitative technique utilized when the deformation of the tissue of interest is assumed to be uniform.

It depends on **Young's modulus** of stiffness/elasticity, which reflects the relationship between the deformation of a solid structure and the constraint applied to it. This force was first induced by the ultrasound transducer and later by the arterial pulsations [8]. This vibration is so slow that it is considered quasi-static. The transducer will collect data in real time, thus enabling identification of the nodule and normal tissue deformation. Color (or gray-scale) encoding allows differentiation between tissues based upon their intrinsic deformation and, hence, information on their stiffness (inverse of the deformation). The viscoelasticity of the tissue remains a problem [9] (Fig. 1).

Strain elastography is widely available from many US manufacturers.

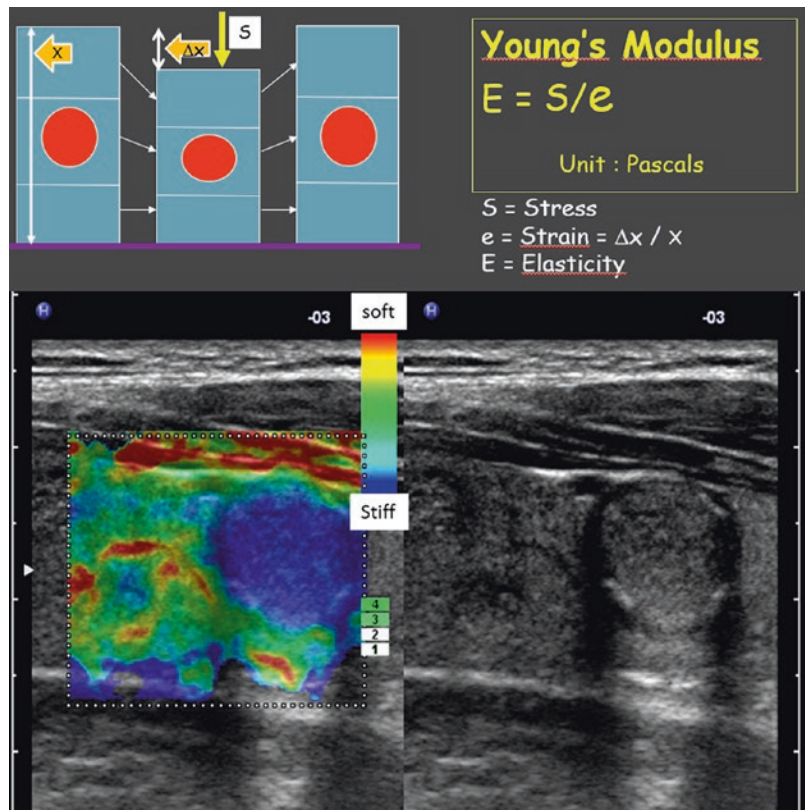
Because the colorimetric analysis is not always easy, to avoid the subjectivity of this analysis, studies using quantification of the map color were conducted, with inconstant results (Fig. 2).

Semi-quantitative analysis provides numerical values that correspond to the deformation ratios. The machine calculates a ratio between the regions of interest (ROI) localized by the operator on the nodule and the healthy tissue. The calculation can thus be made using the rates of deformation of the structure (strain rate) (Fig. 3).

The appearance of a nodule according to color mapping must be compared with the appearance of normal surrounding tissue. In some cases, this comparison is not possible due to a lack of available normal tissue.

- Huge nodule
- Nodule in empty thyroid bed
- Abnormal neighboring tissue (autoimmune disease)

Fig. 1 Strain elastography: schema of compression/relaxation and stiffness calculated by Young's modulus. Elastogram of a stiff nodule (papillary cancer) (Hitachi)



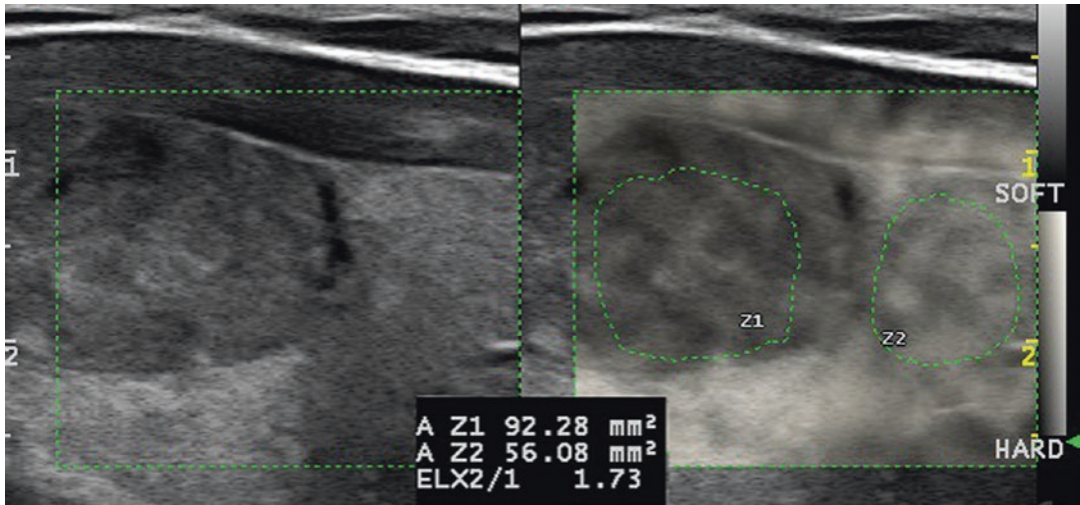


Fig. 2 Strain elastography map color quantification. Benign nodule with intermediate ratio (Esaote)

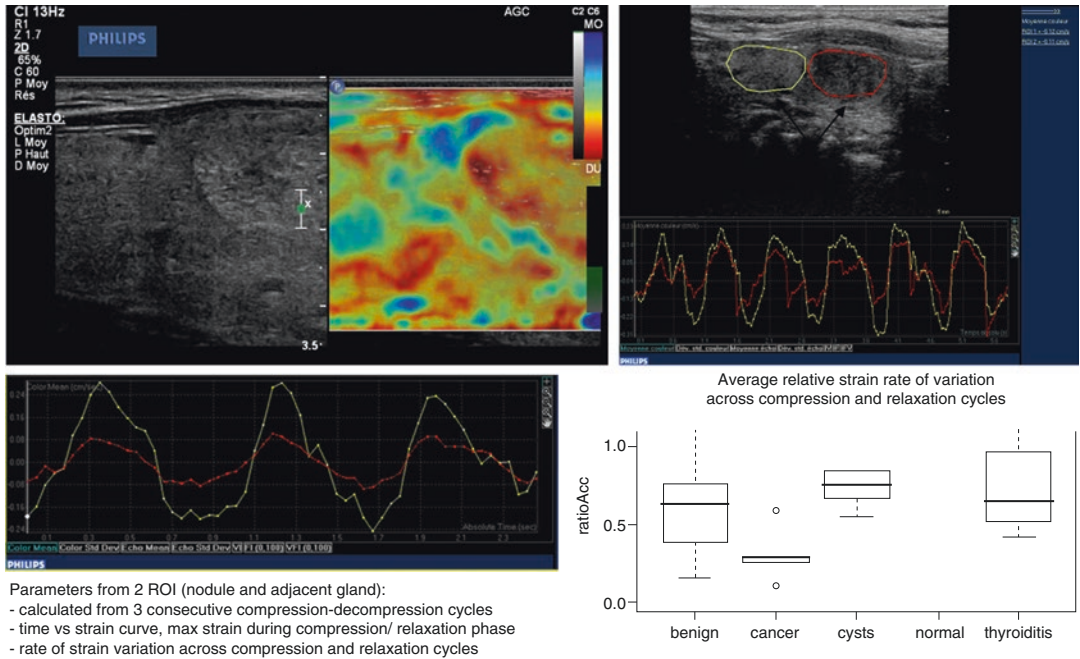


Fig. 3 Strain elastography with semiquantitative analysis. Two ROIs are localized on the strain image. Calculation of stiffness index is realized with Q-Lab software using the strain rate (Philips)

Without semiquantitative analysis, the comparison of map color is frequently subjective.

Dynamic Methods

The probe creates a focused ultrasonic beam (cone beam) with a finite duration. The energy of

the beam is converted into a force, namely, acoustic radiation force impulse (ARFI). It generates a brief localized displacement characterizing the viscoelastic property of the tissue. A shear wave (SW) (or transverse wave) is created, perpendicular to the wave propagation direction. It spreads parallel to the skin plan. The speed of the shear waves increases in accordance with tissue stiff-

ness, and the elasticity measurement can be expressed in m/sec or converted into kilopascals (ARFI-shear wave velocity (ARFI-SWV)) (shear modulus and then Young's modulus). In the case of a stiff nodule, the velocity increases and thereby the stiff value (in kilopascal-kPa) [10, 11].

Shear Wave Speed Measurement

1. Transient elastography (TE) allows quantitative evaluation of tissue stiffness based upon the measurement of the shear wave velocities propagating perpendicular to the US beam direction. It provides a single point measurement without imaging capabilities and has been validated for the diagnosis of liver fibrosis (Fibroscan®, Echosens, Paris, France).
2. Point shear wave elastography (pSWE)—ARFI quantification. The measurement is performed in a single small region of interest (ROI) less than 1 cm³ that can be moved upon an anatomical B-mode image (point quantification) (Siemens. Philips).

Shear Wave Speed Imaging (SWE)

Shear velocity information, which is quantitative and is displayed for imaging, provides a real-time map of elasticity. The elastogram is overlaid with the B-mode image or with side-by-side modality. As in semiquantitative QSE, the ROIs are positioned in the nodule and in the surrounding healthy tissue. The screen is refreshed each second (SuperSonic Imagine, Aix-en-Provence, France; Toshiba MS, Nasu, Japan; General Electric Healthcare).

Supersonic Imaging (Aixplorer): This device is able to monitor shear wave propagation at frame rates above 10,000 Hz (due to an ultrafast beam former) and to keep the dynamics of the acquisition thanks to UltraFast imaging processing. It eliminates many of the limitations of conventional shear wave elasticity imaging techniques by avoiding the repetition of successive shear wave tracking sequences and tracking in real time the propagation of the shear waves in a single ultrafast acquisition (Fig. 4). Multiple ROIs with variable shapes can be positioned upon the area of interest. For each ROI, the software instantly calculates the mean, minimum, and maximum stiffness as well as the standard deviation (the latter

increases with increasing tissue elasticity heterogeneity). It also provides an elasticity ratio between the two ROIs (Fig. 5).

Toshiba (Applio Platinum): The acquisition modality is different, using a “line-by-line” emission technique. The shear wave propagation is displayed, enabling the choice of the best frame for calculation of the stiff value (Fig. 6).

General Electric (LogisE9 XDclear): The system uses the same technique as that of Toshiba.

Siemens (ACUSON S3000): The new device provides a 2D SWE image with Virtual Touch™ Quantification (VTq) (Fig. 7). The VTIQ image is a color-coded display of shear wave velocity within the ROIs. The shear wave speed may be quantified in these ROIs.

Reproducibility

It is suitable for quasi-static elastography, with a correlation coefficient ranging from 0.73 to 0.79 for inter-operator reproducibility and 0.73 to 0.84 for intra-operator reproducibility [11, 12].

Regarding shear wave, all the studies attest of the high level of reproducibility [13–15].

Elastography of the Thyroid

Elastography was first used in thyroid imaging in 2005.

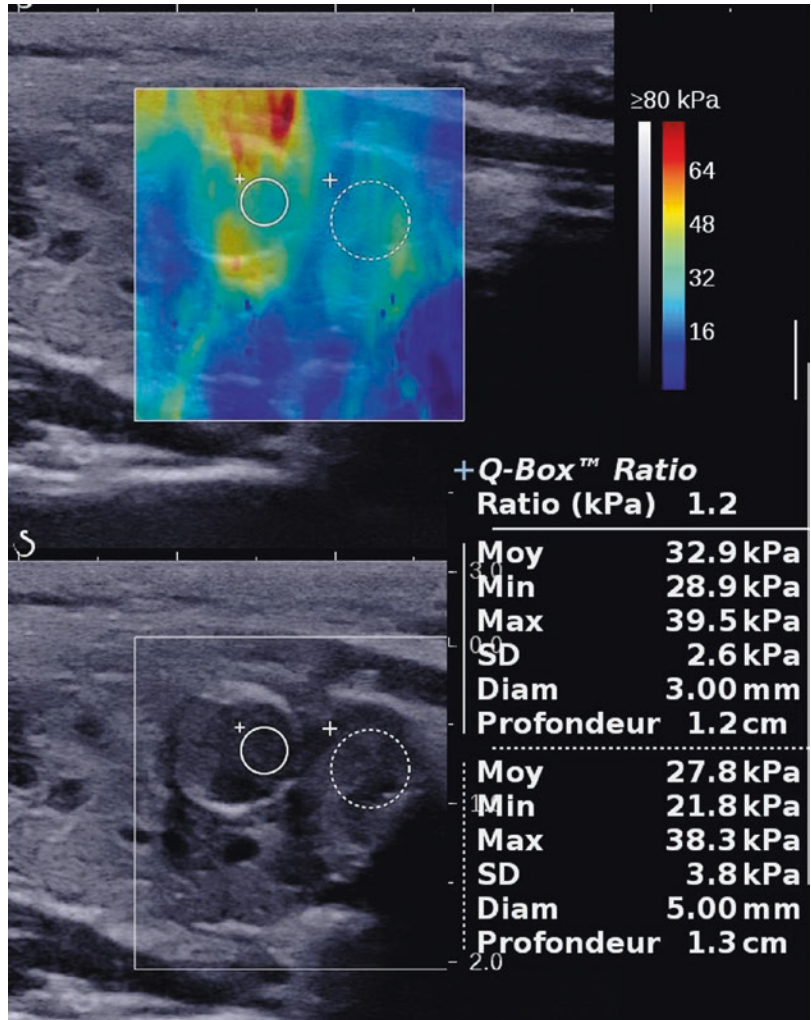
Andreas Lyshchik et al., in an in vitro study, [16] described the “Elastic moduli of thyroid tissues under compression.” He found a very significant difference between papillary cancers and healthy tissue (Table 1).

A few months later he published the first in vivo study, “Thyroid gland tumor diagnosis at ultrasound elastography” [17].

Practical Examination [18]

One must however bear in mind that, while elastography can provide useful additional information for nodule characterization, it should not be

Fig. 4 Shear wave elastography. Discontinued egg-shell nodule generates an anterior artifact. Nevertheless, the stiffness analysis is possible. The ratio between nodule and surrounding healthy tissue is normal. The elastographic scale and the ROI location are correct (Supersonic Imagine)



considered as a substitute for conventional ultrasound examination [19].

In routine clinical practice, each nodule must be stratified according to a TIRADS score (Table 2) and accurately located within the gland based on a highly sensitive color map. At least two elastographic acquisitions are used for each nodule. The examination is painless; the patient may be asked to hold his breath for a very short period. The ultrasound probe is positioned in front of the nodule (sterile water can be used as connecting gel if FNAC is provided in the same procedure). Regions of interest are determined after each screenshot, but postprocessing studies are often carried out. Although the acquisition does not take long, it increases the total duration

of the US examination (that do not exceed 10 min in routine practice). The stiff score noted in the report for each nodule has the potential to modify the basic TIRADS score [20].

Quasi-static Elastography

The carotid beats generate a sufficient deformation to create a quantitative map image on which the regions of interest are located. The difference in color encoding between the nodule and the surrounding tissue is analyzed, the score classification having been established by Rago et al. [21], Tranquart et al. [22], and Asteria et al. [23]. The nodules that show low stiffness with a homogeneous or predominantly homogeneous pattern are consistent with benign lesions. On the other

Fig. 5 Shear wave elastography. Papillary thyroid cancer. The nodule is very stiff (maximum 162 kPa), heterogeneous due to necrotic areas (standard deviation = 34) with a very high stiffness ratio (6.6)

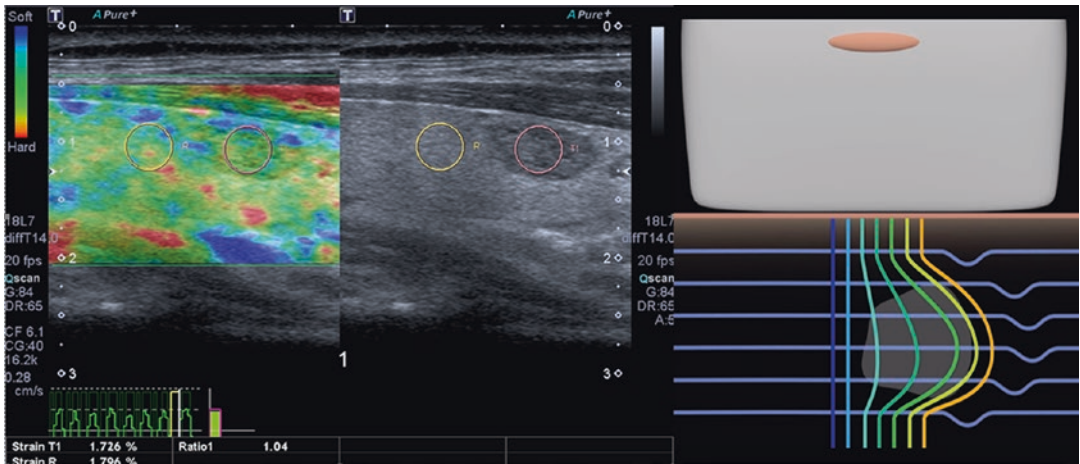
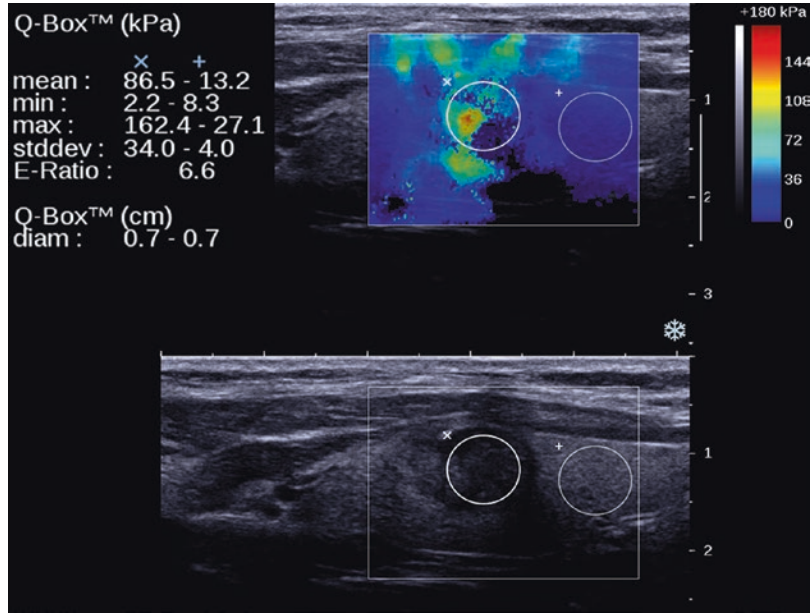


Fig. 6 Shear wave elastography: real-time map of elasticity and shear wave propagation. Benign nodule with normal stiff ratio (Toshiba)

hand, stiff nodules are considered malignant (Fig. 8).

The best approach is to add a semiquantitative analysis to the colorimetric study providing a good level of reproducibility, as mentioned in some preliminary studies.

Shear Wave Elastography

The ultrasound pulse is generated by the probe. The pressure on the patient’s skin must be very

light (because of the risk of creating a “push” effect artifact). The dual screen displays (B-mode and B-mode with elastogram) precise the location of the ROIs. It is important to move the first (small) ROI in the nodule; once the area with the higher signal is found, the diameter of the ROI should be magnified until the standard deviation remains low (analysis of a homogeneous sample). Ideally, the second ROI must be located at the same first deep level. The stiffness

value with its strain ratio appears automatically in the Q-Box.

Some studies have proposed thresholds beyond which cancer should be suspected [15].

- 35–90 kPa for maximum stiffness
- 3.7 for maximum ratio

Other publications using the ARFI system have produced the same results.

Setting principles for the Aixplorer (no major difference from the Applio-Toshiba setting):

- The thyroid presetting is too high (180 kPa); thus the stiffness measurement of a nodule will be wrong due to the mislocation of the ROI. The maximum value of the elastography scale must definitely be lowered, to around 80 kPa. If the tumor exhibits a very high

stiffness value, this value will be increased. The value recorded in numerous publications has been reduced due to the conservation of the original presetting (Fig. 9).

- The intensity of the signal must be sufficient to conduct the examination. In the event of a weak signal, the deep area should be colorless or uniformly low. Next, the “pen” presetting must be used for penetration, or the probe must be replaced by a linear probe with lower frequency (SL10).
- The gain can be increased until the elastographic sound appears.
- Artifacts must be avoided: due to excess pressure with the probe (“push” effect) and in the deep area due to stiffer organs—the trachea and carotid. This explains the difficulties for the analysis of an isthmus nodule. In this case, the coronal approach is useful.

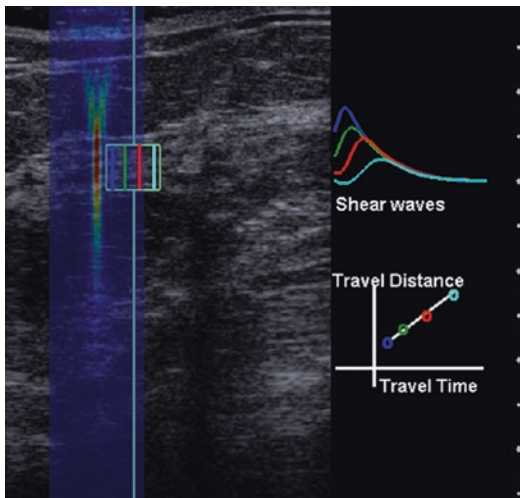


Fig. 7 ARFI system: Virtual Touch™ Quantification (VTq). The focused push pulse generates shear waves. The tracking beams detect SW peak, and shear velocity is computed using linear regression (Siemens)

Summary of the Literature

The preliminary report of Lyschchik in 2005 was followed by numerous papers on quasi-static elastography with manual compression of the thyroid or carotid shear stress. They all showed a high rate of malignancy associated with stiff nodules, whereas benign nodules were soft in most cases.

Rago et al. reported in 2007 the clinical application of thyroid elastography using a five-point scale. Using this criterion, Rago’s study includes 92 consecutive patients with a single nodule. The sensitivity was calculated to be 97% and the specificity 100% [21].

Asteria et al. described a classification using a four-point scale: in 86 nodules, sensitivity and specificity were calculated at 94.1% and 81%, respectively [23].

Table 1 Rigidity of different thyroid tissues compared with normal tissue: in vitro measurement [16]

Histology	Stiffness / normal
Colloid adenoma	x 1.7 – 2.4
Papillary cancer (mild compression)	x 5
Papillary cancer (heavy compression)	x 17
Follicular cancer	x 1

Table 2 French TIRADS classification (Courtesy G. RUSS) [20]

TI-RADS SCORE	MEANING
1	NORMAL EXAMINATION
2	BENIGN
3	VERY PROBABLY BENIGN
4A	LOW SUSPICION
4B	HIGH SUSPICION
5	PRACTICALLY CERTAINLY MALIGNANT

In 2010, the meta-analysis carried out by Bojunga et al. concerned 8 studies with surgery as the gold standard and 639 studied nodules [24]. Quasi-static elastography has a sensibility of 92% and a specificity of 90% for the diagnosis of thyroid cancer. However, there was an important selection bias, since the prevalence of cancer was 24%, which is very different from that of a normal ultrasound report.

Concerning semiquantitative QSE, three studies confirmed the good results of colorimetric analysis.

The first used is Q-Lab software (Philips US, Bothell, WA, USA) [25]. The calculation of the deformation slope ratio between the nodule and healthy tissue shows significant differences depending on the nature of the lesion (Fig). Cantisani et al.'s study included 97 patients referred for thyroid surgery [26]. An elasticity ratio greater than 2 made it possible to obtain the following results: sensitivity of 97.3, specificity of 91%, PPV of 87.8%, and NPV of 98.2%. Elastography was more sensitive and specific than all the other ultrasound data. Vorlander's study, involving a large number of patients (309), found a NPV of 100% for a ratio of 3.2 and a PPV of 42% for a ratio of 6.7 [27].

Regarding quasi-static elastography, a number of publications question the value of the technique [28, 29]. This could possibly be due to the absence of semi-quantification and the lack of

reproducibility during the learning curve *with* due to compression by the probe (devices without indication of stress level).

SWE was first reported for diagnosing thyroid nodules in 2010 by Sebag et al. [13]. The author shows that the combination of B-mode US and SWE provides enhanced sensibility and specificity. The emphasis was on certain specificities of the technique: quantitative, operator-independent, and reproducible. These results were confirmed 2 years later by the same team, with a threshold stiffness value of 65 kPa [30].

In 2013, the first SWE meta-analysis by Zhang et al. concerned 5 publications and 698 nodules [15]. The author concluded that SWE is a highly reproductive procedure, applicable to all type of nodules. The heterogeneity for the specificity and positive LR is principally due to the lower results of one of the studies [31]. The explanation is probably the wrong setting of the machine (the maximum value of the elastography scale was 180 kPa on the figures included in the publication). The same problem appeared in Szczepanek-Parulka et al.'s publication and Tian's meta-analysis [32, 33] and probably accounts for the disappointing result of SWE in comparison with QSE.

Liu's meta-analysis shows the high sensitivity and specificity of ARFI for differential diagnosis between benign and malignant nodules while also confirming the current interest in the combination with conventional ultrasound [34].

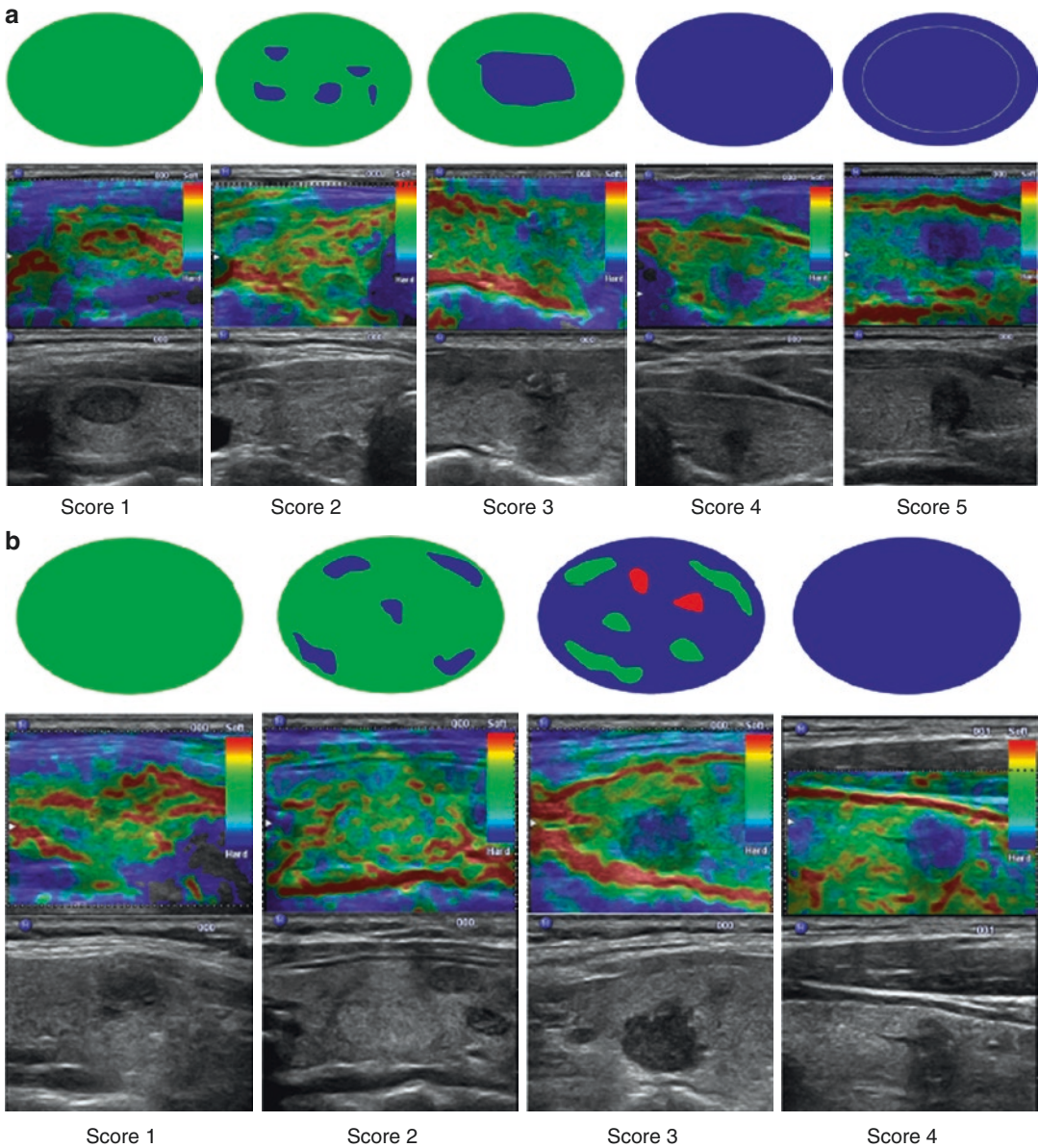


Fig. 8 Qualitative assessment of strain elastography. Scores by Rago (a) [21] and Asteria (b) [23]. Homogenous green pattern indicates soft nodule and homogenous blue pattern indicates stiff nodule

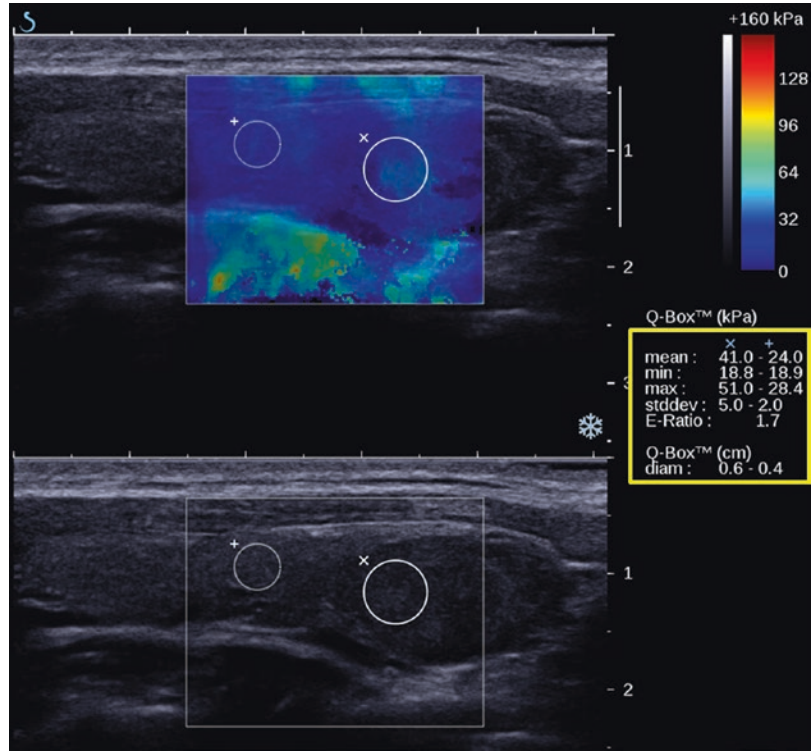
Moreover, Park et al. in 2015 showed that quantitative parameters of SWE are an independent predictor of thyroid malignancy [35].

In 2013, the European Federation of Societies for Ultrasound in Medicine and Biology published EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography [36]. With regard to the thyroid, two of the recommendations were:

- Elastography is an additional tool for thyroid lesion differentiation.
- Based on expert opinion, elastography may be used to guide the follow-up of lesions negative for malignancy at FNA.

Some recent developments are not preconized by these recommendations: the authors of a recent meta-analysis propose the omission of

Fig. 9 Shear wave elastography: wrong setting of the machine. High maximum value of elastography scale in case of soft nodule (Supersonic Imagine)



FNA cytology in the case of a completely soft nodule (Asteria score 1) [37].

The World Federation for Ultrasound in Medicine and Biology (WFUMB) recently published the WFUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography: Part 4. Thyroid [38]. The 25 recommendations are issued on the level of evidence of the published literature and on expert group consensus. They compared strain and SWE elastography.

A recent meta-analysis (Hu) points to better specificity of strain elastography [39]. The He et al. study shows an equality of efficacy between the Aixplorer and Applio-Toshiba systems [40].

Thyroid Pathology: Information/Data Provided by Elastography

Nodular Analysis

According to most of the reported series, elastography enables enhancement of the positive predictive value (PPV) and the negative predictive value

(NPV) [41, 42] of malignancy obtained via conventional ultrasound studies. It is therefore predicted to become the eighth parameter for thyroid nodule characterization. It was included in the French TIRADS classification. This point was recommended by domestic society (French Endocrine Society) [43] and ultrasound international societies (Fig. 10) [44]. The recent EU-TIRADS score does not confirm this proposition [45].

It is however of note that the above observed improvement in PPV and NPV in nodule characterization seems to be closely related to operator experience and skill. When the two scores are high, information obtained from elastography provides less benefit than that of the conventional US. This probably accounts for the disappointment felt among certain expert colleagues possessing great expertise in thyroid ultrasound analysis [29].

Notably, elastography is useful for the location of cystic nodules (Fig. 11) with viscous component (resembling hypoechoic solid nodules) and pseudonodules. In these cases, it is a time-saving application.

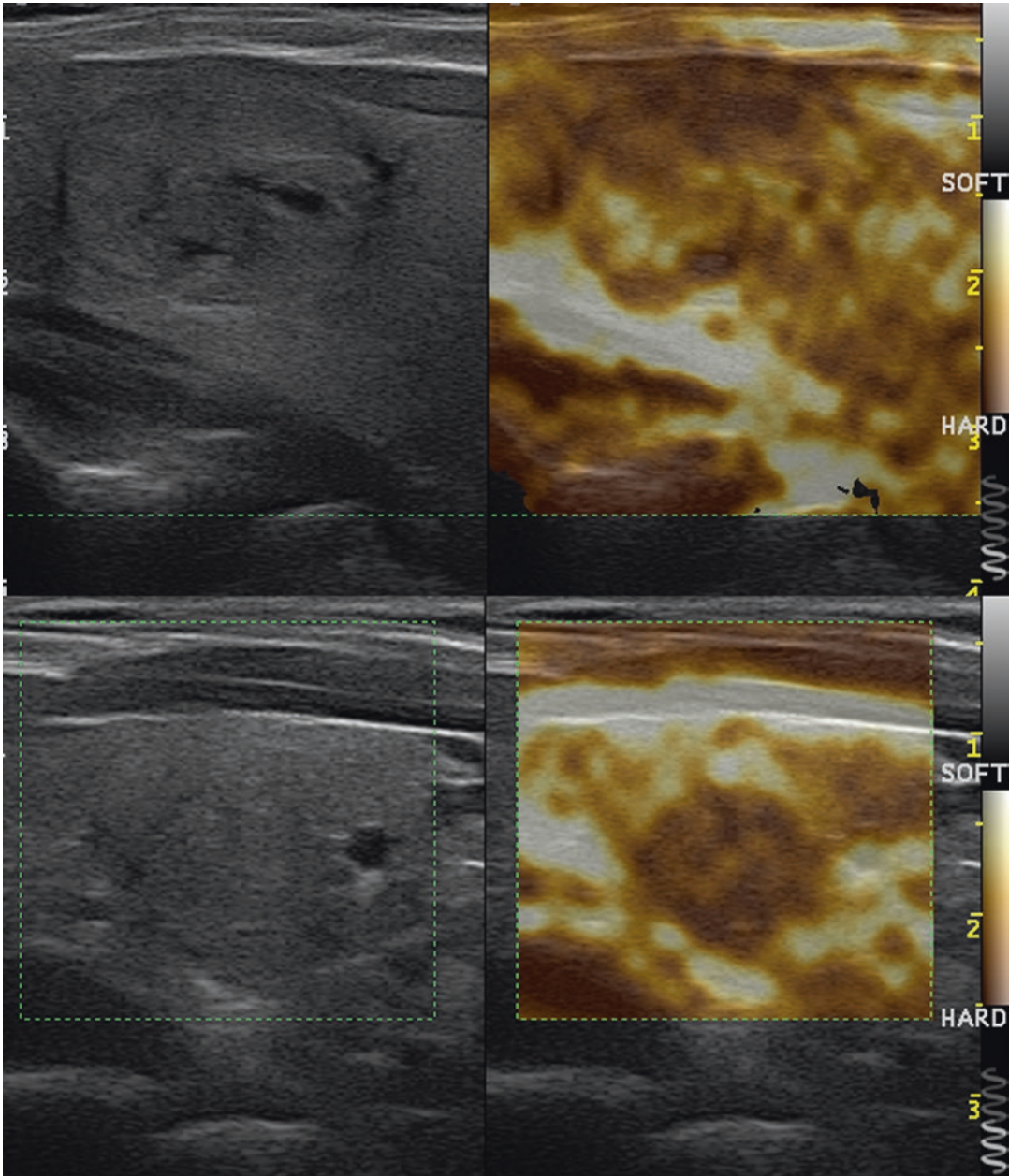


Fig. 10 Improvement of TIRADS by QSE elastography: two nodules TIRADS 3. Top image, the nodule is probably soft; bottom image, suspicious of malignancy (TIRADS 4b)

Other Thyroid Diseases

Shear wave elastography enables objective tissue stiffness quantification by providing a numerical value varying between 10 and 40 kPa for healthy tissue with some studies proposing the use of SWE for the characterization of non-nodular thyroid disease.

- Autoimmune thyroiditis (AIT). In the event of nodule(s) occurring during AIT, the stiffness ratio will likely be artificially low and thus falsely reassuring. The numerical stiffness value therefore needs to be considered [46, 47]. On the other hand, SWE was recently proposed to select patients with a higher

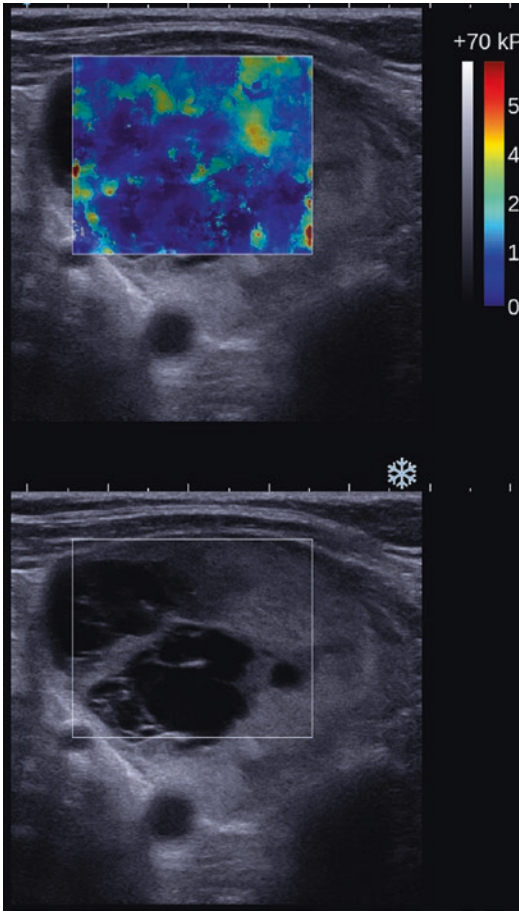


Fig. 11 Nodule with important fluid component the dark blue color of the cystic area corresponds with lack of shear wave propagation in fluid

stiffness value requiring biological investigations [48, 49].

- Riedel’s thyroiditis. This rare form of thyroiditis due to IgG4 exhibits a very high stiffness value, and SWE is a good method to unmask the possibility of this diagnosis (Fig. 12) [50].
- Thyroid bed after surgery. In the case of thyroidectomy for cancer, the emphasis of solid hypoechoic vascularized tissue in the thyroid bed is suspicious for recurrence. The possibility of parathyroid adenoma is not rare, but its ultrasound data are the same as those for cancer recurrence. SWE may provide the solution.

Other Cervical Diseases

- Lymph nodes. Elastography can also be useful to investigate cervical lymph nodes. In QSE, metastatic thyroid adenopathy has a very different appearance compared with normal lymph node. Without any surrounding healthy tissue, the comparison is impossible. In this case, SWE seems to be easier to select lymph nodes for fine needle aspiration cytology [51]. In addition, the detection of cystic component (lack of SWE signal) is an important sign of malignancy (Fig. 13).
- Parathyroid. A recent study described the high sensitivity and specificity of SWE (ARFI) to differentiate parathyroid adenoma from benign and malignant thyroid nodules (especially in case of posterior nodule(s)) [52].

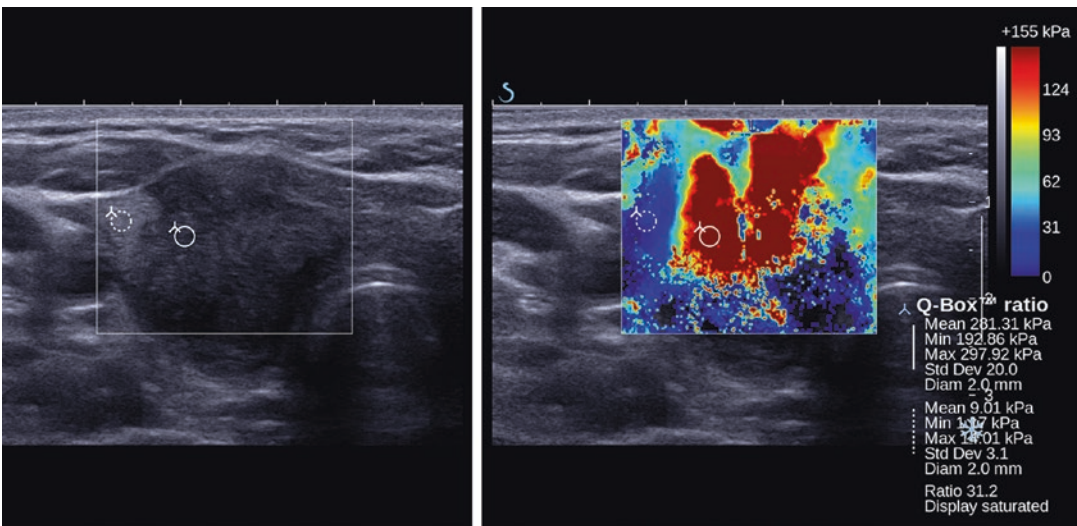


Fig. 12 Riedel’s thyroiditis. Hypoechoic nodule, with very high maximum stiffness value and ratio (Supersonic Imagine)

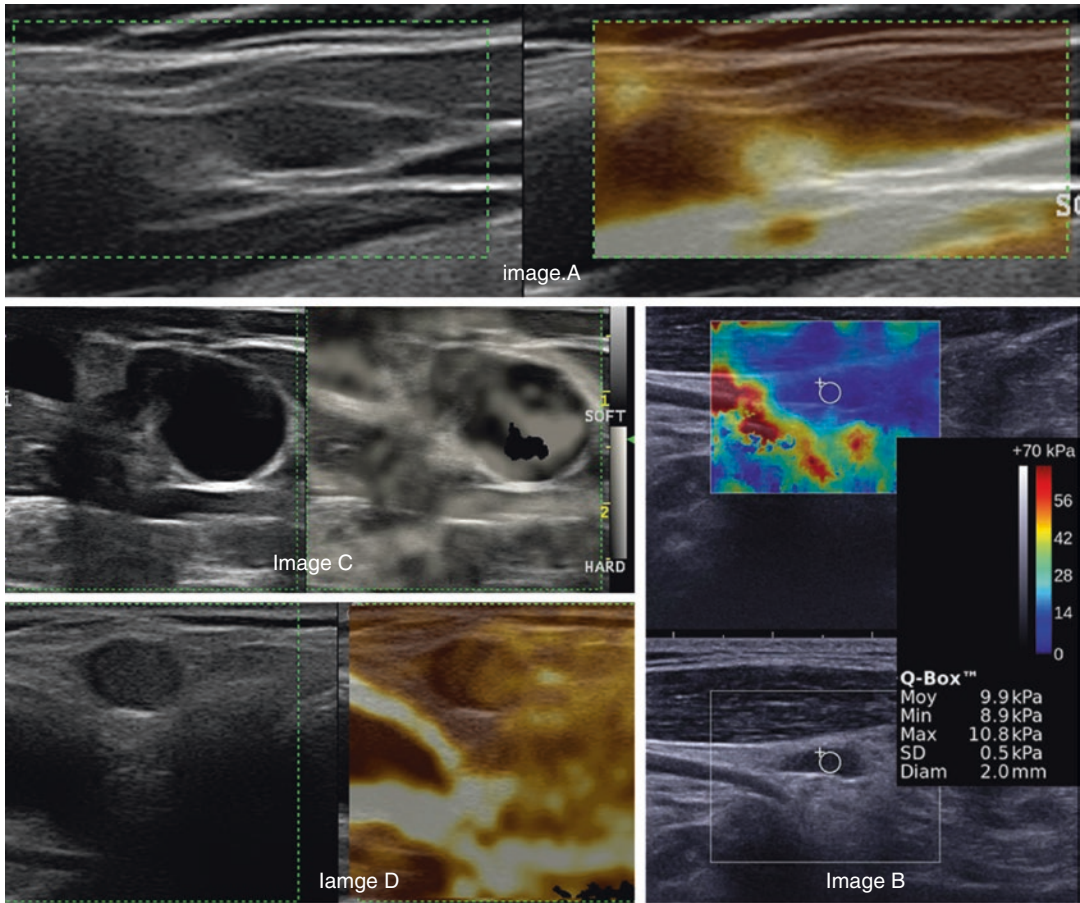
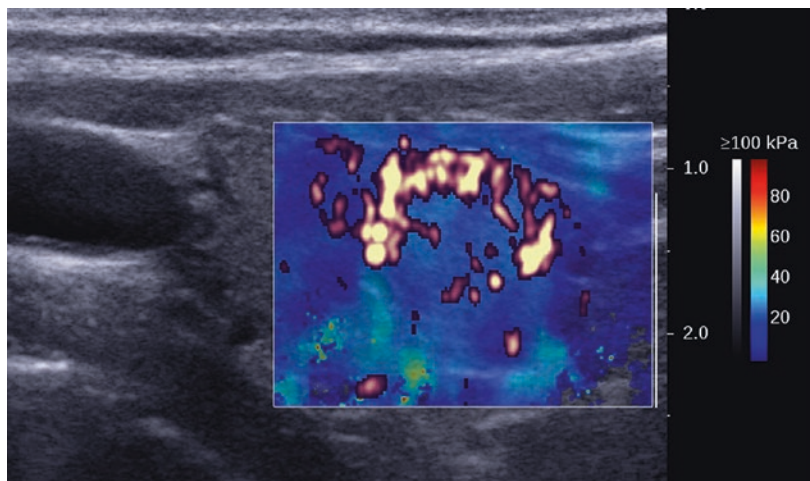


Fig. 13 Lymph node elastography. Normal lymph node. QSE (image a) SWE (image b) Lymph node metastasis: QSE: Cystic (image c) and stiff (image d)

Fig. 14 Shear wave elastography with power Doppler encoding (Supersonic Imagine)



Thyroid Elastography: Today and Tomorrow

Such an Important Technique Is Always in Research and Development (R&D)

- In the case of a deep nodule, the problem of the loss of signal is now resolved, thanks to new adapted probes.
- Some hyper-vascularized nodules may behave like stiff nodules. Supersonic imaging is used to develop a new application incorporating SWE and Doppler on the same screen (Fig. 14).
- The future may be twin procedures (shear wave elastography + contrast-enhanced ultrasound (CEUS)).

So Today, What Does Elastography Bring to the Thyroidologist?

The elastographic score is the eighth data component of TIRADS (Table 2), providing as it does an enhancement of ultrasound nodule characterization together with an increase in PPV and NPV and an improvement of TIRADS (negatively correlated with the expertise of the operator). It thus represents a reduction in the number of cytologies [53] and probably of surgeries. It cuts down the time for the examination of multinodular goiter, cystic nodules, and pseudonodules of thyroiditis (Fig. 15).

But What Additional Information Do We Need to Obtain?

Indeterminate cytologies (15% of samples) remain a major problem for thyroidologists. According to the Bethesda score [54], type 3 (AUS) and type 4 (follicular neoplasm) characterize, respectively, 10% and 25% of follicular cancers. Could elastography shed more light on these ambiguous cases (Table 3)?

The results of publications reporting on QSE devices are not unanimous [55–58].

SWE alone seems to be a valuable tool for determination of the preoperative malignancy risk of follicular-pattern nodules [59, 60]. The first part of the French SWEETMAC study has not, meanwhile, confirmed these results [61]. It is one of several ongoing studies, coupled with other investigations, using SWE (e.g., molecular biology, miRNA).

Concerning the nodules with non-diagnostic cytologies, Capelli's study [57], confirming Rago et al.'s study [62], shows that QSE alone is able (after two FNAC Bethesda one) to diagnose 12/15 cancers and all the cancers in association with conventional sonographic features.

What Information Will We (Probably) Never Obtain?

Elastography will never be substituted for histology. We know that tissue stiffness increases with stroma proportion and numerous malignant tumor cancers are devoid of stroma (follicular cancers, follicular variant of papillary cancers, poorly differentiated cancers). The aim of elastography is not to explain why a particular cancer is soft and why some benign lesions are stiff.

Conclusions in the Form of Reflections

Thanks to the relatively recent development of elastography, we have had the privilege of living a particularly exciting page of scientific history, whose progressive advances are typical in the field of innovative technology.

Thirteen years after the first description of the technique, endocrinologists discovered its application to the thyroid. While the very first response was one of simple curiosity about this discovery, more enterprising colleagues quickly realized its considerable potential and proceeded to serious studies and investigations. *It was the age of pioneers.*

Their publications produced a *period of ever-increasing interest and enthusiasm* in the medical community and numerous teams set about using QS elastography, reporting their finds in a lot of papers, the first meta-analysis being published in 2010. SWE confirmed the QSE studies, and, today, elastography is on its way to becoming fully established in technical procedures.

On the other hand, some eminent voices have raised doubts about the true significance of the technique. In fact, during this period, the value of nodule characterization was considerably enhanced while OR though meanwhile TIRADS has revolutionized our practices, with or without

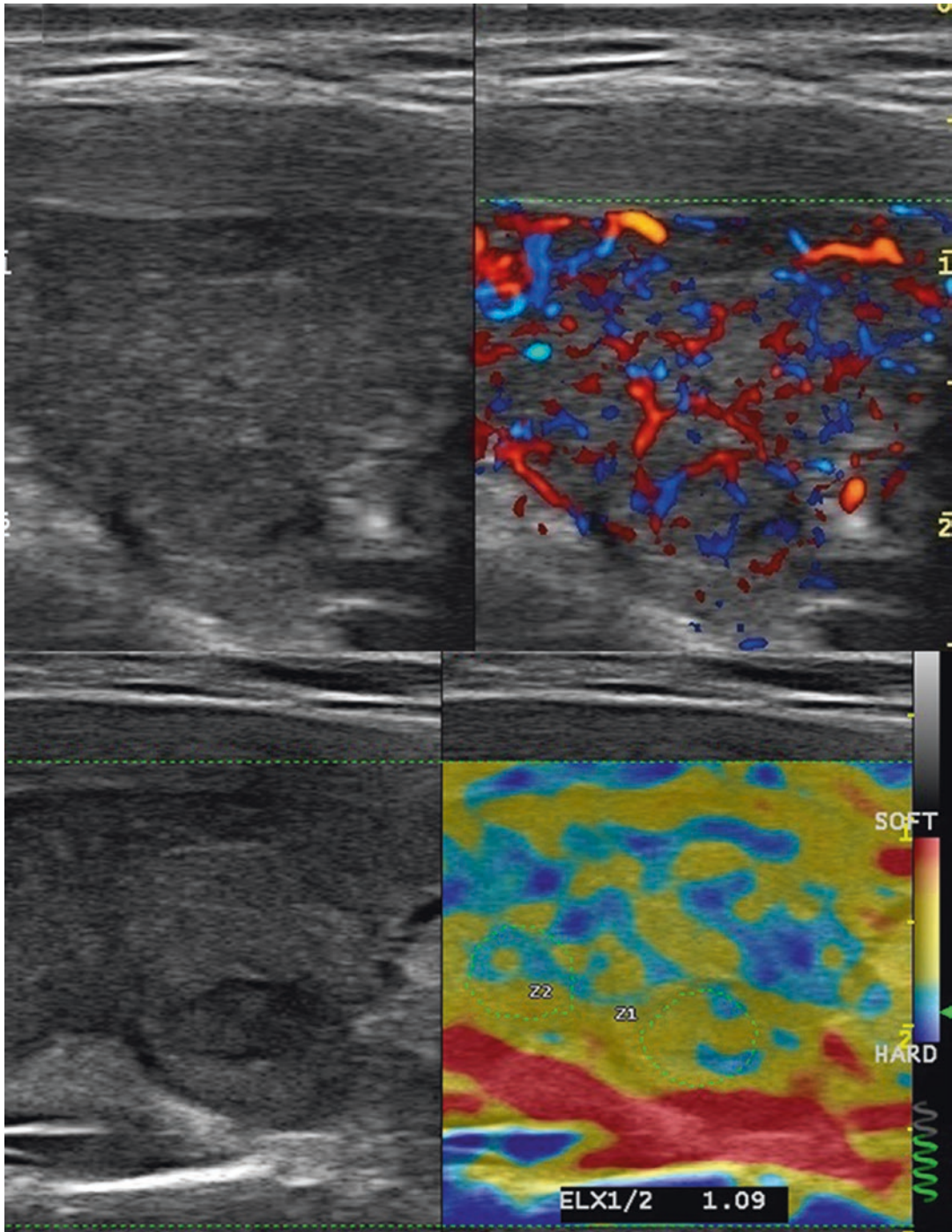


Fig. 15 Pseudonodular appearance during autoimmune thyroiditis: lesion without precise shapes in gray scale, without ring vessels in color Doppler, without stiffness ratio in strain elastography

elastography. Thus, *a period of loss of confidence has come about*. This however has not stemmed the flow of papers on the subject (280 between

2012 and 2016), though it has generated *the present time of reflection* in correlation with the huge technical developments brought about by R&D.

Table 3 Bethesda system [49]

• Cytological aspect	Cancer risk
• 2 Benign	<1%
• 3 Follicular lesions	5-15%
• 4 Follicular Neoplasm +/- oncocysts	15-30%
• 5 Suspect of malignancy	50-75%
• 6 Cancer	90%

The next step will probably be *the age of reason*, in other words, the realization that elastography constitutes an essential element of nodule analysis in conjunction with—and not in place of—classical ultrasound characterization [63], also incorporating CEUS, scintigraphy, molecular biology, and miRNA in the event of difficult cases.

Until the advent of a new technique.....???

Glossary

AIT Autoimmune thyroiditis

ARFI Acoustic radiation force impulse

AUS Atypia of undetermined significance

CEUS Contrast-enhanced ultrasound

ETA European Thyroid Association

EFSUMB European Federation of Societies for Ultrasound in Medicine and Biology

FNA Fine needle aspiration cytology

IgG4 Immunoglobulin G4

kPa Kilopascal

miRNA Micro-RNA

NPV Negative predicting value

PPV Positive predicting value

QSE Quasi-static elastography

RD Research and development

ROI Region of interest

SE Strain elastography

SWE Shear wave elastography

TE Transient elastography

TIRADS Thyroid imaging reporting and data system

TM Time motion

VTq Virtual touch quantification

2D Two dimensional = B-mode = Gray scale

US Ultrasound

References

1. Mai KT, Perkins DG, Yazdi HM, Commons AS, Thomas J, Meban S. Infiltrating papillary thyroid carcinoma: review of 134 cases of papillary carcinoma. *Arch Pathol Lab Med.* 1998;122(2):166–71.
2. Eisencher A. *Echosismographie.* 1980.
3. Dickinson RJ, Hill CR. Measurement of soft tissue motion using correlation between A-scans. *Ultrasound Med Biol.* 1982;8(3):263–71.
4. Krouskop TA, Dougherty DR, Vinson FS. A pulsed Doppler ultrasonic system for making noninvasive measurements of the mechanical properties of soft tissue. *J Rehabil Res Dev.* 1987;24(2):1–8.
5. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrasound Imaging.* 1991;13(2):111–34.
6. Cespedes I, Ophir J, Ponnekanti H, Maklad N. Elastography: elasticity imaging using ultrasound with application to muscle and breast in vivo. *Ultrasound Imaging.* 1993;15(2):73–88.
7. Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: basic principles and technology. *Ultraschall Med.* 2013;34(2):169–84.
8. Bae U, Dighe M, Dubinsky T, Minoshima S, Shamdasani V, Kim Y. Ultrasound thyroid elastography using carotid artery pulsation: preliminary study. *J Ultrasound Med.* 2007;26(6):797–805.
9. Bercoff J, Tanter M, Muller M, Fink M. The role of viscosity in the impulse diffraction field of elastic waves induced by the acoustic radiation force. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2004;51(11):1523–36.
10. Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2004;51(4):396–409.
11. Park SH, Kim SJ, Kim EK, Kim MJ, Son EJ, Kwak JY. Interobserver agreement in assessing the sonographic and elastographic features of malignant thyroid nodules. *Am J Roentgenol.* 2009;193(5):W416–23.
12. Lim DJ, Luo S, Kim MH, Ko SH, Kim Y. Interobserver agreement and intraobserver reproducibility in thyroid ultrasound elastography. *Am J Roentgenol.* 2012;198(4):896–901.
13. Sebag F, Vaillant-Lombard J, Berbis J, Griset V, Henry JF, Petit P, et al. Shear wave elastography: a new ultrasound imaging mode for the differential diagnosis of benign and malignant thyroid nodules. *J Clin Endocrinol Metab.* 2010;95(12):5281–8.
14. Kim H, Kim JA, Son EJ, Youk JH. Quantitative assessment of shear-wave ultrasound elastography in thyroid nodules: diagnostic performance for predicting malignancy. *Eur Radiol.* 2013;23(9):2532–7.

15. Zhang B, Ma X, Wu N, Liu L, Liu X, Zhang J, et al. Shear wave elastography for differentiation of benign and malignant thyroid nodules: a meta-analysis. *J Ultrasound Med.* 2013;32(12):2163–9.
16. Lyschik A, Higashi T, Asato R, Tanaka S, Ito J, Hiraoka M, et al. Elastic moduli of thyroid tissues under compression. *Ultrason Imaging.* 2005;27(2):101–10.
17. Lyschik A, Higashi T, Asato R, Tanaka S, Ito J, Mai JJ, et al. Thyroid gland tumor diagnosis at US elastography. *Radiology.* 2005;237(1):202–11.
18. Monpeyssen H, Tramalloni J, Poiree S, Helenon O, Correas JM. Elastography of the thyroid. *Diagn Interv Imaging.* 2013;94(5):535–44.
19. Wemeau JL, Sadoul JL, d'Herbomez M, Monpeyssen H, Tramalloni J, Leteurte E, et al. Recommendations of the French Society of Endocrinology for the management of thyroid nodules. *Presse Med.* 2011;40(9 Pt 1):793–826.
20. Russ G, Royer B, Bigorgne C, Rouxel A, Bienvenu-Perrard M, Leenhardt L. Prospective evaluation of thyroid imaging reporting and data system on 4550 nodules with and without elastography. *Eur J Endocrinol.* 2013;168(5):649–55.
21. Rago T, Santini F, Scutari M, Pinchera A, Vitti P. Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. *J Clin Endocrinol Metab.* 2007;92(8):2917–22.
22. Tranquart F, Bleuizen A, Pierre-Renoult P, Chabrolle C, Sam Giao M, Lecomte P. Elastasonography of thyroid lesions. *J Radiol.* 2008;89(1 Pt 1):35–9.
23. Asteria C, Giovanardi A, Pizzocaro A, Cozzaglio L, Morabito A, Somalvico F, et al. US-elastography in the differential diagnosis of benign and malignant thyroid nodules. *Thyroid.* 2008;18(5):523–31.
24. Bojunga J, Herrmann E, Meyer G, Weber S, Zeuzem S, Friedrich-Rust M. Real-time elastography for the differentiation of benign and malignant thyroid nodules: a meta-analysis. *Thyroid.* 2010;20(10):1145–50.
25. Monpeyssen H, Correas JM, Gauthier T, Tramalloni J, Helenon O. Quantitative elastography of thyroid nodules: preliminary results. *Chicago: RSNA; 2008.*
26. Cantisani V, D'Andrea V, Biancari F, Medvedeva O, Di Segni M, Olive M, et al. Prospective evaluation of multiparametric ultrasound and quantitative elastography in the differential diagnosis of benign and malignant thyroid nodules: preliminary experience. *Eur J Radiol.* 2012;81(10):2678–83.
27. Vorlander C, Wolff J, Saalabian S, Lienenluke RH, Wahl RA. Real-time ultrasound elastography—a noninvasive diagnostic procedure for evaluating dominant thyroid nodules. *Langenbeck's Arch Surg.* 2010;395(7):865–71.
28. Unluturk U, Erdogan MF, Demir O, Gullu S, Baskal N. Ultrasound elastography is not superior to gray-scale ultrasound in predicting malignancy in thyroid nodules. *Thyroid.* 2012;22(10):1031–8.
29. Moon HJ, Sung JM, Kim EK, Yoon JH, Youk JH, Kwak JY. Diagnostic performance of gray-scale US and elastography in solid thyroid nodules. *Radiology.* 2012;262(3):1002–13.
30. Veyrieres JB, Albarel F, Lombard JV, Berbis J, Sebag F, Oliver C, et al. A threshold value in shear wave elastography to rule out malignant thyroid nodules: a reality? *Eur J Radiol.* 2012;81(12):3965–72.
31. Bhatia KS, Tong CS, Cho CC, Yuen EH, Lee YY, Ahuja AT. Shear wave elastography of thyroid nodules in routine clinical practice: preliminary observations and utility for detecting malignancy. *Eur Radiol.* 2012;22(11):2397–406.
32. Szczepanek-Parulska E, Wolinski K, Stangierski A, Gurgul E, Biczysko M, Majewski P, et al. Comparison of diagnostic value of conventional ultrasonography and shear wave elastography in the prediction of thyroid lesions malignancy. *PLoS One.* 2013;8(11):e81532.
33. Tian W, Hao S, Gao B, Jiang Y, Zhang S, Gu L, et al. Comparison of diagnostic accuracy of real-time elastography and shear wave elastography in differentiation malignant from benign thyroid nodules. *Medicine (Baltimore).* 2015;94(52):e2312.
34. Liu BJ, Li DD, Xu HX, Guo LH, Zhang YF, Xu JM, et al. Quantitative shear wave velocity measurement on acoustic radiation force impulse elastography for differential diagnosis between benign and malignant thyroid nodules: a meta-analysis. *Ultrasound Med Biol.* 2015;41(12):3035–43.
35. Park AY, Son EJ, Han K, Youk JH, Kim JA, Park CS. Shear wave elastography of thyroid nodules for the prediction of malignancy in a large scale study. *Eur J Radiol.* 2015;84(3):407–12.
36. Cosgrove D, Piscaglia F, Bamber J, Bojunga J, Correas JM, Gilja OH, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: clinical applications. *Ultraschall Med.* 2013;34(3):238–53.
37. Nell S, Kist JW, Debray TP, de Keizer B, van Oostenbrugge TJ, Borel Rinkes IH, et al. Qualitative elastography can replace thyroid nodule fine-needle aspiration in patients with soft thyroid nodules. A systematic review and meta-analysis. *Eur J Radiol.* 2015;84(4):652–61.
38. Cosgrove D, Barr R, Bojunga J, Cantisani V, Chammas MC, Dighe M, et al. WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: part 4. Thyroid. *Ultrasound Med Biol.* 2017;43(1):4–26.
39. Hu X, Liu Y, Qian L. Diagnostic potential of real-time elastography (RTE) and shear wave elastography (SWE) to differentiate benign and malignant thyroid nodules: a systematic review and meta-analysis. *Medicine (Baltimore).* 2017;96(43):e8282.
40. He YP, Xu HX, Wang D, Li XL, Ren WW, Zhao CK, et al. First experience of comparisons between two different shear wave speed imaging systems in differentiating malignant from benign thyroid nodules. *Clin Hemorheol Microcirc.* 2017;65(4):349–61.
41. Veer V, Puttagunta S. The role of elastography in evaluating thyroid nodules: a literature review

- and meta-analysis. *Eur Arch Otorhinolaryngol.* 2015;272(8):1845–55.
42. Trimboli P, Guglielmi R, Monti S, Misischi I, Graziano F, Nasrollah N, et al. Ultrasound sensitivity for thyroid malignancy is increased by real-time elastography: a prospective multicenter study. *J Clin Endocrinol Metab.* 2012;97(12):4524–30.
 43. Wemeau JL, Sadoul JL, d'Herbomez M, Monpeyssen H, Tramalloni J, Leteurtre E, et al. Guidelines of the French society of endocrinology for the management of thyroid nodules. *Ann Endocrinol (Paris).* 2011;72(4):251–81.
 44. Leenhardt L, Erdogan MF, Hegedus L, Mandel SJ, Paschke R, Rago T, et al. 2013 European thyroid association guidelines for cervical ultrasound scan and ultrasound-guided techniques in the postoperative management of patients with thyroid cancer. *Eur Thyroid J.* 2013;2(3):147–59.
 45. Russ G, Bonnema SG, Erdogan MF, Durrante C, Ngu R, Leenhardt L. European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur Thyroid J.* 2017;6:225–37.
 46. Fukuhara T, Matsuda E, Endo Y, Takenobu M, Izawa S, Fujiwara K, et al. Correlation between quantitative shear wave elastography and pathologic structures of thyroid lesions. *Ultrasound Med Biol.* 2015;41(9):2326–32.
 47. Liu B, Liang J, Zhou L, Lu Y, Zheng Y, Tian W, et al. Shear wave Elastography in the diagnosis of thyroid nodules with coexistent chronic autoimmune Hashimoto's thyroiditis. *Otolaryngol Head Neck Surg.* 2015;153(5):779–85.
 48. Vlad M, Golu I, Bota S, Vlad A, Timar B, Timar R, et al. Real-time shear wave elastography may predict autoimmune thyroid disease. *Wien Klin Wochenschr.* 2015;127(9–10):330–6.
 49. Ruchala M, Szmyt K, Slawek S, Zybek A, Szczepanek-Parulska E. Ultrasound sonoelastography in the evaluation of thyroiditis and autoimmune thyroid disease. *Endokrynol Pol.* 2014;65(6):520–6.
 50. Slman R, Monpeyssen H, Desarnaud S, Haroche J, Fediaevsky Ldu P, Fabrice M, et al. Ultrasound, elastography, and fluorodeoxyglucose positron emission tomography/computed tomography imaging in Riedel's thyroiditis: report of two cases. *Thyroid.* 2011;21(7):799–804.
 51. Jung WS, Kim JA, Son EJ, Youk JH, Park CS. Shear wave elastography in evaluation of cervical lymph node metastasis of papillary thyroid carcinoma: elasticity index as a prognostic implication. *Ann Surg Oncol.* 2015;22(1):111–6.
 52. Batur A, Atmaca M, Yavuz A, Ozgokce M, Bora A, Bulut MD, et al. Ultrasound elastography for distinction between parathyroid adenomas and thyroid nodules. *J Ultrasound Med.* 2016.
 53. Kim MH, Luo S, Ko SH, Jung SL, Lim DJ, Kim Y. Elastography can effectively decrease the number of fine-needle aspiration biopsies in patients with calcified thyroid nodules. *Ultrasound Med Biol.* 2014;40(10):2329–35.
 54. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. *Thyroid.* 2009;19(11):1159–65.
 55. Trimboli P, Treglia G, Sadeghi R, Romanelli F, Giovanella L. Reliability of real-time elastography to diagnose thyroid nodules previously read at FNAC as indeterminate: a meta-analysis. *Endocrine.* 2015;50(2):335–43.
 56. Lippolis PV, Tognini S, Materazzi G, Polini A, Mancini R, Ambrosini CE, et al. Is elastography actually useful in the presurgical selection of thyroid nodules with indeterminate cytology? *J Clin Endocrinol Metab.* 2011;96(11):E1826–30.
 57. Cappelli C, Pirola I, Gandossi E, Agosti B, Cimino E, Casella C, et al. Real-time elastography: a useful tool for predicting malignancy in thyroid nodules with nondiagnostic cytologic findings. *J Ultrasound Med.* 2012;31(11):1777–82.
 58. Cantisani V, Maceroni P, D'Andrea V, Patrizi G, Di Segni M, De Vito C, et al. Strain ratio ultrasound elastography increases the accuracy of colour-Doppler ultrasound in the evaluation of Thy-3 nodules. A bi-Centre university experience. *Eur Radiol.* 2016;26(5):1441–9.
 59. Samir AE, Dhyani M, Anvari A, Prescott J, Halpern EF, Faquin WC, et al. Shear-wave elastography for the preoperative risk stratification of follicular-patterned lesions of the thyroid: diagnostic accuracy and optimal measurement plane. *Radiology.* 2015;277(2):565–73.
 60. Zhao CK, Xu HX, Xu JM, Sun CY, Chen W, Liu BJ, et al. Risk stratification of thyroid nodules with Bethesda category III results on fine-needle aspiration cytology: the additional value of acoustic radiation force impulse elastography. *Oncotarget.* 2017;8(1):1580–92.
 61. Bardet S, Ciappuccini R, Pellot-Barakat C, Monpeyssen H, Michels JJ, Tissier F, et al. Shear wave elastography in thyroid nodules with indeterminate cytology: results of a prospective bicentric study. *Thyroid.* 2017.
 62. Rago T, Scutari M, Santini F, Loiacono V, Piaggi P, Di Coscio G, et al. Real-time elastosonography: useful tool for refining the presurgical diagnosis in thyroid nodules with indeterminate or nondiagnostic cytology. *J Clin Endocrinol Metab.* 2010;95(12):5274–80.
 63. Remonti LR, Kramer CK, Leitao CB, Pinto LC, Gross JL. Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. *Thyroid.* 2015;25(5):538–50.