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Elastography: A New Ultrasound Technique in Nodular Thyroid Pathology

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Abstract

Elastography is a new technique for evaluating the stiffness of nodules. It is generally recognised that malignant thyroid lesions are harder than benign lesions. Different elastographic techniques are presented, with characteristics, advantages and limitations. Qualitative and semiquantitative methods are described. Comparison of the main existing techniques, static and dynamic elastographies, is presented in this chapter. Strain elastography seems to have a better diagnostic quality than shear wave elastography in the diagnosis of thyroid cancer disease. A positive elastogram, suggestive for malignancy is more useful in diagnosis than a positive grey-scale ultrasound evaluation. Elastography increases the specificity of grey scale ultrasound (US), it should be always integrated with its information and should be considered as a complement of conventional US.

Keywords: thyroid cancer, elastography, strain, shear wave, cutoff values

1. Introduction

Thyroid nodular disease is one of the most frequent endocrine pathologies in everyday practice. Epidemiologic studies have shown a prevalence of palpable thyroid nodules of 4–8% in iodine deficient areas [1], and up to 5% in women and 1% in men living in iodine sufficient areas [2]. The ultrasound (US) studies have revealed a much higher prevalence, up to 68% [3, 4]. The most

important challenge in thyroid nodular disease is the correct identification of cancer cases, which occur in 7–15% of all thyroid nodules [5, 6].

The incidence of thyroid nodules has increased due to exposure to medical radiation, iodine intake, obesity and insulin resistance, genetics and inorganic phosphates [7, 8] with a 300% increase in the annual thyroid cancer rate [9].

Not only has the incidence of thyroid cancer significantly increased, but also there is an increase in demand for precise detection techniques, capable of dealing with small, incidentally discovered nodules: over 39% of all recently diagnosed thyroid cancers were below 1 cm [9]. High-resolution ultrasound evaluation is considered the most sensitive diagnostic modality for the detection and evaluation of thyroid nodules [10] being the first evaluation that is recommended in patients with suspect thyroid lesions.

There is a general consensus in all major guidelines [11–14] that fine needle ultrasound guided aspiration (FNAB) is the diagnostic of choice in order to establish the proper therapeutic option: refer to surgery or reevaluation. All guidelines recommend FNAB evaluation in cases of suspicious ultrasound characteristics, but these characteristics are not 100% superimposable: the American Thyroid Association (ATA) has stated that FNAB is the procedure of choice for the evaluation of thyroid nodules. FNAB should be performed in the presence of thyroid nodules >5 mm with suspicious US findings, hypoechoic solid nodules >1 cm, mixed cystic-solid nodules >1.5–2 cm with suspicious US findings, nodules with microcalcifications or abnormal cervical lymph nodes. The American Association of Clinical Endocrinology (AACE) recommends FNAB for hypoechoic solid nodules >1 cm, nodules with malignant US findings, regardless of size, and in patients with a special malignancy history. The Korean Guideline recommends FNAB in all suspicious nodules (taller than wide shape, irregular margins, marked hypoechoic texture, micro and macro-calcifications, speculated margins, extracapsular invasion) regardless of size and selective biopsy in probably benign nodules larger than 2 cm. The British Guidelines do not make any recommendation but suggest universal FNAB in cases with U3 (intermediate), U4 (suspicious) and U5 (malignant) nodules on ultrasound. Not only is it unclear which nodules should be referred to FNAB and which to follow up, but also there are a lot of data regarding the reluctance of the population to the FNAB procedure per se. FNAB results are not 100% accurate, with sensitivity and specificity up to 80% in very good centres [15]. They are considered a prediagnostic method and not a golden standard diagnostic method [16] due to the sensitivity achieved of 70 [17] to 85% [16] and also an application rate of 66% [17] use and accuracy of fine-needle aspiration cytology in histologically proven thyroid carcinoma according to an audit using a national anthology database [Cancer 2000; 90(6): 330–334]. The FNAB findings reported only 47 [17] to 55.3% [18] of proven cancers. The rate of false negative and false positive results of FNAB remains a challenge for this diagnostic method [16].

Elastography is a new method that evaluates the stiffness of the tissue since all thyroid nodules that are firm on palpation are suspicious for malignancy, which adds diagnostic value in respect of malignancy prediction [19, 20]. However, elastography is not widely used in clinical practice and not included in the major endocrine guidelines, but brings important information regarding the inelasticity of thyroid nodular lesions [21].

2. Elastography

Changes in tissue stiffness are present in cancerous disease, fibrotic changes or atherosclerosis. The vast majority of imaging techniques, such as computer tomography, magnetic resonance imaging and positron emission tomography, are focused on morphologic or functional characteristics; elastography assesses the stiffness of the tissue. Elastography is an application of the ultrasound technique, with specialised software that allows the measurement of different tissue stiffness [22].

The stiffness of the biological structures, viscous, anisotropic and non-linear is dependent on the degree of deformation. This deformation is obtained by external pressure, internal transversal deformation of tissue, induced by focused ultrasound beams called acoustic radiation force impulse (ARFI) excitation [23] or by inducing short duration focused acoustic beams, which generate shear waves that propagate transversally in the examined tissue.

These techniques bring qualitative information, imaging in colour maps with colour codes proportional to the tissue stiffness, or numerical evaluation of the stiffness, and are almost always a part of the ultrasound evaluation. The final diagnostic decision is a combination of conventional ultrasound and elastography [24]. There are important differences between manufactures, machines and techniques, and not all the results are comparable and therefore cannot be judged as a head-to-head comparison [25].

2.1. Elastography methods – strain elastography

Strain elastography requires an external palpation that induces a deformation of the subjacent tissue, parallel to the direction of the deformation force or endogenous stress such as vascular beam movements [26]. Repeated movements are registered. The stiff tissue moves less and shows lower deformation compared with the elastic tissue. The elastic images are added on the conventional 2B mode and displayed in a colour map from red (soft tissue) to blue (hard

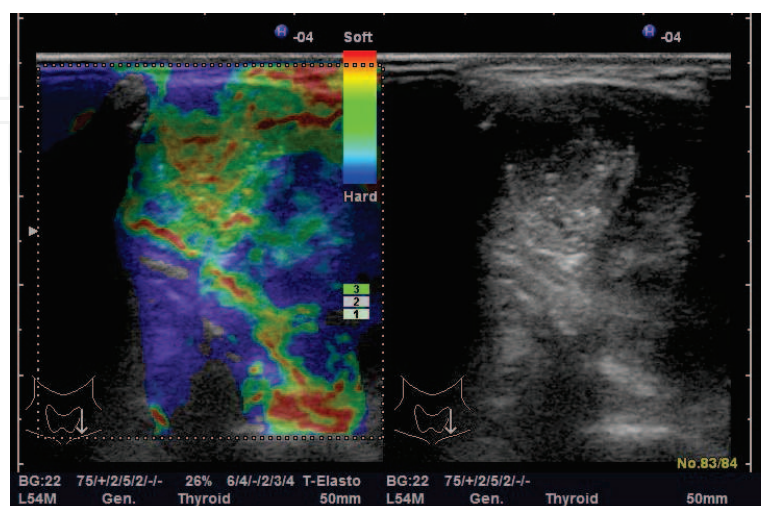


Figure 1. Hitachi device. Image on the left: strain elastography, red-green-blue colour map convention, soft nodule: green nodule. Image in the right: grey scale US: solid thyroid nodule, transversal section.

tissue). This qualitative evaluation is different in different manufacturers: in parallel with 2B images, superimposed to the grey scale images, at a refresh rate equal to that of grey scale = real-time elastography (RTE), offered by Hitachi Systems [27] or is displayed as a single image, representing the mean relative anelasticity strain over a time loop, predefined by the examiner, in the Toshiba machines.

Figures 1–3 show examples of solid thyroid nodules evaluated by strain elastography with different devices.

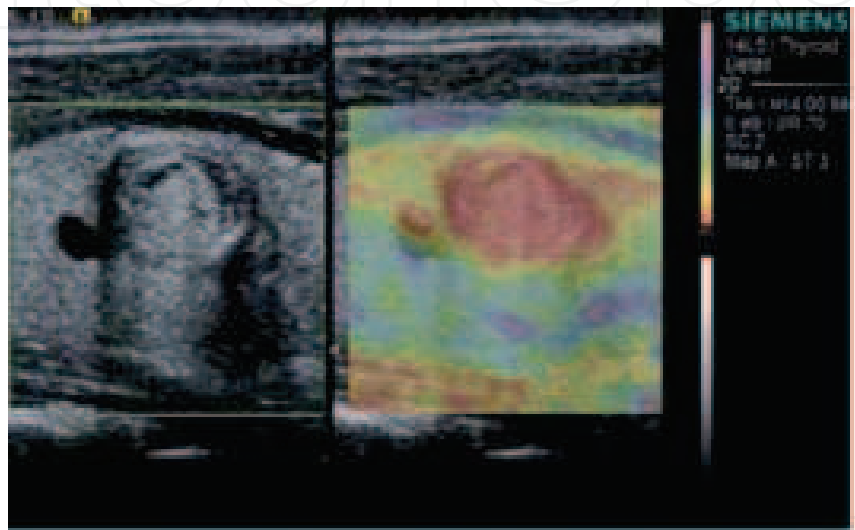


Figure 2. Siemens machine. Image on the left: grey scale US: solid thyroid nodule, longitudinal section. Image on the right: strain elastography, blue-green-red convention map: hard thyroid nodule: red colour.

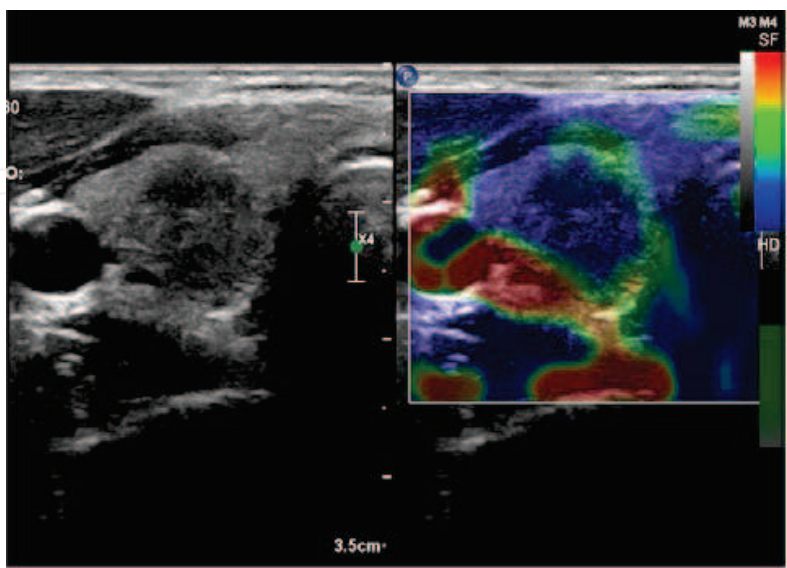


Figure 3. Phillips machine. Image in the left: grey scale US: solid thyroid nodule, transversal section. Image on the right: strain elastography, red – green – blue color map convention, hard nodule: blue nodule.

Also it allows a semiquantitative measurement, with the comparison of tissue strain in the Region of interest (ROI), the nodule, compared with healthy surrounding tissue, with automatic computing of the strain ratio (SR). **Figures 4 and 5** show the way of computer-assisted strain ratio evaluation. Internal pulsation of the carotid artery used in thyroid elastography allows both qualitative images (RTE) and also a semiquantitative evaluation, computing the strain ratio (SR) and the elasticity contrast index, in Samsung devices [28]. The higher the SR, the higher the likelihood of malignancy [29].

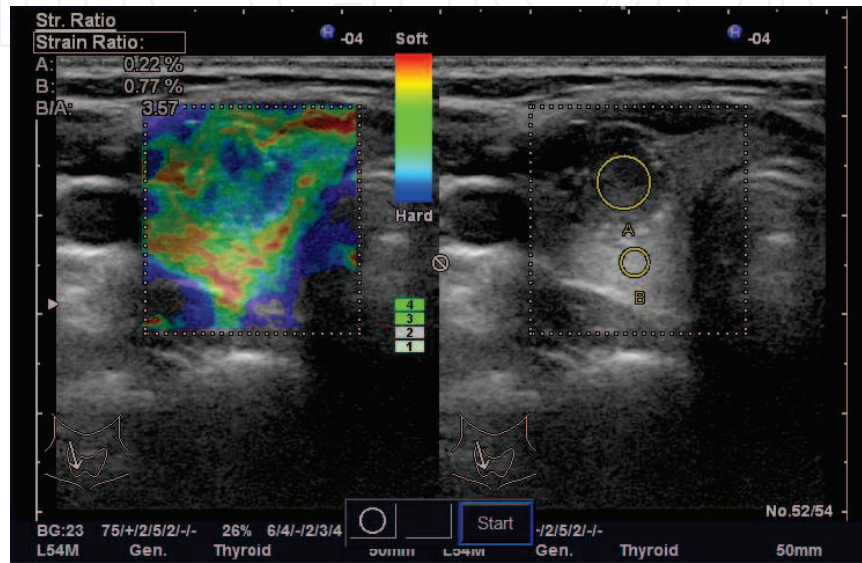


Figure 4. Hitachi device. Image on the left: strain elastography, soft nodule, low strain ratio: average = 3.57. Image on the right: grey scale US: solid thyroid nodule, transversal section.

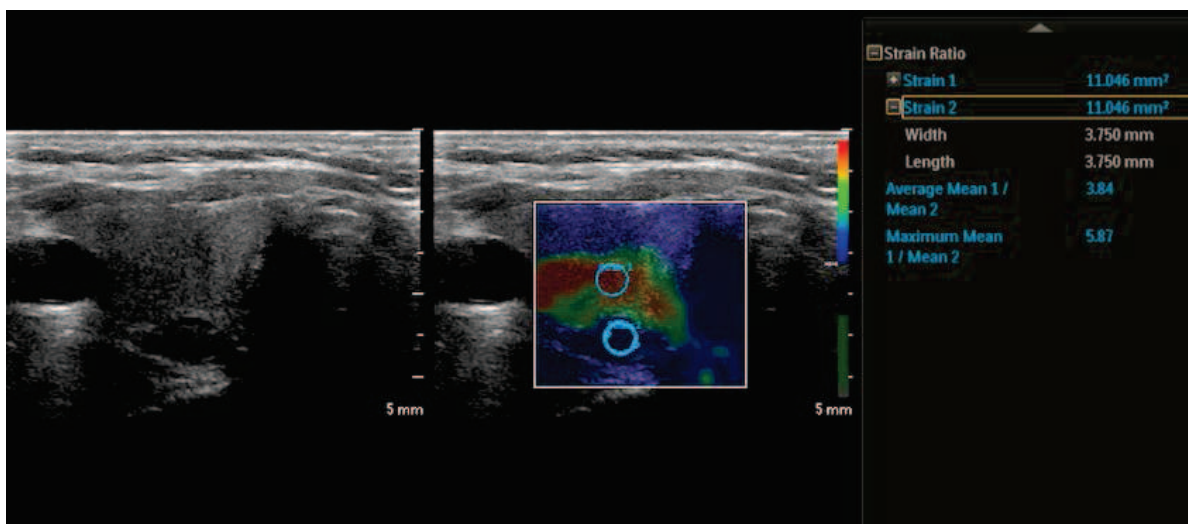


Figure 5. Philips device. Image on the left: grey scale US: solid thyroid nodule, transversal section. Image on the right: strain elastography, hard nodule: red colour (blue-green-red convention map), increased strain ratio: average = 3.84, maximum = 5.87.

The parameters used in strain elastography are strain (colour map), strain ratio geometric measures and elastography to B-mode size ratio (EI/B) ratio [30].

Strain elastography can be performed also by internal force, using transversal displacement of the tissue, without any external compression, secondary to the acoustic radiation force impulse imaging, used by Siemens devices, using the analysis of single images or a predefined time loop but not a real-time evaluation [27].

The following devices using strain elastography: ElaXto (Esaote), RTE (Hitachi Aloka), elastography (General Electric, Philips, Toshiba, Ultrasonix), eSieTocuh: (Samsung, Siemens), respectively, ARFI: VirtualTouch Imaging: (Siemens) are currently present on the commercial ultrasound machine market [30].

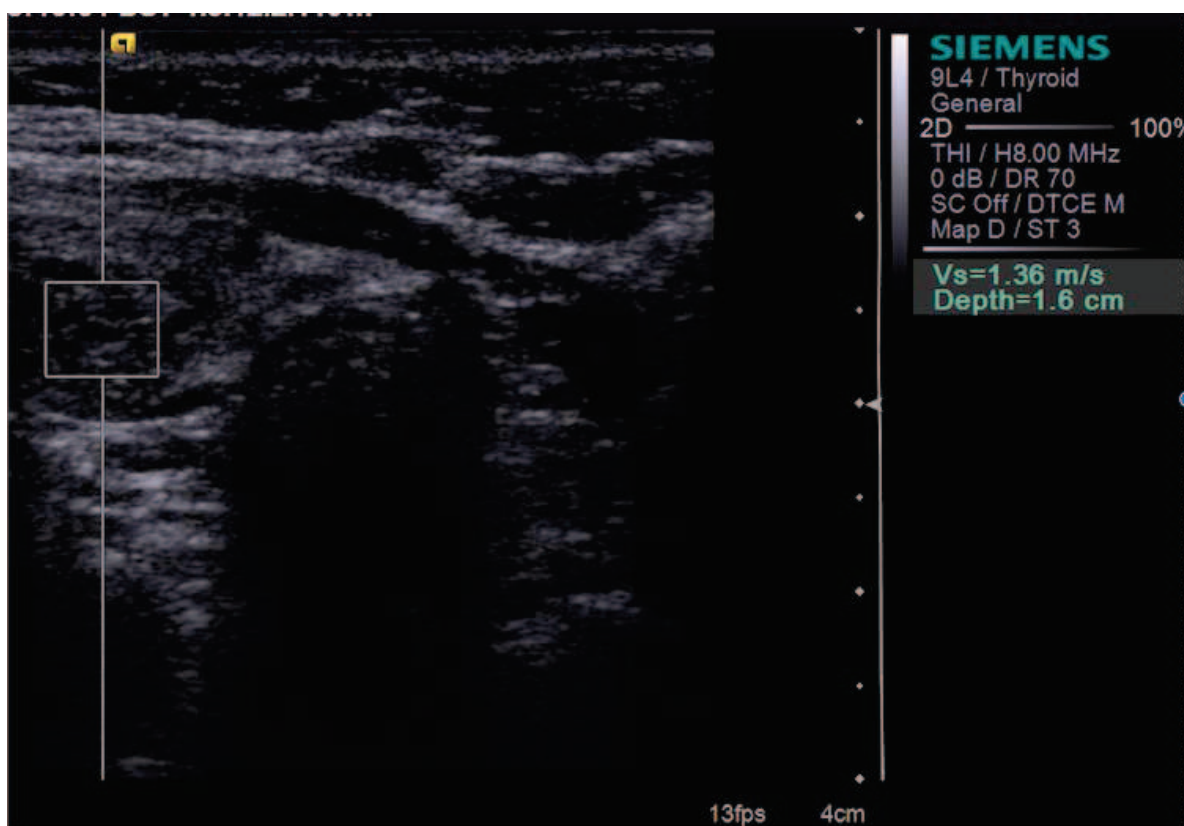


Figure 6. ARFI technique in a solid thyroid nodule: grey scale only evaluation, automatic ROI (1 mm), evaluation of SWE speed (m/s) in the nodule = median value of 10 serial measurements.

It is worth mentioning that the amount of external applied pressure has to be medium and is quantified for each device: for Hitachi machines, the compression scale is displayed always, and the pressure should be between 3 and 4 [31, 32]; in Siemens machines, it should be respectively a quality factor about 50 [33] and for Philips devices, it should maintain a steady pressure level displayed on the screen [34].

2.2. Elastography methods – shear wave elastography

Shear wave elastography assesses the elasticity of the tissues by evaluating the attenuation of the shear waves, which are transverse components of particle displacements, and they move in the tissue, with a speed that is dependent on the stiffness of the tissue [27]. There are two applicable methods: the supersonic shear wave and the acoustic radiation force impulse (ARFI) [35].

Focused ultrasound-induced waves are used in thyroid imaging, the supersonic shear waves, with a measurement of wave velocity (m/s) as the wave attenuates along a perpendicular direction to the transducer, or measuring directly the elasticity of ROI (kilopascals). The colour map displays the soft tissues as blue and hard tissues as red [36].

ARFI uses short-duration acoustic pulses that excite the tissue within the ROI and measures only the speed (m/sec) in these lesions, without any colour-coded images [37]. **Figures 6 and 7** represent ARFI evaluation for solid and cystic thyroid lesion.

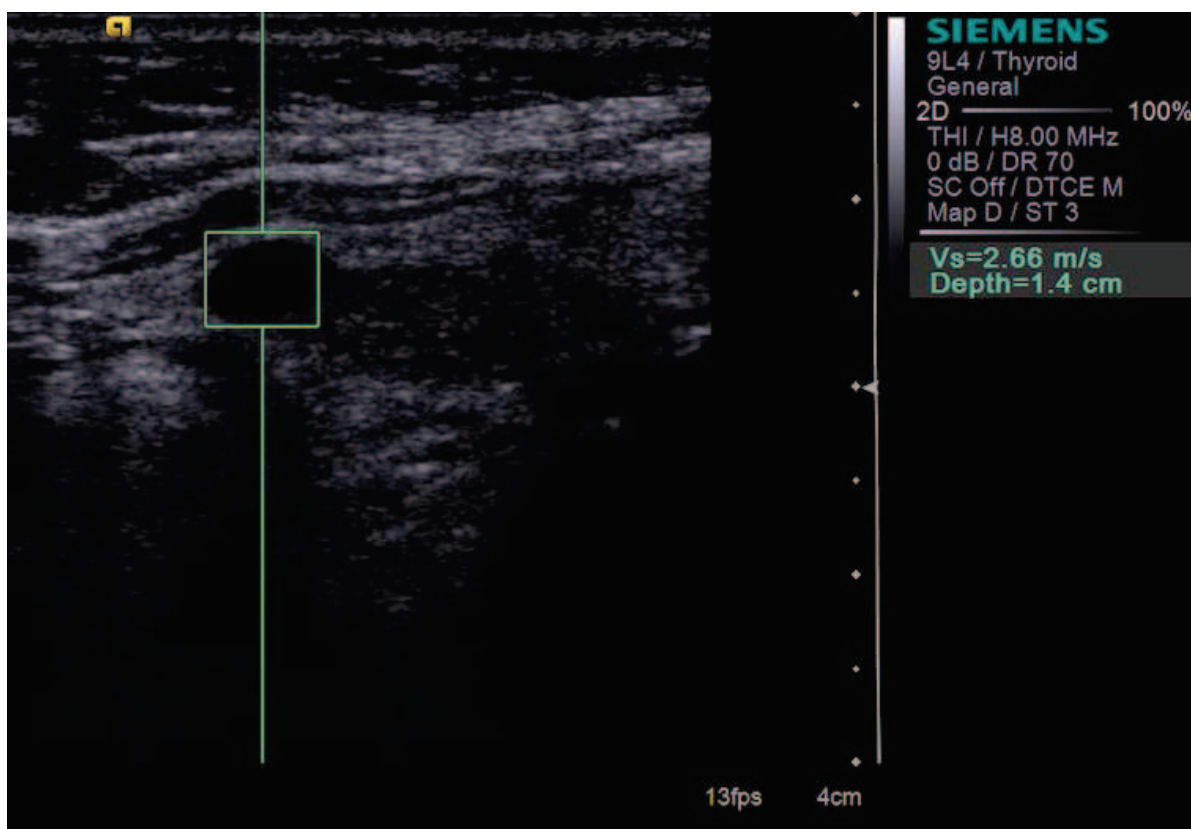


Figure 7. ARFI technique in a solid thyroid nodule: grey scale only evaluation, automatic ROI (1 mm), evaluation of SWE speed (m/s) in the cystic lesion = median value of 10 serial measurements.

The following devices using shear wave elastography are currently present on the market: Virtual Touch (Siemens and Philips) and speed imaging (SuperSonic Image) [30]. Supersonic

devices offer, as in strain elastography, both qualitative images: colour map images related to strain of the nodules, respectively, qualitative evaluation, with measurement of the elasticity of the lesion. **Table 1** summaries the qualitative and quantitative SWE information (**Figure 8**).

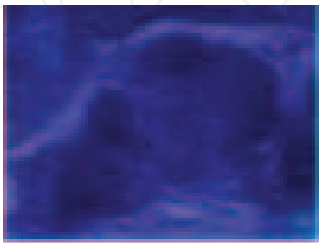
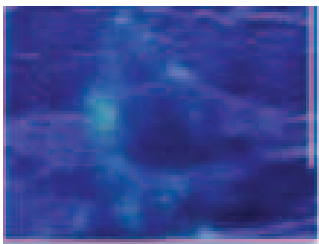
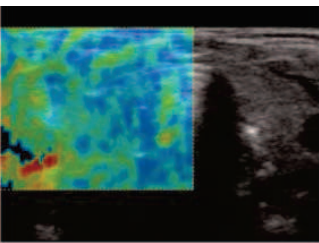
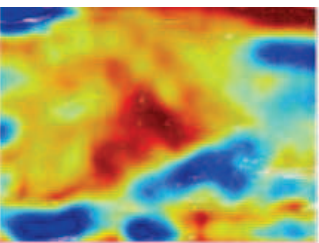
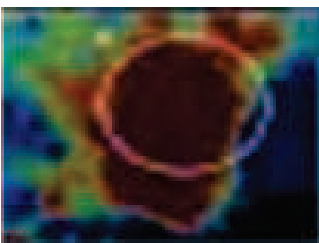
	Colour	kPa	Type
	Dark blue	>0-36	Benign
	Light blue	>36-72	
	Green	>72-108	
	Orange	>108-144	
	Red	>144-180	Malignant

Table 1. Qualitative (colour map) and quantitative (kPa) results in SWE—SuperSonic Aixplorer Machine.

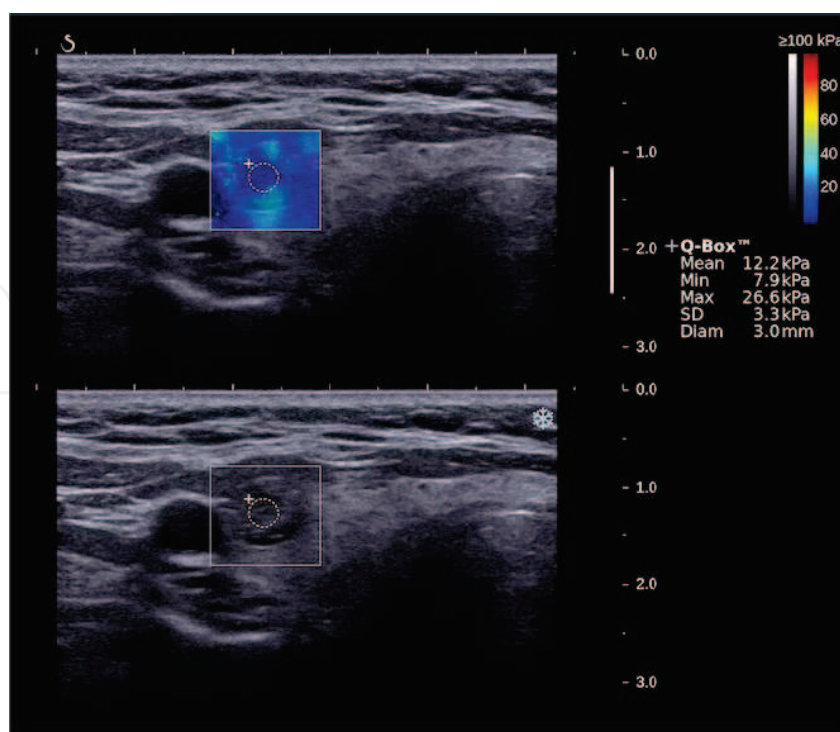


Figure 8. SuperSonic machine. Image below: conventional grey scale evaluation, solid thyroid nodule. Image above: SWE elastography: soft thyroid nodule, 12.2 kPa elasticity = benign lesion. Score 1: even soft elasticity in the whole nodule; Score 2: elasticity in a large part of the nodule; Score 3: elasticity in the peripheral part of the nodule; Score 4: no elasticity in the whole nodule; Score 5: no elasticity in the nodule and the area surrounding the nodule.

2.3. Elastography techniques

2.3.1. Strain elastography

The first information regarding elastography in thyroid nodular pathology came from the Rago group [22] which used the Ueno scale for breast lesions, adapted for thyroid, describing qualitative strain elastography evaluation: score 1 elasticity in the whole lesion, score 2 mostly soft, score 3 soft periphery, score 4 entire hard nodule and score 5 an elasticity beyond the 2B margins of the nodule = infiltration of the surrounding tissue initial described and used by Hitachi Machines (**Figure 9**). Other common colour schemes for thyroid RTE is the Asteria's 4-point scale based on Itoh scale for breast [38]: score 1 = entirely elastic, score 2 = mostly soft nodule, score 3 = mostly hard nodule, score 4 = entirely hard nodule initial described and used by Hitachi Machines (**Figure 10**). Generally, in RTE elastography, nodules with Rago scores 4 and 5, or Asteria scores 3 or 4 are considered highly suspicious for malignancy [24]. The initial result of the second evaluation showed a sensitivity of 97% and specificity of 100% for Rago's criteria [22], respectively, 94.1 and 81% for Asteria's criteria. Since these first reports, there has been much data describing the quality of RTE, with excellent meta-analysis: Moon [39], Sun [40], Dudea [21] and Wuguo [41] and also suggesting that the elastography evaluation is always made after the grey scale ultrasound and the observer integrates the 2B ultrasound

information with the RTE information, for a better diagnostic performance of thyroid cancer [24].

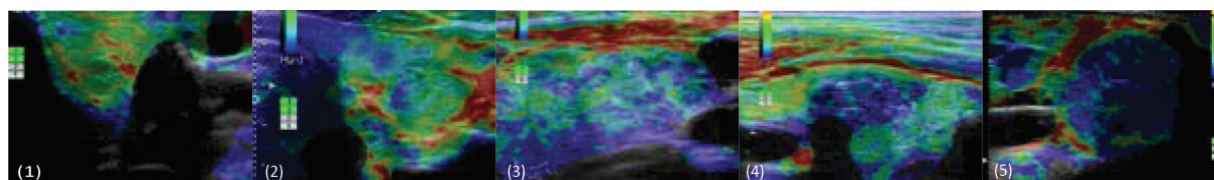


Figure 9. Rago criteria for qualitative strain elastography images. Score 1: even soft elasticity in the whole nodule; Score 2: elasticity in a large part of the nodule; Score 3: elasticity in the peripheral part of the nodule; Score 4: no elasticity in whole nodule; Score 5: no elasticity in the nodule and the area surrounding the nodule.

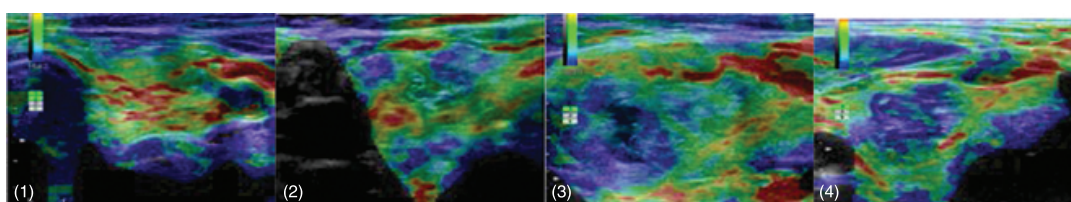


Figure 10. Asteria criteria for qualitative strain elastography images. Score 1: Elasticity in the whole nodule; Score 2: Elasticity in the large part of the nodule; Score 3: Stiffness in the large part of the nodule; Score 4: Nodule without elasticity.

When using the ES system, the diagnostic capacity of differentiating malignant lesions was high, calculated for a group of 4668 patients with 5481 nodules [40] with a pooled sensitivity of 0.79 (95% CI 0.77–0.81) of colour map elastography, confirmed by other more recent meta-analysis: sensitivity of 0.787% (95% CI: 0.793–0.861) and specificity of 0.812 (95% CI: 0.736–0.852) on 10,001 thyroid nodules [41]. The diagnostic results are good also for the ARFI strain elastography devices [20]

The semiquantitative approach of strain elastography was reported from the beginning of the use of this type of elastography in thyroid diseases [42]. The technique uses a comparison of the nodules with the surrounding non-nodular thyroid tissue, similar in depth (difference of depth less than 1 cm) [32]. The strain ratio evaluation, the semiquantitative approach, associates higher diagnostic values compared with qualitative elastography, with a pooled sensitivity of 0.85 (95% CI 0.81–0.89), respectively, a pooled specificity of 0.80 (95% CI 0.77–0.83) [40]. The only problem of the strain approach is the absence of a consensus: the threshold value should be used for the diagnostic.

In the EFSUMB guidelines, different articles are cited with different strain ratio values: 2.0 [43] sensitivity, specificity, positive predictive value (PPV) and NPV of 97.3, 91.7, 87.8 and 98.2%, respectively, value of 0.31 [44] that assures a NPV of 100% and a PPV of 42% using a cutoff of <0.15, respectively, a 2.05 value [31], with the mention that these studies used Q elastography/ARFI strain technique. The most published articles use strain ratio values between 2.5 and 4.5: 3.79 [45]; 2.73 [46]; 3.85 [47]; 4.225 [48]; 4.0 [49]; 4.0 [41], 3.75 [50]. The same values are seen in

a recent meta-analysis [40, 41], where the quantitative elastographic approach was better in the cancer risk evaluation than the qualitative color map evaluation. There are some differences when comparing the strain ratio values in different studies: retrospective analysis of confirmed cancer cases of FNAB or pathology reports [40] or previous calculated strain ratio value, specific for each center [51]. There are no specific values for different types of thyroid carcinoma: 5.02 ± 2.07 for papillary carcinoma, 4.95 ± 2.12 for follicular carcinoma, respectively, 6.54 ± 0.55 for undifferentiated carcinoma [52]. But there are correlations between the SR and Bethesda score on FNAB evaluation: mean SR = 1.94 ± 2.12 for Bethesda I + II, versus 7.07 ± 5.46 for Bethesda V + VI [53].

The WFUMB recommendations are yet to be published, but the breast guidelines have not recommended any clear value for strain ratio [30], so it would be difficult to give a universal recommendation.

There are also some other parameters used in strain elastography:

- Area ratio (AR) used in VTI devices, where the area of the nodule is measured and compared with the area of a surrounding thyroid tissue, three different measurements, and the mean value is considered [54]. The described threshold value for AR suggestive for malignancy is a ratio of 1.08 with a sensibility, specificity, PPV and NPV of 91.3, 86.6, 82.3 and 93.4%, respectively [54].
- Hard area ratio measures the ratio of the hard area within the nodule versus the whole nodule area, with a cutoff value of 0.6 suggestive for malignancy: 92.9% sensibility, 91.3% specificity and 92% accuracy [55], with difficulties when the hard area is not compact [46].
- Strain ratio nodule to sternocleidomastoid muscle: the muscle is considered the reference area for strain calculation and not the healthy thyroid tissue, with reasonable results: 90% sensitivity and 50% specificity for a cutoff value of 1.5 [56].
- Strain index is a ratio between the strain from the whole nodule divided with the strain of the soft part of the nodule, with a cutoff value of 2.05 [57].
- Stiffness ratio is a special ratio calculated by the Philips devices by comparing the stiffness of the nodule versus the surrounding apparent healthy tissue, with a described cutoff value of 3.16 [32].
- Systolic thyroid strain index = compares the highest strain near the carotid artery versus the lowest strain in the thyroid nodule, on a special fixed ROI of 2 mm × 2 mm [58]. No clear cut values are described.
- Elasticity contrast index = the technique is specific for Samsung machines—obtains a strain oscillation map, with malignant lesions showing a higher contrast versus a benign lesion [28]. The measurement should be done at least twice, in transverse section, with consideration of the greatest value [20, 28]. The cutoff value described in the literature is between 3, 5 and 4 [20, 59, 60]. It should be considered that the results are influenced by age, atherosclerosis, hypertension and conditions associated with tachycardia [61].

There are some limitations when observing RTE results: calcification, cyst and position of nodules [62], but the data are not clear, since there are other studies describing the excellent value of RTE in nodules with calcifications [20].

The main described limitations/special situations are the following:

- Nodule size: there are some studies suggesting that large nodules, over 3 cm maximum diameter can underestimate the stiffness of the nodule [63]. This aspect is not recognised universally, since there are studies saying that the diagnostic quality of RTE is unaffected by the nodule size [29].
- Position of nodule: profound nodules, especially in overweight patients, are sometimes difficult to be evaluated by strain elastography if the signal is not deep enough because stress transmission is reduced as the distance increases, with false positive hardening of the nodule [63]. Isthmic nodules should be explored with caution, since they are between hard surfaces and longitudinal scans should be used in order to have also healthy thyroid tissue for semiquantitative evaluation [21]. When evaluating thyroid nodules, especially anterior ones, they should be compared with thyroidal tissue and not with surrounding muscles because they can be false negative evaluated as soft [64].
- Compression intensity per se can change the appearance of the nodules. Strain elastography is dependent on the experience of the examiner. The operator has to perform compression that should not only be reliable but also reproducible. Non-uniform compression produces variability [55]. Several compression cycles are required for a stable and reliable result [55, 65, 66].
- Pre-stress compression can change the displayed stiffness of the nodule by a false increase in stiffness [67] so that the operator should not perform any precompression or palpation before RTE examination [67].
- Bull's eye effect is a typical appearance of the cystic lesion (simple or complex), which has been described in breast elastography, but can be seen in large cystic lesions and also in thyroid.
- The healthy thyroid parenchyma, which is used for a comparison of the stiffness of the lesion, should be at least in more than a half with "green colour" in order not to influence the strain ratio. Thyroid atrophy, diffuse fibrotic changes can affect the relative stiffness of the nodule when compared with the surrounding tissue [21].
- Calcifications inside the nodule are associated with increased stiffness. This is considered the rule, regardless whether there are micro calcifications or rim calcifications [22, 66, 68, 69]. Even if this is generally accepted [61] there are some studies that have demonstrated the contrary: elastography is a helpful differential diagnostic tool in calcified thyroid nodules [20].
- Condition associated with tachycardia—in techniques that use internal compression induced by carotid pulsation, the lesion stiffness is changed.

- Observer experience: after all the previous cited data, experience is required in order to reach the correct degree of external compression, to choose the right position and dimension of ROI, although some authors say [33] that the learning curve is not influenced by the diagnostic performance of RTE.

2.3.2. Shear wave elastography

There are two major types of this elastography, with totally different diagnostic characteristics [24]. They use different ways of generation transversally propagating waves that propagate with different speed in the thyroid tissue, proportionally to the stiffness of the tissues: acoustic radiation force impulse quantification techniques and real-time shear wave elastography.

ARFI quantification estimates the stiffness of the tissue by measuring the speed of ultrasound-generated waves [70]. During a pause in breathing, the ARFI option of the device is turned on, the standard ROI (5 mm diameter or 2 cm diameter) is positioned on the nodule in the solid part and the device registers the speed [35]. Five to ten successive measurements are recommended for each nodule in order to obtain a valid evaluation [29, 71]. The normal interval of speed is between 0 and 9 m/sec [35], the higher the speed, the higher the tissue stiffness.

There are some studies evaluating the ARFI diagnostic quality in the differential diagnosis of thyroid nodules. The differences suggested by ARFI between benign and malignant thyroid is the value of speed, with different cutoff described values with a different sensitivity and specificity: 2.75 m/s [72] 2.9 m/s, sensibility of 91.3% and specificity of 85.10% [54], 2.85 m/s sensibility of 94.4% and specificity of 85.3% [72], 2.55 m/s, sensibility of 86.36% and specificity of 94.42 [73] 2.87 with 75% sensibility and 82.2% specificity [35], or 3.1 m/s with a specific of 91% [70]. All the values were retrospectively calculated with no clear recommendation of a used value [61] not even with a recommendation regarding values on the normal population [61]. The European guideline concluded that there was not sufficient data for reaching any conclusion at this time.

The method has some significant technical limitations:

- The dimensions of ROI are fixed, with two options: 5 mm/2cm large window. The majority of the studies are performed in nodules that are larger than 2 cm in diameter [70, 73]. In smaller nodules, not only is the measurement inaccurate [21] but also the velocity of the US wave is not stable [74].
- Nodule composition: inhomogeneity due to calcifications or cystic degenerescense makes the placement of ROI inside the nodule impossible [75].
- The penetration depth of ARFI is a maximum of 5.5 cm or so? Deeper lesion; big goitres or overweight patients are not suitable for ARFI evaluation [76].
- The devices measure speeds with values between 0 and 9 m/s [35]. Higher speed cannot be measured so very stiff nodules cannot be evaluated [29, 35, 77].
- Experienced operators are needed for the evaluation to avoid pressure on the evaluated skin in order not to influence the measurement [24].

ARFI evaluation is a simple evaluation, but further studies are required before considering it a valuable stiffness evaluation tool in nodular thyroid disease.

2.3.3. Real-time shear wave elastography (supersonic elastography SSE)

The SSE is performed like a conventional ultrasound, with a linear probe at the end of the conventional US evaluation, with the patient in apnoea [24]. The procedure was first used in 2010 [78], since then numerous papers have evaluated the diagnostic performance of SSE. The evaluation is operator independent, requires no external compression or no?, generating qualitative information: colour maps with following colour code: blue = soft tissue, red = hard tissue, respectively, quantitative information evaluated by elasticity index (EI) expressed in kilopascal [24, 78]. As strain elastography, SSE is displayed in parallel with grey scale US, with placement of ROI on the nodular lesion. For quantitative evaluation at least three loops should be recorded [79] with no movements of the transducer.

The diagnostic qualities of the qualitative, colour map SSE are fair, with a sensibility of 95.5% and specificity of 45.7% for elasticity II score (predominantly soft), 72.7 and 84.5% for elasticity III score (elastic on edges and rigid middle, respectively, 54.5 and 97.4% for elasticity IV score (markedly increased stiffness) [80].

Most of the studies report different threshold values for EI as a cutoff for differentiating benign versus malignant lesions.

The described cutoff values are comprised between 34.6 and 90.34 kPa without being able to identify a unique cutoff value [81]: 65.0 kPa (sensitivity = 85.20%, specificity of 93.90% [78], 6.00 kPa (sensitivity = 80.0%, specificity = 90.50% [82], 34.50, sensitivity of 76.90% and specificity of 71.10% [78], 90.34 kPa (sensitivity of 90.34% and specificity of 86.89% [80], 45 kPa (sensitivity of 83.30% and specificity of 91.40% [83].

Interestingly enough, one study [80] evaluated the different diagnostic values of SSE using different cutoff values for the same group of cases (cancer prevalence of 21.35%): sensitivity of 95.2%/specificity of 67.1% for hardness ≥ 50 kPa, sensitivity of 90.5% and specificity of 72.2% for hardness ≥ 59 kPa, sensitivity of 81.0% and specificity of 77.3% for hardness ≥ 65 kPa, sensitivity of 85.7 % and specificity of 81.3 % for hardness ≥ 49 kPa, sensitivity of 90.5% and specificity of 73.5% for hardness ≥ 42 kPa, respectively, 95.2% sensitivity and 70.3% specificity for a threshold for hardness of ≥ 38 kPa. This is the best example that there is still a lot to do in respect of unifying the SSE information. Still, increased hardness values are considered independent predictors of thyroid malignancy with high sensitivity (95.0–95.5%) [84]. The European guideline does not offer any clear information regarding SSE [61], only the comment that the higher the EI, the higher the probability of malignancy. There is still no standardised method for measurement of thyroid lesions; no clear EI cutoff value is described, not even for the same machine [78–80].

However, the method can guide the FNAB, avoiding the puncture of benign nodules [85] independent of the coexistence of autoimmune thyroid disease.

There are some limitations described for the SSE technique:

- If external pressure is used, it produces a false positive increase in elasticity with false positive results [79, 86];
- The presence of fluid does not permit the propagation of the shear wave with no information beyond the liquid zone;
- The presence of calcifications alters the accuracy of SSE especially in small nodules [82, 87].
- Vertical artefacts;
- Structure of the neck *per se* can affect the quality of the shear wave; the presence of trachea, carotid artery and surrounding tissue can affect the SSE diagnostic performance [80] especially in deeply located nodules.

More data are still required in order to find the correct location of SSE in nodular thyroid disease evaluation.

2.4. Comparison of strain and shear wave elastography

Regardless of the type of elastography, the used principle and the evaluated parameters, the evaluation of the hardness of lesions is an important aspect that adds diagnostic information and value compared with classical sonography. There are some studies that have attempted to answer the direct question: which elastography technique should be used for a better differential diagnosis of thyroid cancer [41, 72, 88, 89]?

A recent meta-analysis [89] evaluation of 10,001 thyroid nodules showed better diagnostic sensitivity (0.830, 95% CI: 0.793–0.861 versus 0.787, 95% CI: 0.727–0.847) and specificity (0.812, 95% CI: 0.763–0.852 versus 0.805, CI 95%: 0.712–0.873) with better area under receiver operator curve (AUROC) of 0.885 for RTE compared with AUROC of 0.842 for SWE [41].

Another comparative analysis [88] evaluated the diagnostic performance of RTE versus SSE, comparing a Hitachi Ascendus device, with a 5–13 MHz linear probe versus an Aixplorer Device, with a 4–15 MHz linear probe, on the same 49 consecutive patients with thyroid nodular disease. After analysis of the pathology report, the two diagnostic approaches were compared, with similar results for sensitivity, specificity positive and negative predictive value, regardless of the nodule size: below 1 cm, between 1 and 3 cm or bigger. Sensitivity was higher for RTE than for SWE (79.0% versus 68.4%) with better accuracy (82.8% versus 81.3%) and Negative predictive value (90.5% versus 86.7%), but the differences were not statistically significant. Moreover, coarse calcified nodules were false-positive results in RTE and true-negative results in SWE. The limitation of the study was the low number of the cases, the authors recognising that the studied population may not be representative of a screening population [88]. Another head-to-head comparative study, comprised 30 consecutive patients, with the pathology report as the golden standard diagnostic [72], comparing the RTE technique with the ARFI evaluation, using the same machine, Acuson Siemens 2000 device, concluding that the AUROC of ARFI (0.94) was higher than that of RTE (0.78). However, the number of cases was very small, the heterogeneity of the nodules high, uninodular and polynodular goitre were included, with exclusion of nodules smaller than 1 cm, and the results of this study were not confirmed by other studies. The performance of two of the above-mentioned devices,

Hitachi machine and Siemens S 2000, were also compared on a head-to-head evaluation, performed in 80 consecutive patients, also with a pathology report as the golden standard [90]. Elastographic patterns demonstrated a moderate and high degree of consistency for compression elastography (RTE) and VTI (ARFI); there was no conclusive result by measuring absolute velocities (ARFI) with an overlapping of shear wave velocity for malignant nodules with the velocities for benign nodules; shear wave techniques were inferior to strain elastography.

Without being conclusive, till now, evidence suggests that strain elastography seems to be better in the diagnostic of thyroid nodular disease.

3. Conclusion

The estimation for 2019 is that PTC will be the third most common cancer in women [90]; the correct identification of suspect cases and targeted diagnostic for high-risk lesions is still the challenge in thyroid nodular disease. There is substantial evidence showing that elastography indicators are more predictive for malignancy than conventional grey-scale patterns, such as hypoechogeneity, inhomogeneity, microcalcifications, irregular margins, no halo sign, taller than wide or intranodular vascularisation [91]. A positive elastogram, suggestive of malignancy is more useful in the diagnostic than a positive grey-scale ultrasound evaluation [91].

The association of grey scale US and elastography facilitates the evaluation of nodules with intermediate cytology [92]. The appearance of the nodules of elastography can change the attitude towards FNAB. In the cases of soft nodules, without any grey-scale suspicious characteristics, the FNAB can be delayed or postponed [93]. Authors [94] consider that nodules classified as Asteria 1 and Asteria 2 should not undergo FNAB because of the high NPV of elastography. Presence of a hard nodule on an elastogram should indicate the need for FNAB, regardless of the aspect in grey scale US [93].

Thyroid elastography should be considered in conjunction with other ultrasound characteristics, such as in breast cancer. Low risk nodules with increased stiffness should be referred to FNAB, regardless of dimensions or conventional ultrasound characteristics; medium risk nodules with low stiffness should be followed up instead of FNAB, and medium and high risk nodules with increased stiffness should be recommended for FNAB. Elastography increases the specificity of grey scale US; it should be always integrated with its information and should be considered as complementary to conventional US.

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