Chapter

Elastography Methods in the Prediction of Malignancy in Thyroid Nodules

Andreea Borlea, Laura Cotoi, Corina Paul, Felix Bende and Dana Stoian

Abstract

Ultrasonography provides a primary stratification of the malignancy risk of thyroid nodules for selecting those that need further evaluation by fine-needle aspiration cytology (FNAC). Ultrasound elastography (USE) methods have been more recently proposed as a promising tool, aiming to increase the accuracy of baseline ultrasound. By means of USE, stiffness is assessed as an indicator of malignancy. Strain elastography was the first method used in thyroid imaging, with very good accuracy in discerning thyroid cancer. More recently, 2D shear-wave elastography also confirmed to be a valuable tool with similar outcomes. The advantages, limitations, and technical details of the elastography methods currently used in assessing thyroid morphology, particularly thyroid nodules, will be presented and compared in this chapter.

Keywords: thyroid imaging, elastography, strain, shear wave, malignancy risk

1. Introduction

Thyroid nodules are among the most common thyroid pathologies, and their etiology is diverse [1, 2]. They represent masses of abnormal proliferation, formation, and structure within the thyroid parenchyma [3]. The prevalence of thyroid nodules increases with age, reaching up to 50% after 65 years, and they are more commonly found in women [4]. The diagnosis of nodules less than 1 cm, as well as lesions with a deep location, is most commonly missed at physical examination; thus, thyroid imaging techniques have drawn increasing clinical attention [5]. Conventional neck ultrasound (US) is still the preferred method for assessing thyroid morphology, including the presence and appearance of thyroid nodules [6–9].

Thyroid cancer accounts for the most common endocrine malignancy, with a slowly increasing incidence [10, 11]. Its prevalence reaches 7–15% in the group of thyroid nodules [12], and it does remain one of the cancers with the least risk of death [13]. There are certain categories considered at greater risk for cancer, such as young adults, children, and patients with a history of neck irradiation [14]. Size also seems to impact the prevalence of malignancy; nodules larger than 2 cm were more often malignant compared to smaller lesions [15], but multinodular goiters do not seem to increase the likelihood of malignancy [16].

Fine-needle aspiration cytology (FNAC) represents the procedure of choice for further examining the thyroid lesions with high-risk features documented by means of clinical or US evaluation [17]. Thyroid cytology is most commonly reported using the Bethesda classification (I-VI), with different prediction of malignancy for each category, which is meant to guide the case management decision [18]. A less aggressive approach to diagnosis and treatment was introduced starting with the 2015 American Thyroid Association (ATA) guidelines, which advise reducing FNAC indications and endorse "active surveillance" of tumors with very low risk [19].

Ultrasound elastography (USE) proved to be a valuable imaging tool in predicting the risk of malignancy of thyroid nodules [20, 21] and also in decreasing the FNAC indication [17, 22]. It assesses tissue distortion in reply to stress, assuming that a hard lesion presents an increased likelihood of cancer.

2. Ultrasound of the neck

The current recommendations regarding the stratification of risk for Thyroid nodules (TN) include a thorough anamnesis, clinical evaluation, and neck US characterization. The B-mode (2B) evaluation is performed using linear probes, with high frequency (7.5–15 MHz) for excellent details and a resolution of 0.7–1 mm up to 5-cm depth. In most of the cases, frequencies of 10–14 MHz or higher are preferred, and linear transducers with lower frequency are required in selected cases, ensuring depth penetration [23, 24].

High-resolution US is the most widely used evaluation of thyroid nodules, both for screening purposes and in presurgical settings [25–27]. US of the neck currently represents the most affordable, sensitive, and efficient imaging method for evaluating thyroid morphology, and it is widely available; its role in differentiating cancerous nodules from nonmalignant ones is crucial [19, 28–30].

Considering the large accessibility to US equipment, the current trend is to have standardized homogeneous reports, describing the general aspect of the thyroid, its volume, the presence or the absence of nodules, the number of nodules, their size, position, extracapsular relations, and the following US characteristics: internal composition (solid, cystic, or mixed), shape, margins, echogenicity, echotexture, the presence of echogenic foci, and the Doppler vascular pattern [31].

Certain US features [24, 32–35] have been described to be highly specific for malignancy, such as solid or mostly solid composition, the presence of microcalcifications, spiculated margins, markedly hypoechoic texture, extrathyroidal extension, and "taller than wide" shape, namely, the vertical diameter exceeds the transverse one. These findings are established especially for papillary carcinomas [36]. The US characteristics of follicular cancers are highly similar to follicular adenomas, and no typical appearance was described for medullary thyroid cancer (MTC), but some small studies found that half of the studied MTCs were solid, and hypoechoic and microcalcifications were more prevalent (16%) than in the benign controls [37]. Benignity-related features include smooth margins, a spongiform appearance, and completely cystic composition [38]. **Figure 1** displays the images of US low- and high-risk thyroid nodules.

After the comprehensive examination of thyroid morphology, the presence of cervical lymph nodes (LNs), their number, and appearance should be looked for,

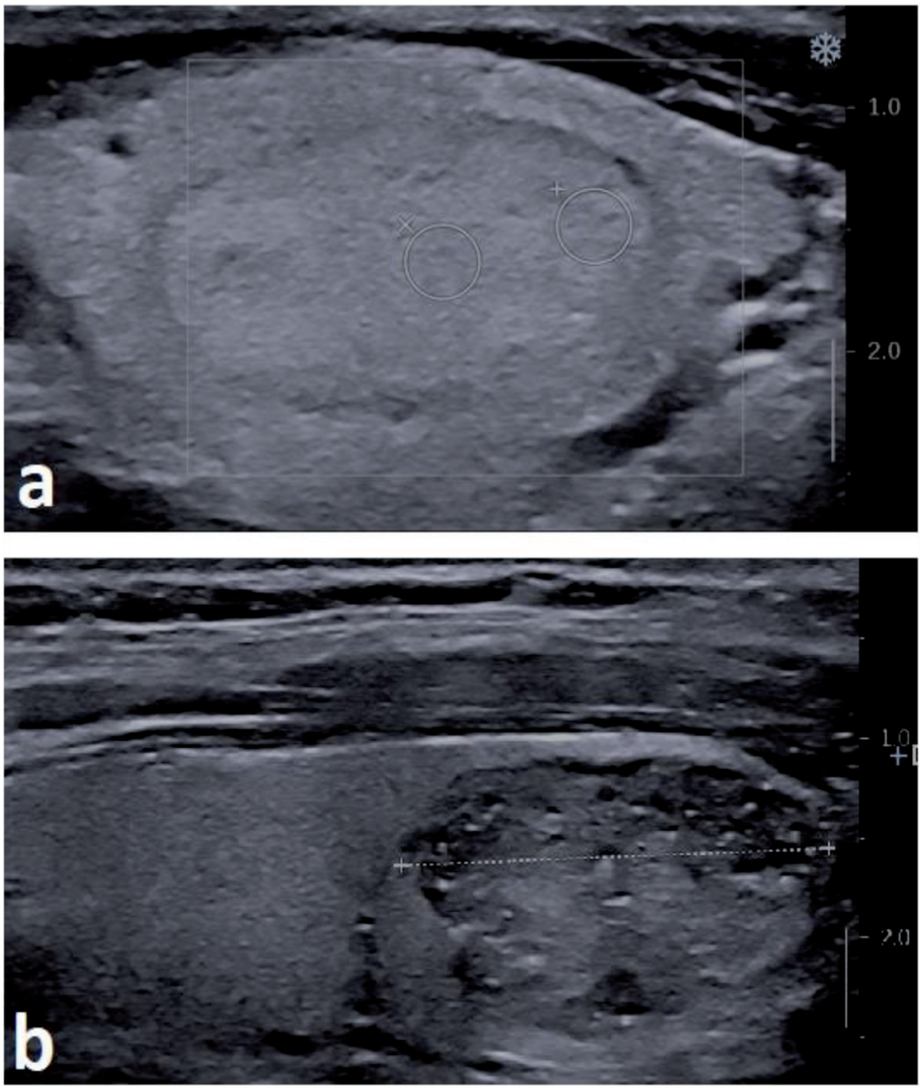

Figure 1.
B-mode image of a thyroid nodule with (a) low-risk US appearance (oval-shaped, isoechoic, peripheral halo, regular margins), benign nodule and (b) high-risk US appearance (inhomogeneous, hypoechoic, punctate echoic foci, and irregular borders), papillary thyroid cancer.

particularly in cases with intermediate- and high-risk nodules [9]. Hilum absence does not diagnose malignancy, but its presence removes its suspicion [39]. An enlarged short-axis diameter is predictive of malignancy, but it is not relevant for the long axis [39–42]. When evaluating multinodular goiters, all the lesions should be described, and their appearance should be assessed in all the cases. If more than one nodule presents features of risk, each of them should be further assessed by FNAC [7, 8, 24].

The concept of thyroid imaging reporting and data system (TI-RADS) was introduced by Horvath et al. in 2009 [43]; these quantitative US classifications are currently used for a more accurate stratification of the US risk of malignancy [44–46].

3. Elastography in the evaluation of thyroid nodules

US elastography noninvasively estimates the stiffness of a thyroid nodule by measuring the tissue displacement, respectively, the internal or external mechanic constraint induced to the tissue. The distortion appears when the nodule is compressed by a controlled external pressure, as in strain imaging, or the shear waves (SWs) induced by the US probe itself—in shear-wave elastography (SWE) [9]. It grants for "virtual palpation" of the thyroid nodules, which otherwise may not be palpable. Stiff nodules are considered to have an increased risk due to the desmoplastic transformation, disclosing firm, and tumor stroma, characterized by abundant myofibroblasts and collagen fibers [47].

Thyroid elastography was recognized starting with the 2016 American Association of Clinical Endocrinology (AACE) guidelines in the diagnosis of thyroid nodules, complementary to grayscale, and importantly, they do recommend that stiff nodules should be further evaluated by FNAC [48]. It is imperative to take into account the recommendations formulated by the 2017 World Federation for Ultrasound in Medicine and Biology (WFUMB) guidelines on the clinical use of ultrasound elastography in thyroid diseases, which validate the use of USE as an additional tool in thyroid evaluation, no matter the technique [24]. Thyroid elastography was also employed for diffuse diseases, including autoimmune thyroid disease, aiming to assess the severity of fibrosis [49]. As for multinodular goiter, elastography should be used to assess the firmness of each nodule within the thyroid, when the technique is available to the examiner [7, 24]. Together with color Doppler evaluation, it can be of help, when aiming to distinguish between one heterogeneous nodule and the aspect of multiple overlaid lesions appearing as one.

Currently available elastography techniques have various limitations related to the shear properties of the tissue. Nonetheless, in some cases, they may be complementing each other [20]. Elastography can be easily used in the assessment of the thyroid gland taking into account its conveniently superficial position, but it is still not largely embraced in practice, nor comprised in all the risk stratification systems [24].

Still, there are some open questions: Could we upgrade the risk category in nodules with high stiffness, as suggested by the previous mentioned guidelines? Is there a recommended threshold for qualitative measurements suggestive for a special risk category, as seen in breast elastography guidelines, which elastography technique should we use?

3.1 Strain elastography

Strain elastography (SE) was the first to be used, and it proved to be of great value in thyroid imaging. It displays tissue stiffness, defined as the difference in length along compression divided by the length ahead of compression. Elasticity is expressed as the Young's modulus, the relation between the stress that is applied and strain (E = stress/strain) [20]. The compression can be external, slightly applied manually by the operator and verified by the US machine scale (**Figure 2**); it can be generated by acoustic radiation force impulse (ARFI), or it can be internal, endogenous, by minimal physiologic movement (vascular pulsations and muscle contraction) [20, 50]. The direct quantification of stress is not attainable by the US machines, and strain is displayed relatively through elastograms [51].

3.1.1 Qualitative SE

The first approach in evaluating strain elastograms (**Figure 3**) is through qualitative pattern-based scoring systems such as the ones described by Asteria et al. [52] on a scale from 1 to 4, with scores 3 and 4 being usually considered suggestive for malignancy and the four-pattern score by Rago et al. [53], where high risk includes scores 4

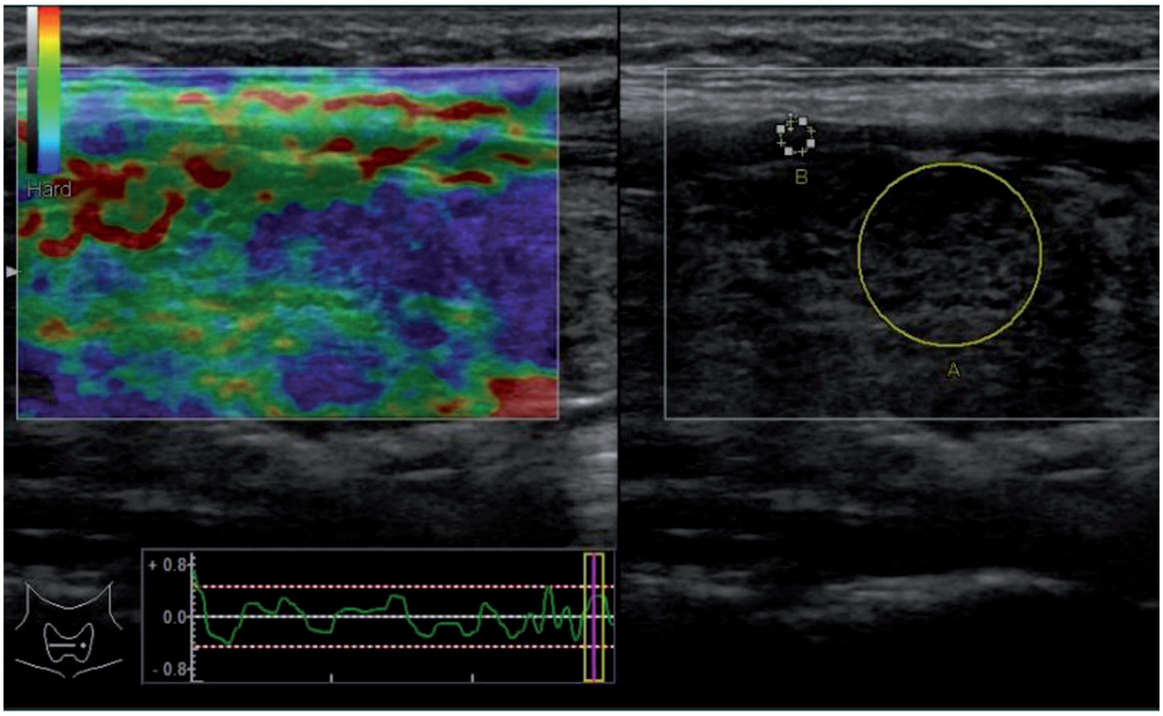

Figure 2.
Pressure scale (bottom, left) for acquiring optimal elasticity images. Elastogram obtained on a Hitachi Preirus device.

and 5. The color-map display settings are not currently standardized, and elastograms are carefully interpreted in accordance with the legend on the screen.

Qualitative elastography proved very good diagnostic quality [54, 55]. A meta-analysis that comprised 20 studies assessing the diagnostic value of SE in discriminating cancerous nodules and even its role in reducing FNACs presented a pooled specificity (Sp) of 80%, a sensitivity (Se) of 85%, the positive predictive value (PPV) of 40%, and the negative predictive value (NPV) of 97% [30, 55].

Nevertheless, some authors reported poor inter- and intraobserver agreement for qualitative elastograms [56], but the results were improved for studies using the carotid pulsations (k = 0.79) [57].

3.1.2 Semiquantitative SE

The strain ratio (SR) (**Figure 4**) provides a numeric value that offers a more objective approach, with less interobserver variability (k = 0.95 [58]) and easier to learn. This semiquantitative parameter is obtained by comparing two manually selected regions of interest (ROIs) within the same captured image, ideally located at the same depth: the first one on the target nodule and the second one on the adjacent reference thyroid parenchyma [59]. Neighboring muscle may be used in cases when thyroid gland is affected by a diffuse disease or there is not enough thyroid tissue found in the image.

SE showed encouraging results in predicting thyroid malignancy, with improved performance over time. A 2013 meta-analysis including 24 studies yielded better diagnostic performance for SE compared to conventional US features (Se = 82% and Sp = 82% for the qualitative score and Se = 89% and Sp = 82% for the strain ratio) [60]. A 2017 meta-analysis reported Se = 84% and Sp = 90% [61]. The cutoff values for the SR in real-time elastography vary in different studies and with the equipment

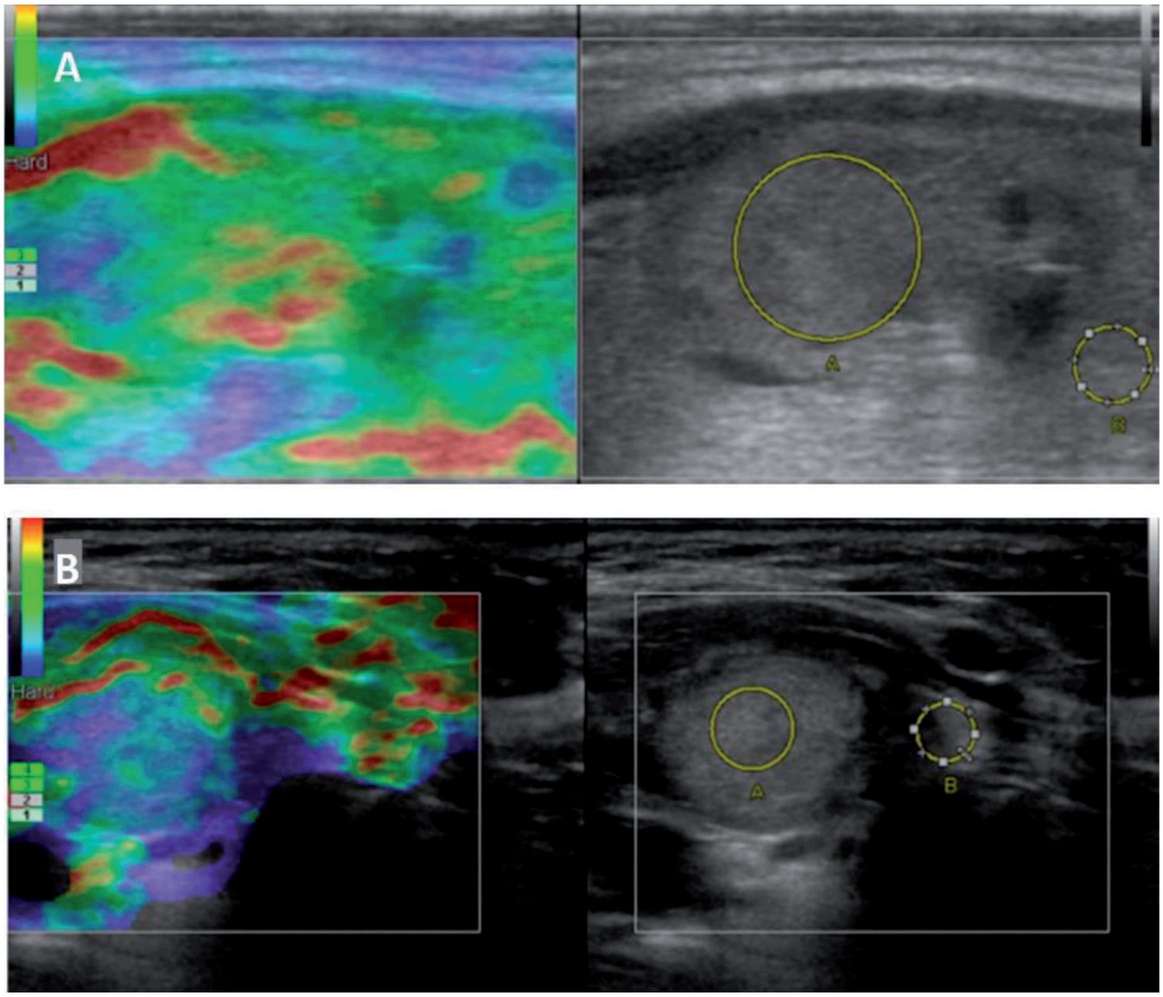

Figure 3.
Qualitative strain elastograms: A—Soft nodule, Asteria 1, benign nodule; B—Mostly stiff nodule, Asteria 3, papillary carcinoma (Hitachi Preirus equipment—The color blue displays hard tissue).

that was used: SR > 4 with 96% specificity and 82% sensitivity [62]; SR >2.7 with 93.6% accuracy [63]; SR > 2 with 93.8% accuracy [64]; SR > 2.45 with 73.9% sensitivity and 73% specificity; and SR > 4 with 95% accuracy [65].

3.1.3 2B us + SE

An approach combining conventional US and elastography was proposed. Initially, results were conflicting. Moon et al. found no significant improvement in diagnosis when combining the two imaging methods [66]. However, other studies found excellent results when adding SE to the standard US evaluation. Trimboli et al. reported for the combined assessment Se = 97% and NPV = 97% versus US-only Se = 85% and NPV = 91% [67]. Russ et al. presented a TI-RADS classification including SE parameter "stiffness" in the risk-assessment strategy, obtaining increased sensitivity (96.7% vs. 92.5%), but decreased specificity [68].

The role of strain elastography was assessed for the category of micronodules (less than 10-mm diameter). A small study including 86 patients demonstrated the value of the technique in detecting microcarcinomas with good diagnostic value in area under the receiver operating characteristic (AUROC): 0.743, with the sensitivity (Se) of 88.9% and the specificity (Sp) of 89.3%. In addition, the missed diagnosis rate was significantly lower for SE compared to conventional ultrasound ($p < 0.05$) [3].

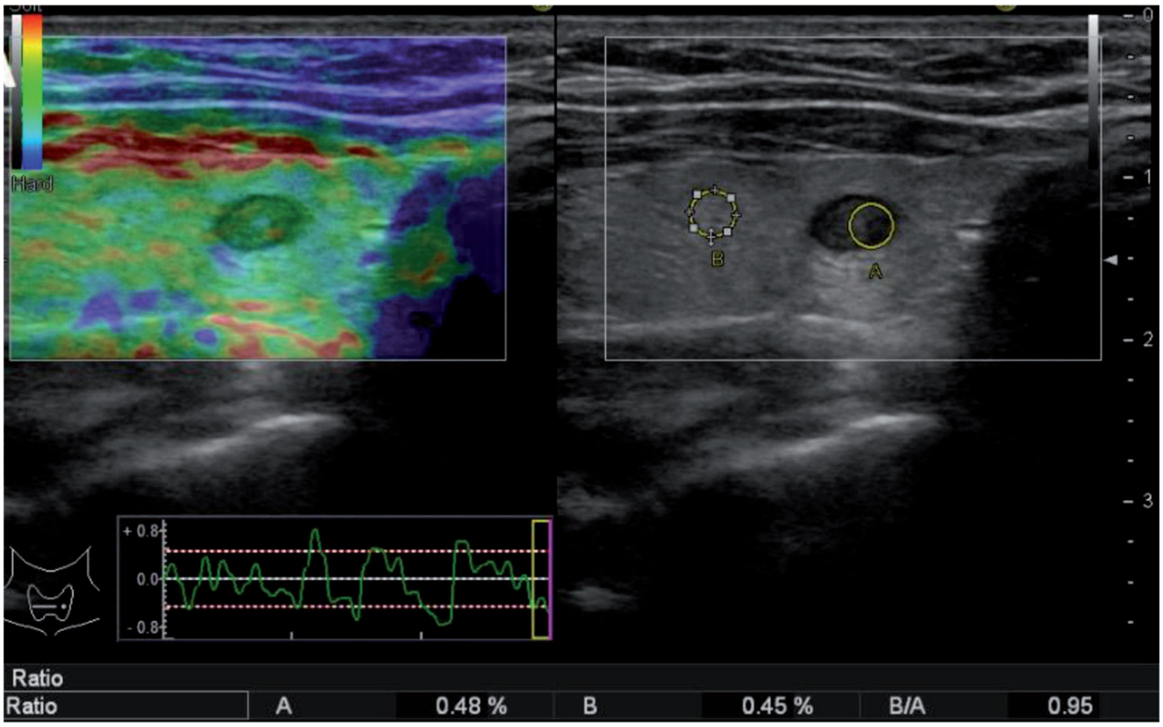

Figure 4.
Strain ratio—Nodule-to-parenchyma—Is 0.95. Soft nodule, similar strain as reference neighboring thyroid tissue; benign micronodule.

Some of the drawbacks of the technique consist in its subjectivity and its dependency on the operator and on compressibility [61]. Some authors outlined an altered performance for nodules bigger than 3 cm, as well as for very small ones, and for coalescent nodules [22, 24, 69].

Increased stiffness can be identified in benign nodules with fibrosis or coarse calcification, generating false-positive results [70, 71]. **Figure 5** illustrates an artifact generated by intranodular calcification that may falsely indicate a stiff thyroid nodule.

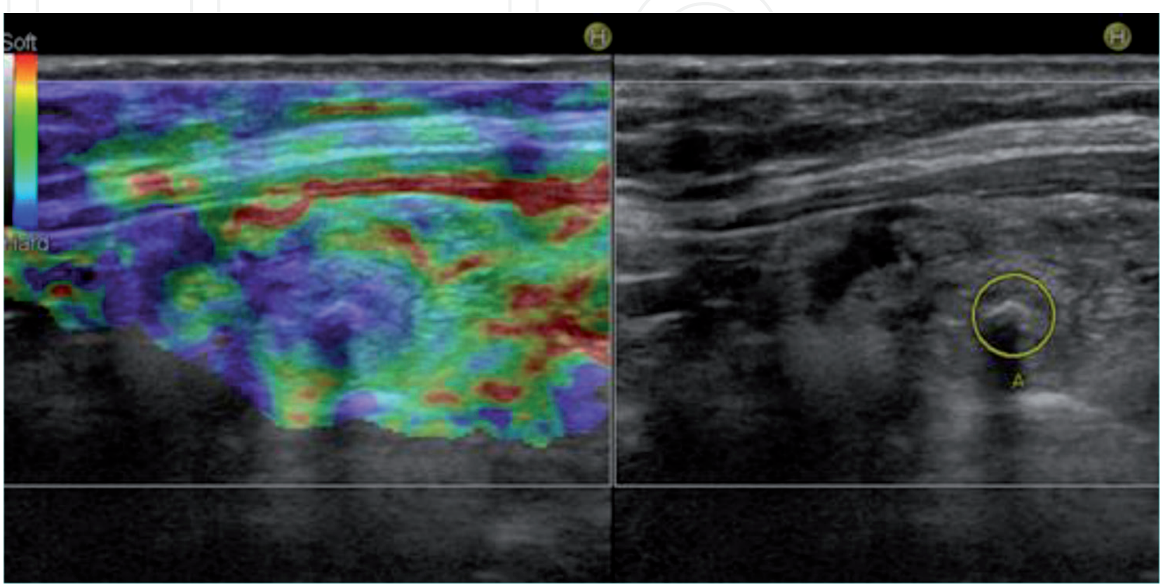

Figure 5.
SE false-positive result: Intranodular calcification in the ROI.

Presently, it is well established that follicular carcinomas may appear misleadingly elastic in SE; therefore, elastography may not be appropriate for diagnosing this particular category (44% false-negative results); other nonpapillary cancers or metastasis may also be soft [24, 70].

3.2 Shear-wave elastography

Shear-wave elastography provides the quantitative measurement that SE does not offer. It is also less dependent on the operator and, consequently, is more reproducible [72]. These dynamic techniques comprise ARFI imaging, point-SWE (pSWE), and 2D-SWE, and rely on acoustic impulses from the US probe that induce tissue movement and generate transverse shear waves. The quantitative elasticity measurement is obtained by assessing the shear wave speed, measured in meters per second or the elasticity index (Young's module) measured in kilopascals [21, 50].

Transient elastography integrates the US transducer and an exterior vibrating "punch" to create shear waves. It is largely employed (FibroScan and Echosens) for evaluating liver fibrosis but is not feasible for thyroid evaluation [73].

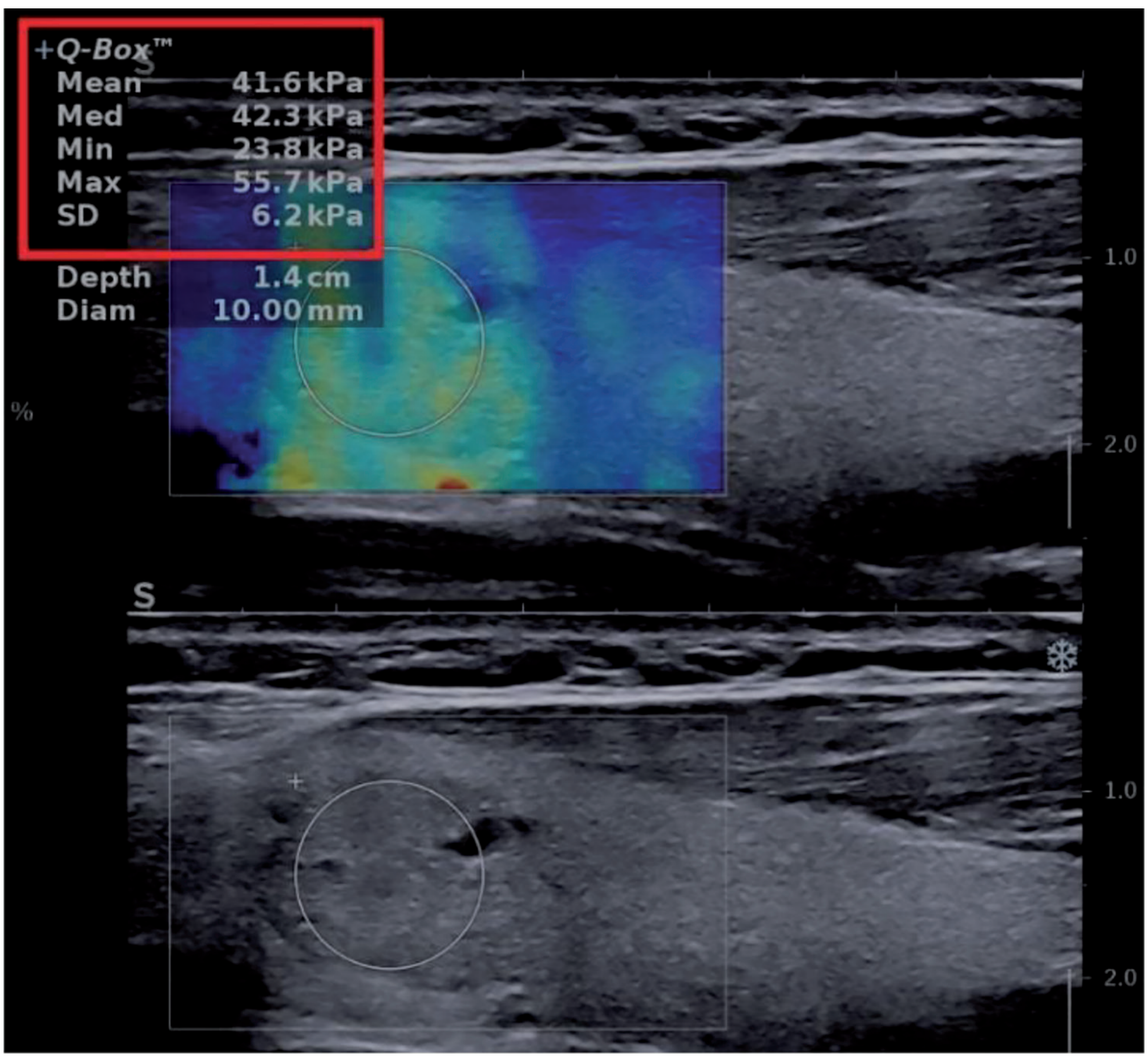

Figure 6.
2D-SWE elasticity parameters of a thyroid nodule with stiff areas displayed by the Hologic SuperSonic Mach 30 equipment, Aixplorer. Q-box parameters: EI mean = 41.6 kPa; med = 42.3 kPa; min = 23.8 kPa, max = 55.7 kPa; standard deviation (SD) = 6.2 kPa; ROI at 1.4-cm depth; ROI diameter = 10 mm.

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In monoplane SWE (point-SWE—pSWE), the ARFI mechanically stimulates the tissue in the ROI applying acoustic push pulses that create local tissue displacement in the axially and shear wave (SW) velocity is estimated (m/s), providing a numerical value (Siemens, VirtualTouch Quantification, VTQ; Phillips ElastPQ) [73].

Biplane SWE (2D SWE) and 3D SWE provide a real-time imaging of a quantitative color elastogram superimposed over 2B images and an estimation of SW speed. Supersonic shear wave employs focused ultrasonic beams, which spread through the entire imaging region and show on a color map the speed of the SW or plainly the

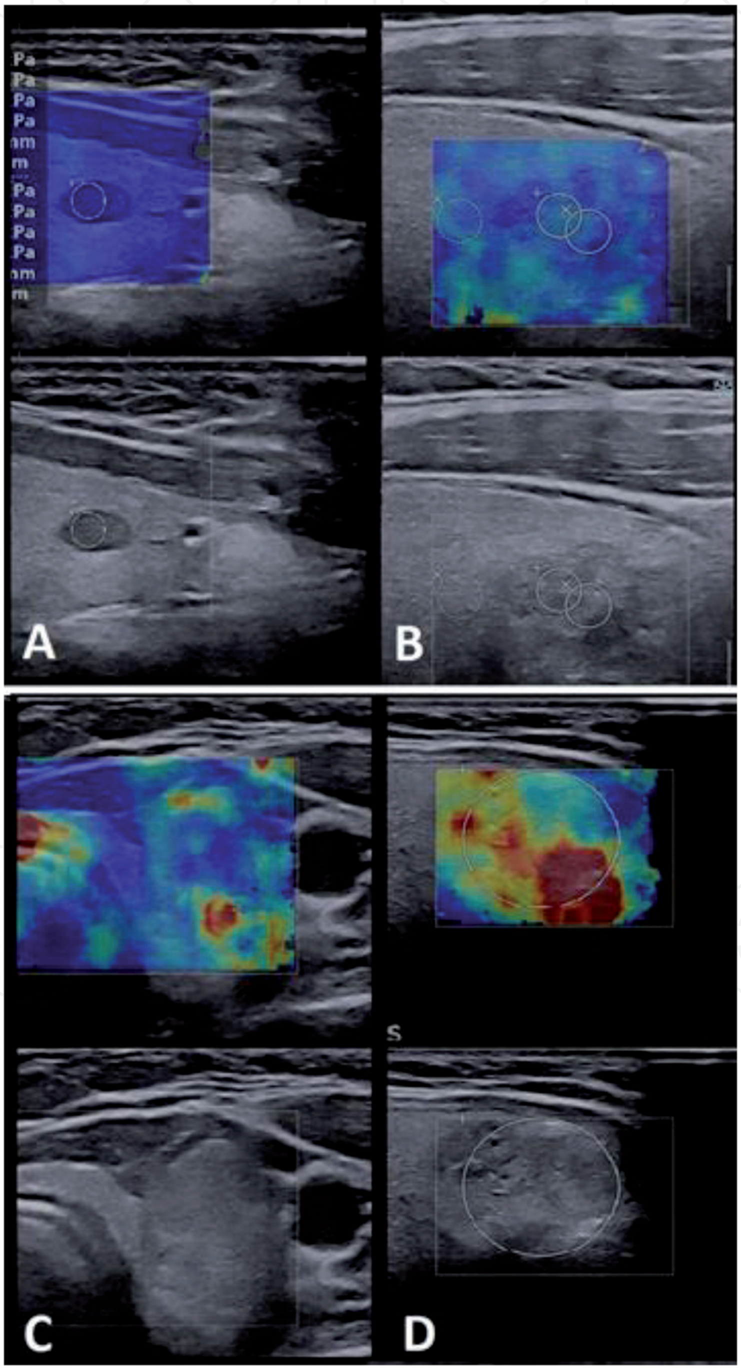

Figure 7.
2D SWE qualitative images: Negative results: A—Entirely soft nodule (homogeneously blue) and B—Mostly soft nodule (heterogeneously blue with green spots), and positive results: C—Nodule with stiff areas (heterogeneous, with patches green, yellow, and red) and D—Completely stiff nodules (heterogeneous multicolored with irregular red, orange, green, and blue areas).

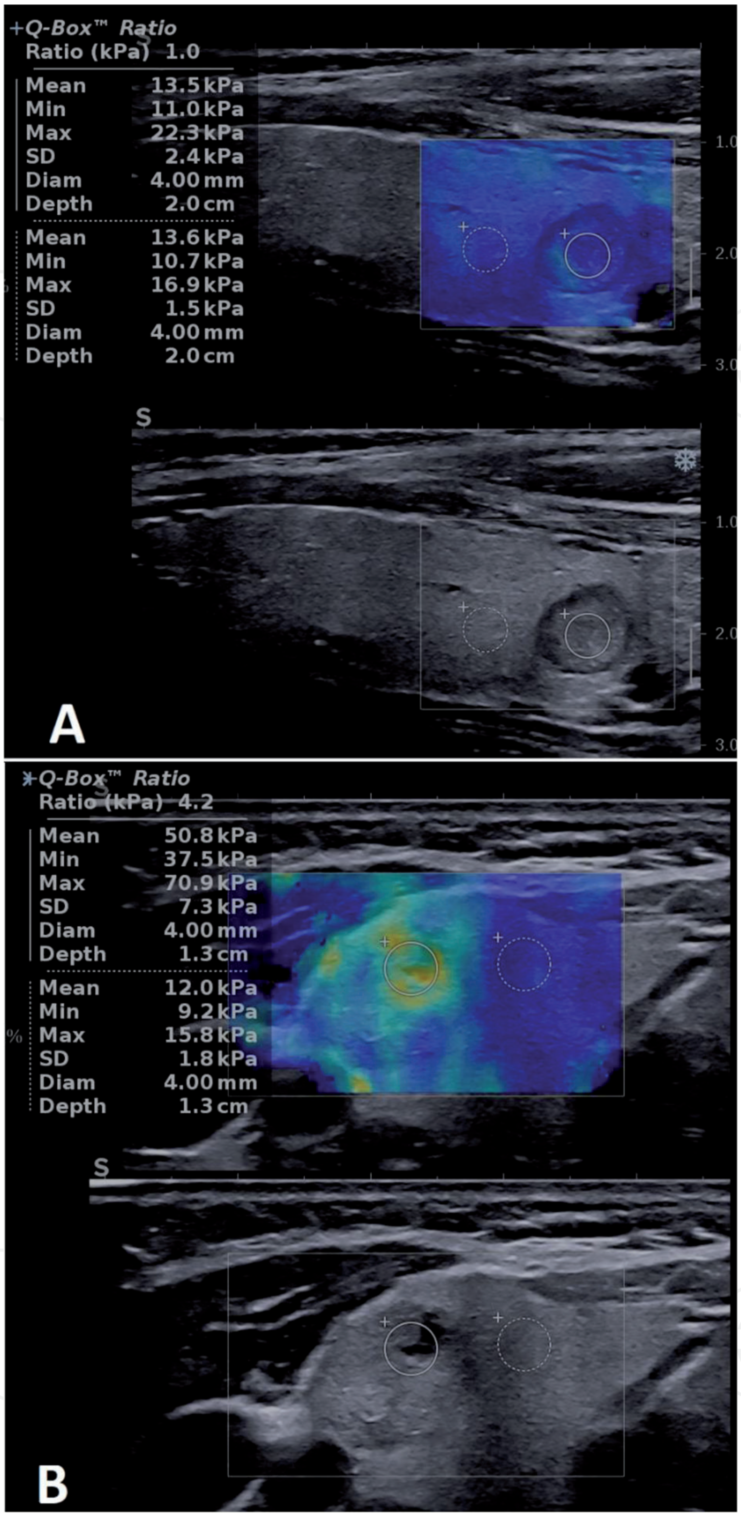

Figure 8.
The nodule-to parenchyma SWE ratio measured on a Hologic Supersonic Mach 30 device—The Q-box ratio. A—Soft nodule, elasticity similar to surrounding healthy thyroid tissue (EI mean = 13.5 kPA and Q-box ratio = 1); B—Nodule with heterogeneous elasticity map, with stiffer areas with EI mean = 50.8 kPa and Q-box ratio = 4.2.

elasticity index (kPa) for each pixel in the ROI. A set of parameters can be quantified in the ROI: the maximum, minimum, and mean E, and the standard deviation, as displayed in **Figure 6** [72, 73]. Currently accessible available technologies on US equipment include: SuperSonic Imagine—2D-SWE; Siemens—Virtual Touch Imaging Quantification, VTIQ; Toshiba—Acoustic Structure Quantification; Philips—SWE; and GE Healthcare—2D-SWE [73].

The qualitative assessment can be made also for 2D SWE. A group from China proposed a modified four-category scale adapted to the physical characteristics of SWE technique and measurements. Patterns 1 (homogeneous lesion with no meaningful color signal corresponding to high stiffness) and 2 (high stiffness signal limited to the capsule surroundings) are interpreted as low risk. Patterns 3 (marginal stiffness) and 4 (interior stiffness) are viewed as high risk; the authors described a very good diagnostic value with 89.1% sensitivity, 74.6% specificity, and the AUROC of 0.79 [74].

A standardized, systematic assessment of qualitative, color-coded elasticity maps is of great importance for discarding artifacts and ensuring reliable quantitative measurements of elasticity [21, 75]. **Figure 7** illustrates the examples of 2D SWE images for soft (A, B) and hard (C, D) thyroid nodules.

Comparable to SE, an SWE ratio can be generated by comparing the stiffness of the nodule to the bordering normal parenchyma or neighboring muscle [24]. **Figure 8** displays the SWE ratio on a SuperSonic Mach 30 machine (the Q-Box™ ratio).

The cutoff values for the elasticity index reported in SWE studies are also different. For Supersonic 2D SWE, the most accurate parameter, as described in most studies, was the E mean, and a poorer diagnostic value was obtained for the E mean. For the E mean, the following cutoffs were reported: ≥42.1 kPa with 76.9% sensitivity and 71.1% specificity [76]; ≥65 kPa with 71% accuracy [77]; ≥39.2 kPa with 81% accuracy [78]; ≥34.5 kPa with 84% sensitivity, 78% specificity, and 82% accuracy [79]; and ≥ 24.6 kPa with 84% accuracy [80]. The evaluation is not standardized; thus, the number of determinations varied between 3 and 10 per patient; the size of the ROI also varied between 2 mm and 10 mm in the reported studies.

4. Strain versus shear-wave elastography

Both SE and SWE are efficacious instruments in the stratification of malignancy risk in thyroid nodules, used complementary to grayscale assessment, as specified by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines and proven by diverse studies [24], with a broad range of values for sensitivity and specificity resulting from the comparison of the two elastography methods.

Although the majority of literature data suggest that SE is slightly superior in diagnosing thyroid cancer, there is presently no consensus about which technique is superior, and both SWE and SE demonstrated to present important additional value to the classic US assessment in the preoperative examination strategy for thyroid nodules.

To date, only a few small studies have provided a head-to-head comparison of SE and SWE in the same population. More data are available for comparing the two methods. A large meta-analysis including 71 studies and 16,624 patients revealed that SE is hardly better in discriminating thyroid malignancy. The pooled results included the sensitivity of 82.9% for SE and of 78.4% for SWE and the pooled specificity of 82.8% for SE and of 82.4% for SWE [81]. Another meta-analysis assessing 22 studies revealed a pooled sensitivity of 79% (95% confidence interval (CI): 0.730–0.840) and a specificity of 87% (95% CI: 0.790–0.920) for SWE. On the other hand, a pooled sensitivity of 84% (95% CI: 0.760–0.900) and a specificity of 90% (95% CI: 0.850–0.940) were reported for SE, considerably higher than the values recorded for SWE ($p < 0.05$) [61].

2D SWE evaluation is superior when it comes to the assessment of nodules that coexist with thyroid autoimmunity, while SE has lower feasibility in this particular setting [81, 82]. The operator's experience in performing each technique is essential, especially for strain elastography evaluation, as SWE proved better reproducibility. Even so, factors such as the manual compression on the US probe may influence the measurements. In SWE, the most common evaluation errors are artifacts generated by the operator. For these reasons, although SWE is easier to learn, it is important that both the elastography techniques are always performed by experienced examiners [83].

5. Conclusions

Thyroid elastography is a promising instrument for the assessment of thyroid nodules and the detection of thyroid malignancy, regardless of the technique. It does improve the diagnostic confidence in thyroid imaging and helps achieve the final purpose: an accurate selection of the nodules that are at risk and need further management from the ones that are at low risk and benefit from follow-up.

Conflict of interest

The authors declare no conflict of interest.

Author details

Andreea Borlea*, Laura Cotoi, Corina Paul, Felix Bende and Dana Stoian
University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania

*Address all correspondence to: borlea.andreea@umft.ro

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