Chapter

Advanced Ultrasound Techniques in Preoperative Diagnostic of Thyroid Cancers

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Abstract

The most precise evaluation of thyroid masses is by high-sensitive ultrasound. Complementary to B-mode ultrasound, elastography can add valuable information by determining tissue stiffness—an important predictor for malignancy. All major guidelines recommend nodules with high suspicious ultrasound characteristics larger than 1 cm to be addressed to ultrasound-guided fine needle aspiration biopsy (FNAB) to rule out malignancy. The main limitation of this procedure is represented by indeterminate cytology, which accounts for up to 20–25% of biopsy results. Molecular markers imply elevated costs and their performance needs further study. Elastography may be helpful in establishing the optimal therapeutic attitude for this cytological category. Currently, there are two ultrasound elastography methods available for assessing tissue stiffness using the parallel deformation to the applied force direction (strain) or the perpendicular deformation to the force direction (shear wave). These methods will be presented and compared in this chapter, with their indications and limitations for a better understanding of their application in nodular thyroid pathology.

Keywords: thyroid cancer, ultrasound, elastography, strain, shear wave, malignancy risk assessment

1. Introduction

Thyroid cancer incidence increased in the last three decades by up to 211%, not only as a result of a better ability to detect very small lesions, by means of high-resolution ultrasonography, but also secondary to a real increase of thyroid cancer incidence, regardless of size, gender, or age groups [1, 2]. Even in these conditions, the prevalence of thyroid cancer, in the entire group of thyroid nodules, reaches a percentage of 15% [3], the main challenge for clinicians being the correct identification of which nodules to refer to fine needle aspiration cytology (FNAC) or directly to surgery, and which to follow by means of ultrasound evaluation [2, 4].

"A thyroid nodule is defined as a discrete lesion within the thyroid gland that is ultrasonographically distinct from the surrounding thyroid parenchyma" [4]. Nodules are usually noticed either by the patient when causing clinical disturbances or compressive symptoms, or by the clinician when performing a thyroid screening or a radiologic procedure such as carotid ultrasound or computed tomography of the neck [5].

When evaluating a thyroid nodule, first line step is represented by running laboratory tests (thyroid-stimulating hormone and thyroid hormones) and performing ultrasound evaluation of the gland. Evaluation goals include identification of the small percentage of malignant nodules, of those that impair thyroid function and of compressive symptoms (dysphonia and dyspnea) [6, 7].

Personal or family history of thyroid cancer, significant exposure to radiations, increases the malignancy risk of the nodule and should be screened for [8].

It is desired to have uniform and standardized reports, given the increased accessibility of the ultrasound equipment and considerable number of clinicians that perform this type of evaluation. Reports will always record nodule position, number, extracapsular relations, and the following features of the lesions: size, shape, margins, echogenicity, echo texture, internal composition (solid, cystic, or mixed), presence of calcifications, and vascular pattern [2].

There are some US features described that are considered highly specific for malignancy, as the presence of microcalcifications, rim calcifications, infiltrative margins, extrathyroidal extension, mostly solid composition, marked hypoechoic texture, and "taller than wide" shape, respectively, the vertical diameter bigger than the transverse diameter. Spongiform appearance, smooth margins, and cystic composition are associated with benignity [6].

Vascularization assessment is considered to have poor interobserver agreement and it has highly dependent on the US equipment used [9].

Additionally, abnormal cervical lymph nodes should be assessed, especially in patients with intermediate- and high-risk thyroid nodules [10].

Various authors and societies proposed risk-stratification systems for thyroid nodules on US. They were initially introduced by classifying thyroid nodules which displayed any suspicious feature as malignant. Thus, starting with Kim et al. in 2002, risk-stratification systems were conceived as qualitative grading systems.

Assessment based on a combination of US features has been proposed as a better method of risk stratification. The system developed into a quantitative scoring system, on which the concept of thyroid imaging reporting and data system (TI-RADS) is based. Horvath et al., inspired by the previously existing breast imaging reporting and data system (BI-RADS) score, introduced it in 2009. Since then, the concept has permanently developed; each new concept proposed having its advantages and limitations regarding their practical application [11]. There are also data suggesting TI-RADS quantification is better than individual assessment of the US characteristics [12].

Different diagnostic qualities are described for each model: Park model: Se = 82%, Sp = 65% [13]; Kwak model: Se = 97.4%, Sp = 29.3% [14, 15].

Diagnostic accuracy for Russ' TI-RADS model was evaluated comparatively on gray scale alone and associated with elastography score. When compared to cytological results, the study showed Se = 95.7, Sp = 61%, and NPV = 99.7% for gray scale only; Se = 98.5%, Sp = 44.7%, and NPV = 99.8% for the combined model using gray scale + elastography. For the operated group, these models were also compared to pathology results showing Se = 93.2% for gray-scale TI-RADS and Se = 96.7% for gray scale + elastography. It was estimated that the number of nodules sent to FNAB decreased by 33.8% [9, 10, 16].

Stoian model also calculated strain ratio for each nodule, apart from qualitative SE scoring, with excellent diagnostic value (AUC = 0.95761, 95% confidence interval (CI)). In this case, Se = 97.93%, Sp = 86.20%, and NPV = 97.26%. Nodules required for FNAB decreased by 43.7% [17].

The 2017 ACR–TIRADS applied on 100 thyroid nodules showed an overall Se = 92% and Sp = 44%, with a 29% reduction in the number of nodules that require biopsy [18].

US-guided FNAB represents the next step in thyroid nodule evaluation and is considered to be the most accurate and cost-efficient preoperative method for identifying malignancy in thyroid nodular lesions, but its indications are broad and differ in the guidelines [19, 20]. Complications are rare and are usually represented by local pain or minor hematomas, but patients are still sometimes reluctant to undergo this procedure [21]. Prior the FNAB, the patients can be questioned for the use of blood thinner drugs and hematologic disease such as bleeding-clotting disorders.

A category-based reporting system was developed and standardized for thyroid FNAB specimens by The Bethesda System for Reporting Thyroid Cytopathology (and it has been broadly adopted). Based on this reporting system, thyroid nodule cytology can be classified in one of the following six categories: (I) nondiagnostic, (II) benign, (III) atypia or follicular lesion of undetermined significance (AUS or FLUS), (IV) (suspicion of) follicular neoplasm, (V) suspicious for malignancy, and (VI) malignant [22–24].

Each category has its evidence-based recommendation for further clinical behavior according to its estimated malignancy risk. The real challenge concerns the management of indeterminate cytology lesions (Bethesda categories III–V) [22].

Benign cytology accounts for 60–70% of FNAs, malignant findings for about 5%—papillary thyroid carcinoma (PTC) being the most common, and indeterminate cytology for 10–20% of specimens—atypical modifications, follicular or Hurthle cell cancers. The indeterminate category has anywhere from 15 to 60% risk of malignancy, depending on the specifics of the report. Studies recently showed that molecular markers can help future distinction between benign and malignant nodules in this cytological category but there are no recommendations currently in use [20].

The American Association of Clinical Endocrinology 2016 guidelines recommend FNAB for nodules with high US risk if they are ≥10 mm, for intermediate US risk nodules ≥20 mm, and low US risk lesions >20 mm that are increasing in size or have thyroid cancer history. For nodules between 5 and 10 mm in diameter with high-risk US characteristics, they recommend FNAC or watchful waiting. Functioning nodules on scintigraphy that lack suspicious US characteristics do not have recommendation for FNAC [4].

The American Thyroid Association (ATA) Management Guidelines refer to FNAC also for intermediate risk nodules >10 mm [19].

The Korean Thyroid Association (KTA) 2016 Revised Guideline recommends that highly suspicious nodules <1 cm should undergo FNAC in order to avoid unnecessary long-term follow-up, given that 20–40% of nodules in this category are benign [25].

The number of nodules addressed to FNAC could be reduced, as 60–80% of FNACs reveal benign lesions; this low percentage of malignancy detected in the nodules sent to FNAC based on US imaging criteria points out the real need for a more accurate US diagnostic evaluation [4, 6].

There are some drawbacks regarding FNAC results. About 5% of cases are considered qualitative or quantitative insufficient for diagnostic, and Bethesda III and IV categories are inconclusive for a final treatment recommendation. In the presence of indeterminate cytology, the clinical judgment relies again on patient background (clinical risk categories) and ultrasonography aspect [22, 26].

2. Ultrasound elastography—nodule stiffness as a malignancy risk-stratification parameter

US elastography noninvasively evaluates the stiffness of a thyroid nodule by measuring the distortion that appears when the nodule is compressed by external

pressure (strain elastography) or by assessing the attenuation of the shear waves (shear-wave elastography) generated by the transducer [10].

Elasticity is the ability of tissue to resist deformation when an external force is applied, or to resume its original shape after the force is removed [27]. Loss of elasticity of a tissue on palpation or elastography ("virtual palpation") generates suspicion of malignancy. Most solid tumors are mechanically different from adjacent tissues, presenting increased stiffness (decreased elasticity) owing to desmoplastic transformation—more collagen and myofibroblasts [27, 28].

There are some fibrous benign tumors that can be hard on elastography (histiocytofibromas) and some malignant nodules with nonmodified elasticity that can be missed by elastography (follicular carcinomas) [28, 29].

The different US elastography techniques that are currently available carry various limitations in relation to the tissue shear properties and they may be in some cases complementary [30]. Elastography can be easily used in the evaluation of the thyroid gland considering its conveniently superficial location, but it is still not widely adopted in practice or included in all the risk-stratification systems [31].

Presently, only one thyroid US elastography guideline has been published—the "European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines and Recommendations." Recommendations are in favor of using elastography as an extra tool to gray-scale ultrasound and for the follow-up of nodules formerly benign in FNAB [32].

2.1 Strain (quasistatic) elastography

Strain elastography (SE) was the first to be used and most implemented technique on US systems. Usually, very slight external pressure is applied by the operator (or by acoustic radiation force impulse (ARFI)), or more recently, it has the sensitivity to detect minimal endogenous physiological motion (vascular beam movements and muscle contraction) [28, 30]. The imaging methods are a little different for each manufacturer so each equipment will display images with slightly different characteristics [33].

SE equipment does not offer direct quantification of stress. Elastograms illustrate relative stiffness and are calculated from the signal differences previously and after compression, being displayed in parallel with B-mode image (split-screen) or overlaid on the conventional B-mode image. Stiffness of the tissue is displayed usually in a continuous color map from red (soft or no strain) to green (intermediate or equal strain) to blue (hard or no strain). There are some systems available on the market that use a reverse color scale [34, 35].

A visual colorimetric analysis based on the displayed qualitative map image will be made [32]. Two scoring systems have been proposed for the qualitative assessment of nodule elasticity: the Asteria and Rago systems. Asteria classifies nodules on a scale from 1 (entirely elastic nodule) to 4 (entirely stiff nodule). Rago includes the first four Asteria classes with the addition of the fifth score (entirely stiff nodule, infiltrating in the posterior shadowing area) [35]. Lesions that appear homogenous or with low stiffness are considered benign, while lesions that present increased stiffness are considered to have high malignancy risk [28].

SE machines use special software for an objective semiquantitative determination providing a numeric value: *the strain ratio* (*SR*). This method of elasticity assessment represents the ratio between strain value in the neighboring thyroid parenchyma and the mean nodule strain (parenchyma-to-nodule ratio) or between the strain in a neighboring strap muscle and the thyroid nodule (muscle-to-nodule ratio) [32]. Probability of cancer grows with a higher strain ratio [35]. A study conducted by Aydin et al. in 2014 showed that there are no significant differences

between muscle-to-nodule ratio and parenchyma-to-nodule ratio, suggesting that the first ratio could be safely used instead of last ratio in evaluating malignancy risk when the thyroid parenchyma is abnormal [36]. SR is considered to be more accurate than qualitative elasticity assessment. The final value will represent the average of three measurements [37].

Widely different cutoff values have been described for the SR (between 1 and 5), currently there is no general agreement: ≥ 2 (Se = 97.3%, Sp = 91.7%) [38]; ≥ 2.09 (Se = 90.6%; Sp = 93%) [39]; ≥ 2.73 (Se = 89.3%; Sp = 73.2%) [40]; and ≥ 3.79 (Se = 97.8%; Sp = 85.7%) [41]. Most of these studies included only solid nodules.

Elastography imaging to B-mode size ratio (EI/B ratio) has been suggested to be useful in evaluation of breast lesions [42].

The area ratio (AR) is a semiquantitative assessment for SE in virtual touch equipment that compares the nodule area on virtual touch image and B-mode, calculating the mean of the three most accurate measurements. A malignancy cutoff of 1.08 was suggested [43].

Hard area ratio is the ratio between the nodule hard area and the whole nodule area. Different cutoff values for malignancy have been proposed: ≥ 0.45 (Se = 98.2%; Sp =81.2%) [40] and ≥0.6 (Se = 92.9%, Sp = 91.3%). This parameter is highly dependent on the examiner and has poor reproducibility [37].

The elasticity contrast index is available on Samsung machines and measures the strain oscillation within a nodule and then uses complex calculation to determine local contrast. In a malignant lesion, there are large differences between low and high strain regions, inducing important local contrast [44].

When choosing the place of the ROI, some aspects have to be taken into consideration. It should be as proximal to the transducer as possible, it should cover the entire nodule and "as much of the adjacent parenchyma as possible." Manual compression is quantified on most of the machines for better reproducibility: optimal compression in Hitachi machines is considered between 3 and 4 and > 50 in Siemens machines [32, 37].

There is a huge body of evidence regarding the diagnostic qualities of the SE method in defining benign versus malignant lesion.

In a meta-analysis conducted in 2010 by Bojunga et al. that included eight studies (639 nodules), RTE recognized thyroid malignancy with overall mean Se = 92% (88–96 CI) and mean Sp = 90% (85–95 CI). A significant heterogeneity was found for specificity of the different studies [45].

Rago et al. conducted a study on 195 nodules, which concluded that RTE elastography had Se = 94.9%, Sp =90.3%, PPV = 71.1%, and NPV = 98.6% in predicting malignancy in nodules with indeterminate or nondiagnostic cytology. Worth mentioning is the high NPV of high elasticity-score nodules, which strongly predicts benignity [46].

Another valuable study from Italy evaluated SE diagnostic accuracy on 498 nodules showing Se = 97% and NPV = 97% when at least one suspicious US parameters was also present [47].

A meta-analysis that included 20 studies evaluating SE diagnostic value in benign or malignant nodules showed a pooled Se = 85% (95% CI, 79–90%), Sp = 80% (95% CI, 73–86%), NPV = 97% (95% CI, 94–98%), and PPV = 40% (95% CI, 34–48%) [48].

Some of SE limitations are represented by its subjectivity, operator-dependency, and compressibility-dependency [49].

Increased stiffness can be found in benign nodules with coarse calcification or fibrosis, leading to false-positive results [45, 50].

When the evaluated lesion is located deeper, an elastogram can be obtained if lesion can be visualized in the B-mode image, but it may require application of

more stress by the examiner, which could alter the color map for more superficial structures. If nodules are too deep, a false-positive stiff image can appear as a result of reduced stress transmission [32].

Nodule size is not considered to interfere with SE evaluation accuracy, although there are some studies that reported affected performance on nodules larger than 3 cm or very small lesions. WFUMB guidelines consider nodules larger than 3 cm cannot be evaluated correctly because of their deeper parts and lack of healthy adjacent tissue. Coalescent nodules can also not be assessed by SE [32, 37, 51].

Carotid pulsations interfere when external pressure is applied, particularly in transverse incidence, the incidence being preferred for elastography with internal force [32].

The reference surrounding parenchyma in the ROI should have at least 50% green color to obtain an accurate strain ration [37].

Other limitations of SE are presence of peripheral rim calcification—increased stiffness; large cystic component—SE in nodules with cystic components should be assessed only for the solid component; necrosis—can present soft areas; nodules under 5 mm—although a low size limit for SE use was not established; and obese patients [50, 51].

It is clear that strain elastography accuracy is highly dependent on the examiner's training. The interobserver variability has been evaluated by several studies that recently showed excellent agreement between multiple observers [32]. It seems that strain ratio is easily learned compared to elasticity score interpretation [52].

Different pathologies of the thyroid nodules can have an impact on SE appearance. Currently, it is known that follicular carcinomas may appear elastic on SE, so elastography is not a useful tool for evaluating this type of thyroid malignancy (44% false-negative findings). Other particular pathologies that appear soft on elastography and may lead to false-negative results are medullary carcinomas and metastatic carcinomas [32, 45].

2.2 Shear-wave elastography

Shear waves are defined as transverse elements of particle displacement which are very quickly attenuated by the tissue. Shear represents a modification of shape, without a modification of volume [35, 53]. Tissue propagation of shear waves is much slower in comparison to longitudinal waves. They do not propagate well in water, being rapidly attenuated, but they do propagate in elastic media [54].

Shear-wave elastography (SWE) is more operator-independent, and therefore, more reproducible [35]. Quantitative and qualitative assessment of tissue elasticity can be obtained by measuring the shear wave speed. Several applicable methods are available [27].

1D Transient elastography is widely used for estimating liver fibrosis (Fibroscan and Echosens). It cannot be performed with a standard transducer on regular ultrasound equipment. The probe used by this device incorporates an US transducer as well as a vibrating device that exerts an external vibrating "punch" to generate shear waves that will propagate through tissues [27].

In monoplane shear-wave elastography (pSWE), ARFI mechanically excites the tissue in the region of interest (ROI) using acoustic push pulses which generate localized tissue displacements in the US axial direction—perpendicular to the surface. Shear wave speed measurements can be made up to 8 cm in depth (m/s) [14, 30]. This approach is implemented on devices produced by Phillips (ElastPQ) and Siemens (VitualTouch Quantification, VTQ) [27].

Biplane shear-wave elastography (SWE, 2D SWE, 3D SWE) offers a real-time display of a color quantitative elastogram overlaid on a B-mode image and

assessment of shear wave speed [27]. Supersonic shear wave uses focused ultrasonic beams that spread through the whole imaging area, displaying on a color map the velocity (m/s) of the shear wave or directly the elasticity (kilopascals) for every pixel in the ROI. A series of parameters in the ROI can be measured: maximum stiffness, mean stiffness, and standard deviation (SD) [35].

The following 2D-SWE technologies are currently available on US machines by: Siemens (Virtual Touch Imaging Quantification, VTIQ), SuperSonic Imagine (SWE), Philips (SWE), Toshiba (Acoustic Structure Quantification), and GE Healthcare (2D-SWE) [27].

The largest recent meta-analysis by Zhang et al. included 16 studies that used ARFI-generated SWE to evaluate 2436 nodules had mean Se = 0.80 (95% CI, 0.73–0.87) and Sp = 0.85 (95% CI, 0.80–0.90) in detecting malignancy. Both Se and Sp were found significantly heterogeneous in all the included studies [55].

Another meta-analysis (Dong et al.) on 13 retro/prospective studies detected high ARFI VTQ efficacy in detecting thyroid cancer, with pooled Se = 86.3% (95% CI, 78.2–91.7) and Sp = 89.5% (95% CI: 83.3–93.6) [56].

A meta-analysis by Lin et al. included 15 studies that used point-SWE or 2D SWE to investigate 1867 nodules. The pooled Se = 84.3% (95% CI, 76.9–89.7%), Sp = 88.4% (95% CI, 84.0–91.7%), PPV = 27.7–44.7%, and NPV = 98.1–99.1% [57].

All the mentioned meta-analyses concluded that SWE (pSWE and 2-D SWE) are useful in detecting thyroid malignancy as a complementary tool to gray-scale US, which is also a stated recommendation of WFUMB 2017 guidelines [32].

Five to ten consecutive measurements are needed in order to obtain a valid median result [32].

Cutoff values again range widely and have been reported for shear-wave velocity between 2.4 and 4.7 m/s [32].

One study on 476 nodules established an EI cutoff mean value of above 85 kPa (Se = 95%) or one maximum value of above 94 kPa [58]. Another study on VTQ of ARFI reported a cutoff point for velocity = 2.87 m/s and for SWV ratio = 1.59. The study also pointed out this SWE method has highest diagnostic value for nodules >20 mm [59].

Other studies reviewed in the WFUMB guidelines showed cutoff values ranging from 2.55 to 2.75 m/s [60–63].

Interobserver and intraobserver reproducibility were reported to be high. One study conducted by Grazhdani et al. showed high concordance rate (k = 0.75) between two observers [64].

For the characterization of the thyroid lesion, a quantitate measurement for the mean value or maximum value of an elasticity is used. Similar to SE, an SR can be obtained by comparing adjacent normal parenchyma or surrounding muscle [32].

Some of ARFI technique limitations will be briefly presented.

The size of the ROI is fixed (5 × 6 mm or 20 × 20 mm)—small nodules cannot be accurately measured. Also for nodules smaller than 20 mm, wave velocity is not stable. Composition of nodules: cystic composition or calcifications cannot be evaluated—it is impossible to place the ROI inside the nodule. Depth is an important limitation for both pSWE and 2D SWE—the ARFI cannot penetrate nodules deeper than 4–5 cm; ARFI can measure velocities only up to 9 m/s—harder nodules or areas will not be evaluated properly: the value "x.xx m/s" will be shown. Nodules that are located on the thyroid isthmus are a challenge due to their interposition between the stiff trachea and the skin [32, 37].

Again, not all malignant nodules are elastic. Follicular carcinomas are described as soft lesions and are difficult to differentiate from benign lesions. A study by Samir et al. proposed a cutoff value of 22.3 kPa for distinguishing thyroid follicular cancer from benign follicular lesions (Se = 82%; Sp = 88%) [65].

For accurate results, an experimented examiner should always perform SWE evaluation of the thyroid. The pressure applied on the transducer can influence the evaluation results [32].

There are also clear recommendations that in the presence of a stiff nodule, the FNAB is recommended, regardless the conventional US characteristics.

In the AACE guidelines, a nodule with high stiffness is directly included in the intermediate risk group, elevated stiffness being listed as one of the AACE criteria for FNAB. There is a grade-B recommendation for nodules that are stiff on elastography to be addressed to FNAB [7].

Also, in the presence of indeterminate cytology findings, they suggest that elastography to be considered for extra information. Combined elastography and B-mode US is presented to be more trustworthy when excluding nodules from biopsy evaluation [7].

ATA guidelines acknowledge usefulness of US elastography for noninvasive assessment of malignancy risk when accurate evaluation can be made, but it can neither recommend its universal adoption, nor its replacement of classic US assessment [19].

European Thyroid Association (ETA) guidelines also state that elastography, with its high NPV, can be a helpful instrument for thyroid nodule evaluation and it may be used together with gray-scale US, but not replace it [10].

2.3 RTE versus SWE elastography

As mentioned in the EFSUMB guidelines and showed in literature data, both SE and SWE represent a useful tool in thyroid nodule stratification of malignancy risk, complementary to gray-scale evaluation [32].

Different studies have reported a wide range of values for Se and Sp when comparing the two-elastographic methods.

A big meta-analysis on 71 studies with a total of 16,624 patients showed that RTE is slightly better in differentiating benignancy from malignancy in thyroid lesions, with pooled Se = 82.9% for RTE; Se = 78.4% for SWE and Sp = 82.8% for RTE; and Sp = 82.4% for SWE [66].

A head-to-head comparison of two elastographic methods was made only in a few studies.

In a publication by Liu et al., 49 patients (64 nodules) underwent both SWE and RTE evaluation and results were compared to pathology results. For SE, qualitative assessment was made using Rago classification (score 4–5 considered as malignancy suspicious) and for SWE—min and max mean elasticity were measured, cutoff mean value was 38.3 kPa, with Sp = 68.4%; Se = 86.7%; NPV = 86.7%; PPV = 68.4% for SWE and Sp = 79%; Se = 84.4%; NPV = 83.3%; PPV = 64.7% for RTE. The study established that SWE is a promising method for the evaluation of thyroid malignancy risk, with similar value to RTE, its sensitivity being a little lower and its specificity a little higher [67].

A 2017 meta-analysis (Hu et al.) is evaluating 22 studies, which simultaneously evaluated diagnostic performance for thyroid malignancy using both RTE and SWE techniques. The results showed that the pooled Se = 0.79 (95% CI, 0.73–0.84), Sp = 0.87 (95% CI, 0.79–0.92) for SWE compared with Se = 0.84 (95% CI, 0.76–0.90), Sp = 0.90 (95% CI, 0.85–0.94) for RTE, was significant lower for SWE technique ($p < 0.05$) [49].

Another study evaluated 138 nodules using gray-scale US, ARFI imaging and qualitative strain elastography. Combination of ARFI and RTE specificity for detecting malignancy increased by 20% (Sp = 92 vs. 72% for RTE only), but sensitivity decreased by 28% (Se = 48 vs. 76% for RTE alone). When ARFI cutoff was adapted

for the combined methods (ES 3–4 and ARFI ≥1.11 m/s), sensitivity was unchanged, specificity increased by just 3%. Therefore, there was no significant change in accuracy of finding malignant nodules when combining the two methods [63].

Although most literature data suggest RTE is slightly more powerful in differentiating thyroid cancer, there is currently no consensus about which method is better and both SE and SWE proved to add important value to classic US evaluation in the preoperative approach of thyroid nodules.

2.4 Elastography: place in indeterminate cytology results

Nondiagnostic and indeterminate cytology represent the great limitations of FNAC and gray-scale US can sometimes be poorly predictive. About half of these nodules can avoid surgery by performing a second biopsy [68]. There was one study that reported higher prevalence of cancer on repeat FNAB, maybe as a consequence of the class of high-risk nodules that underwent second FNAB [69].

For the clearance of this cytological category, there is currently a general proposal to use molecular markers, but there is still no consensus regarding which panel should be used [70].

Several molecular markers have been studied in indeterminate FNAB cytology findings. The most studied mutations/rearrangements include BRAF, RAS, RET/PTC, and PAX8/PPARγ. These markers can predict ("rule in") malignancy with very high sensitivity, having a high positive predictive value (PPV) but if they are not present, malignancy cannot be "ruled out," having a low sensitivity and negative predictive value (NPV) [70, 71].

The most common molecular tests used in this rapidly developing field will be shortly presented. The Afirma Gene Expression Classifier (GEC) is a microarray test which investigates mRNA expression of 167 genes [72]. This test has been reported to have high NPV (up to 95%) in the Bethesda III and IV categories, but low PPV (14–57%), which makes it useful only as a "rule-out" test [72, 73]. ThyGenX test identifies over 100 mutations associated with thyroid cancer, using a next-generation-sequencing (NGS). ThyraMIR is a newer test (used complementary to the ThyGenX) that analyzes 10 different microRNA molecules that are considered to contribute to cell differentiation and proliferation in thyroid pathology. Combining ThyGenX and ThyraMIR in nodules with indeterminate cytology showed Se = 89%, Sp = 85%, NPV = 94%, and PPV = 74% [72, 74]. ThyroSeq v2 includes analysis of a panel of >1000 mutations and RNA alterations, with Se = 90%, Sp = 93%, PPV = 83%, and NPV = 96%, suggesting that this test may be useful as both "rule-in" and "rule-out" test for Bethesda III and IV cytology [72, 75]. It has been suggested that the thyrotropin receptor (TSHR) mRNA test can be useful in indeterminate nodules, its expression being helpful for early diagnosis of PTC [72, 76, 77].

Currently, there is no individual molecular marker that can certainly rule out malignancy in indeterminate nodules and it is still debatable if there is a cost-effective combination of these markers that can be used [4, 70, 71].

Elastography has been suggested to define more accurately the presurgical malignancy risk in this cytological category to help clinician's decision whether to repeat biopsy or follow-up [32].

A study by Rago et al. tried to refine diagnosis in this category of nodules (142 indeterminate and 53 nondiagnostic). All patients have been examined by gray-scale US, color Doppler, and qualitative RTE (modified Ueno score). Indeterminate cytology score 1—highly elastic nodule—was found strongly predictive of benignity ($p < 0.0001$); combination of scores 2 and 3 showed Se = 96.8%, Sp = 91.8%, and NPV = 99.0% for predicting malignancy. In nondiagnostic cases, Sp, Se, and NPV

showed poorer Se, Sp, and NPV for all elastography scores. When considering both indeterminate and nondiagnostic, the overall Se = 94.9%, Sp = 90.3%, and NPV = 91.3% for scores 2 and 3 [46].

In another study, qualitative RTE failed to make a correct distinction between benignity and malignancy in thyroid nodules, cancer was found in 50% of nodules scored 1 or 2 on elastogram and in 34% of score 3 nodules. Quantitative assessment of elasticity was suggested [78].

A comparison between 2D-SWE (VTIQ) and molecular testing (Afirma GEC) was made in a prospective study in nodules with indeterminate FNAC. SWV cutoff for malignancy risk was defined at above 3.59 m/s with Se = 83.9% and Sp = 79.2%. SWV measurements were made in the stiffest section; authors mention that measurements of a larger area may result in a decreased SWV. The GEC-suspicious group had Se = 90.3% and Sp = 74.2% (PPV of only 47.5%, but NPV of 96.7%). The study concluded that both SWV and GEC can independently predict thyroid cancer with similar diagnostic value and are particularly useful in this cytological category [79].

A more complex study compared diagnostic efficiency of SWE, semiquantitative SE (strain index), classic US, CEUS, and BRAF mutation test in indeterminate cytology, but the number of evaluated nodules was relatively small. The study outcomes confirmed a slightly better efficiency for RTE compared to SWE in distinguishing malignancy; strain index was the one parameter that showed significant correlation with pathology results. RTE and SWE do not seem interchangeable but may be used complementary. Interestingly, when strain index, SWV, and BRAF mutation were considered together, Sp was enhanced, but Se was lower compared to US findings alone [68].

This cytological category still remains uncertain in diagnosis, and in some cases, a strategy that combines advanced ultrasound methods was documented to provide higher accuracy in diagnosis than use of a single technique [68]. More studies are required concerning this approach.

2.5 Contrast-enhanced ultrasound (CEUS)

The use of contrast agents in ultrasonography has widely expanded in clinical use and may play an important role in identifying thyroid cancers by evaluating tumor microcirculation. New-generation contrast agents (SonoVue) are administered intravenously and contain sulfur hexafluoride microbubbles that stay in the blood flow for a while. The examiner focuses the US image on the ROI and a contrast-enhanced image is displayed, detecting microvascular changes in the lesion that classic Doppler cannot display [80].

CEUS has already changed approach in management of liver lesions, significantly improving the number of unnecessary biopsy indications [81].

In studies where CEUS was performed on thyroid lesions, malignity was indicated by hypoenhancement and heterogeneity [80]. Hypoenhancement can be explained by the absence of blood supply in the central area of the tumor, due to thrombus formation, vascular compression, and necrosis. Neovascularization is mainly marginal, promoting tumor expansion [82]. Heterogeneity is explained by the complex and aberrant composition of cancerous lesions (fibrotic, presence of calcifications, and necrosis areas) [80, 82].

Other indicators of malignancy are the time of wash-in and wash-out, but results are controversial. Some studies described early wash-in and wash-out in malignant lesions [83, 84], while others have shown late-phase enhancement for thyroid cancers compared to perinodular tissue [85] or no significant difference in the time of enhancement for benign versus malignant nodules [86].

Adenomas are characterized by homogeneity and peripheral ring enhancement [80].

Two recent meta-analyses on CEUS diagnostic accuracy showed the pooled Se = 0.88 (95% CI, 0.85–0.91); pooled Sp = 0.90 (95% CI, 0.88–0.92) [87]; and a pooled Se = 0.853, pooled Sp = 0.87 [88].

Some benign nodules showed pattern described for malignant ones and vice versa, so an assessment of both elastography and CEUS was combined in some articles.

A study by Zhan et al. aimed to evaluate the aid of CEUS in diagnosis of thyroid malignancy. First, 200 thyroid nodules were evaluated using ARFI technique. A number of 40 nodules that were in the "gray zone" underwent CEUS. ARFI accurately diagnosed 82% of the total nodules, while CEUS accuracy was 90% ($p < 0.05$) [89].

Cantisani et al. compared Q-elastography with CEUS in thyroid cancer assessment. Study results showed that both methods outclassed gray-scale US, but Q-elastography was more sensitive than CEUS (Se = 95%, Sp = 88% for Q-elastography; Se = 79%, Sp = 91% for CEUS) [83].

However, more studies are required for evaluating the true usefulness of this relatively new and promising technique in the differentiation of malignant from benign thyroid nodules.

3. Conclusions

Given the great number of thyroid lesions and the rising incidence of thyroid cancer, a correct preoperative distinction between benignity and malignancy in nodular pathology is crucial.

Ultrasound elastography represents the most important advance in US imaging since Doppler. It proved to serve as an important tool in selecting candidates for surgery. Elastography is a noninvasive, nonirradiating method that can be easily learned, adds only a few minutes to classic US evaluation, but provides truly valuable additional information. Unfortunately, this technique is still quite new and not widely used in clinical practice, so its universal adoption cannot be recommended by the guidelines, but there is important evidence of its clinical utility and its application in current practice is increasing. As any imaging technique, it holds its limitations [90].

This technique cannot replace the classic, gray-scale ultrasound, and should be used complementary to it [7, 10, 25].

Due to its high NPV, thyroid nodules that are scored soft on elastography are highly likely to be noncancerous and can be followed-up, avoiding FNAB [91]. Therefore, elastography reduces the need for FNA by up to 43% of cases compared to gray-scale risk stratification [17]. It also identifies stiff nodules that need biopsy and can be missed by gray-scale US alone. Even lesions with low-risk features, but high stiffness, are recommended for FNAB [91].

In the case of indeterminate cytology, clinical judgment can be a real challenge for practitioners. Elastography proved to predict malignancy better than B-mode parameters and can be essential in further management decision for nodules in this category.

For an accurate result, it is important that the evaluation should be performed by an experienced operator.

Conflict of interest

There is no conflict of interest.

Abbreviations

FNAB	fine needle biopsy
US	ultrasonography conventional
Se	sensitivity
Sp	specificity
NPV	negative predictive value
PPV	positive predictive value
AACE	American Association of Clinical Endocrinology
ATA	American Thyroid Association
ETA	European Thyroid Association
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
WFUMB	World Federation for Ultrasound in Medicine and Biology
AR	area ratio
ARFI	acoustic radiation force impulse
SE	strain elastography
SWE	shear-wave elastography
CEUS	contrast-enhanced ultrasound
AUS	atypia of undetermined significance
FLUS	follicular lesion of undetermined significance
ROI	region of interest
EI/B ratio	elastography imaging to B-mode size ratio

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