

## Review Article

# Ultrasonographic and Elastographic Diagnostic of Parathyroid Lesions – A Literature Review

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High-sensitive ultrasound is a simple, accurate and a reproducible method to assess parathyroid pathology. One of its main advantages is that it is a non-invasive and non-irradiating method. Complementary to conventional ultrasound, Doppler imaging and elastography can increase the sensitivity and specificity of diagnosis.

Hyperparathyroidism is a common disorder of the parathyroid glands and the third most frequent endocrinopathy, especially among elderly women. Surgery is currently the curative treatment of the disease, appropriate preoperative localization, excluding multi glandular disease and determining the best surgical approach.

Elastography can be an effective tool in diagnosis parathyroid lesion, by differentiating possible parathyroid lesion from thyroid disease, cervical lymph nodes and other anatomical structures. There are currently no guidelines recommendations and no established values on the elasticity of parathyroid lesions. Hence the need of a review on the current elastography studies in the literature.

**Keywords:** Parathyroid; Adenoma; Ultrasonography; Elastography**Abbreviations**

PTH: Parathyroid Hormone; pSWE: Point Shear-Wave Elastography; PHPT: Primary Hyperparathyroidism; SE: Strain Elastography; sHPT: Secondary Hyperparathyroidism; ARFI: Acoustic Radiation Force Impulse; MEN 1: Multiple Endocrine Neoplastic Type 1; VTQ: Virtual Touch Quantification; MEN 2: Multiple Endocrine Neoplastic Type 2; VTI: Virtual Touch Imaging; MIP: Minimally Invasive Parathyroidectomy; AR: Area Ratio; KDIGO: Kidney Disease Improving Global Outcomes; SWV: Shear Wave Velocity; US: Ultrasonography; 2D-SWE: 2Dimensional Shear-Wave Elastography; ROI: Region Of Interest; 3D-SWE: 3Dimensional Shear-Wave Elastography; TE: Transient Elastography; EI: Elasticity Index; SWE: Shear-Wave Elastography

**Introduction**

Hyperparathyroidism is a disorder of the parathyroid glands, characterized by overproduction of Parathyroid Hormone (PTH). The disorder can be categorized as primary, secondary, or tertiary [1], Primary Hyperparathyroidism (PHPT) being the most frequent parathyroid disease, respectively a frequent endocrine disease [2]. Secondary Hyperparathyroidism (sHPT) may result due to chronic hypocalcaemia that can be caused by chronic kidney disease, or digestive causes: vitamin D deficiency, impaired gastrointestinal absorption, Crohn's disease, celiac disease, post-bariatric surgery, or due to hyperphosphatemia or drug induced [2,3].

Since 1970s, when the biochemical-screening test of serum calcium concentration was available, the clinical portrait of hyperparathyroidism changed. Patients with primary hyperparathyroidism could be now diagnosed in stages with mild

hypercalcemia, with no specific symptomatology [4]. The spectrum of disease varies from asymptomatic cases, to cases with severe complication, such as nephrocalcinosis or severe osteoporosis with fragility fractures or neuromuscular illness.

Primary Hyperparathyroidism (PHPT) is the third most endocrinopathy after type 2 diabetes and thyroid disease, caused by overactive parathyroid glands with high Parathyroid Hormone (PTH) secretion and consequent increase in serum calcium [4-9]. Routine calcium serum easements has changed the clinical presentation of PHPT, the incidence increasing 4-5 times [9]. Asymptomatic PHPT has a high incidence in postmenopausal women over 50 years old (female – male ration 3-4:1) [1,4,10,11].

The incidence of PHPT has increased in Europe, probably reflecting the active screening. A Swedish study identified PHPT in 3% of women and 0.7% of men, over the age of 60 [12]. A prevalence study in Denmark, evaluating the time span of 1999 to 2010 reported an annual rate of 16 per 100.000 [13]. Another study conducted in Scotland, UK, over a 20-year period (1997–2006) showed an raising incidence in PHPT especially in females [14,15].

Unique parathyroid adenoma is one of the most common lesion found in PHPT [16], sporadic single parathyroid adenomas representing 85-90% of PHPT cases [7]. Multi glandular disease accounts for 20% of the cases and less than 1% is due to parathyroid carcinoma [6–8].

Familial primary hyperparathyroidism accounts for 5-10% of cases of PHPT and it relates to a various of syndromes and hereditary disease, including multiple endocrine neoplastic type 1 (MEN 1) and type 2 (MEN 2), hyperparathyroidism-jaw tumor syndrome, and

isolated familial hyperparathyroidism [5-7,17].

The etiology of PHPT remains ambiguous in the majority of cases. A history of external neck irradiation, may contribute to the development of PHPT. The risk was substantial, high levels of PTH were associated with acute radiation syndrome [5,18,19]. Chronically ingestion of medications such as lithium or thiazides diuretics may also be involved [1,14,20].

Secondary Hyperparathyroidism (sHPT) occurs as a compensatory response to hypocalcemic states due to chronic renal failure, malabsorption syndromes, low vitamin D levels and other chronic illness. In this case, sHPT could be corrected by treating the underlying affection, however chronically stimulated parathyroid glands could become autonomous, thus resulting in persistent hypercalcemia, transforming in tertiary hyperparathyroidism [1,6,21].

Extended stimulation by high extracellular concentration, low extracellular calcium concentration and considerably low concentrations of calcitriol lead to increased synthesis of PTH. The development of sHPT begins at early stages of chronic kidney disease by decreasing or desensitizing the calcium-sensing receptors and vitamin D receptors, inducing parathyroid hyperplasia [22].

The prevalence in Europe of sHPT due to chronic kidney disease on patients on stages 3-5 is estimated at around 8.5% in the United Kingdom, 8.2% in France respectively 6.8% in Spain and 6.1% in Portugal [23].

sHPT is a common complication of chronic kidney disease, associated with high cardiovascular morbidity and mortality 4-8 [24,25].

The treatment options are related to the type and severity of hyperparathyroidism:

- Follow up in cases with asymptomatic primary hyperparathyroidism;
- Surgical treatment in symptomatic primary hyperparathyroidism and in upgraded asymptomatic primary hyperparathyroidism;

The Canadian guidelines with international consensus (2017 guidelines) recommend that both symptomatic and asymptomatic primary hyperparathyroidism should undergo parathyroid surgery.

The main indications for surgery in PHPT are: age less than 50 years, serum calcium exceeding with 1 mg/dl the upper normal limit, limit of the reference interval for total serum calcium or  $> 0.12$  mmol/l for ionized calcium, a DXA measured T score under -2.5 of bone mass density at any site, in postmenopausal women or men over 50 years of age, presents an indication for surgery, or the appearance of a of fragility fractures, respectively a glomerular filtration rate lower than 60 ml/min, the presence of nephrolithiasis or nephrocalcinosis, or Calciuria over 400 mg/day.

Parathyroidectomy should be considered for all patients under 50 years, including children due to the increased severity of the disease in adolescence [26].

Minimally Invasive Parathyroidectomy (MIP) is recommended

if preoperative localization of parathyroid adenomas was successful and multiglandular disease was excluded. MIP has high surgical success (95-98%) and low complication rates (1-3%).

Surgery is recommended in older patients meeting the criteria for parathyroidectomy only if they have a stable medical condition.

Monitoring and medical treatment should be considered for asymptomatic patients for whom the guidelines for surgery do not apply or are unable or unwilling to undergo parathyroidectomy. Yearly monitoring of biochemical profile and bone density mass is recommended. Medical treatments include vitamin D, in case of vitamin D levels below 50 nmol/l, bisphosphonates or Denosumab, in cases with bone disease. Cinacalcet is an effective drug in lowering the serum calcium for symptomatic patients who cannot undergo surgery. It can be used in combinations with bisphosphonates in selected patients [26].

The American Association of Endocrine Surgeons guidelines (2016) recommend parathyroidectomy as the only definitive treatment of PHPT both for symptomatic patients, because of clear benefits, and in asymptomatic cases, for improved quality of life.

Strong recommendations for surgery are:

- Total serum calcium is 1 mg/dl higher than the upper normal range, regardless symptomatology;
- The presence of osteoporosis, fragility or vertebral compression fractures;
- Patients under 50 years, regardless complications
- Clinical or biochemical evidence of parathyroid carcinoma;
- Lack of compliance to observational protocols (e.g. neurocognitive or neuropsychiatric symptoms);

Weak recommendations for surgery are:

- Renal involvement: silent nephrolithiasis, nephrocalcinosis, glomerular filtration rate below 60 ml/min or hypercalciuria ( $> 400$  mg/dl/ 24 hours urine);
- Cardiovascular disease, other than hypertension, if reduction of the cardiovascular morbidity and mortality can be achieved;
- Nontraditional symptoms: muscle weakness, altered functional capacity and abnormal sleep patterns [27,28].

MIP is recommended in cases with solitary adenomas, but not routinely recommended if multiglandular disease is suspected or diagnosed. If during MIP, multiglandular disease is discovered bilateral exploration is strongly recommended [27,28].

In cases with sHPT, phosphate binders, calcium supplements, active vitamin D analogues and calcimimetics are used in renal form of disease, vitamin D supplements in digestive form of disease, surgical treatment being used only in refractory cases, defined as severe, persistent, with growing elevations of serum PTH that cannot be lowered by medical treatment, without causing severe metabolic complications, according to the KDIGO guidelines [29]. KDIGO guidelines suggest a serum level of PTH to be maintained between two to nine times the upper normal level for patients in

dialysis, but literature reports suggest that a serum PTH level over 800 pg/ml and a sustained hypercalcemia, defined as serum calcium higher than 10.4 mg/dl, and hyperphosphatemia, as an absolute indication for parathyroidectomy, especially in patients before renal transplantation, regardless symptoms [29,30].

Considering the treatment options, both in PHPT and sHPT, a correct identification of the location of the parathyroid glands is mandatory before referring to surgery.

Current options are scintigraphy, ultrasonography, MRI and Tomography (CT). Ultrasonography (US) and scintigraphy are the most available imaging techniques for the localization of parathyroid disease. There are numerous literature studies that compare these techniques showing similar sensitivities and specificities for single adenoma detection. CT and MRI are also cited as imaging techniques for parathyroid disease, but more often for ectopic sites, such as mediastinal glands [31].

US is widely available and it the most frequent examination in thyroid disease. US has stated a crucial role the management and diagnosis of thyroid nodules. It can also be used to perform diagnostic and therapeutic techniques as fine needle aspiration and percutaneous interventions – ethanol, radio frequency or laser ablation [32].

### Grey Scale Ultrasonography

Technical development of Ultrasonography (US) has gained increasing accessibility in endocrine disease becoming a gold standard in thyroid disease. US is a non-invasive, cheap and it allows repeatable, real-time assessment of organs. One of the major advantages of US is that it does not expose patients to radioactive isotopes or Roentgen rays, it has a short duration and it is comfortable for the patients, it can be performed on children and pregnant women [33,34]. During a parathyroid examination, the patient lies in supine position, with hyperextension of the neck, a shoulder role could facilitate exposure. It is important for the examiner to maintain constant and precise adherence of the probe to the area of examination [33,35,36].

Examination of the parathyroid glands must include longitudinal and transverse images from the the carotid arteries to the hyoid bone and extending from the superior carotid artery bifurcation to the inferior thoracic inlet [36,37]. Normal parathyroid glands are rarely visualized on ultrasound due to their small size and posterior location. Enlarged glands, however, appear as ovoid, hypoechoic structures, measuring approximately 0.8-1.5 cm [35].

Parathyroid ultrasonography can evaluate anatomic relationship of enlarger glands with surrounding tissues. Abnormal parathyroid glands have an oval or bean shape form and they can rarely appear as multi lobulated hypo echoic mass posterior or inferior to the thyroid gland on ultrasound examination. In addition, auxiliary techniques such as Color or Power Doppler could help demonstrate an extrathyroidal feeding vessel entering in one of the poles. Thyroid nodules or cervical lymph nodes can give negative or positive false results. US cannot examine retrosternal or mediastinal parathyroid lesions [32]. Superior glands are usually first assessed, due to the fact that they are less likely to be ectopic. Collateral techniques such as rotating the head or swallowing should enhance visualization of ectopic adenomas by deviating them into the sonographic window. However, the evaluation of ectopic glands is limited by

poor penetration of bone structures and air-filled structures [35]. If visualized, location size and number of the parathyroid glands should be documented. Measurements in three dimensions and volumes with the ellipsoid formula should be calculated [36]. Thyroid gland should be always evaluated for concomitant thyroid pathology or presence of intrathyroidal parathyroid adenoma [37]. Literature studies have found occurrence of thyroid disease in 29-51% of patients with PHPT, impacting the therapeutical approach [38,39].

Precision of localizing parathyroid adenomas by US is dependent by the location and size of the tumor [40], by body habitus and gland morphology and also by the experience of the practitioner [35].

There is a significant body of evidence evaluating the diagnostic quality of US, in locating parathyroid adenomas: with a sensitivity described as 76% [41], 79% [42] up to 80% [43] even 90% of parathyroid hyperplasia [44] and a specificity of 93.2% [41]. The sensitivity decreases in multiglandular disease, around 35% (95% CI, 30–40%), even less in double adenoma 16% (95% CI, 4–28%) [42].

False positive results are also described, with a very vast variation, between 40-100%[40] due to thyroid nodules, lymph nodes, muscles, vessels and oesophagus [45,46].

The novel applications of ultrasound, including Doppler techniques, 3D imaging, contrast-enhanced ultrasonography and elastography techniques have enhanced the diagnostic value of ultrasound in the diagnostic of hyperparathyroidism [33], by decreasing the false positive cases.

Colour Doppler sonography is an useful complementary technique in localization of parathyroid disease, especially parathyroid adenomas [47] because of the typically element, a peripheral vascular rim and an abnormal increased blood flow compared to the thyroid tissue[48], respectively the central hilum vascularisation seen in lymph nodes.

Various flow patterns were reported. Including no flow, spot of fire, central vessels, peripheral vessels and combined vascularity, central and peripheral [49]. Doppler imaging increases accuracy by 54% and sensitivity by 54%, respectively 10% compared to grey scale imaging [50].

### Ultrasound Elastography

Elastography is a relatively novel developed technique that can be helpful in assessing, among other complementary techniques of ultrasonography, with additional information on tissue stiffness, not explored by any other imagistic techniques [51]. Developed in the 1990's, its main purpose is to replace clinic palpation in the evaluation of tissue rigidity. Ultrasonography is a imaging technique widely used in medical practice for more than 40 years for its low cost, portability, accessibility and the ability to perform real-time evaluation [52].

An increase of the tissue stiffness can be found in neoplastic disease, fibrous tissues or atherosclerosis. Neoplastic development can be seen in early stages because of the changes in the tissue matrix, where due to the overproduction of connective tissue, the increased blood vessels density and the changes in the cell density the overall tissue becomes stiffer [53]. Elastography has the potential of detecting the differences of benign and malignant tissues from the early stages of the disease and also can offer a greater sensitivity and resolution for

deep situated structures [54].

Elastography uses ultrasound to provide the estimation of tissue stiffness, by measuring the degree of distortion under a compression force, because softer body tissues distort more easily than harder ones [55]. The distortion in elastography can be obtained by external pressure, usually applied manually via ultrasound transducer [55], or by internal crossing deformation, induced by converged ultrasound beams or by short duration focused acoustic beam, that will generate shear waves that diffuse transversally through the tissue. Elastography techniques deliver qualitative information about tissue stiffness through colour maps and colour codes and quantitative information through numerical values [51].

There are described two basic principles used for ultrasound elastography: “examination of the strain or deformation of a tissue due to a force (static elastography) and analysis of the propagation speed of a shear wave (shear wave elastography)” [56]. The results are delivered using three major type of characteristics:

- Qualitative criteria = maps, presented in grey or colour scales, depending on the manufacturer, displaying the distribution of elasticity in the Region Of Interest (ROI). A ration can be calculated between the width of nodules on B-mode compared with elastography.

Other parameters are also used in strain elastography, some specific to the manufacturer:

- a. Area Ratio (AR) reported on Virtual Touch Imaging (VTI), comparing the lesion surface with the adjacent tissue.
- b. Hard area ratio comparing the hard area with the rest of the lesion.
- c. Strain index, comparing the strain of the whole lesion with the strain of soft part of lesion
- d. Stiffness ratio, specific to Philips devices, compares lesion stiffness with the surround tissue. Elasticity contrast index is a specific technique for Samsung machines that delivers a strain map, with malignant lesions showing a higher contrast [51,57,58].

- Semi-quantitative criteria are estimation of deformation ratios or elasticity ratios between different ROIs, usually called stiffness ratio. Strain elastography can also provide semi-quantitative determinations using the Strain Ratio (SR) allowing comparison of tissue strain in the Region Of Interest (ROI) with the adjacent healthy tissue. High values of SR are correlated with high chances of malignancy [51,59].
- Quantitative criteria available only on shear wave devices, measuring shear wave propagation speed. It is a dynamic method that contains various subtypes of techniques: Transient Elastography (TE) that calculates only values, without images, Point Shear-Wave Elastography (pSWE) and shear-wave elastography that includes 2D SWE and 3D SWE [60]. They give numerical data in m/s or kPa, calculated in Young modulus [56].

In this elastography technique an active stress is implemented by using a vibrating device in 1D transient elastography or acoustic

radiation force in point Shear Wave Elastography (pSWE) and 2D Shear Wave Elastography (2D SWE). The excitation created by the waves is quantified and reported as the shear wave speed or in Young’s modulus E [61].

In strain elastography physical displacement parallel to the applied normal stress is measured, in comparison, shear wave elastography applies a dynamic stress that produce shear waves in parallel or perpendicular dimensions, generating qualitative and quantitative results of tissue elasticity. There are three SWE techniques: Dimensional Transient Elastography (1D-TE), point Shear Wave Elastography (pSWE) and 2Dimensional Shear Wave Elastography (2D-SWE) and the newer technique 3Dimensional Elastography (3D-SWE) [61].

In point shear wave elastography, ARFI induces displacement of tissue in a single focal location, similar to ARFI strain. In contrast with ARFI strain, in pSWE measures a portion of longitudinal waves converted through the absorbtion of acoustic energy in shear waves. The speed of shear waves is directly reported or converted in Young’s modulus E to determine the tissue elasticity. pSWE can be operated on any ultrasound machine using the a standard ultrasound transducer. This can be performed using Virtual Touch™ Quantification (VTQ/ARFI) and Elast-PQTM [61].

VTQ measures and quantifies tissue stiffness by sending short duration acoustic pulses (0.03-0.04 ms) from the probe, generating small (1-10µm) tissue dislocation in the Region Of Interest (ROI). The tissue deformation is then calculated to a numeric value called Shear Wave Velocity (SWV) [62].

Two-dimensional shear wave elastography is the newest technique based on the acoustic radiation force. Compared to ARFI strain imaging and pSWE where there is a single focal location, 2D SWE uses multiple focal zones examined with greater speeds than shear waves, forming a cone, called Mach’s cone that allows real-time interrogation, generating quantitative elastograms [60]. This technology can be found on Virtual Touch™ Imaging Quantification (VTIQ/ARFI), Shear Wave™ Elastography, Shear Wave Elastography, Acoustic Structure Quantification™ and 2D-SWE [53,60]. The major advantages are real-time quantitative elastograms overlap on B-mode image [63], assesing information both anatomical and of tissue stiffness [61].

There are limitations to these techniques, false positive results can be generated if applying external pressure [64,65], shear wave cannot propagate through liquid zones, calcifications also change accuracy of this technique [66] and also the local anatomy (trachea, carotid artery) can alter the quality of examination [51,67].

## Virtual Touch Imaging Quantification

Acoustic Radiation Force Impulse (ARFI) is a SWE mode that asses elasticity of tissues placed in a Region Of Interest (ROI) by measuring the velocity of shear waves. 13 Two methods are described, Virtual Touch Quantification (VTQ) and Virtual Touch Imaging Quantification (VTIQ). Both measure quantitatively tissue elasticity by Shear Wave Velocity (SWV) in meters/seconds (m/s). By comparison, VTIQ uses a smaller Region Of Interest (ROI) and during examination an color map is shown, allowing the correct



placement of the ROI [34].

VTIQ is an elastographic technique based on the principle of acoustic radiation force method. By directing ARFI, a sound impulse to a tissue, a matching shear wave is created [68]. Speed wave in VTIQ is 1-10 m/s [69]. Shear Wave Velocity (SWV) represents a qualitative parameter and it has an inverse relation with tissue stiffness, hard tissues are correlated with a faster wave, whereas soft tissues with a slower wave. VTIQ can be a potential useful tool in assessing parathyroid lesions [68].

Ultrasound elastography is cost effective and widely available as a diagnostic tool. The value of the method is demonstrated in breast, thyroid, prostate and liver disease [69]. It has been proven to be a beneficial diagnostic tool of focal lesions in thyroid, breast, lymph nodes and pancreatic tumors. However it cannot replace tissue biopsies, but on selected cases it can be a valuable tool of diagnostic [54].

The effectiveness of elastography in parathyroid diseases is less studied. Consecutively to B-mode ultrasound and colour Doppler, elastography could be performed as an adjuvant method in evaluating parathyroid lesions [70]. Normal parathyroid glands cannot be visualized on ultrasound because of their small size, deep location and the increased amount of adipose tissue. Parathyroid adenomas and parathyroid hyperplasia can normally be visualized on US. Parathyroid adenomas have a low amount of adipose tissue compared to the normal parathyroid glands, whereas hyperplasia preserves somehow the fat tissue. They have a hypoechoic appearance of US because of the high cellularity and low fat tissue, that reduce the reflecting of sound [34]. Decreased adipose tissue in parathyroid glands and the capsule surrounding the adenoma can contribute to an increased stiffness [62].

The role of strain elastography in elasticity of parathyroid lesions was examined in several studies, which have shown that elastography is a helpful technique in differentiating different parathyroid pathologies. In the first study, carried out on 92 patients with parathyroid lesions, Unluturk et al. [71] found that parathyroid adenomas appear as stiff lesions (median SR=3.56), while parathyroid hyperplasia have a higher elasticity and lower stiffness (median SR=1.49). Isidori et al. [72] evaluated 79 patients with parathyroid disorders on Elastoscanner Core Index (ECI) and compared the finding with the lymph nodes. They found that ECI values of adenomas have lower elasticity than hyperplasia and reactive lymph nodes, helping in the differential diagnosis.

Based on the literature experience with elastography on neck pathology, SWE could be an effective tool in diagnosing parathyroid adenoma since parathyroid adenoma has a different tissue composition, vascularity pattern, and subsequent tissue stiffness compared to thyroid pathology [69].

Prospective literature studies have assessed stiffness in parathyroid adenomas and parathyroid hyperplasia, but the results depend on the elastographic method used, and, are sometimes contradictory. Elastography is a newly developed method of examination and currently there are no established values in parathyroid pathology.

Azizi et al. [69] examined 57 patients with parathyroid adenomas

using SWE VTIQ and compared it with normal thyroid tissue. They reported a mean SWV of parathyroid adenoma at 2.01 m/s ( $\pm 0.24$ ), which was significantly lower than the mean SWV in the normal thyroid tissue - 2.77 m/s. They also found a polar vessel present, including also adenomas from ectopic locations, in 86% of patients, suggesting that it can be used as a sonographic parameter in the diagnosis of parathyroid adenomas.

Batur et al. [73] conducted a study on 21 patients with parathyroid adenomas using ARFI imaging 2DSWE and compared the mean SWV obtained with elastographic measurements on thyroid benign and malignant pathology. The reported results indicate a higher stiffness in parathyroid adenomas (mean SWV=3.09  $\pm 0.75$  m/s) compared with thyroid benign nodules (2.20 $\pm 0.39$  m/s) and a lower stiffness compared to the malignant thyroid lesions (3.59 $\pm 0.43$  m/s). The main limitation of this study was the depth of ARFI penetration, of 5 cm, and the impossibility of measuring high velocities.

Chandramohan et al. [74] used the same diagnostic algorithm (comparison with thyroid nodular pathology), in 43 patients with parathyroid lesions using ARFI VTI. Mean SWV of parathyroid lesions was 1.6 $\pm 0.78$  m/s, whereas benign thyroid nodules had a mean of 2.11 $\pm 0.8$  m/s and malignant thyroid nodules had mean of 4.3 $\pm 2.71$  m/s. Authors concluded that parathyroid adenomas have a lower SWV compared to thyroid lesions. They established a cut-off value for parathyroid adenomas to 1.72 m/s with a sensitivity of 75.3% and a specificity of 71.1%. They also stated that a speckled appearance is highly characteristic to parathyroid adenomas.

Another study performed by Hattapoglu et al. [62] evaluated 36 patients with parathyroid lesions using VTQ method of point SWE and compared it to normal thyroid parenchyma and thyroid nodules. The reported mean SWV (shear wave velocity) of parathyroid adenoma (2.28 $\pm 0.50$  m/s) was higher than the parathyroid hyperplasia (1.46 $\pm 0.23$  m/s), there were no significant difference between parathyroid adenoma and thyroid nodules (2.25 $\pm 0.51$  m/s) and parathyroid adenomas were significantly stiffer than normal thyroid parenchyma (1.62 $\pm 0.20$  m/s). They established a cut-off value of 1.73 m/s for parathyroid adenomas with a sensitivity and specificity of 90.0%, respectively 80.6%. There were limitations to the study, the reduced number of parathyroid hyperplasia and the use of VTQ technique [34].

Polat et al. [34] examined 66 patients with parathyroid lesions using SWE VTIQ method and compared the shear wave velocity of parathyroid lesions with inflammatory cervical lymph nodes. The mean SWV of parathyroid adenomas was 2.16 $\pm 0.33$  m/s, a mean SWV of 1.75  $\pm 0.28$  m/s was found in parathyroid hyperplasia and 1.86 $\pm 0.37$  m/s was found in cervical lymph nodes. The elasticity of parathyroid adenomas was lower than parathyroid hyperplasia and cervical lymph nodes, however they could not establish a significant difference between parathyroid hyperplasia and lymph nodes. A cut-off value greater than 1.92 m/s for diagnosing parathyroid adenoma had a sensitivity of 80% and a specificity of 82%. Authors did not compare parathyroid lesions with thyroid tissue or lesions and this represents a limitation to the study.

Adam et al. [75] performed 2D-SWE on 65 patients with parathyroid adenomas and compared stiffness with benign thyroid

nodules. A mean Elasticity Index (EI) of parathyroid adenomas was found  $5.2 \pm 7.2$  kPa, whereas the mean EI of thyroid nodules was  $24.3 \pm 33.8$  kPa, indicating that parathyroid adenomas are significantly more elastic than benign thyroid nodules.

Golu et al. [76] conducted an elastography study, using 2D-SWE technology, on 22 patients with parathyroid lesions and compared the EI with normal thyroid tissue elasticity. The mean EI measured in parathyroid lesions was  $10.2 \pm 4.9$  kPa and the mean EI in normal thyroid tissue was  $19.5 \pm 7.6$  kPa, establishing that parathyroid lesions are more elastic than thyroid normal tissue. A cut-off value of 12.5 kPa was found, with a specificity of 86% and a sensitivity of 93%. However, there are limitations to this study, the low number of parathyroid lesions and the lack of thyroid explorations of normal subjects.

### Contrast Enhanced Ultrasound (CEUS)

There are currently no studies with CEUS of primary hyperparathyroidism. Researching the literature, we found one study on CEUS [77] conducted on patients with secondary hyperparathyroidism. The study was included 42 patients with sHPT. The patients were divided in three groups (light, moderate and severe sHPT) by the PTH levels.

In sHPT, patients first present parathyroid enlargement due to diffused hyperplasia and numerous studies have shown that the natural tendency of diffuse hyperplasia is to transform in nodular hyperplasia [78]. Conventional ultrasound can be performed and it can easily show the location of parathyroid glands and the surrounding anatomy, but it cannot assess the severity of sHPT. According to the authors of the study, CEUS can detect nodular hyperplasia before the appearance of sHPT resistant to medical treatment. They found a CEUS model that can evaluate the severity of sHPT, light sHPT was characterized by "slow-in, fast-out and low enhancement", moderate sHPT was characterized by "fast-in, fast-out and higher-enhancement", while severe sHPT was characterized by "fast-in, low-out and higher-enhancement" [77].

The major problem of elastography, and US evaluation, regardless device or technique is the possibility of ectopic or supernumerary parathyroids. The reported incidence of supernumerary glands varies from 3% to 13%, the most common cited ectopic site being the thymus [35,79,80].

Ultrasound is not the best modality to assess ectopic parathyroid adenomas, especially when located in the thymus or posterior mediastinum.

Literature reports showed that 10% of parathyroid adenomas are situated intrathyroidal, leading to false-positive results in patients with concomitant thyroid nodular goiter or enlarged lymph nodes and false-negative results due to the small size of parathyroid adenomas [81,82].

Ultrasound sensitivity reported in the diagnosis of ectopic parathyroid adenomas is 25% [83]. Auxiliary techniques, like graded compression and axial rotation of the patient's head or swallowing should facilitate visualization of ectopic adenomas by bringing them under the ultrasound probe. Regardless of these techniques, the capacity of ultrasound to evaluate ectopic glands is restricted

due to the air filled (trachea, oesophagus) and osseous structures. Complementary imaging techniques such as MRI or CT may be necessary, especially in patients with multiglandular disease and ectopic glands in the mediastinum [31,32,82,84].

A single literature study examined ectopic parathyroid adenomas using SWE VTIQ, Azizi et al. found the median SWV for ectopic adenomas (three intrathyroidal and two in the right neck) is 2.18 m/s and all ectopic adenomas presented a polar vessel in Doppler mode [69].

### Conclusion

Elastographic techniques, especially shear wave elastography can be a useful tool in the diagnosis of parathyroid adenomas. Elastography does not offer by itself a decisive diagnosis of parathyroid lesions, but as an additional tool it can add significant value to the ultrasound examination, especially if cut off values are used to differentiate parathyroid versus thyroid parenchyma.

Currently there are no current guidelines recommendations on the technique or established values in order to properly evaluate the stiffness of the parathyroid glands. After reviewing the literature, and assessing thyroid recommendations, we can make some remarks.

There are some basic setting principles when evaluating (with 2D-SWE) parathyroid disease:

1. Elastography scale – thyroid and lymph nodes studies use a scale between 20-40 kPa for a homogenous colour code [85]. Since the literature studies showed a comparable stiffness of parathyroid adenomas to benign thyroid disease and parathyroid hyperplasia stiffness resembling to that of the lymph nodes, when evaluating parathyroid disease same scale should be embraced. The maximum value of the scale on thyroid disease is 80 kPa.
2. Observing a very low value, near 0 indicates the presence of a liquid lesion. It is also important to verify the signal intensity, in case of deep lesions, where the signal is uniformly low, one could opt for a linear probe with lower frequencies.
3. Elastographic noise can be decreased by increasing gain.
4. Trachea could generate artefacts; superior or intrathyroid parathyroid lesions could be affected.
5. The external pressure on the probe must be minimal in order to prevent false positive values [86].

When considering a therapeutic method, the final decision should take into consideration conventional ultrasound and elastography, as additional diagnostic tool. Even if there are important differences between the different elastographic techniques, current studies performed on parathyroid lesion established that parathyroid adenomas are usually stiffer than parathyroid hyperplasia and cervical lymph nodes. However, depending on the elastographic method, the stiffness of parathyroid lesions is contradictory when comparing it to normal thyroid tissue or thyroid lesions. Further studies are needed due to the disagreeing results of some studies conducted on different elastography techniques.

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