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Phd THESIS

DIAGNOSTIC PERFORMANCE OF REAL TIME ELASTOGRAPHY IN PREDICTING THYROID NODULES MALIGNANCIES

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T i m i ș o a r a
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Contents

GENERAL PART

CHAPTER I. BENIGN AND MALIGNANT THYROID NODULE

Thyroid nodules are commonly seen in clinical practice and are found in 50 – 60% of people with a good general health status, especially in women. [1]

Diagnostic imaging techniques currently available allow the identification of very small thyroid nodules (0.2 cm), and this is linked to the increasing incidence of the disease [2], with various authors considering that we are rather assisting to improved detection of thyroid nodules than to an actual increased incidence.

The 5-year prevalence of thyroid cancer worldwide, expressed as proportion (per 100,000) of the population suffering from this disease, was 23.2, with higher rates in women (36) than in men (10.4). [3] In Europe, the prevalence was 33.6 (49.4 for women and 16.2 for males), while in Romania was 16.6% (27.6 for women and 4.6 for males) [4]

I.2. ETIOLOGY AND PATHOGENESIS

Etiologically, the thyroid nodule may occur in benign conditions, such as multinodular goiter, focal thyroiditis, thyroid and parathyroid cysts, thyroid gland, gill duct, residual hyperplasia following destructive processes of thyroid parenchyma, compensatory lobe hyperplasia in case of agenesis of the other lobe, as well as in benign and malignant tumors such as carcinomas of various types, primary thyroid malignant lymphoma, bone marrow cancer, etc.

Many exogenous factors contribute to thyroid disorders, particularly in the development of thyroid cancer, of which we mention exposure to ionizing radiation or iodine availability. In areas with iodine deficiency, the multinodular goiter is a frequent disorder because the thyroid does not synthesize sufficient amounts of thyroid hormones.

However, the greatest source of concern for thyroid nodules is that they may be malignant. Etiopathogenic factors of thyroid cancer include exposure to radiation or pollutants, which can cause carcinogenic mutations, but also genetic factors. Among the endogenous causes of thyroid cancer, we mention TSH level disorders, autoimmune thyroiditis, obesity and insulin resistance.

CHAPTER II. DIAGNOSIS OF BENIGN AND MALIGNANT THYROID NODULE

II.1. ANAMNESIS AND CLINICAL EXAM

Anamnesis focuses on collecting information about family and personal history of thyroid disease, previous cervical irradiation, the time of appearance or observation, as well as the development of the nodule, dysphonia, dysphagia or dyspnea, cervical sensitivity or pain, symptoms of hypo- or hyperthyroidism. [5]

II.2. BIOLOGICAL DIAGNOSIS

Laboratory investigations to detect one or more thyroid nodules begin with the measurement of serum TSH, which is the best test for thyroid function. Other laboratory tests will be performed according to the TSH level, as follows:

- If TSH is low, free thyroxine (FT4) and free triiodothyronine (FT3) are measured;
- If TSH levels are increased, anti-thyroid peroxidase (anti-TPO) and FT4 are determined.

II.3. CYTOLOGICAL EXAM

Cytology by fine needle aspiration is an important step in the diagnosis of thyroid nodules along with ultrasound. The National Guideline on Thyroid Nodule Management [5] recommends the cytological evaluation of any firm or hard solitary nodule. FNAC is considered the most appropriate method of evaluating thyroid nodules due to the high rate of positive results correlated with a low rate of false negative results, thus guiding the selection of patients requiring surgery. [6]

II.4. HISTOPATHOLOGICAL EXAM

Histopathological diagnosis is the diagnosis of certainty in case of thyroid nodules. Although a recent study [7] has drawn attention to the fact that interobserver variability may lead to discordant diagnosis of benign or malignant disease, the histopathological examination remains the gold standard. Histopathological diagnosis includes the staging of thyroid cancer based on criteria established by the international TNM staging system and is reported according to histological classification of thyroid tumors by the WHO.

II.4.1.HISTOLOGICAL CLASSIFICATION OF THYROID TUMORS

Thyroid tumors are classified as benign epithelial: follicular adenomas [8], other adenomas (non-follicular), and malignant (follicular, papillary, medullary, undifferentiated or other types); benign and malignant non-epithelial derived from tumors of the pharynx, larynx, trachea, and esophagus, as a consequence of the direct extension of the primary tumor to which metastasis is added from primary lung, breast, digestive or renal malignant tumors. [9.10]

II.4.2. EPITHELIAL TUMORS

Benign epithelial tumors are classified as follicular adenomas or other adenomas (non-follicular).

Malignant epithelial tumors can be follicular, papillary, medullary (C-cell), undifferentiated (anaplastic), or other types.

II.4.3. OTHER TYPES OF TUMORS

Benign and malignant non-epithelial tumors, as well as secondary tumors, are rare. Tumor-like lesions include diffuse and nodular hyperplasia, thyroid cysts, ectopic thyroid tissue, and chronic or fibrous thyroiditis (Riedel).

II.5 DIAGNOSTIC IMAGING TECHNIQUES

Scintigraphy is useful in patients with hyperthyroidism and in the detection of thyroid tissue after thyroidectomy in the treatment of thyroid cancer. Computed tomography or nuclear magnetic resonance imaging are not recommended in routine thyroid node evaluation, and positron emission computed tomography is considered useful in preoperative staging of malignant nodules with aggressive features.

II.5.1. THYROID ULTRASOUND

Thyroid ultrasound is recommended [1,5] especially in patients with palpable nodules or multinodular goiter, in those with palpable cervical adenopathy suspicious of malignancy, in patients at risk of familial thyroid cancer and in those who have been irradiated in the head and neck area, especially in childhood, as well as in the monitoring of thyroid nodules.

The main ultrasound parameters for which information can be yielded are [1]: size and location of the nodules, shape of the nodules, with emphasis on the margins shape and the ratio between the anterior and posterior diameter, the composition of the nodules (solid, cystic, spongiform) (hypo-, iso-, or hyperechoic), presence or absence of halo sign, presence and type of calcifications, vascularization (intra-, perinodular or absent).

Thus, based on the data from the literature [11,12,13,14], the authors specify the ultrasound features suggestive of malignancy given their significant correlation with a certain diagnosis of thyroid cancer, namely: solid composition, marked hypoechoic), irregular or spiculated margins, presence of microcalcifications and anterior-posterior diameter larger than transverse.

Rago et al. [15] showed that the association between the absence of halo sign and the presence of point microcalcifications had the highest predictive value in their study, while other studies showed that hypoechogenicity, the presence of microcalcifications, irregular or spiculated margins, a ratio greater than 1 cm between the anterior-posterior and the transverse diameters, [16] the lack of homogeneity, the absence of the halo sign, the intranodular vascularization and the nodule shape [17] represented the most useful features of malignant nodules.

In our studies [18,19,20] we identified the following ultrasound features to be predictive of malignancy: intranodular or perinodular blood flow, transonic areas, microcalcifications, irregular margins, echogenicity and homogeneity.

II.5.2. ELASTOGRAPHY

Elastography, a technique that measures the elasticity differences between the suspect region (nodule) and the adjacent thyroid tissue (normal tissue) [21].

II.5.2.1. Strain Elastography

The principle underlying the strain elastography is that of transmitting ultrasounds in tissue by applying an external pressure by means of a transducer, thus assessing the elasticity/rigidity of a lesion following the appreciation of the degree of deformation that occurs when external force is applied to the nodule. [14] The software embedded in the special elastography equipment compares the degree of deformation of the nodule to that of the adjacent tissue, calculates and displays a strain index.

The Tsukuba score, developed by Itoh and Ueno for elastographic investigations on breast cancer, [22] uses a 5-point scale, which applies to thyroid nodules as well. According to this scale, nodules with a score of 1 to 2 are mostly elastic and soft, nodules with score 3 are those with a rigid center, while scores 4 and 5 are hard-weighted nodules. [23] The semi-quantitative method has also been shown to be useful in the diagnosis of malignant thyroid nodules, as shown by the study of Cantisani et al., [24] who demonstrated that a strain ratio (SR) greater than 2 claims additional investigations, being associated with malignancy. A more recent study [25], which aimed to compare the clinical utility of SR with the elastographic score, concluded that the first had a sensitivity of 81% and a specificity of 83% with the best cutoff calculated at 4.2.

Our retrospective study on strain elastography [20] produced similar results to those reported in the literature, a SR greater than 2 being predictive of malignancy, with 92.3% sensitivity, 67.7% specificity, 100 % positive predictive value and 88.57% negative predictive value of. The results obtained in this study at elastography also correlated with those of conventional ultrasound and Doppler ultrasound.

II.5.2.2. Shear Wave Elastography

Depending on the generation of propagated waves crossing thyroid tissue, the shear-wave elastography is of two types: ARFI (Acoustic Radiation Force Impulse) and SSE (Supersonic Elastography). Supersonic elastography involves a shear source that travels through the tissue at supersonic speed, moving faster than the induced shear waves. The shear source is created by successively focusing the wave at different depths [26]. Studies related to shear wave elastography performance have produced promising results from the beginning. Thus, the first published study [27] prospectively evaluated a group of patients and found an index for malignant nodules of 150 +/- 95 kPa. For the benign nodules, the index was 36 +/- 30 kPa and for normal thyroid tissue, 15.9 +/- 7.6 kPa (p / 0.001), with 93.9% specificity and 85.2% sensitivity. Similar results were reported by Veyreires et al., [28] the cutoff for malignant nodules being 115-60.4 kPa, and for the benign ones 41-25.8 kPa. In both studies, the optimal cutoff was 65-66 kPa.

Subsequent studies have reported various cutoffs, between 34.5 kPa and 90.34 kPa. Bhatia et al. [29] obtained a cutoff of 34.5 kPa for the average elasticity index, and Szczepanek-Parulska et al. [30] reported the best cutoff as 50 kPa, with high sensitivity but lower specified. Finally, the greatest cutoff was 90.34 kPa, reported by Wang et al. [31].

A meta-analysis [32] of 15 studies comprising 1,867 thyroid nodules detected in 1,525 patients calculated the sensitivity and specificity in identifying malignant thyroid nodules at 84.3% and 88.4%, respectively, the positive predictive value of the studies being between 27.7% and 44.7%, while the negative predictive value ranged between 98.1% and 99.1%. Another meta-analysis, [33] which included 5 studies with a total of 469 patients and 698 thyroid nodules, of which 130 were malignant, the following values were calculated: 0.84 sensitivity, 0.90 specificity, 7.39 positive predictive value and 0.20 negative predictive value.

In our study [18], we calculated the sensitivity, specificity, positive and negative predictive values for the four studied parameters, namely SWE-mean, SWE-max, SWE-SD and SWE-ratio, the results being comparable to those in the literature. We also calculated a cutoff for the average elasticity index of 20.08 kPa and 53.95 kPa for SWE-max.

ORIGINAL PART

CHAPTER III. PERSONAL CONTRIBUTIONS

III.1. AIM AND OBJECTIVES

The **aim** of this thesis is to evaluate the role of real-time elastography in prediction of malignant thyroid nodules.

The proposed **objectives** were:

- Analysis of anthropometric parameters of patients diagnosed with thyroid nodules.
- Evaluation of the characteristics of thyroid nodules by two methods, namely: real-time elastography and strain elastography
- Analysis of correlation of elastographic characteristics of thyroid nodules and their malignancy established by histopathological examination
- Determining the predictors of malignancy
- Comparing the methods used to determine the malignancy of thyroid nodules

III.2. MATERIAL AND METHOD

The first study was a prospective study conducted between January 2012 and December 2016 at the County Emergency Clinical Hospital Timisoara. We included 32 patients (28 women and 4 men) with an average age of 54.5 years (at least 29 years, maximum 76 years) who refused fine needle aspiration biopsy, out of 42 cases in which the diagnosis of multinodular goiter has been confirmed.

Patients included in this study had solitary thyroid nodules or multinodular goiter with nodule volumes ranging from 0.02 to 20.2 ml (SD ± 5.4) and thyroid volumes between 5.15 and 48.28 ml (SD ± 11 47). Fifty-two nodules were analyzed using elastography, as well as conventional ultrasound and Doppler ultrasound. All patients underwent either lobectomy or total thyroidectomy at II Surgery Clinic of SCJUT, and the final histopathological diagnosis performed on excised thyroid tissue served as the reference standard.

We used a 2D-SWE ultrasound system AixplorerTM (SuperSonic Image, Aix-en-Provence, France) using a SC5-1 linear transducer. All patients were examined during a single procedure by conventional ultrasound (Module B), Doppler ultrasound and shear wave elastography using the same equipment.

The second study was a retrospective study that included 44 nodules found in 31 patients (28 women and 3 men), mean age 52.3 years (minimum 17 years, maximum 70 years). The study was conducted between August 2016 and September 2017 at Korall Clinic in Satu Mare. All patients underwent surgery, and the final histopathological diagnosis performed on excised thyroid tissue served as the reference standard. We included patients who presented with solitary thyroid nodules or multinodular goiter at the conventional ultrasound examination, Doppler, and by strain elastography.

We used a SIUI (Shantou Institute of Ultrasonic Instruments Co., Ltd.) ultrasound equipment, Apogee 1200 model, with a 8 MHz 50mm linear transducer.

We performed the statistical analysis using the SPSS program (version 17.0 for Windows, SPSS Inc., Chicago, Illinois, USA) and the EpiInfo program (version 7). We analyzed a sample of 52 nodules and divided the sample into two parts, malignant nodules (25%, 14 nodules) and benign nodules (75%, 38 nodules) in the first study and 44 nodules in the second study. The proportion obtained from these groups was compared using a quadratic square test ($p < 0.001$). A $p < 0.05$ was considered statistically significant. Histological diagnosis has served as reference standard.

III.3. RESULTS

III.3.1 Shear Wave Elasthography Evaluation of Thyroid Nodules

In the study group, 24 nodules had irregular margins, 44 of the nodules were hypoechoic to the conventional ultrasound, seven isoechoic and only one was hyperechoic, 40 of the nodules were inhomogeneous, the halo sign was present in only 15 nodules, the microcalcifications were present in only 8 nodules, and the transonic areas were seen in 30 nodules.

During Doppler ultrasound, we observed the absence of vascularization in 13 nodules, and perinodular blood flow in 17 nodules. Intranodular blood flow was present in 20 nodules, while two nodules had both perinodular and intranodular vascularization.

Following the histopathological examination of the surgically removed nodules, 14 of the 52 nodules were found to be malignant, and the remaining 38 were benign. Of note, the nodules were malignant in half of the women, whereas all nodules found in men were benign. Among the malignant nodules one is diagnosed as Hürthle cell adenoma, 9 are classified as degenerative goiter, and 4 as chronic autoimmune thyroiditis.

We applied the t-student test, which revealed statistically significant differences only for the elastographic parameters and those determined at the Doppler ultrasound. The higher the vascularization, the greater the chance that the nodule is malignant; the same is true for elastographic parameters, which have higher values for malignant nodules.

The parameters recorded in the shear-wave elastography were SWE-mean (mean elasticity index), SWE-max (maximum elasticity index), and SWE-SD (standard deviation in the elasticity index of normal thyroid tissue). The values recorded in our study for the four quantitative parameters were rather dispersed between the two groups. However, mean and median values were higher for malignant nodules, all four parameters reaching statistical significance.

We calculated in our study a sensitivity of 71.4% and a specificity of 52.6% with AUC of 0.718 and PPV = 35.7% for SWE-mean. For the SWE-Max parameter, we calculated a sensitivity of 64.3% and a specificity of 60.5% with AUC of 0.701, PPV of 37.5%. For SWE-SD, the sensitivity is 64.3% and the specificity of 60.5% with a value of AUC = 0.652. For the SWE-ratio, the sensitivity is 71.4% and the specificity of 60.5% with an AUC = 0.740, PPV = 42.3%. We conclude that shear wave elastography has shown good performance in differentiating benign nodules from malignant ones.

III.3.2. EVALUATION OF STRAIN ELASTOGRAPHY AS A DIAGNOSIS METHOD IN MALIGNANT THYROID PHATOLOGY

For evaluation of strain elastography as a diagnostic method in thyroid malignant pathology, we studied 31 patients evaluated at the Korall Clinic in Satu Mare between August 2016 and September 2017. The average age of the patients included in the study was 52.33 years ± 14.50, with a minimum of 17 years and a maximum of 70 years.

Forty-four nodules were diagnosed, with the majority (54.5%) located in the right lobe, 4.23% in the left lobe and only 2.3% in the isthmus. Regarding the echogenicity of the nodules, 81.8% were hypoechoic, 15.9% isoechoic and only 2.3% hyperechoic; 59.1% were found to be inhomogeneous, 27.3% of the nodules had a perinodular halo, the microcalcifications were present in 22.7% of the nodules and the transonic areas in 43.2% of the nodules, while 86.4% of the nodules had regular margins. Perinodular vascularization was present in 54.5% of the nodules, whereas both peri- and intranodular vascularization was seen in 27.3%.

We compared the two groups of benign and malignant nodules, revealing a statistically significant difference between the descriptive characteristics of the two histopathological forms.

Malignancy suspicion based on these measurements was confirmed by histopathological examination. Thus, there were 13 malignant nodules out of 44. The sensitivity of the method was 92.3% and the specificity was 67.7%, PPV 100% and NPV 88.57%, which shows that all patients with malignant nodules were diagnosed with this method, the measurements being accurate.

In conclusion, the information we have obtained demonstrates the validity of the strain elastography, given that the results obtained have matched both those from conventional ultrasound and color-flow Doppler, as well as histopathological diagnosis.

III.3.3. EVALUATION OF DIAGNOSTIC CAPACITY OF REAL-TIME ELASTOGRAPHY IN THE ASSESSMENT OF NODULES IN PATIENTS WITH AUTOIMMUNE THYROIDITIS

We particularly studied the predictive ability of real-time elastography to detect malignant nodules in the onset of chronic autoimmune thyroiditis. To assess the ability of SWE to diagnose correctly benign and malignant thyroid nodules in patients with autoimmune thyroiditis, we performed a retrospective study and analyzed 19 thyroid nodules by conventional ultrasound and color-flow Doppler, as well as by shear wave elastography (SWE). Thus, we extracted only those nodules found in patients with autoimmune thyroiditis, confirmed by histopathological diagnosis.

The study was conducted from October 2015 to February 2016 in the Endocrinology Department of the Victor Babes University of Medicine and Pharmacy Timisoara (UMFVBT) and the Second Surgery Clinic of the Pius Brinzeu County Clinical Hospital Timisoara (SCJUT). Of the 43 evaluated thyroid nodules, we extracted the 19 thyroid nodules found in 11 patients with autoimmune thyroiditis, all women, with an average age of 58.36 years. The nodules were divided into two subgroups, benign (n = 13) and malignant (n = 16). All nodules were surgically removed at SCJUT II Surgery Clinic, and histopathological diagnosis served as the reference standard.

We performed ultrasound and shear wave elastography during a single procedure on the same equipment, an AixplorerTM (SuperSonic Imagine, Aix-en-Provence, France) ultrasound system using a SC5-1 linear transducer. The t-test study was used to compare the data and the $p < 0.05$ values were considered statistically significant.

The histopathological diagnosis was performed according to the World Health Organization's instructions, revealing six papillary carcinomas, the other 13 nodules being benign.

At conventional ultrasound, the presence of transonic areas was the only parameter that reached statistical significance at $p = 0.033$. In our series, only seven nodules had irregular margins, most of the nodules (n = 16) were hypoechoic, more than half of the nodules had an inhomogeneous appearance, the halo sign being absent in 12 nodules.

At color-flow Doppler, 4 of the 6 malignant nodules had intranodular blood flow, 2 had perinodular blood flow, while all avascular nodules (n = 5) were benign. These results were found to be statistically significant at a p value of 0.043. We found that the tissue rigidity of malignant nodules in patients with simultaneous autoimmune thyroiditis is significantly higher for all SWE parameters. There were large differences between the highest values recorded in the two subgroups, as follows: SWE-mean of 59.1 kPa in a malignant nodule and 33.2 kPa in a benign one; SWE-max 96.06 kPa / 46.5 kPa; SWE-SD 14.4 kPa / 4.9 kPa; SWE-ratio of 2.03 kPa and 1.53 kP, respectively.

We calculated a sensitivity of 66.7% and a specificity of 53.8% for SWE-mean with an AUC of 0.692. For the SWE-max parameter, we calculated a test sensitivity of 66.7% and a specificity of 46.2% with an AUC of 0.756. For the SWE-SD parameter, we calculated a test sensitivity of 66.7% and a specificity value of 30.8%. The AUC is 0.712. For the SWE-ratio parameter, we calculated a 50% test sensitivity and a higher specificity value than the other 72.7 %% parameters. The AUC is 0.864. In addition, in order to appreciate the correct identification of the real positive nodules, we calculated the positive and negative predictive values. For SWE-mean, PPV is 21.1% and NPV is 36.8%, with no statistical differences between the two groups. As with the other parameters, for SWE-SD, PPV and NPV are similar without statistically significant differences.

CHAPTER IV. DISCUSSIONS

A meta-analysis calculated the sensitivity, specificity, PPV and NPV of 0.84, 0.90, 7.39 and 0.20, respectively, with good diagnostic accuracy. The cutoff values in these studies were from 34.5 to 90.34 kPa. In our study, we calculated the sensitivities, specificities, PPV, NPV, AUC, and cutoff values for each of the four SWE-mean, SWE-max, SWE-SD and SWE-ratio parameters. SWE-mean showed the highest sensitivity (92.3%), although with a lower specificity (47.4%), the best being SWE-max (81.6% with a sensitivity of 53, 8%). The positive predictive value was between 37.5 and 50%, according to literature data. Similarly, we obtained negative predictive values for all four SWE parameters, proving a potential to reduce unnecessary invasive diagnostic procedures in patients with benign masses

Cut-off values reported in the literature range from 34.5 kPa to 90.34 kPa. Bhatia et al. evaluated the SWE's reliability in 176 throat lesions, of which 40 thyroid nodules, and achieved a cut-off of 34.5 kPa for the average elasticity index, while Szczepanek-Parulska et al. 18 had the best cut-off at 50 kPa, with very high sensitivity, but less specificity. Sebag et al. and Veyrieres et al. found values very close to differentiation between benign and malignant masses, namely 65 kPa and 66 kPa, respectively. Wang et al. reported the greatest cut-off, 90.34 kPa.

We have established in our study a cut-off for the mean elasticity index of 20.08 kPa, with a very high sensitivity and lower specificity, and a higher cut-off for SWE-max, i.e. 53.95 kPa, with high specificity and low sensitivity. For SWE-mean and SWE-max the negative predictive value was very high (94.70% and 83.8%, respectively), while the precision was 60% for the first and 74.5% for the second.

According to the data available in the literature, several features of the nodules (irregular margins, hypoechogenicity, inhomogeneity, absence of halo sign, presence of microcalcifications, transonic areas and blood flow) predict malignancy in the thyroid nodules when taken together, and in our study we have found that intranodular blood flow is statistically significant.

Rago et al. used the elasticity score for thyroid nodule elastography and concluded that scores 4 to 5 were predictive of malignancy, with 97% sensitivity, 100% specificity, and 98% positive predictive value.

The semi-quantitative approach has also been proved correct in the diagnosis of malignant thyroid nodules, as shown by Cantisani et al., who reported 93% sensitivity, 89% specificity, 82% PPV and 94% NPV. Another study intending to evaluate the clinical value of the strain ratio compared to the elasticity score, found 81% sensitivity and 83% specificity for the first. Similar to these studies, our retrospective analysis shows that a foreign index greater than 2 is highly predictive of malignancy, with 92.3% sensitivity, 67.7% specificity, 100% predictive value and 88.57% negative predictive value. In our study, the results obtained in foreign elastography also correlated with the results obtained at conventional ultrasound and Doppler.

CHAPTER V. CONCLUSIONS

- ✓ The first study was a prospective study carried out between January 2012 and December 2016 at the Emergency County Clinical Hospital Timisoara, which included 32 patients (28 women and 4 males) with an average age of 54.5 years.
- ✓ The second study was a retrospective study that included 44 nodules found in 31 patients (28 women and 3 men), an average age of 52.3 years between August 2016 and September 2017 at the Korall Clinic Satu Mare.
- ✓ In both studies, the majority of patients were women (87.5%).
- ✓ Patients were diagnosed with 1, 2 or 3 nodules located only in the left lobe, only in the right lobe or bilateral.
- ✓ The following features of the nodules were found in the first study:
    - o Statistically significant differences between the two groups of nodules were demonstrated only for elastographic parameters and those determined in color-flow Doppler, namely nodular blood-flow
    - o A statistically significant positive correlation between malignancy and nodular blood-flow, a value of elastographic parameters was proved.
    - o Elastographic parameters and nodular blood-flow were shown to be malignancy predictors.
- ✓ In evaluating the shear wave elastography as a diagnostic method we obtained the following results: we calculated a sensitivity of 71.4% and a specificity of 52.6% with AUC of 0.718, PPV = 35.7%, for the SWE-max parameter I calculated a sensitivity of 64.3% and a specificity of 60.5% with AUC of 0.701, PPV of 37.5%; for the SWE-SD the sensitivity is 64.3% and the specificity of 60.5% with a value of AUC =

0.652, PPV of 37.5%, SWE-ratio sensitivity is 71.4% and specificity of 60, 5% with an AUC = 0.740, 42.3%.a AUC=0.652, PPV de 37,5%, în cazul SWE-ratio sensibilitatea este de 71,4% și specificitatea de 60,5% cu un AUC=0.740, 42,3%.

- ✓ In assessing strain elastography as a method of diagnosis of thyroid nodules and measurements obtained as predictors of malignancy, the sensitivity of the method was determined, namely 92.3%, and the specificity, i.e. 67.7%.
- ✓ The positive predictive value was 100% and the negative predictive value was 88.57%, which shows that all patients with malignant nodules were diagnosed by this method, the measurements being accurate.
- ✓ Strain elastography is constantly demonstrating its diagnostic value in thyroid disorders, being able to identify malignancies with high precision. As it is a recent technique, studies are still needed to confirm its precision.
- ✓ Regarding real-time shear wave elastography, despite the generally lower levels of the four SWE parameters obtained in our study compared to those in the literature, we believe that this research adds evidence that real-time elastography has a great potential for reliable and accurate diagnosis of thyroid malignancies.

REFERENCES

[1] Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for The Diagnosis and Management of Thyroid Nodules-2016 Update. Endocrine Practice. 2016;22(Suppl 1).

[2] Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, Negri E. Thyroid cancer mortality and incidence: a global overview. International Journal of Cancer. 2015;136(9):2187-95.

[3] Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

[4] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403. doi: 10.1016/j.ejca.2012.12.027.

[5] Ordinul nr. 1324/2010 privind aprobarea ghidurilor de practică medicală pentru specialitatea endocrinologie, Anexa 7, Ghid de diagnostic și terapie al nodulilor tiroidieni pentru România. Monitorul Oficial al României nr 799 din 30.11.2010.

[6] Pitman MB, Abele J, Ali SZ, Duick D, Elsheikh TM, Jeffrey RB, Powers CN, Randolph G, Renshaw A, Scoutt L. Techniques for thyroid FNA: A synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagnostic cytopathology. 2008 Jun 1;36(6):407-24.

[7] Cibas ES, Baloch ZW, Fellegara G, LiVolsi VA, Raab SS, Rosai J, Diggans J, Friedman L, Kennedy GC, Kloos RT, Lanman RB. A prospective assessment defining the limitations of thyroid nodule pathologic evaluation. Annals of internal medicine. 2013 Sep 3;159(5):325-32.

[8] McHenry CR, Phitayakorn R. Follicular adenoma and carcinoma of the thyroid gland. The Oncologist. 2011 May 1;16(5):585-93.

[9] Mirallié E, Rigaud J, Mathonnet M, Gibelin H, Regenet N, Hamy A, Bretagnol F, de Calan L, Le Néel JC, Kraimps JL. Management and prognosis of metastases to the thyroid gland. Journal of the American College of Surgeons. 2005 Feb 1;200(2):203-7.

[10] Papi G, Fadda G, Corsello SM, Corrado S, Rossi ED, Radighieri E, Miraglia A, Carani C, Pontecorvi A. Metastases to the thyroid gland: prevalence, clinicopathological aspects and prognosis: a 10-year experience. Clinical endocrinology. 2007 Apr 1;66(4):565-71.

[11] Fish SA, Langer JE, Mandel SJ. Sonographic imaging of thyroid nodules and cervical lymph nodes. Endocrinology and Metabolism Clinics. 2008 Jun 1;37(2):401-17.

[12] Ghervan C. Thyroid and parathyroid ultrasound. Medical ultrasonography. 2011 Mar 1;13(1):80.

[13] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016 Jan 1;26(1):1-33.

[14] Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, Jung HK, Choi JS, Kim BM, Kim EK. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology. 2011 Sep;260(3):892-9.

[15] Rago T, Scutari M, Santini F, Loiacono V, Piaggi P, Di Coscio G, Basolo F, Berti P, Pinchera A, Vitti P. Real-time elastosonography: useful tool for refining the presurgical diagnosis in thyroid nodules with indeterminate or nondiagnostic cytology. The Journal of Clinical Endocrinology & Metabolism. 2010 Dec 1;95(12):5274-80.

[16] Hong Y, Liu X, Li Z, Zhang X, Chen M, Luo Z. Real-time ultrasound elastography in the differential diagnosis of benign and malignant thyroid nodules. Journal of Ultrasound in Medicine. 2009 Jul 1;28(7):861-7.

[17] Stoian D, Cornianuz M, Dobrescu A, Lazar F. Nodular thyroid cancer. Diagnostic value of real time elastography. Chirurgia (Bucur). 2012 Jan 1;107(1):39-46.

[18] Oprea MC, Vlad M, Golu I, Sporea I, Fulger L. Diagnostic Value of Real-Time Shear Wave Elastography in Diagnosing Thyroid Cancer. REVISTA DE CHIMIE. 2017 Dec 1;68(12):2818-22.

[19] Oprea MC, Fulger L. Usefulness of real-time shear wave elastography in the diagnosis of malignant thyroid nodules in patients with autoimmune thyroiditis. Fiziologia-Physiology. 2016 Oct 1;26(4):32-36.

[20] Oprea MC, Fulger L. Diagnostic Performance of Strain Elastography for Thyroid Nodules. Fiziologia - Physiology 2017;27(2):17-20.

[21] Cosgrove D, Barr R, Bojunga J, Cantisani V, Chammas MC, Dighe M, Vinayak S, Xu JM, Dietrich CF. WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part 4. Thyroid. Ultrasound in Medicine and Biology. 2017 Jan 1;43(1):4-26.

[22] Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, Yamakawa M, Matsumura T. Breast disease: clinical application of US elastography for diagnosis. Radiology. 2006 May;239(2):341-50.

[23] Asteria C, Giovanardi A, Pizzocaro A, Cozzaglio L, Morabito A, Somalvico F, Zoppo A. US-elastography in the differential diagnosis of benign and malignant thyroid nodules. Thyroid. 2008 May 1;18(5):523-31.

[24] Cantisani V, D'Andrea V, Biancari F, Medvedyeva O, Di Segni M, Olive M, Patrizi G, Redler A, Enrico De Antoni E, Masciangelo R, Frezzotti F. Prospective evaluation of multiparametric ultrasound and quantitative elastosonography in the differential diagnosis of benign and malignant thyroid nodules: preliminary experience. European journal of radiology. 2012;81(10):2678-83.

[25] Ning CP, Jiang SQ, Zhang T, Sun LT, Liu YJ, Tian JW. The value of strain ratio in differential diagnosis of thyroid solid nodules. European journal of radiology. 2012;81(2):286-91.

[26] Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. IEEE transactions on ultrasonics, ferroelectrics, and frequency control. 2004 Apr;51(4):396-409

[27] Sebag F, Vaillant-Lombard J, Berbis J, Griset V, Henry JF, Petit P, Oliver C. Shear wave elastography: a new ultrasound imaging mode for the differential diagnosis of benign and malignant thyroid nodules. The Journal of Clinical Endocrinology & Metabolism. 2010 Dec 1;95(12):5281-8.

[28] Veyrieres JB, Albarel F, Lombard JV, Berbis J, Sebag F, Oliver C, et al. A threshold value in Shear Wave elastography to rule out malignant thyroid nodules: a reality? Eur J Radiol. 2012;81:3965-3972.
[29] Bhatia K, Tong CS, Cho CC, Yuen EH, Lee J, Ahuja AT. Reliability of shear wave ultrasound elastography for neck lesions identified in routine clinical practice. Ultraschall Med. 2012;33:463-468.
[30] Szczepanek-Parulska E, Woliński K, Stangierski A, Gurgul E, Biczysko M, Majewski P, Rewaj-Łosyk M, Ruchała M. Comparison of diagnostic value of conventional ultrasonography and shear wave elastography in the prediction of thyroid lesions malignancy. PLoS One. 2013 Nov 29;8(11):e81532.
[31] Wang T, Zhang YX, Feng YQ, Tao CM. Quantitative assessment of realtime shear wave elastography imaging in differentiating benign and malignant thyroid nodules. Chin J Med Imaging. 2012; 20:684-687.
[32] Lin P, Chen M, Liu B, Wang S & Li X. Diagnostic performance of shear wave elastography in the identification of malignant thyroid nodules: a meta-analysis. European radiology. 2014;24(11):2729-2738.
[33] Zhang, B., Ma, X., Wu, N., Liu, L., Liu, X., Zhang, J., ... & Niu, T. Shear Wave Elastography for Differentiation of Benign and Malignant Thyroid Nodules. Journal of Ultrasound in Medicine. 2013;32(12):2163-2169.