ROLE OF IMAGING INVESTIGATIONS IN DETECTING THYROID NODULE MALIGNANCY. A RETROSPECTIVE STUDY

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Abstract

Nodular thyroid pathology is a topical public health problem that is increasingly targeted and discussed by the general population. The prevalence is around 10%, but rates up to 68% are reported in the literature. In Romania, according to statistics from the National Institute of Public Health, the incidence of thyroid diseases has tripled between 2010 and 2016 and is increasing, which can also be explained by improved patient access to specialized medical services and diagnostic tests. High-resolution thyroid ultrasound is deemed the preferred screening examination for the diagnosis of thyroid lumps, using the Ti-RADS system it identifies nodule types and assesses malignancy risk. Elastography is a newly introduced dynamic method applying software in ultrasound to appraise tissue rigidity by projecting distortion caused by external forces, like palpation, during thyroid evaluations in physical exams. These tests used both could improve the accuracy of diagnosis of thyroid nodules.

Keywords: Ti-RADS, Thyroidian nodules, Elastography, ultrasound.

INTRODUCTION

1. *General review of thyroid*

The thyroid gland plays an important role in regulating multiple processes in the human body such as metabolism, energy consumption, as well as heart and brain function.

The hypothalamic-pituitary axis is responsible for generation and distribution of thyroid hormones. Thyrotropin, also known as thyroid- stimulating hormone (TSH) is secreted by the anterior pituitary, stimulated by thyrotropin-releasing hormone secreted in hypothalamus.

As a feedback to TSH emission, follicular cells synthesize thyroglobulin, an non-active protein, which reacts like a colloid moving from the surface into the follicles.

Levothyroxine serves as the primary thyroid secretion and is also called thyroid hormone. It is the product of two tyrosine molecules, each binding two Iodine molecules. The main function of this hormone is to incorporate, concentrate and store Iodine molecules in the circulation even against a concentration gradient.

The main transporter is the NIS (Na-Iodine symporter), which is located in the basement membrane of thyroid cells and has the function of transporting inorganic iodine to thyroid cells, as shown in Figure 1. As a result of this process, the iodine concentration in thyroid cells increases about 20-40 times that in the blood. Once in the cell, iodine becomes organic and is incorporated on tyrosine residues present on the amino acid sequence of thyroglobulin. This process occurs at the apical membrane of the thyroid cell and is supported by thyroidperoxidase (TPO) in the presence of hydrogen hydroxide, pendrin and possibly the calcium-activated anionic membrane channel anoctamine 1. [27]

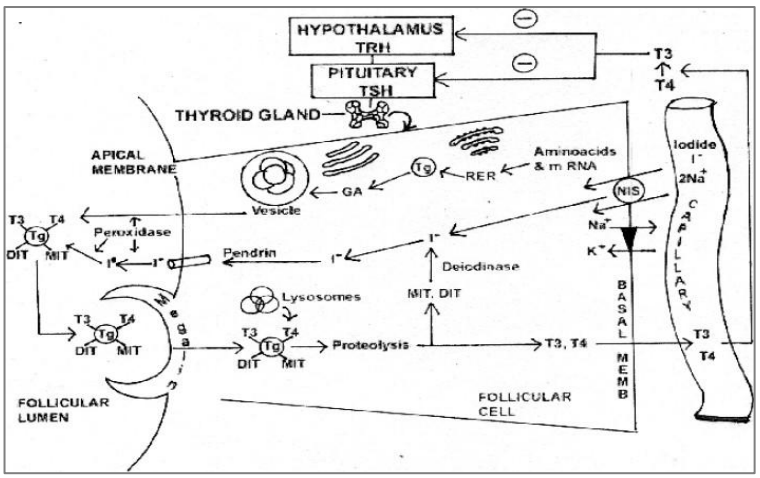

Figure 1. *Synthesis and Release of thyroid hormones [Khurana I. Textbook of Medical Physiology. India: Reed Elsevier; 2006. Endocrinal System; pp. 710–715.]*

Under the influence of TSH- via the process of pinocytosis the thyroglobulin in the colloid enters the thyroid cell, where it is destroyed by endopeptidase, so that the thyroid hormone that is incorporated into its amino acid is released into the circulation as levothyroxine.

Thyroid hormones circulate in the bloodstream bound predominantly to the thyroxine-binding protein.[5]

2. *Thyroidian nodules*

According to American Thyroid Association (ATA), thyroidian nodules are characterized as "separate lesions of the thyroid , radiologically clear from the surrounding thyroid parenchyma". They may be incidentally detected through palpation during a routine physical examination or during imagistic investigations performed for routine evaluations such as carotid duplex ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or ^{18}F- fluorodeoxyglucose positron emission tomography (18FDG- PET).

While approximately 7-15% of thyroid nodules are malignant; [36] the rest of cases are represented by benign masses (**Table 1**). An effective approach on management of nodular tissue depends on the clinician's aptitude to differentiate a malignant nodule from a benign one with high accuracy and without additional costs.

Table I. The classification of thyroid nodules

Benign thyroid nodules	**Malignant thyroid nodules**
Multinodular goiter - colloid nodule	Papillary carcinomas
Hashimoto's thyroiditis with nodularization	Follicular carcinomas
Colloid cysts, simple or hemorrhagic	Anaplastic/differentiated carcinomas
Follicular adenomas	Medullary carcinomas
Hürthle cell adenomas	Primary thyroid lymphomas
	Metastatic carcinomas

Etiologically, thyroid nodular disease can be caused by exposure to ionizing radiation. According to studies, ionizing radiation is a well-established risk factor for benign as well as to malignant thyroid nodules. The thyroid nodules can occur at an annual rate of 2% of exposed population. [34] Smoking, obesity, obesity, metabolic syndrome, alcohol consumption, elevated levels of insulin-like growth factor-1 and uterine fibroids are also risk factors for thyroid nodular disease. [36]

2.1.Epidemiology of thyroid nodules

Nodular thyroid disease is a pathology with a higher prevalence among female patients, this aspect is also confirmed in specialized studies, thus, in the Framingam study conducted on a group of 5234 patients over 60 years of age, a female prevalence of 6.4% was found, while men had a ratio of 1.5%. [32] Another study by Tunbridge claims that nodular thyroid disease is prevalent in females with a female:male ratio of 4:1, [31] this radio is explained by the hormonal influences.

The most important challenge in thyroid nodular disease is the correct identification of cancer cases, which occur in 7–15% of all thyroid nodules.[25, 22] The occurrence of both thyroid nodules and thyroid cancer has risen significantly in recent years. Recent data from the United States shows about 63,000 new thyroid cancer cases annually. This rise is largely attributed to early detection through high-resolution ultrasound and the identification of subclinical thyroid nodules.[36] Another theory, attributes the elevated incidence of thyroidian nodules to medical radiation exposure, iodine intake, obesity and insulin resistance, genetics and inorganic phosphates [20, 37] with a 300% increase in the annual rate of thyroid cancer. [6]

Thyroid cancer ranks 7th in the incidence of malignant pathologies worldwide according to Global Cancer Observatory, which registered 821,214 newly confirmed cases of thyroid cancer worldwide in 2022 [4] The incidence of thyroid malignancies worldwide is shown in **Figure 2**.

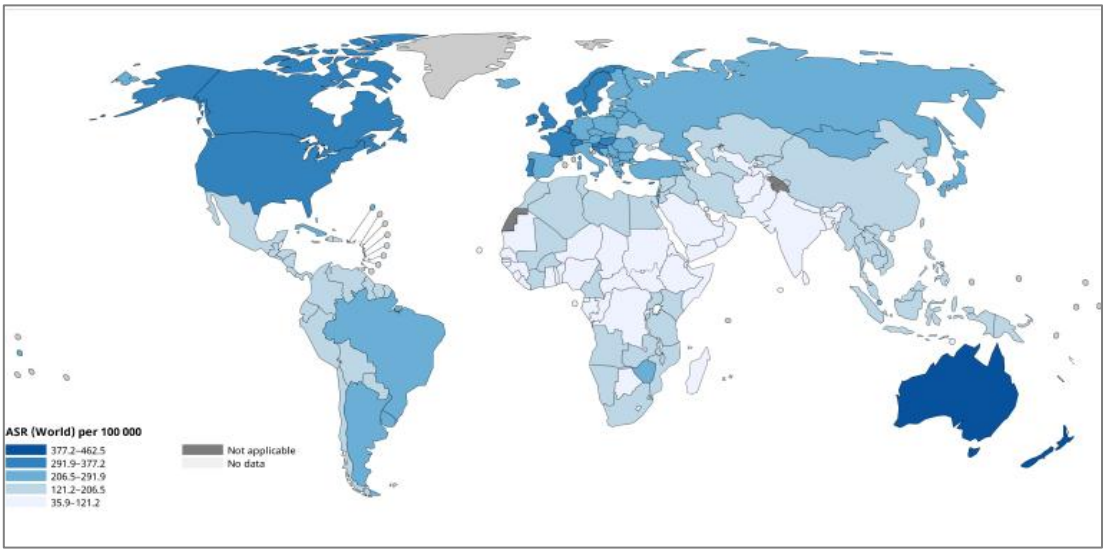

Figure 2. *The worldwide incidence of thyroidian cancer [GLOBOCAN 2022]*

According to the statistics of the International Agency for Research on Cancer, in Romania in 2022 there were 104,661 confirmed cases of thyroid malignancy, a number that places thyroid cancer on the 15th place as incidence of oncologic diseases in our country. [14]

3. Paraclinical investigations of thyroid function

Correct ordering of laboratory tests facilitates early diagnosis of a thyroid disorder and contributes to timely and appropriate treatment. The main laboratory tests for the detection of thyroid disorders are presented in the table bellow.

Table 2. Main thyroid laboratory tests and their clinical significance

Laboratory test	**Clinical significance**
TSH	- Primary screening test for thyroid dysfunction. - Evaluation of thyroid hormone replacement therapy in patients with primary hypothyroidism. - Evaluation of suppressive therapy in patients with follicular cell derived thyroid cancer.
T4	- Detection of thyroid dysfunction in association with TSH. - Evaluation of thyroid hormone replacement therapy in patients with secondary hypothyroidism (free T4). - Evaluation of thyroid dysfunction in pregnancy (total T4).
T3	- Detecting hyperthyroidism - Not useful in the management of hypothyroidism. - May be useful in diagnosing nonthyroid diseases.
Thyroidian antibodies	- Positive in autoimmune thyroid disease. - TPOAb - evaluation of patients with subclinical hypothyroidism and women with recurrent miscarriages. - TRAb - diagnosis of Graves' disease; aids in predicting Graves' patients who may be weaned from antithyroid drugs.
Tireoglobulin	- Evaluating the effectiveness of treatment for differentiated thyroid cancer and monitoring residual or recurrent disease. - Diagnosis of thyrotoxicosis.
Calcitonin	- To diagnose medullary thyroid cancer and to monitor recurrence, progression and response to treatment.

4. Imagistic tests of thyroid gland

The gold-standard imaging methods to explore the thyroid gland are:

- High-resolution ultrasound;
- Elastography;
- Scintigraphy.

High-resolution ultrasound

High-resolution ultrasonography (USG) is the most accurate imaging technique currently available for evaluating the thyroid gland and its associated conditions. The benefits of ultrasound scanning include non-invasivity, accesibility, cost-effectivenes and it is free from ionizing radiation. Further, real time ultrasound imaging is useful in guidance diagnostic and therapeutic interventional procedures in cases of thyroid disease. The most important limitation of ultrasound in thyroid imaging is its inability to assess thyroid function, such as whether the gland is hypoactive, hyperactive, or functioning normally. This evaluation typically requires a blood test or a radioactive isotope uptake test.[29, 4]

Indications for thyroid USG, following the American Association of Clinical Endocrinologists (AACE) and Associazione Medici Endocrinologi (AME) recommendations, [9] are as follows:

- To assess the existence of a thyroid nodule when findings from the clinical examination are inconclusive.
- To define one or more thyroid nodules by accurately measuring their dimensions, assessing their internal structure, and evaluating vascularization.
- To distinguish a malignant thyroid mass from a benign one based on their sonographic characteristics.
- To distinguish a thyroid nodule from other cervical masses.
- To assess difuze changes in thyroidian parenchyma.
- To identify postoperative residuals and tumoral masses, also identifying methastases in cervical lymph nodes.
- To follow up the patients at high risk for thyroid malignancy.
- To assist in guiding diagnostic procedures and interventional techniques.

TI-RADS classification

TI-RADS, short for Thyroid Imaging Reporting and Data System, [30] is an ultrasound-based classification system designed to quantify characteristics of thyroid nodules, modeled after the ACR BI-RADS system used in breast imagistics. In 2017, the American College of Radiology (ACR) TI-RADS Committee of the American College of Radiology (ACR) introduced a new risk classification system for grouping thyroid nodules based on their appearance on ultrasonography. [30] The ultrasound features in the ACR TI-RADS are classified depending on risk of malignancy. Points are assigned based on the ultrasound features of a nodule, with more concerning features receiving higher scores. **Figure 3** displays these features organized according to the five lexicon categories. [11]

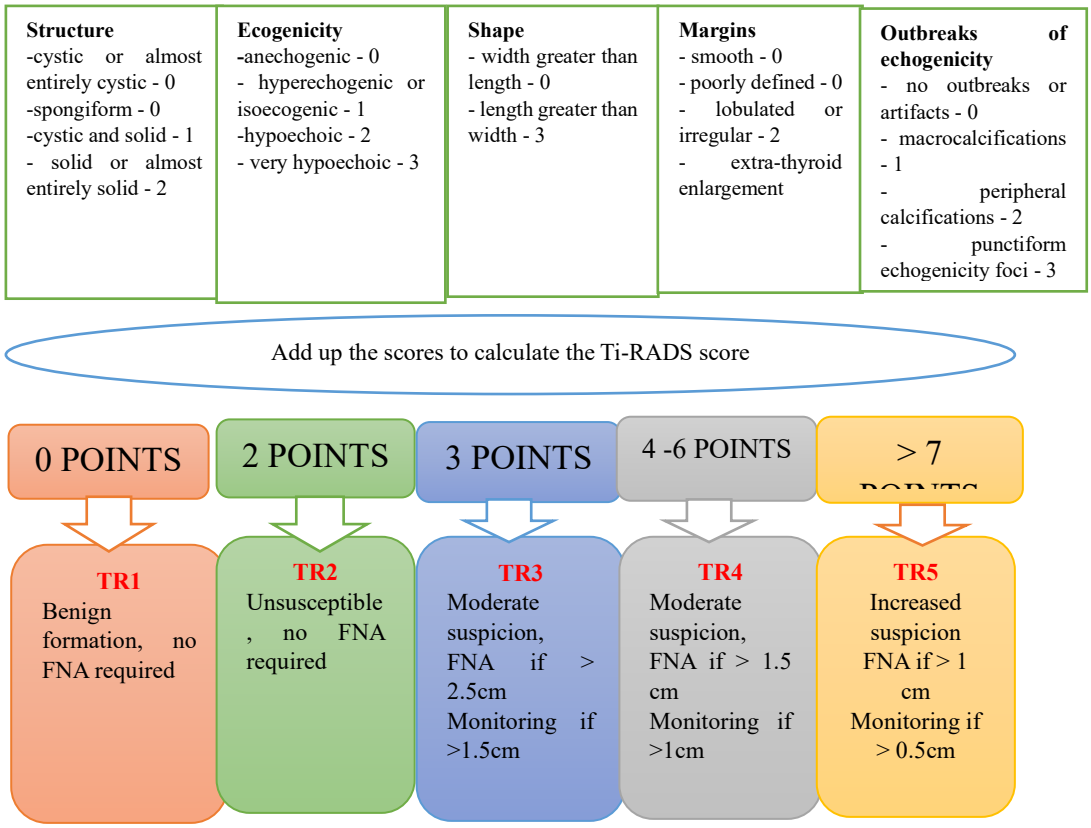

Figure 3. *Sonographic features and associated points grouped according to the five ACR TI-RADS categories*

The sum of the assigned points defines malignancy risk according to 5 grades, corresponding to low or high suspicion of malignancy. This system does not include subcategories and no TR 0 group to indicate normal thyroid.

The criteria for performing fine-needle aspiration or indication for USG monitoring are based on the final ACR TI-RADS score and the biggest nodule diameter. For risk grades including TR3 and TR5, there are established some size limits, at or above this limit is indicated performing of fine-needle aspiration. There were also established lower limits for nodules classified as TR3, TR4, TR5, that should be ultrasound monitotored, in order to reduce the number of repeated examinations for nodules which are more likely to be benign. High-risk nodules undergo biopsy only if they are 1 cm or larger, whereas low-risk nodules are further evaluated only when their size reaches 2.5 cm or greater.

The primary objective of ACR TI-RADS is to optimize the detection of clinically significant malignancies while minimizing the risks and costs associated with invasive investigation and treatment of benign nodules or indolent, non-aggressive tumors. The indications for ultrasound follow-up aim to reduce the possibility that significant lesions remain undetected over time.

Comparative studies indicate that the ACR system demonstrates a sensitivity of 75–97% and a specificity of 53–67%. It is reported to either have the highest sensitivity and lowest specificity among the compared systems [38] or, alternatively, the highest specificity.[12, 10]

Thyroidian scintigraphy

This days, the standard initial diagnostic review of a single thyroid lump no longer employs nuclear imaging methods as it was before. Nuclear imagistics are utilized to classify a nodule as warm or cold based on its relative uptake of radioactive isotopes. Hot nodules indicate independently functioning thyroid tissue, warm nodules describe normal thyroid function, and cold nodules represent hypofunctional or nonfunctional tissue. Hot nodules are infrequently malignant, while 5–8% of warm or cold nodules are associated with malignancy. [8]

The indications for this investigation are :a) Defining the functional status of the thyroid gland; b)Thyrotoxicosis, differential diagnosis; c)Thyroid cancer: whole body scanning for detection of distant metastases, estimation of local residual after thyroidectomy, follow-up for recurrence.

The results are interpreted according to the degree of uptake. Benign nodules are classified according to their ability to produce hormones compared to healthy thyroid tissue. They fall into three categories: 'warm', 'cold' and 'normal' nodules. "Warm" nodules are more active than normal thyroid tissue and therefore produce more hormones. 'Cold' nodules, on the other hand, are clumps of tissue with no real ability to produce thyroid hormones compared to normal thyroid tissue. Finally, normal nodules cannot be differentiated from healthy tissue on the basis of their hormone-producing capacity. The majority of thyroid nodules are cold nodules (about 50-85%), while only 10% of nodules are 'warm' and about 40% are 'normal'.

Thyroidian elastography

Elastography shows an elasticity score as a qualitative result and the strain ratio. Benign lesions push but do not invade the surrounding structures, they remain with normal elasticity, unlike hard malignant lesions, which infiltrate and stiffen the neighboring structures, this difference being objectified in the elastographic mode by the increased projection area of the malignant lesions, corresponding to the infiltration of the surrounding structures. Research indicates that elastography can effectively distinguish malignant thyroid nodules from benign ones with high sensitivity and specificity. [26]

Strain elastography

Strain elastograms of nodules are systematically assessed using a gradual scoring method, based on the dominant shade within the nodular tissue. The two principal scoring systems are those classified by Asteria et al. [1] and Rago et al..[26]The first one, based on the breast strain USE scale of Itoh et al..[15] All the aspects are adapted to thiroidian tissue, and evaluate qualitative features of the thyroidian lumps.

Table 3. Criterias for qualitative elastography

Rago criteria for qualitative elastography deformation elastography images.	**Asteria criteria for qualitative strain elastography images.**
Score 1: uniform soft elasticity in the whole knot; Score 2: elasticity in a large part of the knot;	Score 1: Elasticity in the whole knot; Score 2: Elasticity in most of the knot; Score 3: Stiffness in most of the knot;

Score 3: elasticity in the peripheral part of the knot; Score 4: lack of elasticity in the whole knot; Score 5: lack of elasticity of the knot and the area around the knot.	Score 4: Knot without elasticity.

The criteria followed in strain elastography are :

The criteria followed in strain elastography are:

The area ratio, in which the area of the nodule is measured and compared with the area of a surrounding thyroid tissue, three different measurements and the mean value is taken into account. [17] The described threshold value for AR suggestive for malignancy is a ratio of 1.08 with a sensitivity, specificity of 91.3, 86.6, 82.3 and 93.4%, respectively. [17]

Hard area ratio which measures the ratio of the hard area in the nodule to the entire area of the nodule, with a cut-off value of 0.6 suggestive of malignancy: 92.9% sensitivity, 91.3% specificity and 92% accuracy. [21]

Deformation ratio of the nodule to the sternocleidomastoid muscle: the muscle is considered the reference area for calculating the deformity and not the healthy thyroid tissue, with reasonable results: sensitivity 90% and specificity 50% for a cut-off value of 1.5. [16]

Strain index is a ratio of the strain of the whole nodule divided by the strain of the soft part of the nodule, with a cut-off value of 2.05.

The stiffness ratio is a special ratio calculated by Philips devices by comparing the stiffness of the lump to the surrounding apparently healthy tissue, with a cut-off value described as 3.16.

The systolic thyroid stiffness index = compares the highest stiffness near the carotid artery with the lowest stiffness in the thyroid nodule, over an area of 2 mm × 2 mm. No clear values are described.

Elasticity contrast index = technique is specific to Samsung devices - obtains a deformation oscillation map, with malignant lesions showing higher contrast than a benign lesion . The cut-off value described in the literature is between 3, 5 and 4.[3] It should be taken into account that the results are influenced by age, atherosclerosis, hypertension and tachycardia-associated conditions.

Realtime Shearwave elastography

Real-time shear wave elastography is performed like a conventional ultrasound, with a linear probe at the end of the conventional US evaluation, with the patient in apnea. The device generates both quantitative and qualitative information : color-coded color maps with the following color code: blue = soft tissue, red = hard tissue, respectively, quantitative information evaluated by the elasticity index expressed in kilopascal.[14] As in elastography strain ,in elastography shear wave over time is displayed in parallel with the gray scale of the ultrasound, with probe placement on the nodular lesion. At least three loops without transducer motion should be recorded for quantitative evaluation.

The diagnostic qualities of this type of qualitative, color-mapped elastograph generate information with a sensitivity of 95.5% and specificity of 45.7% for elasticity score II (predominantly soft), 72.7 and 84.5% for elasticity score III (elastic at the edges and stiff middle, respectively) , 54.5 and 97.4% for elasticity score IV (significantly increased stiffness).[23]

MATERIALS AND METHODS

This study is based on the anamnesis, laboratory investigations and imaging investigations of the patients enrolled in the study hospitalized in the Endocrinology Department of the County Emergency Hospital "Sfântul Apostol Andrei" of Galati in the period 2020-2022.

In this study TSH and FT4 values, which describe the thyroid hormone balance, were analyzed. The samples were collected on an empty stomach and were analyzed immunochemically in the Laboratory of the County Emergency Hospital "Sfântul Apostol Andrei", Galati.

The ultrasound scans were performed using the ESOATE MyLab X7, which has extensive configuration features. Using the same apparatus via ElaXto which is a non-invasive method for the determination of tissue elasticity, elastographic nodule formations were analyzed. Elasticity differences between tissues were detected and visualized in real time.

The study was retrospective, and attempted to establish the correlation between the results of elastography, scintigraphy, anatomic-pathologic examination and the TI-RADS score.

Data were loaded and processed using statistical functions in SPSS 18.0 at 95% significance level.

RESULTS

Clinical study: Forty female patients were included in this trial aged between 43 and 74 years, with a total number of 122 analyzed nodules. Multiple nodular formations, spread unilaterally or bilaterally, were found in most patients. The distribution of nodules is represented in the table bellow:

Table 4: The correlation of number of nodules and their localization

Localization		**NODULES**							
		1	2	3	4	5	6	N	p
RTL 1	n	4	4	18	8	2	2	38	0,143
	%	10,5	10,5	47,4	21,1	5,3	5,3	95,0	
RTL 2	n			10	8	2	2	22	**0,001**
	%			45,5	36,4	9,1	9,1	55,0	
RTL 3	n			1			2	3	**0,018**
	%			33,3			66,7	7,5	
RTL 4	n						2	2	**0,007**
	%						100	5,0	
LTL 1	n	2	4	16	8	2	2	34	**0,018**
	%	5,9	11,8	47,1	23,5	5,9	5,9	85,0	
LTL 2	n			6	8	2	2	18	**0,001**
	%			33,3	44,4	11,1	11,1	45,0	
LTL 3	n					2		2	**0,007**
	%					100		5,0	
Istm	n		3					3	0,405
	%		100					7,5	
Nr of patiens x nodules		6 x 1	4 x 2	18 x 3	8 x 4	2 x5	2 x 6	122	
		15,0	10,0	45,0	20,0	5,0	5,0	nodules	

There were analyzed echographic aspects of the nodules such as structure, echogenity, shape, margins and outbreaks of echogenity and were classified according to Ti-RADS score with the results bellow:

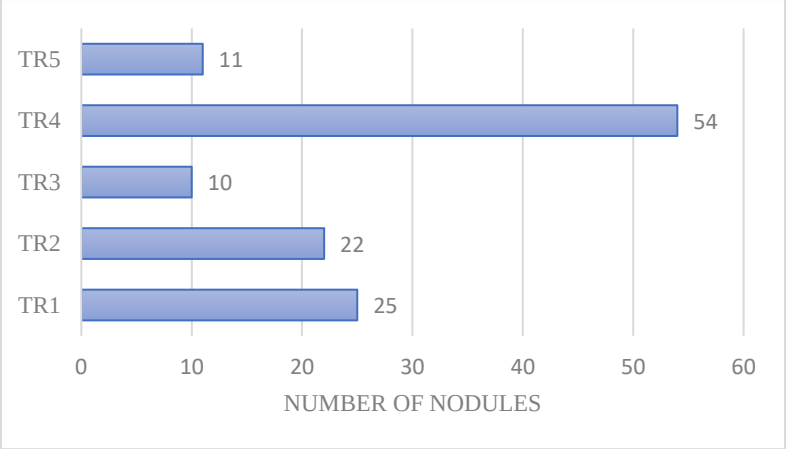

Figure 4. *The distribution of nodules by Ti-RADS score*

According to this distribution the number of nodules with the highest risk of malignity are represented by the nodules with Ti-RADS score 4 and 5, with a percentage of 44,26% respectively 9,02%.

Analyzing the elastography result, the mean hard/soft percentage was higher in the nodular formations on the LTS.

Tabel 5. Hard/soft percentage descriptive data

	LTD1	LTD2	LTD3	LTS1	LTS2	Istm
N	22	6	1	11	5	1
Average	68,64	66,67	60	83,64	48	60
Median	70	70	60	80	50	60
Standard Deviation	12,36	13,66		10,27	20,49	
Variant	18,01	20,49		12,40	42,69	
Skewness Test	-0,737	-0,523		0,448	1,022	
Std. Error of Skewness	0,491	0,845		0,661	0,913	
Minimum	50	50	60	70	30	60
Maximum	80	80	60	100	80	60

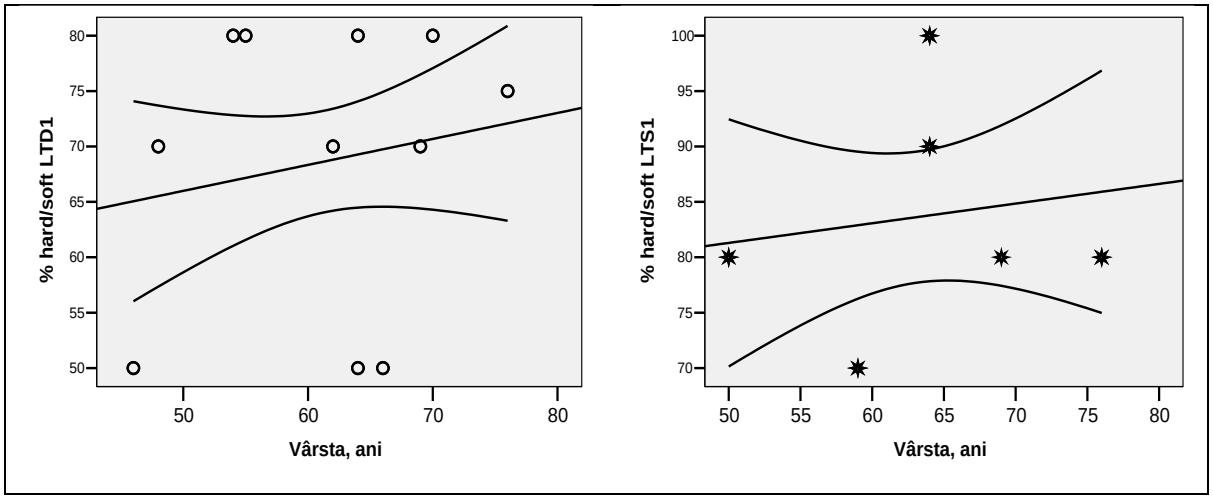

Figure 5. *Correlation between hard/soft percentage and age*

The percentage hard/soft elastography score correlated directly, but reduced in intensity with age, for both LTD (r=0.175; p=0.437) and LTS (r=0.149; p=0.661).

18 out of 40 patients underwent scintigraphy on the recommendation of the endocrinologist, which revealed 20 hypercapping areas, i.e. 'hot' formations, and 6 hypocapping, i.e. 'cold' formations.

All of the 40 patients were referred for surgery. Anatomo-pathologic examination was performed following surgery.

A total of 121 nodules were analyzed post-surgically anatomopathologically, which were categorized into benign and malignant nodules. There were identified 4 medular carcinomas, 8 folicular carcinomas and 12 papilar carcinomas and 97 benign nodules.

Depending on localization, anatomopathologic outcome did not correlate significantly with TI-RADS scores.

Table 6. Correlation of TI-RADS score with anatomopathologic findings

Localization	TiRads	Anatomo-pathology		p
		Malignant	Benign	
RTL1	TR1	12,5%	23,3%	
	TR2	12,5%	20,0%	
	TR3	12,5%	-	0,414
	TR4	50,0%	40,0%	
	TR5	12,5%	16,7%	

RTL2	TR1	-	22,4%	
	TR2	25,0%	22,4%	
	TR3	25,0%	5,6%	0,470
	TR4	50,0%	38,9%	
	TR5	-	11,1%	
RTL3	TR4	-	100%	nc
RTL4	TR1	-	100%	nc
LTL1	TR1	30,0%	20,8%	
	TR2	20,0%	33,3%	
	TR3	10,0%	8,3%	0,865
	TR4	40,0%	37,5%	
	TR5	-	-	
LTL2	TR1	-	12,5%	
	TR2	-	-	
	TR3	-	18,8%	0,379
	TR4	50%	62,5%	
	TR5	50%	6,3%	
Istm	TR3	-	50%	nc
	TR4	-	50%	

-at RTL1 localization, 50% of malignant and 40% of benign outcomes were associated with TI-RADS=4 (p=0.414);

-at RTL2 localization, 50% of malignant outcomes and 38.9% of benign outcomes were associated with TI-RADS=4 (p=0.470);

-at LTL1 localization, 40% of malignant and 37.5% of benign outcomes were associated with TI-RADS=4 (p=0.865);

-at LTL2 localization, 50% of malignant and 62.5% of benign outcomes were associated with TI-RADS=4 (p=0.379).

Depending on the localization of the nodule, correlating the anatomo-pathologic result with Asteria scores, the following aspects were noted :

-at LTD1 localization, all malignant findings and 62.5% of benign findings were associated with Asteria score=3 (p=0.032);

-for LTS1 localization, 66.7% of malignant outcomes and only 16.7% of benign outcomes were associated with Asteria score =4

Table 7. Correlation of Asteria score with anatomopathologic findings

Localization	Asteria	Anatomo-pathology		p
		Malignant	Benign	
LTD1	2	-	37,5%	**0,032**
	3	100%	62,5%	
LTD2	2	50,0%	100%	0,148
	3	50,0%	-	
LTS1	3	33,3%	83,3%	**0,009**
	4	66,7%	16,7%	
LTS2	2	-	80,0%	nc
	3	-	20,0%	
Istm	2	-	100%	nc

DISCUSSIONS

The guidelines indicate that the number of nodules has a low influence on their risk of malignancy, recommending the inclusion of this information in the report generated following conventional ultrasound in situations where individual nodules can be properly assessed and monitored. From the statistical analysis it was found that the majority of nodules were part of multinodular glands and only 6 of the patients had solitary nodules. Regarding the localization of nodular formations, this is not a predictive criterion for malignancy.

In this paper, the TI-RADS score criteria were analyzed. The score results themselves demonstrate that the solid structure of the nodule increases the susceptibility of the nodule to be malignant, just as thyroid overspill increases the susceptibility of malignancy.

Data from the literature state that the risk of malignancy of nodular formations showing intralesional microcalcifications is higher than that of nodules without such changes.

A multicenter retrospective validation multicenter study on 1058 nodules using final histology as the gold standard found a cancer rate in or close to the given range described in the EU-TIRADS guidelines and a satisfactory diagnostic value with 93% sensitivity and 97%. [28]

Based on literature data, a TR1 score has a risk of malignancy of 0.3%, a node with a TR2 score of 1.5%, a node with a TR3 score has a risk of 4.8%, a TR4 node has

a risk of malignancy of 9.1%, and a node with a TR5 score has a risk of malignancy of 35% [19] This study reflected that TR4 and TR5 scores are more often associated with malignant formations.

This study was performed based on the Asteria criteria, which present 4 classes of nodules. Using Asteria's criteria, the researchers calculated sensitivity and specificity to be 94.1% and 81%, respectively, in 86 nodules. [1] This study demonstrates the diagnostic potential of this investigation and reflects a higher percentage of malignant formations in nodules with high Asteria score.

Currently, the TI-RADS score does not analyze the functional status of thyroid nodules, thus scintigraphy presents an important investigation for the management of nodular formations.

Walfish and coworkers concluded that a total reliance on fine-needle biopsy without performing scintigraphy would lead to surgery for benign nodules suspected to be malignant and may increase surgical morbidity. [34]

Analyses performed with reference to the occurrence of thyroid carcinoma among "warm" nodules on scintigraphy have shown that this finding is an extremely rare phenomenon, thus, upon detection of a "warm" formation on scintigraphy, malignancy is excluded and the nodule does not require further investigation to exclude malignancy. [2]

According to the data analyzed in this paper elastographic examination combined with ultrasonographic examination contributes to proper management of thyroid nodular formations, contributing to decrease the number of invasive interventions that pose additional risks to patients.

CONCLUSIONS

Following the study correlation of the results of the performed investigations led to the conclusion that elastography has a significant role in the detection of malignant nodular formations, with an Asteria 4 score being associated with 66.7% of malignant formations in the LTL.The Ti-RADS score 4 was correlated with 50% of malignant formations in RTL. The correlation of imaging findings has a predictive role for

malignancy and are useful for the management of nodular formations, early diagnosis and increasing the quality of life of patients with thyroid nodule pathology.

Abbreviations

TIRADS- Thyroid Imaging Reporting and Data System

TRH- Thyroliberberin

TSH- Thyroid Stimulating Hormone

NIS- Na-Iodine symporter

TPO- Thyroid peroxidase

T4- Thyroxine

T3- Triiodothyronine

ATA- the American Thyroid Association

MIT- Monoiodotyrosine

DIT- Di-iodotyrosine

AACE- American Association of Clinical Endocrinologists

AME - Associazione Medici Endocrinologi

MEN- multiple endocrine neoplasia

FNA- Fine needle aspiration

ACR- American College of Radiology

TNM- Classification of Malignant Tumors

REFERENCES

1. *Asteria C, Giovanardi A, Pizzocaro A, Cozzaglio L, Norabito A, Somalvico F, et al. USelastography in the differential diagnosis of benign and malignant thyroid nodules. Thyroid 2008;18: 523–531.*
2. *Bomeli SR, LeBeau SO, Ferris RL Evaluation of a thyroid nodule. Otolaryngol Clin North Am. 2010;**43**:229–238.*
3. *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.*
4. *Chaudhary V, Bano S. Imaging of the thyroid: Recent advances. Indian J Endocrinol Metab. 2012;16:371–6.*
5. *Costanzo L.S. Thyroid Hormones. In: Cicalese B., editor. Physiology. 4th ed. Philadelphia: Saunders Elsevier; 2010. p. 401–9.*
6. *Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014 Apr. 140 (4):317-22 .*
7. *Eun Ju Ha, Dong Gyu Na, Jung Hwan Baek, Jin Yong Sung, Ji-hoon Kim, So Young Kang. US Fine-Needle Aspiration Biopsy for Thyroid Malignancy: Diagnostic Performance of Seven Society Guidelines Applied to 2000 Thyroid Nodules. (2018) Radiology. 287 (3): 893-900.*
8. *Gates JD, Benavides LC, Shriver CD, et al. Preoperative thyroid ultrasound in all patients undergoing parathyroidectomy. J Surg Res. 2008 Dec 4.*

9. *Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract. 2006;12:63–102.*
10. *Grani, Giorgio, Lamartina, Livia, Ascoli, Valeria, Bosco, Daniela, Biffoni, Marco, Giacomelli, Laura, Maranghi, Marianna, Falcone, Rosa, Ramundo, Valeria, Cantisani, Vito, Filetti, Sebastiano, Durante, Cosimo. Reducing the Number of Unnecessary Thyroid Biopsies While Improving Diagnostic Accuracy: Toward the "Right" TIRADS. (2019) The Journal of Clinical Endocrinology & Metabolism. 104 (1): 95.*
11. *Grant EG, Tessler FN, Hoang JK, et al. Thyroid ultrasound reporting lexicon: white paper of the ACR Thyroid Imaging, Reporting and Data System (TIRADS) Committee. J Am Coll Radiol 2015;12: 1272-9.*
12. *Ha E, Na D, Baek J, Sung J, Kim J, Kang S. US Fine-Needle Aspiration Biopsy for Thyroid Malignancy: Diagnostic Performance of Seven Society Guidelines Applied to 2000 Thyroid Nodules. Radiology. 2018;287(3):893-900.*
13. *Haugen BR, Alexander EK, Bible KC, et al. 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;26(1):1–133. doi: 10.1089/thy.2015.0020.*
14. *https://gco.iarc.fr/today/data/factsheets/cancers/32-Thyroid-fact-sheet.pdf*
15. *Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, Yamakawa M, and Matsumura T, Breast disease: clinical application of US elastography for diagnosis, Radiology. 2006,* ***239****, no. 2, 341–350, 2-s2.0-33646150005.*
16. *Kagoya R, Monobe H, Tojima H. Utility of elastography for differential diagnosis of benign and malignant thyroid nodules. Otolaryngol Head Neck Surg 2010; 143:230–234.*
17. *Kura M, Balarinoa C, Tamagone F, Campagno B, Bertini K, Escalante JG, Vega A, Peresotti B, Vilallonga J, Saubidet A. Relationship between the value of elastography ratio and the Bethesda cutolgical classification in thyroid pathology. Rev Argent Radiol 2014;78(3):128–137.*
18. *Kwak JY, Lim Eun-Kyung. Ultrasound elastography for thyroid nodules: recent advances. Ultrasonography. 2014;33(2):75–82.*
19. *Maloney E, Dougherty P, Dighe M, Relyea-Chew A. The development of a validated checklist for ultrasound-guided thyroid nodule fine-needle aspiration biopsies: preliminary results, Ultrasound Q, 2015;31:159–65.*
20. *Mathews W, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013; 346:f2360. DOI: 10.1136/bmj.f2360.*
21. *Middleton WD, Teefey SA, Reading CC, et al. Multiinstitutional Analysis of Thyroid Nodule Risk Stratification Using the American College of Radiology Thyroid Imaging Reporting and Data System. (2017) American Journal of Roentgenology. 208 (6): 1331-1341*
22. *Panini E, Guglielmi R, Bianchini A et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. JCEM 2002;87 (5):1941–1946.*
23. *Park SH, Kim SJ, Kim EK, Kim MJ, Son EJ, Kwak JY. Interobserver agreement in assessing the sonographic and elastographic features of malignant thyroid nodules. Am J Roentgenol. 2009; 193:W416-W2-423*

24. *Parulska ES, Wolinski K, Stangierski A, et al. Comparison of diagnostic value of conventional ultrasonography and shear wave elastography in the prediction of thyroid lesions malignancy. PLoS One 2013;8(11):e81532.*
25. *Pellegriti Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013; 2013:965212. DOI: 10.1155/2013/965212.*
26. *Rago T, Santini F, Scutari M, Pinchera A, Vitti P. Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. J Clin Endocrinol Metab. 2007; 92:2917–2922.*
27. *Seyed Amirhossein R, Hadduck TA, Gelareh S, et al. Comparative effectiveness of elastographic and B-mode ultrasound criteria for diagnostic discrimination of thyroid nodules: a meta-analysis. AJR Am J Roentgenol. 2013;200(6):1317–26*
28. *Silveira JC, Kopp PA. Pendrin and anoctamin as mediators of apical iodide efflux in thyroid cells. Curr Opin Endocrinol Diabetes Obes. 2015;22(5):374–80.*
29. *Solbiati L, Charboneau JW, Osti V, James EM, Hay ID. The thyroid gland. In: Rumack CM, Wilson SR, Charboneau JW, editors. Diagnostic Ultrasound. 3rd ed. Vol. 1. St. Louis, Missouri: Elsevier Mosby; 2005. pp. 735–70.*
30. *Tessler F.N., Middleton W.D., Grant E.G., Hoang J.K., Berland L.L., Teefey S.A., Cronan J.J., Beland M.D., Desser T.S., Frates M.C., et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J. Am. Coll. Radiol. 2017;14:587–595. doi: 10.1016/j.jacr.2017.01.046.*
31. *Trimboli P., Ngu R., Royer B., Giovanella L., Bigorgne C., Simo R., Carroll P., Russ G. A multicentre validation study for the EU-TIRADS using histological diagnosis as a gold standard. Clin. Endocrinol. 2019;91:340–347. doi: 10.1111/cen.13997.*
32. *Tunbridge WMG, Evered DC, Hall R et al. The spectrum of thyroid disease in the community: the Whickham survey. Clin Endocrinol (Oxf) 1977;7:481–93.*
33. *Vanderpump MPJ. The epidemiology of thyroid diseases. In: Braverman LE, Utiger RD (eds). Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, 9th edn. JB Lippincott-Raven: Philadelphia, 2005,398–496*
34. *Walfish PG, Strawbridge HT, Rosen IB Management implications for routine needle biopsy of hyperfunctioning thyroid nodules. Surgery. 1985;**98**:1179–1188.*
35. *Welker MJ, Orlov D. Thyroid nodules. Am Fam Physician. 2003 Feb 01;67(3):559-66.*
36. *Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic Review of Trends in the Incidence Rates of Thyroid Cancer. Thyroid. 2016 Nov. 26 (11):1541-1552 .*
37. *Wulaningsih WMichaelsson K, et al. Inorganic phosphate and the risk of cancer in the Swedish AMORIS study. BMC Cancer. 2013; 24 (13):257. DOI: 10.1186/1471-2407-13-257.*
38. *Xu T, Wu Y, Wu R et al. Validation and Comparison of Three Newly-Released Thyroid Imaging Reporting and Data Systems for Cancer Risk Determination. Endocrine. 2019;64(2):299-307.*