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Role and importance of elastography in the diagnosis of differentiated thyroid carcinomas regarding the clinical, echosonographic, biohumoral and cytological examination and correlation of these results with definitive histopathological findings – A retrospective study

Uloga i značaj elastografije u dijagnostici diferentovanih karcinoma štitaste žlezde u odnosu na klinički, ehosonografski, biohumoralni i citološki pregled i korelacija nalaza sa definitivnim patohistološkim nalazima – Retrospektivna studija

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Abstract

Background/Aim. Thyroid nodules represent a common problem in medicine. Ultrasound examination of the thyroid glands is a common method for the initial diagnosis of thyroid neoplasia enabling the selection of nodules that should undergo fine needle aspiration biopsy (FNAB). It is a noninvasive method that has a great potential in discovering suspicious lesions, enabling timely actions for further diagnostics and potential treatment. However, it is still not clear enough how the quantitative data collected from Ultrasound elastography correlate with those obtained by other diagnostic tools used for detecting thyroid nodules. The aim of this study was to estimate the importance of ultrasound elastography in diagnostics of differentiated thyroid carcinomas but also to estimate the importance of other diagnostic procedures as well. **Methods.** The research was performed on patients initially referred to the Clinic of Endocrinology in Military Medical Academy, Belgrade to evaluate the status of thyroid nodules. The data from ultrasound elastography was then correlated with those from other diagnostic procedures including clinical examination, echosonography, cytological and histopathological analyses. **Results.** Statistically significant difference between the group of patients with follicular adenoma and the group of patients with differentiated thyroid carcinoma was detected for consistency, nodules immovability, thyroglobulin (Tg) levels, presence of calcifications in the nodules and the elastographic score. Fixed nodules and those with firmer consistency were significantly more common in the group of patients with malignant lesions, in which Tg levels were higher. The elastography score 3–4 showed a high predictive value for the detection of thyroid carcinoma, unlike the elasticity score. **Conclusion**. Ultrasound elastography represents a new non-invasive method that has a very significant, high predictive value for the detection of thyroid carcinoma, especially in correlation with other diagnostic procedures.

Key words:
thyroid diseases; ultrasonography; biopsy, fine-needle; diagnosis; differential.

Apstrakt

Uvod/Cilj. Tiroidni nodusi predstavljaju veoma čest medicinski problem. Ultrazvučni pregled štitaste žlezde je najčešće primenjivana metoda za početnu procenu i izbor nodusa za iglenu biopsiju (*fine needle aspiration biopsy* – FNAB). Između mnogih metoda, ultrazvučna elastografija kao neinvazivna metoda ima veliki značaj u otkrivanja sumnjivih promena i određivanju prirode tumora. Pregled je potpuno bezbolan i jednostavan, a podrazumeva merenje

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otpora mekih tkiva, kvalitativno i kvantitativno. Međutim, još uvek nije u potpunosti jasno u kojoj meri kvantitativni podaci dobijeni ultrazvučnom elastografijom korelišu sa podacima dobijenim drugim dijagnostičkim postupcima za detekciju toroidnih nodusa. Cilj studije bio je da se proceni značaj ultrazvučne elastografije u dijagnostici diferentovanih karcinoma štitaste žlezde, ali i vrednost drugih dijagnostičkih procedura. **Metode.** Istraživanje je obavljeno na bolesnicima koji su inicijalno upućeni u Kliniku za endokrinologiju Vojnomedicinske akademije u Beogradu u cilju evaluacije nodoznih struma. Korelisani su nalazi dobijeni elastografijom sa rezultatima kliničkog pregleda, biohumoralne, morfološke (ehosonografske), citološke obrade i definitivnog patohistološkog nalaza. **Rezultati.** Od svih praćenih parametara, statistički značajna razlika između dve grupe bolesnika sa folikularnim adenomom i diferentovanim tiroidnim karcinomom je detektovana za konzistenciju, nepokretnost nodusa, vrednost tiroglobulina (Tg), prisustvo solidnih nodusa, kalcifikata i elastografski skor. Nepokretni nodusi i oni tvrđe konzistencije su bili statistički značajno češće prisutni u grupi bolesnika sa malignim lezijama, gde je bila viša vrednost T). Elastografski skor 3–4 je pokazo visoku prediktivnu vrednost za detekciju tiroidnih karcinoma, za razliku od skora elasticiteta. **Zaključak.** Ultrazvučna elastografija predstavlja novu neinvazivnu metodu koja ima veoma značajnu, visoku prediktivnu vrednost za detekciju tiroidnih karcinoma, naročito u korelaciji sa drugim dijagnostičkim procedurama.

Ključne reči:
tireoidna žlezda, bolesti; ultrasonografija; biopsija tankom iglom; dijagnoza, diferencijalna.

Introduction

Primary thyroid tumors originate from thyroid follicular epithelia or parafollicular cells of the thyroid gland, and rarely present lymphoproliferative diseases. They are clinically most often represented as localized enlargements of the thyroid gland (nodules).

The prevalence of palpatory detected nodules is about 3% (6.4% of women and 1.5% of men) [1]. In the last 20 years, an increased use of echosonography of the neck has reduced the prevalence of nodules in the general population for about 20–70%[1, 2]. Autopsy studies state that the changes in the thyroid gland due to nonthyroidal disease are found in approximately 50% of the bodies examined after death [2, 3]. Nodules of the thyroid gland are four times more common in women, in the areas with iodine deficiency, in people exposed to radiation, and in people older than 60 years [3]. The incidence of thyroid nodules is about 100 cases *per* 100,000 people *per* year [3, 4]. About 5% of these thyroid nodules are carcinoma [5, 6]. Thyroid carcinoma is not a frequent neoplasm but is the most common malignant endocrine tumor [7]. The highest incidence was recorded in Iceland and Hawaii, especially in ethnic groups of Chinese and Filipinos [8].

Diagnosis of differentiated malignant tumors is established by the standard histopathological (HP) and immunohistochemical analyses in surgical specimens of thyroid tissue after thyroidectomy performed. The diagnostic methods include: clinical examination, biohumoral treatment, ultrasound examination, scintigraphy and cytological diagnosis (FNAB – fine needle aspiration biopsy).

To detect functional nodules that do not show malignant characteristics, the serum level of thyrotropin (TSH) is determined. Functional nodules are proven by scintigraphy. In most cases, they do not have malignant features, so cytological punctures are not generally indicated at that time. Determination of the tumor marker thyroglobulin (Tg) is not routinely applied and is not recommended in the preoperative diagnostics [9, 10]. Determination of serum calcitonin levels should be performed in a patient with a family history of medullary carcinoma of the thyroid gland and multiple endocrine neoplasias [11].

Ultrasound examination of the thyroid gland includes morphological evaluation, tissue mobility analysis, and elastography analyses. The morphological analysis determines the presence, size, and the localization of focal changes, edge shapes, echogenicity, homogeneity, the presence of micro and macrocalcification, the presence of cystic component, hypoechogenic halo, and the pathologically altered lymph nodes of the neck [12]. Vascularization analyses include assessment of blood circulation to the surrounding tissue (graded 0–4) and the type of vascularization (intranodal and perinodal) [13]. It is not possible to diagnose the malignant potential with ultrasound only. Suspicious characteristics of the nodules include their hypoechogenicity, the microcalcifications, their regularly shaped edges, increased vascularization, the shape of the nodule (the anteroposterior diameter of the nodule is larger than the transversal) and the growth rate of the nodule during the sequential ultrasound examinations [14, 15].

Ultrasonic elastography is a non-invasive method in which the resistance of soft tissues to pressure is measured [16,17]. The examination is completely painless and simple. The goal of the measurement is to detect suspicious changes and to assess the malignant potential of the nodules. Resistance to the pressure of the nodules and surrounding tissue is shown in different colors, which we designate as qualitative testing of tissue resistance. The measurements are based on the fact that all tumors, especially malignant, have firmer structures, due to pronounced cell proliferation, increased tissue density, and increased vascularisation. At the pressure of the ultrasonic probe, the colors of normal tissue change from red to yellow, to green, while in tumor altered tissues it has blue or gray-black shades. The resistance can be measured quantitatively as well, both within the change itself and in the surrounding tissues, which is expressed by elastography scores and estimated by the resistance index: strain ratio (SR) [18–21]. Quantitative measurements can show up to twenty times higher resistance of the tumor tissues compared to normal ones.

In addition to the above diagnostic tests, the use of other morphological procedures [computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)] is not performed routinely. In all patients with palpatory detected thyroid glands, it is necessary to perform ultrasound diagnosis [22]. On the other hand, a cytological examination is the most accurate and cost-effective method for the evaluation of thyroid nodules. Thyroid biopsy is usually performed under the supervision of ultrasound [23–27]. Cytological examination of all nodules ≥ 10 mm is recommended as well as smaller nodules if several susceptible features are present [28, 29]. Nowadays with the advancement of ultrasound technology, it is technically possible to make a cytological examination of nodules of size below 5 mm [30]. The cytological interpretation of the findings is most commonly made by the Bethesda classification adopted by the National Cancer Institute (NCI). Cytological findings are classified into 6 diagnostic categories: I – nondiagnostic or unsatisfying; II – benign cytopathological finding; III – follicular lesion/atypia of undetermined significance; IV – follicual neoplasm or suspicious follicular neoplasm; V – suspicious on malignancy; VI – malignancy [31, 32]. Due to the insufficient sensitivity of cytological diagnosis in the distinction of follicular carcinoma from follicular adenoma, an operative procedure is required for the HP verification [17]. Cytologically confirmed benign nodules require only further monitoring. The cytological puncture under control of ultrasound should be done or repeated when an increase of the nodule is registered with palpation or ultrasound [33].

Malignant features are recorded in about 5% of solitary nodules, in the polynodal thyroid gland, or in small not palpable nodules that are randomly detected by ultrasound [34]. The risk of malignancy in patients with multiple nodules is similar to the risk in patients with solitary nodules [35]. As the size of the nodule increases, there is no increase in the risk of malignancy. In patients with multiple nodules, it is necessary to make aspirational biopsy of the suspicious nodules, or the dominant nodule in patients with multiple nodules without suspected features. Nodules suspicious to malignancy are subjected to surgical removal [36].

Most of these methods have a known predictive value during the diagnostic process of nodal changes in the thyroid gland, but for elastography, different and partially contradictory results have been shown [37]. Therefore, this study aimed to examine the significance of ultrasound elastography in the diagnosis of differentiated thyroid gland tumors.

Methods

The research was a retrospective, clinical, noninterventional cross-sectional study aimed to analyze the significance of the diagnostic test – ultrasound elastography. The study covered 58 patients (41 females and 17 males, ages 24 to 78), who were examined in the period between 2015 to 2018 at the Clinic for Endocrinology of the Military Medical Academy in Belgrade, Serbia, and who were subjected to the surgical treatment after the diagnostic procedure performed. Based on a HP analyses, patients were divided into two groups. The follicular adenoma (FA) group included patients who had been diagnosed with a benign focal lesions/follicular adenoma determined by HP and the differentiated thyroid carcinoma (DTC) group containing patients with the existence of malignant lesions (papillary and follicular – DTC) determined by HP.

The survey was conducted based on the following criteria: age > 18 years, a HP analysis verified as FA or DTC. Excluding criteria for the examined population were: patients with thyroid gland tumors that did not belong to FA or DTC, pregnant women and nursing women, patients with previous thyroid gland surgery and other thyroid diseases followed by its dysfunction (thyrotoxicosis, manifest hypothyroidism, acute and subacute thyroiditis); patients with cognitive dysfunction who could not give relevant anamnestic data, patients with other malignancies in the last 5 years (except for skin cancer), patients with multiple endocrine neoplasias, patients with severe liver and kidney failure, patients with radioactive iodine in therapeutic purposes.

The results of the clinical examination were analyzed in terms of the inspection findings or palpatory findings and laboratory analyses. The analysis of the inspection finding included the existence or absence of visible nodule changes in the normal position of the head and in the extension of the neck. The palpatory finding included palpability of the nodules (palpable or non-alopecia), nodules consistency (hard or elastic) and mobility of the nodules (movable or immobile).

Laboratory analyses were carried out at the Institute of Biochemistry of the Military Medical Academy in Belgrade, and included determining the following parameters: free thyroxine (fT4) and TSH were determined from the serum by the chemiluminescence method, on the unicell DxI 800 (Beckman Coulter) using the reference value 7.0–19.0 pmol/L, and 0.340–5.600 mIU/L, respectively; thyroglobulin was determined by chemiluminescence method, on the Elecsys 2010 (Roche) with the reference value 3.50–77.0 mg/L; calcitonin was determined from the serum on the Imulyte 2000 (Siments) using the reference values 7.0–18.0 nmoL/L; antithyroglobulin antibodies (TGAb) were measured from the serum by chemiluminescence method (the reference values were 0.00–4.00 IU/mL); anti-thyroid peroxidase antibodies (anti TPOAb) were determined from the serum using reference values < 9.0 IU/mL.

After a detailed clinical examination and laboratory analyses, all patients were examined by echosonography. Echocardial examination of the thyroid glands was carried out on the ultrasonic device of the brand Toshiba Aplio linear probe 10 MHz. In all patients, standard ultrasound examination in B-mode and ultrasound measurement were performed. Analyzed ultrasound characteristics of the thyroid gland nodule included the following: localization of the nodules, the regularity of the edges, the presence of hypoechogenic halo; homogeneity; echogenicity; presence of calcificate; extrathyroidal extension; marginal calcification; dimensions; analysis of blood flow. We used the Fukunara scoring: the nodules that were the most elastic were assigned to score 1 (mostly benign nodules), and the nodules that are least elastic were assigned to score 4 (malignant nodes) [15]. The re-

sistance was measured both quantitatively, within the same shift as in the surrounding tissues, and is expressed as the resistance index (SR – strain ratio) that represents the software calculated, quantitative measure of elasticity. In this study, all values of SR ≥ 2.5 were considered to be a predictor of malignancy of the nodules.

The finding of a cytological analysis of material obtained during FNAB was marked as a suspect malignant lesion, probably a benign lesion and a non-exclusive finding.

The sample size was calculated based on sensitivity of elastography in the diagnosis of DTC. According to the data from Tanaka et al. [36] the sensitivity of elastography in the diagnosis of differentiated thyroid carcinoma is 89.1%. The study sample was calculated taking $\alpha = 0.05$, the strength of the study $1\beta = 80\%$ and for the detection of a difference of 10% from the assumed sensitivity. By applying the formula, the established criteria for sample size included at least 49 patients. In the analysis of the obtained results, the methods of descriptive and analytical statistics were used. Data for all categories were represented as absolute and relative values. The distribution of data was tested and the data were presented according to the central tendency (arithmetic mean, median) and measurements of variability (standard deviation, range).

The difference between the two groups was analyzed by the Student's *t*-test, Man-Whitney test, chi-square (χ^2) test, and Fischer test, depending on the type and distribution of data. The relationship between the two variables was analyzed using the Person's or Spearman's coefficient of correlation, depending on the type and distribution of data. Diagnostic accuracy of elastography was expressed through the sensitivity, specificity, positive and negative predictive value of this method concerning FNAB. Receiver operating characteristic curve (ROC) was used to calculate the cut off values for continuous variables. Variables with the greatest diagnostic potential were incorporated into the mathematical model, and its diagnostic potential was determined. The significance threshold (α) for all statistical calculations was 0.05. SPSS software package (version 23.0, SRSS Inc. Chicago, IL) was used for statistical data processing of the results obtained.

Results

The study included 33 patients with FA and 25 patients with DTC. The age and gender of patients with malignant (DTC) and benign (FA) lesions were not statistically significantly different between the two groups (Table 1). The fol-

Table 1
Demographic characteristics of patients with follicular adenoma (FA) and patients with differentiated thyroid carcinoma (DTC)

Characteristics	FA (n = 33)	DTC (n = 25)	*p*
Age (year), mean ± SD	47.7 ± 12.9	51.0 ± 14.4	0.383 (*t*-test)
Gender, n (%)			
male	8 (24.2)	9 (36)	0.330 (χ^2-test)
female	25 (75.8)	16 (64)	

Table 2
Clinical and laboratory characteristics of the disease in patients with follicular adenoma (FA) and patients with differentiated thyroid carcinoma (DTC)

Parameters	FA (n = 33)	DTC (n = 25)	*p*
Inspection finding, n (%)			
no visible finding	5 (15.2)	7 (28)	0.412
node visible with neck extension	18 (54.5)	10 (40)	
node visible in normal position	10 (30.3)	8 (32)	
Palpation finding, n (%)			
not palpable	0 (0)	0 (0)	–
palpable	33 (100)	25 (100)	
Node consistency, n (%)			
firm	19 (57.6)	21 (84)	0.031
elastic	14 (42.4)	4 (16)	
Node mobility, n (%)			
not mobile	0 (0)	3 (12)	0.041
mobile	33 (100)	22 (88)	
fT4 (pmol/L), mean ± SD	12.8 ± 3.3	11.6 ± 2.9	0.171
TSH (pmol/L), mean ± SD	1.6 ± 1	2 ± 0.8	0.129
Thyroglobulin (Tg), mean ± SD	77.7 ± 97.7	314 ± 553.6	0.045
Anti TPO Ab (IU/mL), mean ± SD	4.3 ± 5.8	24.3 ± 75.1	0.131
Anti Tg Ab (IU/mL), mean ± SD	3.1 ± 7.0	4.8 ± 10.9	0.486
Calcitonin > 2 nmol/L, n (%)	1 (3.0)	1 (4.0)	1.000

Note: **Data presented as n (%) were analyzed with the χ^2-test; data presented with arithmetic mean and standard deviation (SD) were analyzed with the Student's *t*-test.**
fT4 – free thyroxine; TSH – thyroid stimulating hormone (thyrotropin);
TPO Ab – thyroid peroxidase antibodies; Tg Ab – thyroglobulin antibodies.

lowing parameters were monitored: inspection and palpatory findings, consistency, nodules mobility, and the levels of TSH, fT4, Tg, calcitonin, TPOAb and TGAb. The inspection findings did not differ significantly between DTC and FA groups. All nodes were palpable in both groups of patients. Observing the parameters that were evaluated by clinical examination and laboratory analyses, significant difference between groups was found in the nodules of firmer consistency, immobile nodules and values of Tg (Table 2).

The nodules with a firmer consistency were significantly more present in the DTC group of patients. In the DTC group, there were 84% of patients with firmer consistency nodules and only 16% of elastic nodules. In the FA group there were more elastic nodules (42.42%). Fixed (non mobile) nodules were statistically significantly more present in the DTC group (12%). There were no fixed nodes in the FA group.

Tg levels were significantly higher in the DTC group of patients. The levels of fT4, TSH, TPOAb, and TGAb did not differ between the DTC and FA groups. Calcitonin levels > 2 nmol/L were present in one patient of each group, so there was no statistically significant difference between the DTC and FA groups.

Ultrasound characteristics and measurements of examined nodules are presented in Table 3. The distribution of anatomical localization of the nodules in patients did not differ significantly between the DTC and FA groups. Irregular edges were more common in patients with DTC, and the difference was near the level of statistical significance. The presence of hypoechogenic halo was more common in the DTC group, but the difference between the DTC and FA groups was not significant. Solid nodules were significantly more present in the patients with DTC. Namely, 88% of patients from the DTC group had solid nodules, while 12% of them were cystic. In the FA group, only 33.33% of patients had solid nodules. The homogeneity and echogenicity of the nodules did not differ significantly between the two groups. Micro- and macro-calcifications were significantly more present in the group of patients with DTC. Namely, 97% of the patients in the FA group did not have calcifications. In the

Table 3
Ultrasound characteristics of the disease in patients with follicular adenoma (FA) and patients with differentiated thyroid carcinoma (DTC)

Characteristics	FA (n = 33)	DTC (n = 25)	*p*
Localization, n (%)			
central	25 (75.8)	20 (80)	0.701
peripheral	8 (24.2)	5 (20)	
Anatomic localization, n (%)			
cranial	3 (9.1)	4 (16)	
medial	25 (75.8)	20 (80)	0.316
the caudal third of the lobe	5 (15.2)	1 (4)	
The regularity of the edges, n (%)			
absent	3 (9.1)	7 (28)	0.059
present	30 (90.9)	18 (72)	
Presence of hypoechogenic halo, n (%)			
absent	26 (78.8)	24 (96)	0.121
present	7 (21.2)	1 (4)	
The appearance of the node tissue, n (%)			
solid	11 (33.3)	22 (88)	
mixed	22 (66.7)	3 (12)	< 0.001
cystic	0 (0)	0 (0)	
Homogeneity, n (%)			
homogeneous	5 (15.2)	6 (24)	0.504
not homogeneous	28 (84.8)	19 (76)	
Echogenicity			
dominantly hypoechogenic, n (%)	29 (87.9)	24 (96)	
iso echogenic	3 (9.1)	0 (0)	0.386
hyper echogenic	1 (3)	1 (4)	
Presence of the calcifications, n (%)			
absent	32 (97)	10 (40)	
present, micro	0 (0)	13 (52)	< 0.001
present, macro	1 (3)	2 (8)	
Dimensions (mm), mean ± SD	25.6 ± 6.3	25.0 ± 5.0	0.719
Mobility (present), n (%)	20 (60.6)	21 (84.0)	0.080
Calcification of the edges, n (%)			
absent	29 (87.9)	25 (100)	0.126
present	4 (12.1)	0 (0)	

***Note*: Data presented as n (%) were analyzed with the chi-square (χ^2) test and these presented as arithmetic mean and standard deviation (SD) were analyzed with Student *t*-test.**

DTC group, 52% of the patients had microcalcifications and 8% macrocalcifications. The dimensions of the nodules and calcifications of the edges were not significantly different between the groups. More pronounced vascularization was more prevalent in the group of patients with DTC, and the difference was close to the conventional level of statistical significance (not shown).

The parameters registered with ultrasound elastography in the FA and DTC groups of patients are shown in Table 3. The elastography scores 2 and 3 were significantly more frequent in the group of patients with FA, whereas elastography score 4 was only present in the group of patients with malignant lesions (DTC). 17 patients (68%) in the DTC group had score over 4, whereas in the FA group none of the patients had the score 4. In the DTC group, no patient had the score of lower than 3. The sensitivity of Fukunara score 4 was 68%, and the specificity was 100% for the diagnosis of DTC. The elasticity score, SR > 2.5, was present in almost all patients in the examined groups, but there were no statistically significant differences between them. The SR > 2.5 did not prove to be sensitive sufficiently and specific enough for the diagnosis of DTC, therefore only numerical values were analyzed. The area under the ROC curve (AVC) was statistically significant (Figure 1). The SR ≥ 4.35 was 92% sensitive and 70% specific for the diagnosis of DTC in the examined patients. The results of the cytological analyzes obtained by FNAB showed that FNAB findings in patients with benign lesions (FA) were false positive, which makes this method insufficiently specific for the diagnosis of differentiated thyroid carcinoma.

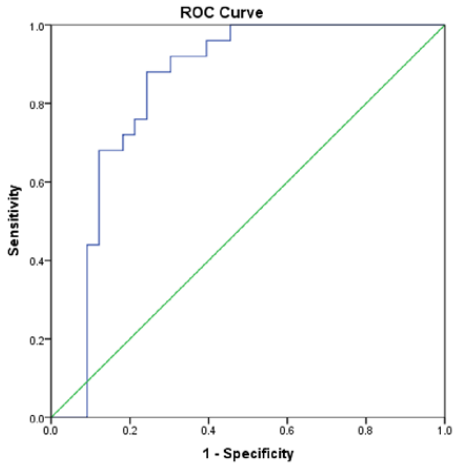

Fig. 1 – Receiver operating characteristic (ROC) curve of specificity and sensitivity of strain ratio in the diagnosis of differentiated thyroid carcinoma (DTC). Scala under ROC curve (95% confidence interval): 0.84. (0.731–0.949); $p < 0.001$.

Discussion

Increasing prevalence of primary thyroid tumors, benign or malignant, have been detected by over the past twenty years. In the general population, the prevalence is about 20–70% [1, 2, 38, 39]. The fact that about 5% of the thyroid nodules are malignant, imposes a need for a more precise detection and preoperative diagnosis of thyroid carcinomas [5, 6]. Regardless of all diagnostic possibilities, the definitive diagnosis of differentiated malignant tumors is made exclusively by the histopathological and immunohistochemical analyses. It is a constant professional need to timely diagnose and cure malignant thyroid gland disease, but also to reduce the number of operated benign nodules. Detailed clinical examination, biohumoral, echosonography, scintigraphy, and cytological analyses are often insufficient to clearly assess and establish an indication for surgical treatment. A high quality elastography measurements could indeed provide the necessary tool for this kind of decision. Therefore, the study was conducted in which 33 patients with FA and 25 patients with DTC were involved.

Both men and women have the lowest incidence of malignant nodules in the 70s. A typical risk of 5% malignancy of thyroid gland nodules varies by age and gender [40]. Patients of the male gender, younger age with individual nodules, have a higher risk of developing DTC. Therefore, the age and gender of a patient should be considered when DTC is suspected in patients with thyroid nodules [41]. However, according to age and gender, the incidence of malignant (DTC) and benign (FA) lesions did not differ significantly in this study.

When it comes to clinical and bio-humoral characteristics, there is a lot of contradictory data in the literature. A physical examination may be limited by the patient's physical characteristics and the subjectivisms of the physician [42]. In this study, a statistically significant difference between the DTC and FA groups was observed only for consistency and elasticity of the thyroid nodules. Namely, nodules of firm consistency and fixed nodules were more common in the group of patients with malignant lesions (DTCs). These data are only partly in line with the other published data. According to these results, an increased risk of thyroid gland cancer include nodules that are larger than 4 cm (19.3% risk of malignancy), palpation with firm consistency, nodules that are fixed to the surrounding tissues, lymphadenopathy of the neck and voice change (hoarseness) [43].

In this study, Tg levels were significantly higher in the group of patients with DTC, which is in correlation with the already published data. A preoperative interpretation of Tg level is often a complex task as they can be elevated in both benign and malignant thyroid diseases. Therefore, Tg use as a diagnostic marker for thyroid gland carcinoma is quite limited [44]. Tg is considered a good marker for follow-up monitoring after surgery and ablative therapy with radioactive iodine (RAI) of well differentiated follicular cell carcinoma. When Tg is not detected in the serum, it can be assumed that the disease is no longer present [45]. So, Tg has a great predictive value in the postoperative period after the RAI ablative therapy. Still, there are postoperative recurrences of diseases that do not go with an increased serum levels of Tg. Some autors [46] pointed out that the preoperative determination of serum Tg is important for identifying patients with a possible relapse of the disease in which there is no higher levels of Tg. Although the results of our research do not show a statistically significant difference between the DTC and FA

groups for TSH, fT4, anti-TPOAb, and anti-TGAb values, there are papers with opposite claims. McLeod et al. [46] have concluded that a higher TSH serum concentration is associated with a higher incidence of cancer in existing thyroid gland nodules. Boelaert et al.[45] noted that with the increasing TSH levels, the risk of malignancy in thyroid nodules increases. Jonklaas et al. [44] suggested that TSH suppression in high-risk patients would affect the reduction of mortality. TSH is an important factor that affects the growth of the thyroid gland and may have a clinical application in the future for the diagnosis of thyroid cancer.

Ultrasound examination is significant in assessing the nature of the nodules, determining their number and size, assessing the existence of lymphadenopathy, but also for ultrasound-guided aspiration biopsies [47–49]. Ultrasound characteristics of malignant nodules include their hypoechogenicity, irregular edges, microcalcifications, intranodal hypervascularity and regional lymphadenopathy. The combination of these characteristics can have a high malignancy prediction value [50, 51]. The characteristics which indicate the presence of benign nodules are completely cystic nodes (< 2% of all nodus), microcystic nodules with over 50% of cystic nodules volume (99.7% benign nature) [52]. The ultrasound characteristics of nodules in this study had a different degree of significance. Namely, a significant difference between the DTC and FA groups was registered only for the presence or absence of calcifications and the nodules appearances. The solid nodules and calcifications were significantly more frequent in the group of patients with malignant lesions (DTC). The sizes of nodules and the frequency of the marginal calcifications did not differ significantly between the two groups. Cappelli et al. [56] pointed out that malignancy is associated with a higher nodules size (especially 30 mm and larger nodes). Frates et al. [53] and Moon et al. [57] claimed that the size of nodules is not a useful category for distinguishing the malignant from benign nodules. In some studies, microcalcifications, but also rough, marginal calcifications, were designated as clear malignant predictors [58]. In other studies, the significance of microcalcification was noted [59] while the correlation of malignancy with rough and marginal calcifications is still a matter of debate. Ramundo et al. [54] have shown that there is a significantly higher risk of thyroid carcinoma in nodules located in the central part of the lobes of the thyroid gland, especially in cases of solid nodules. It was concluded that the nodules of such localization are an independent risk factor for malignancy, regardless of the ultrasound characteristics [53–55].

In our study, nodules localization had no predictive value. Nodules were most often localized in the central part of the thyroid gland (medially). The results of many studies suggested that hypoechogenic nodules and the ones with irregular edges are much more frequent in malignant lesions, i.e. they are considered independent predictors for malignancy of the nodules [54]. However, several studies showed the opposite results. In this study, the irregular edges were more frequent in the patients with DTC, although the difference was not statistically significant. The presence of hypoechogenic halo was also more common in the DTC group, but the difference was not significant statistically. The homogeneity and echogenicity of the nodules did not differ significantly between the two examined groups. Many studies have found that increased blood flow in nodules was a malignancy prediction [55–57], while some consider vascularization levelas a non-specific factor for it. Here, we found that an increased vascularization was more frequent in the group of patients with DTC, but the difference was significant statistically, probably due to lower number of patients involved.

Using the elastography method, qualitative and quantitative resistance of the nodules and the surrounding tissues was evaluated. We used the Fukunari sore [35]. Malignant nodules had a smaller score (3–4), while benign nodules had a greater elasticity (score 1–2). The same score system was used by Wang et al. [60], while the Ueno classification was used by Ciledag et al. [61] and Itoh et al. [62]. Our results indicated that significantly more frequent elastography score 2 and 3 were present in the FA group, while the elastography score 4 was only present in the group of patients with malignant lesions (DTC). The sensitivity of the Fukunara score 4 was 68% and the specificity was 100% for the diagnosis of DTC. In the paper of Rago et al. [63] it was shown that the elastography score 4 has a high predictive value for malignancy, with a sensitivity of 97% and a specificity of 100%, and that the method has a high potential for diagnosing thyroid cancer. Cantisani et al. [64] have shown that the sensitivity and specificity of the elastography are 94% and 81%, respectively, and the accuracy of the method is 83.7%, meaning that it is a promising technique for the detection of malignant thyroid nodules, especially in combination with echosonography. Rago et al. [63] showed that elastography score 1 had a high predictability for benign nodules, as it could be found in 102 of total 111 benign nodules, and only in one of 31 cases of DTC ($p < 0.0001$). It has also been shown that ultrasonic elastography is useful for the selection of patients for surgical intervention, especially in those with unclear cytological appearance [63]. Additionally, it was shown that elastography, especially when performed by the experts, is excellent for detection of malignant changes in the thyroid gland if combined with echosonography [67, 68].

In our study the elasticity score (SR > 2.5) was present in almost all patients in the FA and DTC groups, and there was no statistically significant difference between the two groups. In 12 patients with the SR > 2.5, it was not shown that the method was sufficiently sensitive or specific for the diagnosis of DTC. The SR ≥ 4.35 had 92% sensitivity and 70% specificity for the diagnosis of DTC in both patient groups. Unlike elastographic scoring, the determination of the SR index calculated by software provided quantitative measures of elasticity, therefore more reliable information [18–21]. In our study, the SR values ≥ 4.35 were thus highly specific for making the diagnosis of DTC. Lyshchik et al. [20] have suggested that SR ≥ 4.0 is a strong predictor of nodules malignancy, with a sensitivity of 82% and a specificity of 96%. Kagoya et al. [66] used the SR > 1.5 as a sign of nodules malignancy, with a sensitivity of 90% and a specificity of 50% [65]. When performing this technique, it should be taken into account that the depth of the tissue, in which the elasticity between the nodule and the

normal tissue is compared, is the same or at least similar, as well as that the elasticity estimation is performed on the longitudinal display of the thyroid gland, because on that occasion, a sufficiently large part of normal tissue is used for comparison and calculation of SR index [66]. Rago et al. [21] have shown that the size of the nodules does not affect the SR index and the predictability of elastography. However, other researchers suggested that the size of the nodule can affect this index, so they included the nodules which were up to a maximum size of 3 cm [61]. Other studies included all nodules up to 4 cm [64–66]. In our study we included all nodules up to a maximum of 3 cm. For nodules larger than 3 cm, the pressure applied during elastography cannot be the same in all parts of the nodule so the results of the SR index would be inadequate. For now, there is no reliable information on what the minimum size of the nodule should be before this kind of measurement. Some studies have suggested that when performing this method, one has to take into consideration the position of the carotid artery, since the pacing of the carotid artery may impair the proper interpretation of the elastography image [60, 61]. Our study did not include patients whose nodules were close to the carotid artery, and the method was performed by external compression.

Conclusion

Detailed clinical, biohumoral, echosonography, scintigraphy and cytological examinations are often not sufficient for a safe assessment and a clear indication for definitive surgical treatment of differentiated malignant thyroid tumors, which imposes the need for more precise preoperative evaluation of these patients. On the other hand, there is a constant need to reduce the number of operated on benign lesions. Here we showed that ultrasound elastography represents a new non-invasive method that could have an important role in the detection of thyroid carcinoma, especially in association with findings of other diagnostic procedures. By combining only a few echosonography and elastography characteristics, the sensitivity and specificity of the findings are significantly increased. The presence of at least one of them (solid tissue appearance, presence of calcificates, the Fukunara score ≥ 4, the strain ratio ≥ 4.35) has sensitivity of 100% and specificity of 43.8% for the diagnosis of DTC. The presence of at least two of the listed has 96% sensitivity and 87.9% specificity. The presence of 3 and more of the listed characteristics has 100% sensitivity and 89.2% specificity.

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