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Nodular thyroid cancer. Diagnostic value of real time elastography

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Rezumat

Cancer tiroidian nodular. Valoarea diagnostică a elastografiei în timp real

Premize: cel mai important aspect al diagnosticului nodulului tiroidian este identificarea malignității lui. Elastografia este o tehnică mai nouă, care permite aprecierea elasticității țesuturilor, după aplicarea unei forțe externe, standardizat controlată. Elastografia este actualmente folosită în diferențierea formațiunilor maligne de cele benigne.
Pacienți: acest studiu prospectiv a inclus 69 de subiecți, 2 bărbați și 65 de femei, cu vârsta medie de 50.08±12.43 ani, cu cel puțin un nodul tirodian predominant solid, cu volum de minim 0.20 ml, confirmat la ecografia conventională. Toți pacienții au fost operați. Examenul histopatologic extemporaneu și la parafina a fost efectuat la toate cazurile. Elasticitatea tisulară a fost masurată calitativ și împărțită în scoruri de la 1 (cea mai mare elasticitate) la 5 (lipsa oricărui semnal), corespunzător scalei UENO.
Rezultate: la cei 69 de pacienți evaluați, am identificat 107 noduli, care au făcut obiectul acestui studiu. 27 de fornațiuni nodulareau avut scor elastografic 1, 36 de cazuri au avut scor elastografic 2. Toți acesti noduli au fost benigni la examenul histopatologic. 33 de noduli au avut scorul 3, 32 dintre aceștia corspunzând unei leziuni benigne și doar un caz având cancer tiroidian. Scorul elastografic 4 a fost descris la 10 leziuni, toate cancere tiroidiene. Scorul înalt elastografic este predictiv pentru malignitate, cu o sensibilitate de 90.9%, specificitate de 98.96%, valoare predictivă pozitivă de 100%, respectiv valoare predictivă negativă de 98.6%. Calitatea dagnostică a elastografiei în timp real, a fost independentă de volumul nodular.
Concluzii: sonoelastografia în timp real are o perspectivă bună în diagnosticul cancerului tiroidian, independent de volumul nodulului apreciat, permițând studiul nodulilor mai mici de 0.5 ml.

Cuvinte cheie: nodul tiroidian, cancer tiroidian, sonoelastografie în timp real

Abstract

Background: the most important aspect in the diagnostic approach of thyroid nodule is identifying the malignancy. Elastography is a newly technique that measures the elasticity of tissue, after applying a external force, standardized control. US elastography is currently used in differentiation of malignant from benign lesions.
Patients: this prospective study included 69 patients, mean age 50.08±12.43 years, 67 females and 2 men, with thyroid nodules on conventional US, with a volume higher than 0.20 ml. All patients underwent surgery after complete evaluation. Extemporaneous and postsurgical histopathological exam was performed in all cases. Tissue stiffness was scored from one (greatest elasticity) to 5 (no strain), according to the UENO scale.
Results: in the 69 cases we diagnosed 107 nodules, which we analyzed. 27 nodules had score 1 on US elastography and 37 nodules had score 2. All nodules were benign on histopathological exam. Score 3 was found in 33 cases, 32 benign and

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one papillary carcinoma. Score 4 as found in 10 cases, all carcinomas. ES score of 4 is highly predictive for malignancy (sensitivity of 90.9%, specificity of 98.96%, positive predictive value of 100%, negative predictive value if 98,60%). The diagnostic quality of elastography was independent of the nodule volume.
Conclusion: US elastography has a good potential in diagnosing thyroid malignancy, independent of nodule volume, allowing the study of small nodules, less than 0.5 ml.

Key words: thyroid nodule, thyroid cancer, real tine sonoelastography

Introduction

Cancer suspicion should be present in the presence of any thyroid nodule, thyroid nodule being the most frequent form of manifestation of differentiated thyroid carcinoma (1). Thyroid nodules are a common pathology in our region (2). They are found clinically in 4-8% of cases (3), 19-45% with the use of ultrasound (4), but as high as 50% in autoptic studies (5).

Although thyroid nodules can cause local compression symptoms (dysphagia, dysphonia, irritative couch) or hyperthyroidism due to insuppressible thyroid hormones production, or just esthetic inconvenience, the main concern of the patient and the doctor is detection of malignancy, which normally comprises up to 5% of the total thyroid nodules (6).

The goal of the modern investigation techniques is to discriminate with as high as possible sensitivity and specificity suspicious from unsuspicious thyroid nodules. Fine needle aspiration biopsy (FNAB) has a sensitivity of up to 70% in diagnosing thyroid malignancy (1). Limitations of the use of this technique are compliance of the patients, and the presence of a high qualified cytologist. Ultrasound is considered the most sensitive noninvasive diagnosis tool of the thyroid nodules (7). FNAB There is no consensus regarding the importance of US in selecting the cases for FNAB, guiding the procedure or follow-up US criteria or using US as a screening tool for thyroid cancer detection (4,6,7,8). Size, echogenicity, composition, presence or absence of calcification/halo/irregular margins and also blood flow pattern, typical egg shell appearance are used to classically evaluate the thyroid nodules (9).

A thyroid nodule that is clinically firm and consistent is associated with an increased risk of malignancy (10,11). The principle of elastography imaging is based evaluating on differential tissue characteristics regarding rigidity versus elasticity (12). Elastography is used complementary to classical US for improving the diagnosis of thyroid tumors, that appear harder than the surrounding tissue. Tissue that is found hard on elastography scan is closely correlated with malignant disease (13). Previous studies found a very high sensitivity (82-97%) and specificity (97-100%) of malignancy diagnosis in hard nodules (14,15).

Material and Method

Patients

The study is a prospective study enrolling cases seen in the Endocrinology Office, Center Dr. D, affiliated with the Departmetn of Endocrinology, University of Medicine and Pharmacy "Victor Babes" Timisoara, in the period January-September 2011. There were included cases with one or more thyroid predominant solid nodules, with volumes higher than 0.20 mL, in patients that did not accept FNAB. All of the patients underwent surgery in the 2nd Surgical Clinic of the same University. All patients gave their inform consent to the approach. From a total of 114 cases with suspected thyroid nodule, nodular goiter was confirmed in 89 cases, 69 out of them cases being predominant solid lesions, 67 females and 2 men, mean age 50.08±12.43 (95% LCL = 45.86 years 95% UCL 52.30 age) range 24 to 74 years with confirmed thyroid solid nodules. This 69 patients were included in our analysis. In this cases we observed 107 nodules (mean 1.550 ± 1.4 nodule/patient), that were analyzed with conventional, power Doppler sonography and real time elastography.

The 20 cases with predominant chystic lesions were not included in our analysis because the poor use of elastography in such lesions (14).

Equipment

We performed the final evaluation of each patient on a Hitachi EUB 7500 HV machine with 6-13 MHz variable frequency linear probe, with Doppler and elastography software, with recording of frames of all lesions prospectively on color elastography color map 1 (red-yellow-green-blue color map); Hitachi Medical System, Tokyo, Japan.

Conventional, Power Doppler US and Elastography

In preoperative period all patients were examined by the same operator (D.S.), using High Resolution B-mode grey scale ultrasonography (US), Power Doppler ultrasonography (PD) and Real Time ultrasound elastography (USE) using the same machine. We analyses at each nodule the following parameters: echogenity (hyper-, iso and hyperecoic compared to the normal thyroid parenchyma); presence or absence of halo phenomena; irregular or well defined margins, shape (dominant dimension); intranodular homogeneity; presence of calcification: spot microcalcifications: hyperechoic spots less than 2 mm, without acoustic shadowing, macrocalcifications round solitary/eggshell or nonspecific calcification. Color flow Doppler pattern was defined as: absence of any blood flow, perinodular with no or scare intranodular blood flow, marked intranodular blood flow or unique dominant intranodular vessel (16,17).

The US elastography was performed during the same US examination, by the same observer. The US elastogram was displayed, as usual, over de 2B map, with the scale ranging from red – soft tissue to blue – hard lesions with no strain.

The compression applied to the neck was always between double-checked by the standardized real-time measurement displayed on the screen. Only moderate pressure with the scale 3 to 4 were applied and used for the analysis. This is required because the extent of tissue compression influences both the tissue response and the elasticity score (18). The images were classified by the UENO 5 point scale (18): ES 1 = soft, elasticity (green color) within whole lesion, ES 2 = soft, elasticity (green color) in more than 50% of the lesion, especially in the center, ES 3 = intermediate, blue in circa 50% of the area predominant in the center of the lesion (elasticity only at the periphery of the nodule), ES 4 = hard, no elasticity, predominant blue color, ES 5 = no elasticity in the nodule and surrounding area. (*Fig. 1, Fig. 2)*

Treatment

All patients with predominant solid nodules (69 cases) were referred to surgery. The surgical protocol was: total lobectomy on the site of the nodule. Total thyroidectomy was performed in cases with elastography score of 4. All excised pieces were send th morphopathological department.

Histopathological diagnosis

Each piece extracted from each case was formalin-fixed and paraffin embedded both nodular and apparent healthy thyroid tissue. The histological diagnosis was made by the pathologist on duty on the day of surgery, according to the World Health Organization Guidelines (19). In selected cases imunohistochemical reactions(IHC) were performed: HBME, CH-19, K067 and TTF.

The immunohistochemical reactions were carried out on sections 4-5μ thick, mounted on electrostatic charged slides; for immunostaining we used the IHC technique in the LSAB system (labeled streptavidin-biotin) and visualization with DAB (diaminobenzidine), the kit being provided by DAKO. Formalin-fixed and paraffin-embedded tissue sections were IHC stained using the monoclonal antibodies anti-CK19 (clone RCK108; 1:150), anti-HBME-1 (clone HBME-1; 1:100) and anti-TTF-1 (anti-thyroid transcription factor) (clone 8G7G3/1; 1:50). We assessed the IHC expression of KI-67 antigen using the prediluted monoclonal antibody, clone MIB-1, with pretreatment by boiling.

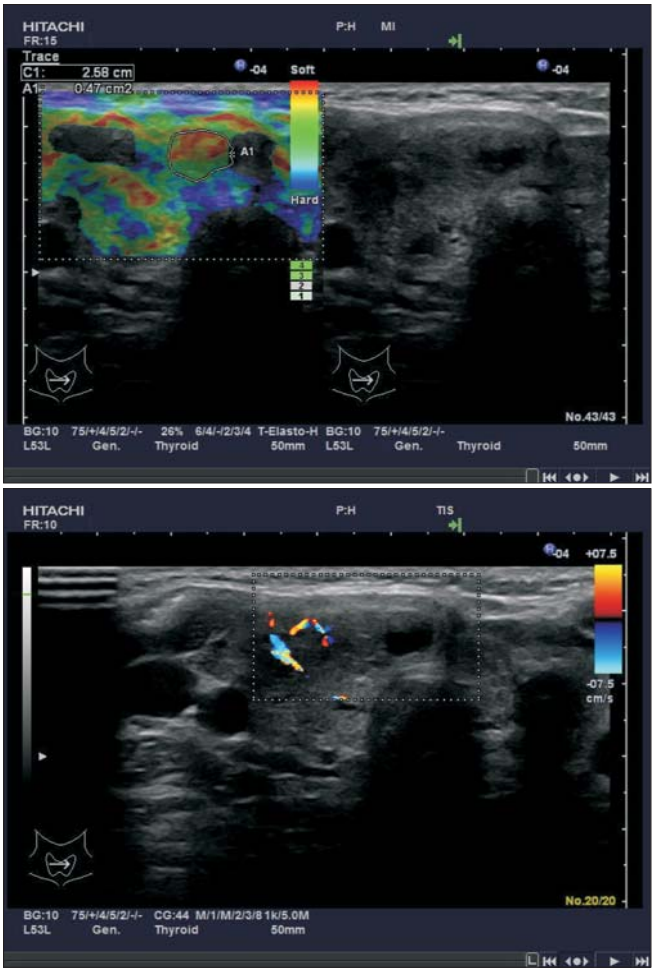


Figure 1. *Fibroadenoma with ES score of 1 and perinodular vascularization*

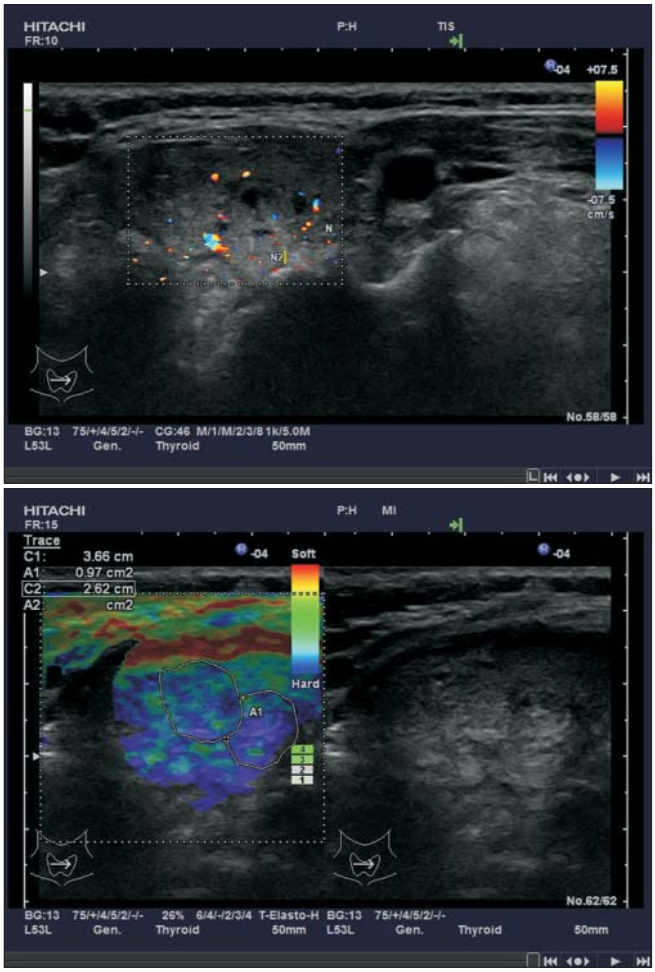


Figure 2. *Papillar thyroid carcinoma (N2) with intranodullar vascularization and ES = 4 associated with a follicular adenoma (N1)*

Statistical analysis

Numerical data (age, number of nodules per patient, TSH value, and nodule volumes are shown in median, minimum, maximum and 95% LCL and 95% UCL levels. Results obtained in different groups were compared using Student's t test two sample. The diagnostic performance of different parameters was evaluated by Receiver Operating Characteristics (ROC) curve. P-values less than 0.002 were considered as statistically significant. Analyses were carried out with NCSS software version NCSS PAAS 2008 v8.0.11.

Results

Histology

Of the 69 patients, 11 (15.94%) had a final diagnosis of thyroid malignancy on histology: 10 cases papillary thyroid carcinoma: 2 classical variant *(Fig. 3)*, 6 follicular variant, one microcarcinoma *(Fig. 4)* and one less differentiated carcinoma; 1 case had follicular thyroid cancer.

From the 58 benign cases (84.04%) we had 26 follicular adenoma, 10 hyperplastic nodules, 11 anisofollicular nodules – coloidochistic degenerative changes, 9 oxyphilic adenomas (with dysplasia or metaplasia), 1 chronic autoimmune thyroiditis with no other associated lesion and 1 parathyroid adenoma.

When we analyzed each separate the 107 nodules we observed: one (0.93%) huge nodule with follicular cancer, 10 cases with papillary carcinoma (9.45%), 41 follicular nodules (38.31%), 19 coloidochistic nodules (17.75%), 12 hyperplastic nodules (11.21%), 14 oxyphilic carcinoma (13.08%), three parathyroid adenomas (2.803%) and seven (6.54%) plain autoimmune chronic thyroiditis (2.803%).

Papillary carcinomas showed an intense and diffuse CK19 expression (cytoplasmic pattern with membranar emphasis), immunoreactivity being more intense in tumors with papillary architecture *(Fig. 5)*, variable in those with follicular pattern and reduced in poorly differentiated carcinomas. Most papillary carcinomas, both classical and follicular variant, expressed HBME-1 with diffuse, intense, membranar immunoreactivity, more prominent in the apical area *(Fig. 6)*. Follicular carcinomas showed focal immunoreaction with variable intensity. We identified nuclear immunoreactivity for TTF-1 *(Fig. 7)* in well differentiated lesions derived from follicular carcinoma, and low, focal expression in poorly differentiated carcinomas.

Immunostaining with MIB-1 demonstrated that the proliferation rate had a tendency to increase from the classic forms *(Fig. 8)* of papillary carcinomas to poorly differentiated tumors.

Conventional ultrasound

When we evaluated the characteristics of ultrasound, classic, Doppler or sonoelastographic, we analyzed all the described nodules, respectively the 107 nodules. All data regarding ultrasound characteristics are described for this number of cases.

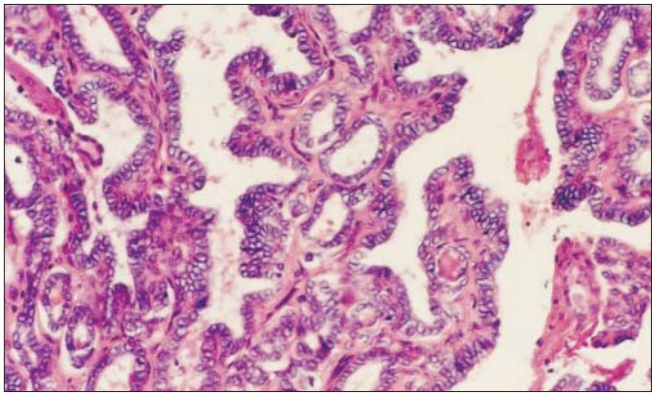


Figure 3. *Papillary thyroid carcinoma – classic variant. HE x 200*

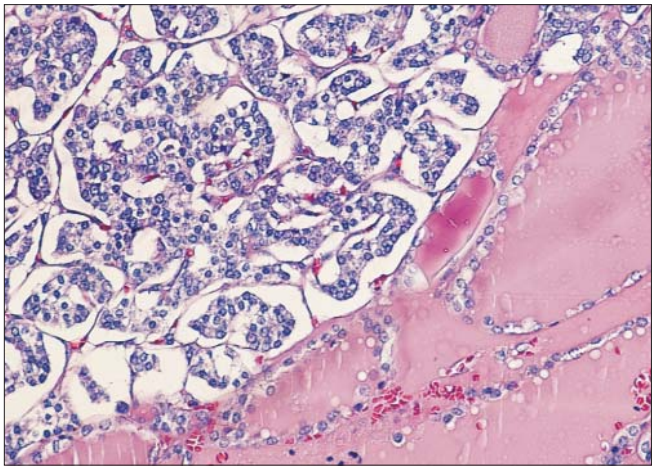


Figure 4. *Papillar microcarcinoma in a thyroid coloid diffuse goiter. HE x 200*

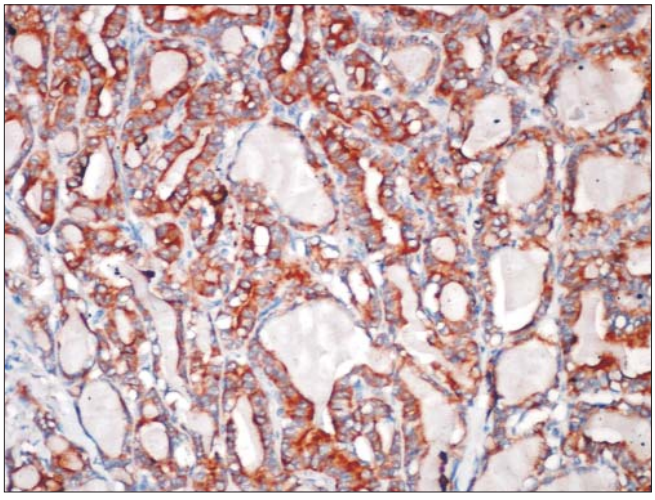


Figure 5. *Papillary carcinoma – follicular variant. CK19 positive immunoreaction. LSAB x 200*

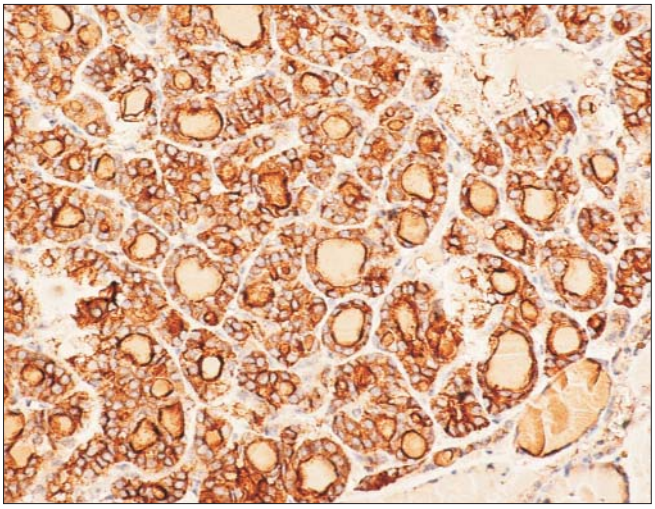


Figure 6. *Follicular variant of papillary carcinoma with intense and diffuse HBME-1 expression. LSAB x 200*

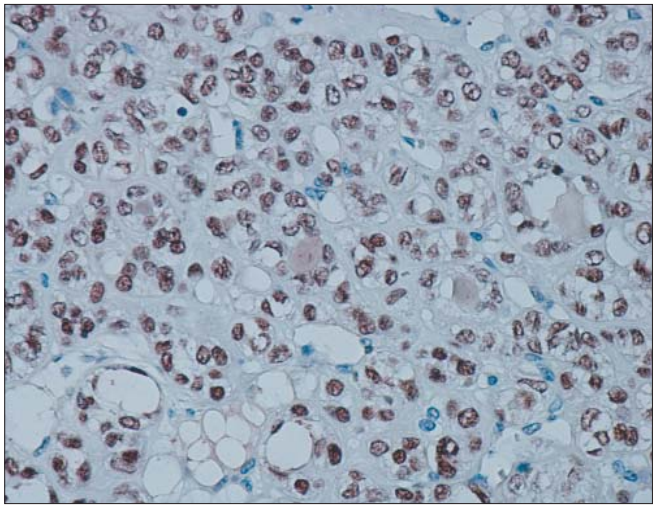


Figure 7. *Papillary carcinoma – follicular variant. Nuclear TTF-1 positive expression. LSAB x 200*

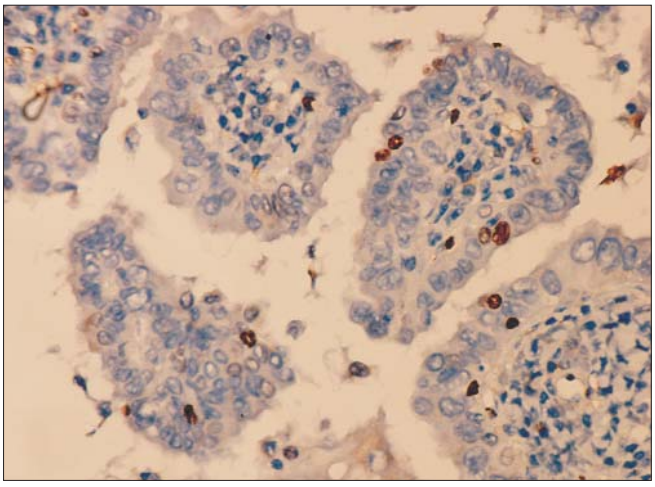


Figure 8. *Papillary carcinoma - classic variant with isolated Ki-67 positive nuclei. LSAB x 400*

Table 1. *Differences in age, TSH value, nodule volume and nodule number in cases with benign lesions (BN) versus cancer (CA)*

Parameter	Mean	SD	SE	95% LCL	95% UCL
Age (years)					
BN	50.63	12.19	1.24	48.16	53.10
CA	47	11.13	3.35	39.51	54.48
TSH (UI/mL)					
BN	1.703	1.32	0.138	1.482	1.978
CA	1.544	0.577	0.182	1.141	1.967
Nodules/patient					
BN	2.269	1.536	0.198	1.872	2.66
CA	1.636	0.684	0.203	1.183	2.089
Nodule volume (ml)					
BN	3.79	6.25	0.638	2.52	5.06
CA	6.510	7.73	2.3	1.71	11.70

The numerical parameters values in benign (BN) and malignant (CA) nodules are presented in *Table 1*. We found no significant differences regarding age (p=0.09), sex (p=1.2), thyroid functional level (p=0.02) or nodule volume (p=0.04) between benign and malign cancers when assessed with equal variance T test. When the differences were calculated by the Aspin Welch Unequal variance test, we found significant difference only in the number of nodules/patient, malignant cases having significant less nodules in the moment of reference to surgery compared with benign cases (p =0.0015).

We evaluated the different characteristics of the conventional echography in the prediction of BN or CA lesion. The data are presented in *Table 2*.

The most predictive parameters, appreciate by the Area under the diagnostic ROC curve (AUC) in descendant order were: inhomogeneity (AUC= 0.7985), dominant intranodular vessel (AUC = 0.789), absent halo sign (AUC = 0.7581), intranodular vascularization (AUC = 0.7206), nodule taller than wide (AUC = 0.712). *(Fig. 9)*

Different types of calcification alone were not predictive, had only a very high negative predictive value, and associated with low sensitivity. (*Table 2*) All types of calcifications had high NPV: microcalfication: 92.15%, round calcification: 91.08%, nonspecific calcifications: 92.23%. This values were comparable only with the NPV of intranodular vascularization (94.5% - 97.33%). Without being very sensitive, the calcifications are specific to malignancy.

US Elastography

When we assessed the clinical elastography: score 1 was found

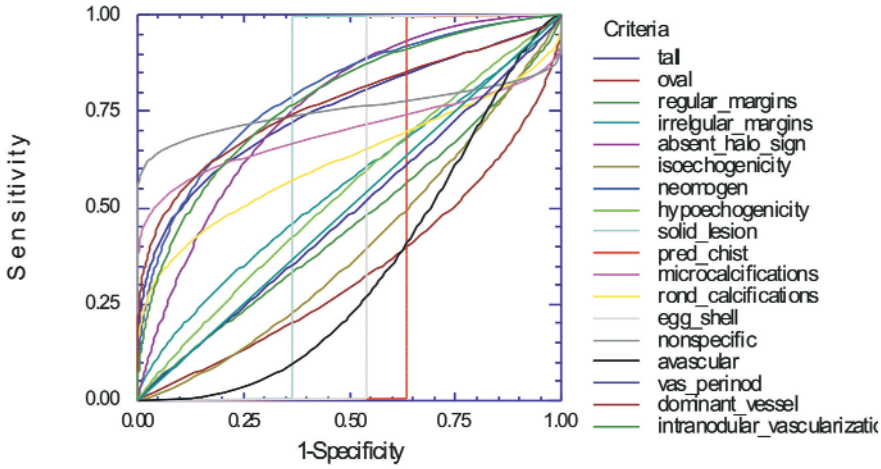


Figure 9. *Diagnostic value of US characteristics on conventional and Doppler US*

in 27 cases, all benign lesions: score 2 in 37 cases, all of the benign lesions, score 3 was described in 33 cases, 1 carcinoma and 32 benign cases, score 4 in 10 cases all carcinoma.

All cases with final benign diagnosis had a ES score below 4, while 10 out of 11 carcinoma cases had a ES score 4. The diagnostic power of each ES value was calculated for the entire group, high ES score having high diagnostic value for cancer, and low ES score having high diagnostic value for benign condition. (*Table 3)*

The predictivity of US elastography was independent from the nodule size, high sensitivity and specificity being observed also in small nodules, medium and huge nodules. (*Table 4)*

Table 2. *Predictivoty of thyroid us parameters in diagnosing carcinoma (CA) versus benign lesion (BN)*

Parameter	Detail	BN (n=96)	CA (n=11)	Sensitivity (%)	Specificity (%)
Shape	Oval	69	5	45.45	26.04
	Tall	25	6	54.54	87.5
Margins	Well defined	78	8	72.73	20.83
	Irregular	18	3	27.27	81.25
Halo sign	Present	60	2	81.82	62.50
	Absent	36	9	18.18	37.50
Echogenicity	Isoecogenicity	43	5	27.27	52.51
	Hypoecogenicity	54	6	63.63	43.75
Homogeneity	Inhomogeneity	50	8	72.72	79.16
Composition	Mostly solid	86	11	100	10.28
Calcifications	Microcalcification	1	3	27.27	72.72
	Round shape	3	2	18.18	95.28
	Egg shell	0	1	0	98.96
	Nonspecific calcifications	1	3	27.27	98.96
Vascularization	Avascular	46	1	9	67.77
	+ Perinodular	50	5	45.45	52.08
	Dominant vessel	10	6	54.55	89.58
	+ Intranodular	23	9	81.18	76.04

The only difference in the relationship ES predictivity and nodule volume, is described in the subgroup of nodules with volume less than 1 cm, were the decreased negative predictive value, in comparison with the whole study group, because there were 2 cases with cancer, one with ES =3, and one with ES of 4, that automatically generated a 50% decrease in the specificity. For a better result, we need larger study group, with more cancer cases.

In the benign group, we observed some differences regarding US and ES information and histological type of lesion. *(Fig. 10)*

We observed that hyperplastic (2.5 ± 0.552) and oxyphilic nodules (2.57 ± 0.646) are associated with higher ES score compared with follicular adenoma (1.87 ± 0.78) and anizofollicular lesions (1.68 ± 0.82): anizofolicular versus hyperplastic: T = - 3.065, p = 0.001, anizofollicular versus oxiphylic metaplasia: T = - 3.343 p=0.001, follicular adenoma versus hyperplastic: T = - 2.585, p = 0.006, follicular adenoma versus oxiphylic metaplasia: T = - 3.279 p=0.001. We did not observe any significant difference between hyperplastic adenoma and oxiphilic adenoma (T = -0.308, p=0.38).

In this particular group of cases we also observed that there were differences in the details regarding vascularization: only one out of 12 hiperplastic nodules were avascular, respectively one oxiphilic nodule was without any vascular signal in Doppler US.

Table 3. *Predictive value of us elastography in patients with histopathological diagnostic*

Score	sensitivity (%)	specificity (%)	PPV	NPV
ES 1 for benign condition	28.12	100	1.0	0.137
ES 2 for benign condition	66.66	100	1.0	0.25
ES 1-3 for benign condition	100	90.9	1.0	0.909
ES 3 for cancer	9.09	66.66	0.03	0.864
ES 4 for cancer	90.9	98.96	1.0	0.986

Table 4. Predictive value of elastography score independent on nodule volume

Size	Score	BN (n=96)	CA (n=11)	sensitivity (%)	specificity (%)	PPV	NPV
< 1 ml	1-3	33	1	100	50	0.97	1
	4	0	1	50	100	1	0.97
1-5 ml	1-3	45	0	100	100	1	1
	4	0	4	100	100	1	1
> 5 ml	1-3	18	0	100	100	1	1
	4	0	5	100	100	1	1

Discussion

Elastography is a newly developed dynamic technique that evaluates the differential tissue characteristics using a tissue rigidity/elasticity ratio = Young modulus (20). It evaluates the degree of distortion of a tissue under the application of a controlled external force, measuring differences between different tissue elasticity (21). Malignant lesions are often associated with changes in the mechanical proprieties of a tissue, and US elastography addresses this feature (16, 22). Elastography has recently been applied in the diagnostic approach to nodular thyroid disease and has shown a high sensitivity and specificity in selected patients (14, 22).

We used the monitoring of the freehand applied compression by the standardized real-time measurement on a numerical scale, provided by the US machine, which a moderate pressure of 3-4. This technique is easy to perform, need up to additional 5 minute per nodule, and minimized the artifacts generated by the applied external pressure (14, 15) and might substitute FNAB in the future (23).

All the high ES score we observed were described in cancer cases. Our results showed a high sensitivity for high ES score in cancer detection (90.9%) comparable with those described in the literature (14,20,24,25,26,27). This high sensitivity is obtained without a decrease of the specificity (24, 26,27), because the method is equally strong in detection of the benign lesions, in cases of ES between 1 and 3 (13,22,24). In this respect, we calculated high positive predictive value for ES 1-3 for benign condition (100%) and also high PPV for ES 4 for malignant lesions (100%), that is congruent with the literature results (13,14,26,27). It is important to mention that the papillary carcinoma with the ES = 3 was a big nodule, with a volume of 9.6 ml, and the carcinoma was a microcarcinoma. This might expein why the score was 3, despite the positive histopathological result.

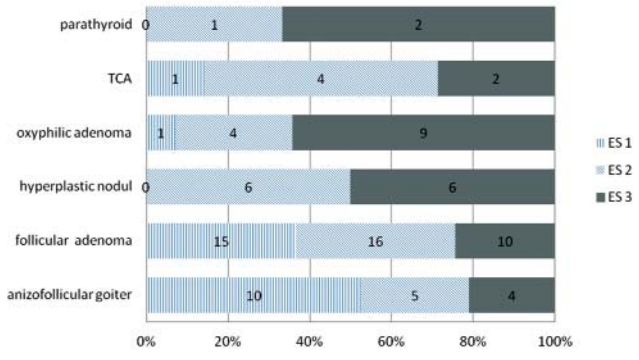


Figure 10. *ES score in the benign nodules*

The possibility to select the region of interest (ROI) for elastography studies allows a correct evaluation of small nodules.

We observed that the predictive value of US-elastographic measurement seems to be independent of nodule size, for small, medium and also large nodules, as compared with the literature (13,20). In our study, we had a difference in sensitivity and specificity of ES in detecting cancer (only 50%), but it was due do the decreased number of cases: one case with ES = 3 and one case with ES = 4). The high diagnostic value is still demonstrated by the excellent PPV (100%) NPV (975) for high elastography score (28).

Because it is known that cystic nodules and nodules shown to have a calcified shell by US are not suitable for US - elastographic evaluation (14, 20) we excluded these cases in our analysis.

The literature describes additional information offered by elastography in respect to nodule cellularity. There is a special pattern for follicular cancer (29) with a difference between the core and the periphery of the nodule, due to the difference of hypercellularity. Because we had only one case with FTC the results were inconclusive. We observed that there is a difference between ES in hyperplastic and oxiphilic adenoma and follicular or anizofollicular benign lesions, but further analysis, on a bigger study group is needed for a conclusion.

We did not observed any bilateral cancer, as described in the literature (30).

The diagnostic value of elastography excided all other conventional US diagnostic criteria. The AUC for qualitative elastography was higher (0.986) compared with any conventional US information (inhomogeneity: AUC= 0.7985, dominant intranodular vessel: AUC = 0.789, absent halo sign: AUC = 0.7581, intranodular vascularization: AUC = 0.7206, nodule taller than wide AUC = 0.712). We could perform this evaluation because of the indubitable surgical outcome with histological diagnostic (31).

The limitations of the method are: predomimant cystic lesions, were the external pressure is not transmited, and shell calcification, were there is no compressibility or the measurement is made for the shell calcification and not for the nodule cellularity (14).

In conclusion, US elastography seems to have a great potential role in stratifying suspect nodules, for FNAB indica-

tion and surgery. It also allows the study of 0.25 ml nodules, which are difficult to be punctured. Larger studies are needed for a better accuracy of the conclusions.

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