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THE EFFICIENCY OF ULTRASOUND ELASTOGRAPHY IN THE DIFFERENTIAL DIAGNOSIS OF THYROID NODULES

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Aim: **To evaluate the efficiency of ultrasound elastography (USE) in the differential diagnosis of thyroid nodules.**
Methods: **One hundred thyroid nodules in 100 patients (79 females, 21 males, age range 18-78; mean age = 45.6 years) were evaluated with real-time freehand USE, using Hitachi EUB 7500 equipment and elasticity scores were obtained. The elasticity was scored as follows: Score 1, elasticity in the entire nodule; Score 2, mainly elastic nodule with the presence of inelastic areas not constant during real time examination; Score 3, constant inelastic areas prevalently arranged at the periphery of the nodule; Score 4, constant inelastic areas prevalently arranged at the center of the nodule; Score 5, no elasticity in the nodule. Also mean strain ratio values were calculated for all nodules.**
Results: **Eighty-four (86%) of cases were benign and sixteen (16%) were malignant. Elasticity score 3 and higher and strain ratio higher than 2.485 had statistically significant relation with malignancy ($p < 0.05$).**
Conclusions: **USE including strain ratio calculations besides subjective evaluation of elasticity scores is an efficient imaging method which may contribute to the differential diagnosis of thyroid nodules.**

Key-words: Thyroid, US.

Nodular disease is the most frequent pathology of the thyroid gland and its incidence is very high in population. Among adults it is 4-8% in palpation, 10-41% in ultrasonographic evaluation and 40-60% in autopsy series (1-7). Especially in the recent years, by the extensive use of ultrasonography and high resolution devices, the frequency of the determination of thyroid nodules has increased in patients without a complaint or a palpable nodule. The majority of these nodules are benign and 7-15% are malignant (8, 9).

Different results had been reported in the studies about the efficiency of ultrasonography in the differential diagnosis of thyroid nodules. Although there are some helpful sonographic findings, none of them is able to provide the diagnosis of malignancy alone (5, 10-12). Following ultrasonography, fine needle aspiration biopsy (FNAB) is the second frequently used method in the differential diagnosis of thyroid nodules. The most of the nodules suspected as malignant in conventional ultrasonography are diagnosed as benign after FNAB or operation and this situation has created a need for a new method which can contribute to differentiate malignant nodules from benign ones and help to decrease the number of nodules undergoing these invasive procedures (13-15).

It is well known that malignant tissue is harder than normal tissues. When a malignant lesion is compressed with the ultrasound probe, it displaces more than a benign lesion. Ultrasound elastography (USE), also called as digital finger, is a relatively new method which measures the degree of strain in different tissues and demonstrates them in different colors. It also provides quantitative information for more objective evaluation.

The aim of this study is to evaluate the efficiency of USE in the differential diagnosis of thyroid nodules.

Materials and methods

In this prospective study, 100 patients with 100 thyroid nodules (79 females, 21 males, age range 18-78; mean age = 45.6 years) sent to Radiology department for ultrasound guided FNAB were evaluated with B-mode, color Doppler ultrasonography and USE, between February 2010 and April 2011. Pure cystic nodules and those with coarse calcifications were not included in the study, due to futility of USE on them. FNAB was applied to all solitary nodules, to the largest ones among multiple similar nodules and to the most suspicious ones among multiple nodules with different gray scale sonographic features.

All patients were evaluated by the same radiologist using a real-time instrument (EUB-7500 HV, Hitachi Medical Systems, Tokyo, Japan) and a 13-8 MHz linear probe in supine position. First, demographic data of the patient was recorded. Then, the nodule was examined by real-time B-mode and color Doppler ultrasonography. The number of nodules (multinodular/solitary), size, margin, echogenicity, inner structure (solid/mixed solid-cystic), presence of peripheral halo, presence of microcalcifications and vascularity of the nodule were evaluated. During this evaluation, spot B-mode images and static and dynamic color Doppler ultrasonography images were recorded digitally. After conventional ultrasonography, real-time elastography examination was performed. Probe was placed on the thyroid gland in vertical position, the slice was found in which the largest size of the nodule was seen and slight freehand pressures were applied on the gland with short intervals. The sufficiency of the compression was decided by an indicator numbered from 1 to 4 on the screen. The images with the value 3 or 4 were accepted to be sufficient for evaluation (Figs. 1 and 2). Dynamic elastography images were recorded digitally to be evaluated later on. Afterwards, strain ratio (the ratio of the strain of normal parenchyma to the strain of the nodule) was measured twice for each nodule and mean strain ratio values were calculated. During this process, both the strain of nodule and the strain of parenchyma were measured on the same image seperately and proportioned automatically (Figs. 1 and 2). Strains of parenchyme and nodule were measured by the help of ROI (region of interest) and ROI of parenchyme was tried to place on the same depth with nodule. Strain ratio measurements were done mostly on transverse images, although sagittal

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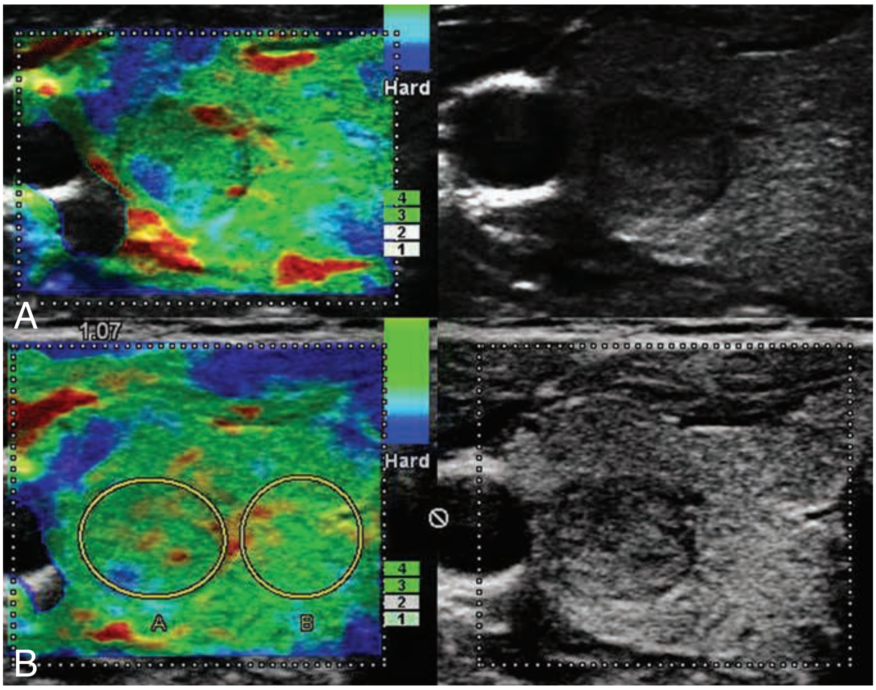

Fig. 1. — Elastogram of a completely elastic nodule with elasticity score 1 in the right thyroid lobe of a 34-year-old female patient (A). Strain ratio measurement of the nodule (B). Mean strain ratio was 1.01 and it was diagnosed as colloid nodule after surgery.

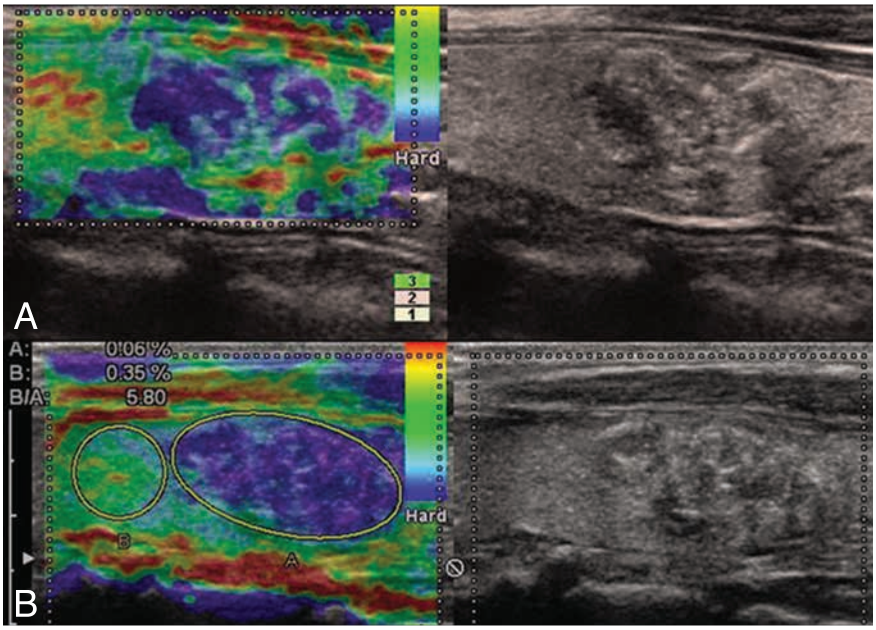

Fig. 2. — Elastogram of a mainly inelastic nodule with elasticity score 4 in the left thyroid lobe of a 20-year-old female patient (A). Strain ratio measurement of the nodule (B). Mean strain ratio was 5.43 and it was diagnosed as papillary carcinoma after surgery.

images were used in some instances due to size and placement of the nodule.

Scoring systems were constituted and used for vascularity and elasticity of nodules by the reference of literature. Vascularity was scored as follows: Score 1, no peripheral or intranodular vascularity; Score 2, there is peripheral vascularity but no intranodular vascularity; Score 3A, peripheral and slight-moderate intranodular vascularity, courses of vessels are regular; Score 3B, peripheral and slight-moderate intranodular vascularity, courses of vessels are irregular (anarchic or suddenly branching vascular structures); Score 4A, peripheral and abundant intranodular vascularity, courses of vessels are regular; Score 4B, peripheral and abundant intranodular vascularity, courses of vessels are irregular (anarchic or suddenly branching vascular structures).

Elasticity was scored as follows: Score 1, elasticity in the entire nodule; Score 2, mainly elastic nodule with the presence of inelastic areas not constant during real time examination; Score 3, constant inelastic areas prevalently arranged at the periphery of the nodule; Score 4, constant inelastic areas prevalently arranged at the center of the nodule; Score 5, no elasticity in the nodule (Fig. 3). In addition, modified TIRADS classification proposed by Russ et al. was used to classify the nodules in terms of B-mode features (Fig. 4) (16).

TIRADS categories, color Doppler ultrasonography and elastography scores of the nodules were decided by two experienced radiologists, who were blind to the histopathologic diagnosis, in consensus. Mean strain ratio of each nodule was also calculated from recorded values.

The statistical analysis of all findings was made by the programme "SPSS for WINDOWS 11.5". Chi-square, Fisher's exact and independent t tests were used for the statistical analysis and *p* values below 0,05 were accepted to be statistically significant.

Results

The largest sizes of total 100 nodules were between 5-65 mm (mean 18.71 mm). Pathologic results of 56 were obtained by cytologic examination, while 44 were obtained by histopathologic examination. Eighty-four were benign and 16 were malignant.

Seventy-seven of benign nodules were colloid nodules and 7 were follicular adenomas. All follicular adenomas were diagnosed by histopathologic evaluation, demonstrating that there was no capsular or vascular invasion. While 15 of malignant nodules were papillary carcinoma, one of them was undifferentiated thyroid carcinoma.

Mean age of patients with benign and malignant nodules were 45.84 and 44.31 respectively and there was no statistically significant difference between the two groups ($p = 0.629$) (Table I). Besides, there was no statistically significant difference between males and female patients in

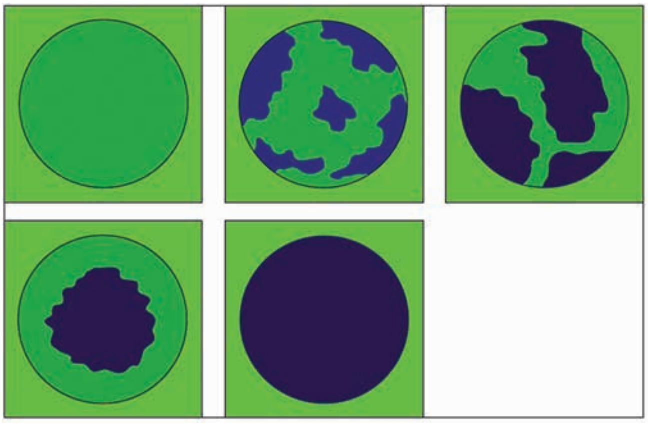

Fig. 3. — Schematic representation of the elasticity scores used. Score 1, elasticity in the entire nodule; Score 2, mainly elastic nodule with the presence of inelastic areas not constant during real time examination; Score 3, constant inelastic areas prevalently arranged at the periphery of the nodule; Score 4, constant inelastic areas prevalently arranged at the center of the nodule; Score 5, no elasticity in the nodule.

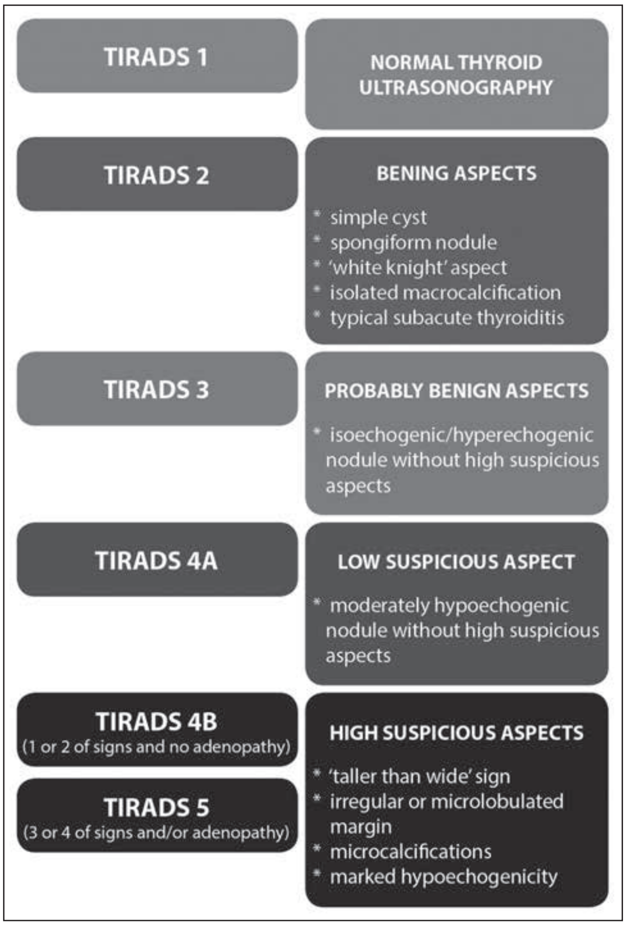

Fig. 4. — TIRADS classification algorithm (16)

terms of the number of benign and malignant nodules ($p = 0.789$) (Table I).

The means of the largest sizes of benign and malignant nodules were 18.71 and 18.69 respectively and there was also no statistically significant difference between them ($p = 0.992$) (Table I).

B-Mode and Color Doppler Ultrasonography

There was no statistically significant relation of solitary nodule, 'taller than wide' sign and solid inner structure with malignancy whereas, hypoechogenicity, blurred margin, presence of microcalcifications and absence of peripheral halo were in statistically significant relation with malignancy (Table II). There was a statistically significant relation of high TIRADS categories with malignancy ($p < 0.001$) (Table III). While irregular course of vessels was in a statistically significant relation with malignancy ($p = 0.001$), intranodular vascularity and abundant intranodular vascularity were not (Table IV).

Presence of microcalcifications was the finding with the highest sensitivity (93.7%), positive predictive value (68.2%), negative predictive value (98.7%) and accuracy (92%) among all B-mode, color Doppler ultrasonography and elastography findings (Table IV). It was also one of findings with the highest specificity together with 'taller than wide' sign (91.6%) (Table V).

Ultrasound Elastography

There was no nodule with Score 5 elasticity among benign nodules and there was only one nodule with Score 5 elasticity among malignant ones. Therefore, the nodules with Score 4 and 5 elasticity were included in the same group to make a meaningful statistical analysis. As a result of this, a statistically significant difference occurred between the groups in terms of malignancy ($p < 0.001$) (Table VI).

The mean strain ratio values of benign and malignant nodules were 1.889 and 3.334, respectively. Cut-off point for strain ratio was found 2.485 by the assistance of SPSS programme and it was seen that there was a statistically significant relation between the strain ratios higher than

Table I. — Distribution of nodules according to the age, sex and the largest size.

		Benign	Malignant	Total	*P*
Age (mean)		45.84 ± 11.13	44.31 ± 12.85	45.60 ± 11.38	0.629
Sex	Female Male	67 (79,8%) 17 (20,2%)	12 (75%) 4 (25%)	79 (79%) 21 (21%)	0.789
Largest size (mean)		18.71 ± 9.059 mm	18.69 ± 10.836 mm	18.71 ± 9.305 mm	0.992

Table II. — Distributions of the benign and malignant nodules according to B-mode ultrasonography findings and p values of the suspicious findings.

		Benign (n = 84)	Malignant (n = 16)	P
Number	Multiple Solitary	65 19	11 5	0.525
'Taller than wide' sign	Absent Present	77 7	15 1	1.00
Echogenicity	Iso-hyperechoic Hypoechoic	55 29	4 12	0.003
Margin	Regular Blurred	61 23	7 9	0.023
Peripheral halo	Present Absent	46 38	4 12	0.029
Microcalcifications	Absent Present	77 7	1 15	< 0.001
Inner structure	Mixed solid-cystic Solid	34 50	5 11	0.488

Table III. — Distribution of the nodules according to TIRADS classification.

TIRADS	Benign (n = 84)	Malignant (n = 16)	Total
3	34 (100%)	0 (0%)	34 (100%)
4A	18 (100%)	0 (0%)	18 (100%)
4B	30 (75%)	10 (25%)	40 (100%)
5	2 (25%)	6 (75%)	8 (100%)
Total	84 (84%)	16 (216%)	100 (100%)

2.485 and malignancy ($p = 0.001$) (Table VII).

Discussion

Palpation is the oldest method in the evaluation of tissue stiffness and it has been used in medicine since Ancient Egypt. It is currently used in physical examination of breast, thyroid and liver. However, evaluation of stiffness by palpation is subjective and insufficient in detection of all mass lesions (17, 18). This fact has lead researchers to look for new techniques to evaluate the stiffness of pathologic tissues.

Elastography is an imaging technique that measures strain responses of tissues against compressive forces applied on them (19, 20). USE was first used in experimental media in the 80s by Ophir et al. It has been commonly used in imaging field for last 10 years, as a result of developments in computer and ultrasound technologies. In previous studies, it has been reported that USE could be used in differential diagnosis of breast and prostate gland disorders (21-24). Like other US techniques, it is cheap, real-time, noninvasive, easy to access and applicate. Also, it does not include ionizing radiation. As a result of all these advantages, USE is gaining popularity in imaging and differential diagnosis of thyroid nodules.

In this study, while hypoechogenicity, blurred margin, absence of halo, microcalcifications and irregular course of vessels were in statistically significant relation with malignancy; sex, number of nodules, 'taller than wide' sign, inner structure, intranodular vascularity and abundant vascularity were not. Presence of microcalcifications was the finding with the highest sensitivity, specificity (together with 'taller than wide' sign), positive predictive value, negative predictive value and accuracy among all B-mode, color Doppler ultrasonography and elastography findings, so it was considered to be enough for the diagnosis of malignancy alone. B-mode and color Doppler ultrasonography findings of this study were also compatible with the literature. While all of the nodules categorized in TIRADS 3 and 4A were benign, six of eight TIRADS 5 nodules were malignant. According to this result, by using modified TIRADS classification proposed by Russ et al., it could be stated that the nodules categorized in TIRADS 3 and 4A are probably benign and malignancy risk is considerably low, and the nodules categorized in TIRADS 5 are probably malignant. Therefore, FNAB or surgery should definitely be recommended for TIRADS 5 nodules, while there's no need for TIRADS 3 and 4A. The nodules categorized in TIRADS 4B could be thought as moderately suspicious and FNAB or follow-up could be recommended. Unfortunately, there hasn't been any TIRADS classification established yet like BI-RADS and all TIRADS classifications are in study phase (16, 25-30). In this study, due to its incomplexity and practicality in usage of all sonographers, modified TIRADS classification proposed by Russ et al. was prefered.

In a similar research on USE, B-mode and color Doppler ultrasonography, Rago et al. reported that high elasticity score, being the finding with the highest sensitivity and spesificity, was in statistically significant relation with malignancy (31). In another study, Rago et al. reported a statistically significant relation be-

Table IV. — Distributions of nodules according to vascularity patterns and p values of the suspicious findings.

		Benign	Malignant	P
Intranodular vascularity	Score 2	4	2	0.174
	Score 3A + 3B +4A + 4B	79	12	
Abundant intranodular vascularity	Score 3A + 3B	50	11	0.051
	Score 4A + 4B	29	1	
Irregular course of vessels	Score 3A + 4A	61	5	0.01
	Score 3B + 4B	18	7	

Table V. — Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of all findings.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Solitary nodule	31.2%	77.4%	20.8%	85.5%	70%
'Taller than wide' sign	6.2%	91.6%	12.5%	83.7%	88%
Hypoechogenicity	75%	65.5%	29.3%	93.2%	67%
Blurred margin	56.2%	72.6%	28.1%	89.7%	70%
Absence of halo	75%	54.7%	24%	92%	58%
Microcalcifications	93.7%	91.6%	68.2%	98.7%	92%
Solid iner structure	68.7%	40.5%	18%	87.2%	45%
Intranodular vascularity	75%	6%	13.2%	55.5%	17%
Abundant vascularity	6.2%	65.5%	3.3%	78%	56%
Irregular course of vessels	43.7%	78.6%	28%	88%	73%
TIRADS ≥ 4B	100%	62%	33%	100%	68%
Strain ratio > 2,485	56.2%	85.7%	42.8%	91.1%	81%
Elasticity score ≥ 3	75%	81%	42.8%	94.4%	80%

Table VI. — Distribution of the nodules according to elasticity scores.

Elasticity score	Benign (n = 84)	Malignant (n = 16)	Total
1	21 (100%)	0 (0%)	21 (100%)
2	47 (92.2%)	4 (7.8%)	51 (100%)
3	12 (75%)	4 (25%)	16 (100%)
4 + 5	4 (33.3%)	8 (66.7%)	12 (100%)
Total	84 (84%)	16 (216%)	100 (100%)

tween low elasticity score and benignity (32). Similarly, in some other studies related to USE, high sensitivity and specificity values were reported related to high elasticity scores and malignancy (33-36).

In addition to these, Ning et al. reported that strain ratio values higher than 4.2 was in statistically significant relation with malignancy, in the study including both strain ratio and elasticity score (36). Moreover, in another study Lyshchic et al. reported a statistically significant relation between the strain ratio higher than 4 and malignancy.

In this study, it was found that there were significant contributions of both real-time examination and strain ratio measurements to the differential diagnosis of thyroid nodules (37). Following the presence of microcalcifications, the other acceptable values of sensitivity, specificity and accuracy were belonged to the elasticity score 3 and higher. Irregular course of vessels and some of other gray scale findings were also in statistically significant relation with malignancy. But, it's obvious that they are not sufficient alone in the diagnosis of malignancy due to their low sensitivity and specificity values. However, real-time elastography seems as a valuable method in the differential diagnosis of thyroid nodules, not alone but together with conventional ultrasonography. According to this study, it could be reasonable to categorize nodules with elasticity score 1 or 2 as probably benign, 3 as moderately suspicious and 4 or 5 as probably malignant and this categorization may be a useful guide for FNAB. As an example, recommending follow-up may be appropriate for nodules with score 1 or 2, and FNAB for nodules with score 3, 4 or 5. In this study, 68 of 72 nodules with elasticity score 1 and 2 were benign, and it was possible to avoid from biopsies for 68% of all patients by using only this scoring.

2.485 was determined as cut-off point of the strain ratio. Although, the strain ratio higher than 2.485 is in

Table VII. — Mean strain ratio values of nodules and distribution of the nodules according to the cut-off point.

	Benign (n = 84)	Malignant (n = 16)	Total
Mean strain ratio	1.889 ± 1.338	3.334 ± 2.703	2.120 ± 1.7
< 2.485	72 (91.1%)	7 (8.9%)	79 (100%)
> 2.485	12 (57.1%)	9 (42.9%)	21 (100%)
Total	84 (84%)	16 (16%)	100 (100%)

statistically significant relation with malignancy ($p = 0.001$), it stays behind the real-time examination due to its low sensitivity (56.2%). It is also lower than the values found in previous studies. It is thought that this is a result of our insufficiency in measuring the strain ratio from correct elastograms reflecting the real strain of the nodules. Hopefully this problem will disappear with the increase of USE experience. This will be possible with more and wide-ranging studies and with the addition of elastography in routine thyroid ultrasonography examinations.

Different scoring systems have been used in the studies related to USE (31-36). In some of these, the scoring system of Ueno and Ito was used for thyroid nodules (31, 32). In this system, inelasticity of tissue around the nodule was also added as criteria. But this criterion represents the desmoplastic reaction seen in breast cancer and it's not necessary and appropriate for the evaluation of thyroid nodules. Moreover, in our experience on real-time examination, we also observed alterations in color codes as a result of serial compression and decompression movements. Because of this, the consistency of inelastic areas throughout the examination was added as criteria in our scorring system. This observation also showed that the strain ratio which could only be measured from spot images, is not sufficient alone due to its higher error margin. Therefore it was seen that the real-time examination is essential in both studies and clinical practice.

Real-time examination is operator dependent and this is its most important limitation. This situation creates a need for a new method presenting quantitative data. The most commonly used value for this aim is the strain ratio, as used in this study. Measuring the strain ratio from images reflecting the real-time examination, making multiple measurements, comparing them with each other and having coherent results are focus points of a correct strain ratio measurement.

Including both real-time examination and strain ratio measurement is the superiority of this study when compared to others. Also, B-mode and color Doppler ultrasonography examinations made it possible to compare efficiencies of USE and conventional ultrasonography.

There were 86 benign (86%) and 16 malignant (16%) thyroid nodules in this study. It seems that the number of the malignant nodules is low compared to whole. In fact, the ratio of malignancies in this study is similar to the ratio in the population (7-15%) (8, 9). All of the malignant nodules except one were papillary carcinoma and this can be considered as a handicap for this study. Due to the fact that the papiller carcinoma is the most common type of thyroid cancers (75-85%), this situation is not suprising. We hope that it will be possible to eliminate this limitation by the help of wide-range studies with wider histopathologic profile.

Conclusion

USE should be considered as an imaging technique to be used in combination with conventional ultrasonography, rather than a magic wand diagnosing malignancy alone. B-mode ultrasonography is unquestionably the most important imaging modality in the differential diagnosis of thyroid nodules. The presence of microcalcifications with the highest sensitivity, specificity and accuracy in this study shows the efficiency of B-mode ultrasonography once again. However radiologists sometimes encounter with confusing cases and this situation is not rare. At this point, USE may play a significant role in the evaluation of the nodules that could not be differentiated by conventional ultrasonography alone. To sum up, USE when combined with strain ratio calculations is a promising ultrasound technique that may contribute to the differential diagnosis of thyroid nodules.

Ethical consideration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

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