Contribution of Ultrasound Strain Elastography to the Differentiation of Benign and Malignant Thyroid Lesions: Randomized Controlled Study

Ultrason Strain-elastografi Tetkikinin Tiroid Nodülleri Benign-Malign Ayrımına Katkısı: Randomize Kontrollü Çalışma

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ABSTRACT

Objective: We aimed to investigate the contribution of strain elastosonography to the distinction of benign and malignant thyroid nodules.

Materials and Methods: The retrospective study included 135 patients who were detected with thyroid nodules on ultrasonography and then underwent fine-needle aspiration biopsy (FNAB). Semi-quantitative strain elastographic evaluation was performed and mean strain ratio was calculated for each nodule. The elastograms were classified using the Tsukuba five-pattern visual scoring system. Accordingly, the lesions with scores 1 and 2 were accepted as soft nodules (benign), score 3 as moderately hard nodules, and scores 4 and 5 as hard nodules (malignant). The nodules were divided as benign and malignant depending on the histopathological results. The FNAB results were compared with elasticity scores.

Results: The patients included 18 (13.3%) men and 117 (86.7%) women. Of the 135 lesions, 113 (83.7%) were benign and 22 (16.3%) were malignant. Strain ratio value was statistically higher in malignant lesions compared to benign lesions (*p*<0.01). When compared with the histopathological results, elastosonography scoring had a sensitivity of 81.8%, specificity of 89.4%, positive predictive value (PPV) of 96.2%, and negative predictive value (NPV) of 64.7%. However, compared with the strain ratio values, elastosonography scoring had a sensitivity of 77.3%, specificity of 87.6%, PPV of 95.2%, and NPV of 54.8% at a cutoff point of 4.850.

Conclusion: Elastosonography is highly effective in the differentiation of benign and malignant lesions.

Key Words: Ultrasound elastography, strain elastography, thyroid nodule

ÖZET

Amaç: Bu çalışmamızda strain elastografi ultrason incelemenin tiroit nodüllerinin benign/malign ayrımına katkısını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamıza ultrasonografi ile tiroit nodülü saptanmış ve sonrasında ince-iğne aspirasyon-biyopsisi (İİAB) yapılan 135 hasta dahil edildi. Tüm nodüllerin semi-kantitatif strain-elastografik değerlendirmesi yapıldı, ortalama strain ratio oranları hesaplandı. Olgular beş kademeli Tsukuba skorlamasına göre değerlendirilerek skorlara ayrıldı. Skor 1 ve 2 yumuşak nodül (benign), skor 3 orta sertlikte (genellikle benign) ve skor 4 ve 5 sert nodül (malign) olarak sınıflandırıldı. Ayrıca nodüllerin İİAB histopatolojik sonuçları benign ve malign olarak sınıflandırıldı ve İİAB ile elastografi sonucları karşılaştırıldı.

Bulgular: Hastaların 18'i erkek, 117'si kadın idi. Lezyonların patolojik incelemesinde 113 nodül benign iken 22'si malign (%17,5) idi. Malign patolojilerde strain-ratio değeri istatiksel anlamlı olarak benign patolojilerden daha yüksek bulundu (p<0,01). Lezyonların elastografik skorlama sonuçları histopatolojik bulgular ile karşılaştırıldığında sensivitesi (%81,8), spesivisitesi (%89,4), pozitif prediktif değeri (%96,2), negatif prediktif değeri (%64,7) olarak hesaplandı. Strain değerlerine göre malign –benign ayrımı için ROC analizi yapıldığında kesim değeri 4,850 alındığında; sensitivite %77,3, spesifite %87,6, pozitif prediktif değeri %95,2 ve negatif prediktif değeri %54,8 bulundu.

Sonuç: Elastografi skorları ve strain-ratio hesaplamaları da dahil olmak üzere ultrason elastografi tetkiki tiroid nodüllerinin benign-malign ayrımına katkıda bulunabilecek etkili bir görüntüleme yöntemidir

Anahtar Kelimeler: Ultrason elastografi, strain elastografi, tiroid nodülü

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Introduction

Thyroid nodules have been reported in 33% of individuals aged 18-65 years and in 50% of individuals aged over 65 years (1,2). Although most of these nodules are of benign character, the prevalence of malignancy has been reported as 5-15% (3). Thyroid function tests, scintigraphy, and ultrasonography (USG) provide valuable information on malignancy; however, they fail to discriminate benign and malignant lesions. In accordance with the American Thyroid Association Guidelines, no single ultrasonographic method or combinations of methods is efficiently sensitive or specific to detect all malignant nodules (4,5). Therefore, fine-needle aspiration biopsy (FNAB) is essential for the nodules larger than 10 mm in size and those with doubtful ultrasonographic features (5). FNAB has been shown to be the most credible preoperative diagnostic technique in the detection of malignant thyroid nodules with a sensitivity and specificity of 65-98% and 72-100%, respectively (6-9).

Elastography is a novel USG-based diagnostic method used for the assessment of tissue elasticity based on external tissue compression. Strain elastography aims at presenting information about the stiffness of the soft tissue surrounding the hard tissue subjected to mechanical pressure through the assessment of the displacement of tissue on the longitudinal plane. Benign thyroid nodules are 1.7 times and the malignant nodules are 5 times stiffer than normal tissue (9). In this study, we aimed to investigate the effectivity of strain elastography in the differentiation of benign and malignant thyroid nodules.

Materials and Methods

The retrospective study comprised 135 patients including 18 (13.3%) men and 117 (86.7%) women with a mean age of 45.6 (range, 18-78) years. All the patients were evaluated by B-mode USG followed by strain elastography prior to FNAB procedure. The nodules with a cystic component and rough calcification were excluded from the study.

The study was confirmed by Van District Training and Research Hospital Nonpharmacological Trials Ethics Committee. An informed consent was obtained from each patient.

B-mode ultrasonography and strain elastography were performed at a single session by an experienced radiologist using Toshiba Aplio 500 Ultrasound System (Toshiba Medical System) with 7-12 MHz linear transducers. Prior to the procedure, the patient was placed in the supine position. After the centralization of the lesion, rhythmic compression-decompression maneuvers were performed with the transducer perpendicular to the skin, lesion, and neck. The elastograms obtained before and after compression were graded using the Tsukuba five-pattern visual scoring system (Table 1). In this scoring system, scores 1 and 2 indicate a soft nodule (benign), score 3 indicates a moderately hard nodule (Figure 1), and scores 4 and 5 indicate a hard nodule (Figure 2).

Fine-needle aspiration biopsy (FNAB) was implemented with a 21-gauge needle attached to a 10-cc syringe under USG guidance. The smears were fixed in 95% ethyl alcohol and then stained

Table 1. Tsukuba scoring in thyroid nodules.

TSUKUBA SCORES	Strain Elastography Features	Macroscopic/Histopathological Features
SCORE 1	Mostly green-coded lesions with equal elasticity with the surrounding tissue	Soft nodule (benign)
SCORE 2	Lesions with nonhomogeneous elasticity and blue-green areas	Soft nodule (benign)
SCORE 3	Lesions coded in blue in the center and green in the surrounding areas	Moderately hard (mostly benign)
SCORE 4	Completely blue lesions with no echogenic halo in the surrounding tissue	Hard nodule (malignant)
SCORE 5	Completely blue lesions with an echogenic halo in the surrounding tissue (loss of elasticity in the surrounding tissue)	Hard nodule (malignant)
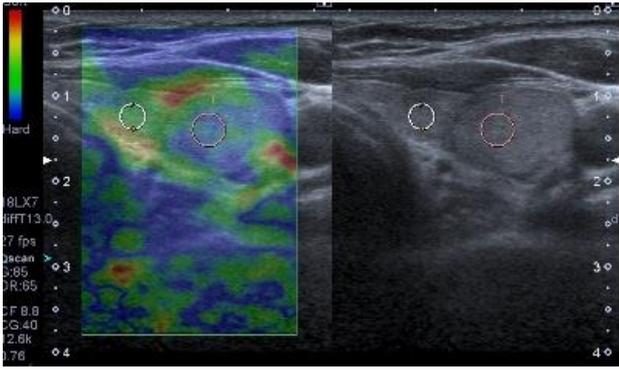
Fig. 1. Real-time ultrasound elastography image reveals elasticity score of 3.
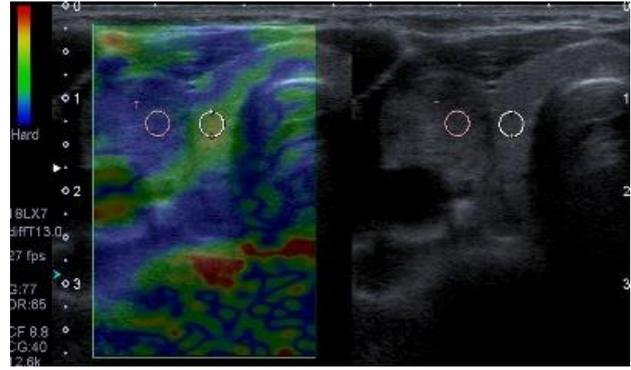
Fig. 2. Real-time ultrasound elastography image reveals elasticity score of 4.

Table 2. Distribution of Types Nodules According to Elastosonography Scores and Final Histopathological Diagnosis

Score	Benign	Malignant	Total
1	33 (29.2)	0 (0)	33
2	29 (25.7)	0 (0)	29
3	39 (34.5)	4 (18.2)	43
4	12 (10.6)	18 81.8	30
Total	113	22	135

with hematoxylin-eosin for pathological assessment. The procedure was repeated in the cases with insufficient material and suspicious results. The lesions were classified as benign and malignant depending on the histopathological results. The FNAB results were compared with the elasticity scores.

Statistical Analysis: Data were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Frequency tables were obtained for the elasticity scores and descriptive statistics were obtained for patient age, strain ratio value, and lesion size. Differences in mean strain ratio values between the benign and malignant lesions were determined using independent samples t-test. Sensitivity and specificity of the elastosonography scoring in the distinction of benign and malignant lesions were calculated. A Receiver Operating Characteristic (ROC) data analysis was implemented to calculate the area under the curve (AUC).

Results

The study comprised 135 patients that presented to our radiology unit with a thyroid nodule, including 18 (13.3%) men and 117 (86.7%) women. The nodule was localized in the left lobule in 73 (54.1%) and in the right lobule in 62 (45.9%) patients. Depending on the pathological results, 113 (83.7%) lesions were classified as benign and 22 (16.3%) as malignant and arithmetic mean values were calculated for patient age, strain ratio value, and lesion size. Mean age was 40.24 years in patients with a benign lesion and 42.38 years in patients with a malignant lesion. Mean lesion size was 16 mm (2-34, 6) in benign lesions and 15 mm (10-28, 18) in malignant lesions. Depending on the elasticity scores, the lesions were classified as follows: elasto-1 33 (29.2%), elasto-2 29 (25.7%), elasto-3 benign 39 (34.5%), elasto-3 malignant 4 (18.2%), elasto-4 benign 12 (10.6%), elasto-4 malignant 18 (81.8%), and elasto-5 0 (0%) (Table 2). Mean strain ratio value was 3.12 in benign lesions and 5.88 in malignant lesions. In the independent-samples t-test, no major distinction was found between benign and malignant nodules with regards to mean strain ratio value ($p<0.01$). Table 3 presents the distribution of benign and malignant lesions and the sensitivity and specificity of elastography scoring in the distinction of benign and malignant lesions. As shown in Table 3, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of elastosonography scoring were 81.8%, 89.4%, 96.2%, and 64.7%, respectively. Table 4 presents the sensitivity and specificity of elastography index in the distinction of benign and malignant lesions. As seen in the table, the best cutoff point for malignant lesions was 4.850 in the ROC analysis (Figure 3). At this cutoff point, the sensitivity and specificity of sonoelastography were 95.7% and 86.7%, respectively. In the ROC analysis, the AUC was 0.994 (95% CI, 0.983-1, $p<0.001$) (Table 5). At the cutoff point of 4.850, the PPV and NPV of strain ratio values were 99.0% and 59.5%, respectively. Strain ratio value was statistically higher in malignant lesions in comparison with benign lesions ($p<0.01$).

Table 3. Sensitivity and Specificity of Elastosonography Scoring for Distinguishing Malignancy

Score	Benign	Malignant	SN (%)	SP (%)	PPV (%)	NPV (%)
1-3	101	4	81.8	89.4	96.2	64.7
4	12	18				
Total	113	22				

Table 4. Sensitivity and Specificity of Elastosonography İndex for Distinguishing Malignancy

Index	Benign	Malignant	SN (%)	SP (%)	PPV (%)	NPV (%)
0- 4.850	99	5	77.3	87.6	99.0	59.5
4.851-7.90	14	17				
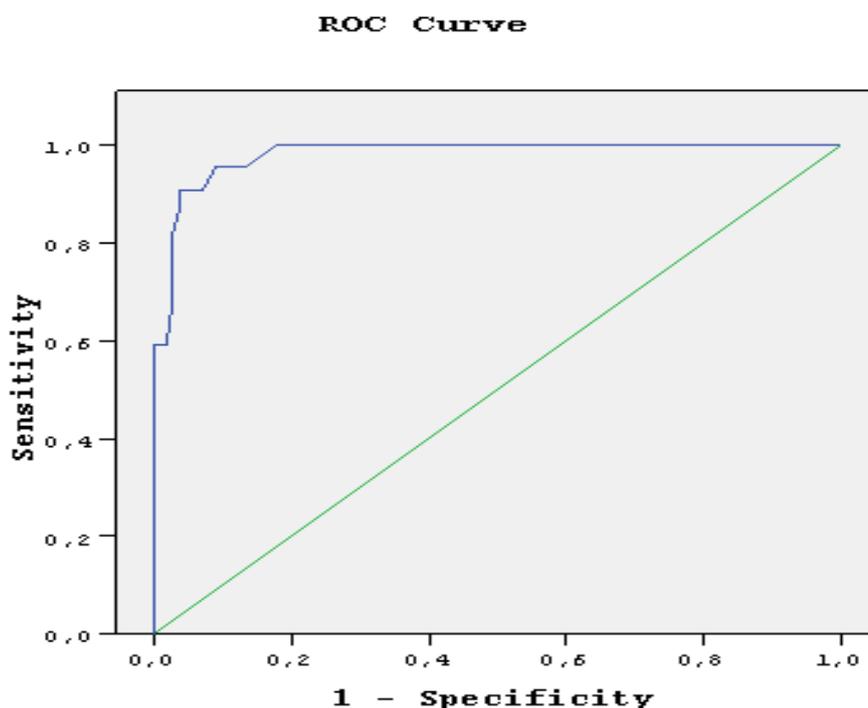
Fig. 3. ROC curve of strain index for distinguishing for malignant from benign nodules.

Tablo 5. AUC of Elastography Scoring and Index

AUC (%)	p	95% confidence interval for AUC
98.1	0.000001	[0.961-1.001]

Discussion

Typical sonographic features of thyroid nodules reported as being suggestive of malignancy include marked hypoechogenicity, nonuniform borders, presence of microcalcifications, a ratio of the lateral to the anterior-posterior diameter of higher than 1 cm, and intranodular vascularity. However, these features usually are not efficiently sensitive or specific to detect all malignant nodules; therefore, FNAB is required in most cases (4). USG has become a popular procedure in the assessment of thyroid nodules. Moreover, the accuracy of USG in the detection of thyroid nodules has become further improved due to the emergence of high-resolution USG devices with high-frequency transducers. As a result of these technological advancements, researchers can obtain better results in the diagnosis of malignant thyroid nodules. Nevertheless, conventional USG does not provide data about the hardness of the nodules. Elastography is a lately advanced technique that allows the evaluation of tissue elasticity (10). This technique is a USG-based technology that provides information on the risk of malignancy by assessing the stiffness of the

lesion (11,12). Moreover, it is also used for evaluating the mechanical and elastic features of the soft tissue. Pathological changes lead to structure alteration in the lesion, thereby resulting in modification of the elastic features of the tissue. Malignant thyroid nodules, particularly papillary carcinoma, tend to be harder than benign nodules (8). In our study, papillary carcinoma was the most common malignant nodule and both the elastography scores and the strain ratio index were importantly higher in malignant nodules than in benign nodules. However, literature shows that increased stiffness may not be present in all malignant tumors and some benign nodules can have high elasticity scores since the fibrosis within both benign and malignant nodules can rise hardness (9). Similarly, in our study, 4 cases of papillary carcinoma had an elasticity score of 3 and a lesion that was diagnosed as follicular adenoma on FNAB had a score of 4.

Rago et al. (13) evaluated 92 cases and reported the sensitivity and specificity of elastography as 97% and 100%, respectively. However, the authors indicated that they obtained these high rates since the study group comprised a select population with cytological suspicion or large nodular size. Similarly, Lyshchik et al. (14) assessed 52 patients with thyroid nodules and reported the sensitivity and specificity of elastography as 82% and 96%, respectively. In that study as well, the study group comprised a select population, most of whom had malignant nodules. Similarly, in our study, the sensitivity and specificity of elastosonography were consistent with those in the literature. In addition, the cutoff point for the elastography scores and the strain ratio values in the distinction of benign and malignant nodules was relatively high, which could also be attributed to the select population in our study.

Strain ratio has been evaluated in numerous studies in the literature. However, none of these studies have reported on a standard cutoff point for the distinction of benign and malignant nodules (15). In one study, a cutoff point of 4.22 resulted in a sensitivity of 81.8%, specificity of 82.9%, and accuracy of 88% (16), whereas 3.79 was the best cutoff point in another study, with a sensitivity of 97.8% and specificity of 85.7% (17). In addition, cutoff points as low as 1.5 and as high as 5 have been suggested in the literature. In our study, the cutoff point of 4.850 yielded a sensitivity of 95.7% and specificity of 86.7%.

Literature shows that the nodules with calcifications and those localized in the isthmus have been either excluded from some studies (18) or included into some other studies (19). In our study, these nodules were excluded from the study.

Unlütürk et al. (20) suggested that elastography is not superior to grey-scale USG in the prediction of malignancy in thyroid nodules. However, our results indicated that both elastography and strain ratio value are valuable techniques in the detection of malignancy in thyroid nodules.

Our study was limited in several ways. First, sonoelastography is a user-dependent method. Second, the internal features of the lesions shown on sonoelastography (calcification, fibrosis, pure cyst) may lead to misleading evaluations and pitfalls. For this reason, we did not include calcified and pure cystic nodules in our study. Another limitation is that the compression maneuvers performed with the transducer may result in deceptively extreme rigidity, particularly in superficial tissues such as thyroid nodules (21). Therefore, in our study, we performed minimal pressure on the lesions before initiating the palpation cycle. The final limitation could be that we did not use non-user-dependent methods such as shear wave elastography and Acoustic Radiation Force Impulse (ARFI) imaging. However, recent studies indicate that there is no significant difference between elastosonography and these two techniques in terms of sensitivity, specificity, and accuracy (22).

In conclusion, elastosonography is highly effective in the distinction of benign and malignant lesions. Moreover, it can be used as a complementary technique for grey-scale ultrasonography and may reduce the need for fine-needle aspiration biopsy.

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