Examining the Contribution of Elasticity Score and Strain Ratio to the Diagnosis and Evaluation of Malignant and Benign Thyroid Nodules

Malign ve Benign Tiroid Nodüllerinin Değerlendirilmesinde Strain Ratio ve Elastisite Skorunun Tanıya Katkısının Araştırılması

Leyla KARACA,[a]
Mecit KANTARCI,[a]
Suat EREN,[a]
Recep SADE,[a]
Hayri OĞUL,[a]
Veysel EŞDUR,[a]
Fatih ERGÜN,[a]
Habib BİLEN[b]

Departments of
[a]Radiology,
[b]Endocrinology and Metabolic Diseases,
Atatürk University Faculty of Medicine,
Erzurum

Geliş Tarihi/*Received:* 03.04.2016
Kabul Tarihi/*Accepted:* 24.11.2016

Yazışma Adresi/*Correspondence:*
Leyla KARACA
Atatürk University Faculty of Medicine,
Department of Radiology, Erzurum,
TURKEY/TÜRKİYE
karacaleyla4@gmail.com

ABSTRACT Objective: Elastography is a novel imaging modality that has been used for characterisation of thyroid nodules in recent years. The purpose of our study is to examine the contribution of real time elastography and the strain ratio in thyroid nodules to the evaluation of malignant and benign lesions. **Material and Methods:** A total of 210 prospective patients who had thyroid nodules were included in our study between February 2014 and February 2015, and a total of 234 nodules were evaluated. These patients received histopathological diagnoses through either surgery or fine needle aspiration cytology. The elasticity score defined by Itoh et al. was used for elasticity evaluation. Patients were also evaluated using strain ratio. **Results:** Twenty-nine nodules were diagnosis as pathologically malignant, among which nine were evaluated as follicular neoplasms, and 20 were evaluated as papillary carcinomas. The elasticity score was significantly higher for predicting nodule malignancy ($p<0.05$). The strain ratio was found to be significantly higher in malignant nodules than in benign nodules ($p<0.001$). ROC analysis revealed a cut- off strain ratio of 3.4 for benign and malignant nodules (AUC: 0.903). **Conclusion:** Both the elasticity score and strain ratio are beneficial parameters in detecting malignant thyroid nodules, and they contribute to the diagnosis process. Further studies to should be conducted with more patients so as to increase the reliability of strain ratio.

Key Words: Thyroid nodule; elasticity imaging techniques

ÖZET Amaç: Elastografi son yıllarda tiroid nodüllerinin karakterizasyonunda kullanılmaya başlayan yeni bir görüntüleme modalitesidir. Çalışmamızın amacı tiroid nodüllerinde strain ratio ve real time elastografinin malign ve benign lezyonları değerlendirmede katkısını araştırmaktır. **Gereç ve Yöntemler:** Şubat 2014 ve Şubat 2015 tarihleri arasında tiroid nodülü olan prospektif 210 hasta çalışmamıza dahil edilmiştir. Toplam 234 nodül değerlendirilmiştir. Bu hastalar ya cerrahi ile ya da ince iğne aspirasyon biopsisi ile histopatolojik tanı almıştır. Itoh ve ark. tarafından tanımlanan elastisite skoru ile elastisiteleri belirlenen hastalar aynı zamanda strain ratio ile de değerlendirilmiştir. **Bulgular:** Nodüllerin 29 tanesi malign patoloji tanısı aldı. Bunlardan 9 tanesi folliküler neoplazm 20 tanesi papiller karsinom olarak değerlendirildi. Elastisite skoru maling nodüllerin tespitinde anlamlı derecede yüksek saptandı ($p<0,05$). Strain ratıo malign nodüllerde benign nodüllere göre anlamlı olarak yüksek saptandı ($p<0,001$). ROC analizinde malign ve benign tiroid nodülleri için cut off değeri 3,4 olarak bulundu (AUC: 0,903). **Sonuç:** Hem elastisite skoru hem de strain ratio malign tiroid nodüllerinin tespitinde yararlı ve tanıya katkı sağlayan parametrelerdir. Daha geniş hasta sayıları ile yapılacak çalışmalar strain ratio'nun güvenilirliğini arttıracaktır.

Anahtar Kelimeler: Tiroid nodülü; elastisite görüntüleme teknikleri

doi: 10.5336/medsci.2016-51629

Turkiye Klinikleri J Med Sci 2016;36(4):185-92

Elastography is an imaging technique that measures the elasticity and stiffness of tissues. Several studies have revealed that malignant tissues are nearly 10 times stiffer than benign tissues. Thyroid nodules are frequently observed in the clinic. Although a majority of thyroid nodules are benign, almost nearly 5%-15% are malignant.[1,2]

Fine needle aspiration cytology (FNAC) has been accepted as the gold standard for evaluating thyroid nodules. However, there are some drawbacks such as the intervention in small nodules being challenging and the repetition with certain intervals. Grayscale ultrasound has been used for the evaluation of thyroid nodules for several years. Hypoechogenicity, irregular border, micro-calcification, increase in blood build-up and absence of halo in grayscale are the findings that make us consider malignancy.[3,4] However, in some cases, malignancy can occur in the absence of these findings or in the presence of some of them. This situation led to an increase in the use of elastography. Ultrasound elastography is an imaging technique that measures the elasticity capacity of a tissue. It was first introduced into use in 1991. Benign lesions are observed as being more elastic than the surrounding tissue, and malignant tissues are observed as being decreased in terms of elasticity capacity when compared with the surrounding tissues.[5] Based on this logic, the tissues are tightened and loosened with the ultrasound probe, and information on the elasticity of the tissues is obtained. In elastography, the color scale, which is called the elasticity score, is used to evaluate the nodules. Over time, quantitative parameters that measure the elasticity of the tissue were put to use, in addition to the qualitative parameter that measures the elasticity. The strain ratio (SR) presents a semi-quantitative measurement that gives the stiffness level of the tissue when compared with the normal tissue. The purpose of this study is to evaluate the contribution of the elasticity score and strain ratio that are used in ultrasound elastography approaches in thyroid nodules for diagnosis and to define a mean strain ratio cut- off point.

MATERIAL AND METHODS

PATIENTS

The study protocol was approved by the Ethical Board of our hospital, and all patients were informed about the examinations and the procedure, and their written consents were received.

A total 210 patients who attended the radiology clinic for thyroid biopsy between February 2014 and February 2015 were evaluated, and a total of 234 nodules were evaluated. Two nodules in 24 patients were examined. Forty- one of these patients received diagnosis with surgery, and the remaining were diagnosed using FNAC. Before the biopsy, both grayscale ultrasound evaluation and elastography examination were performed for all of the patients in one session by a radiologist who was experienced in ultrasonography and elastography. The elastography examination was performed with by using 14- Mhz probe. The patient was laid in the supine position. First, the nodules were evaluated in terms of grayscale findings (calcification, existence of halo, internal blood build-up and hypoechogenity), but the grayscale findings were not used in this study. The colour map was obtained by applying four or five compressions and decompressions after at least four waves, which were obtained in a position where the nodule to be examined was in the centre of the probe. The waves were similar to each other or had co-amplitudes. The elasticity score defined by Itoh et al. was used for elasticity evaluation (Figure 1).[6]

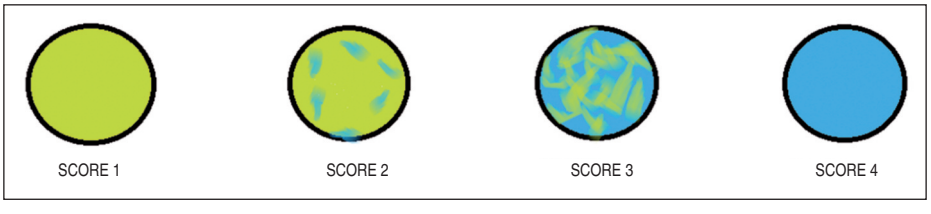


FIGURE 1: Elastography colour Doppler score according to Itoh et al.

Score 1: The nodules are homogenously green.

Score 2: The central part of the nodule is green, and the periphery is blue.

Score 3: The vision is green and blue colours are observed mixed.

Score 4: Completely blue nodules.

The strain ratio and elasticity score were evaluated. A 1.5 cm target region of interest (ROI) was centered on the thyroid nodule for evaluation. As the reference ROI, another ROI of the same size was placed in the normal thyroid tissue, and the distance was specifically at the same distance to the skin with the selected thyroid nodule.

By placing the cursor to the starting point of the compression wave, the device calculated the strain ratio automatically. Each nodule whose elasticity score and strain ratio were measured was diagnosed histopathologically.

Nodules with more than 20% calcification and cystic areas, nodules that did not have sufficient normal thyroid tissue around the target nodule, and those that were neighboring the trachea at the isthmus level were not included in the examination. In addition, patients who had relapse thyroid nodules and were operated earlier, patients whose FNAC results were insufficient and those with an indeterminate-type thyroid pathology were not included in the study.

The results of the cases were classified as benign and malignant, and the obtained strain ratios and elasticity scores were compared. The 210 patients included in the evaluation comprised 174 (82.8%) females and 36 males (17.1%).

STATISTICAL ANALYSIS

SPSS Windows v. 17.0 Program was used for statistical evaluation of the findings. Data were evaluated as mean values with standard deviations (SD). The sensitivity, specificity, PPV, NPV and accuracy were calculated. The *t*-test was used for comparing mean values and SD ($p<0.005$). ROC curves were also used to conclude the optimum cut-off value for SR.

RESULTS

The patients were aged between 24 and 73 years, with a mean age of 40±9 years. The mean nodule diameter varied between 80 mm and 7 mm. In 24 patients, one nodule out of two thyroid lobes was evaluated. Twenty nine nodules were pathologically diagnosed, among which 20 (68.9%) were diagnosed as papillary thyroid carcinoma and 9 (31%) were follicular neoplasms. The remaining patients were diagnosed as benign cytology.

Of the 234 thyroid nodules, 205 (87.6%) were diagnosed as benign cytology. The elasticity scores of 172 (83.9%) benign nodules were determined as 1-2 (Figure 2), and the those of 33 (16.1%) nodules

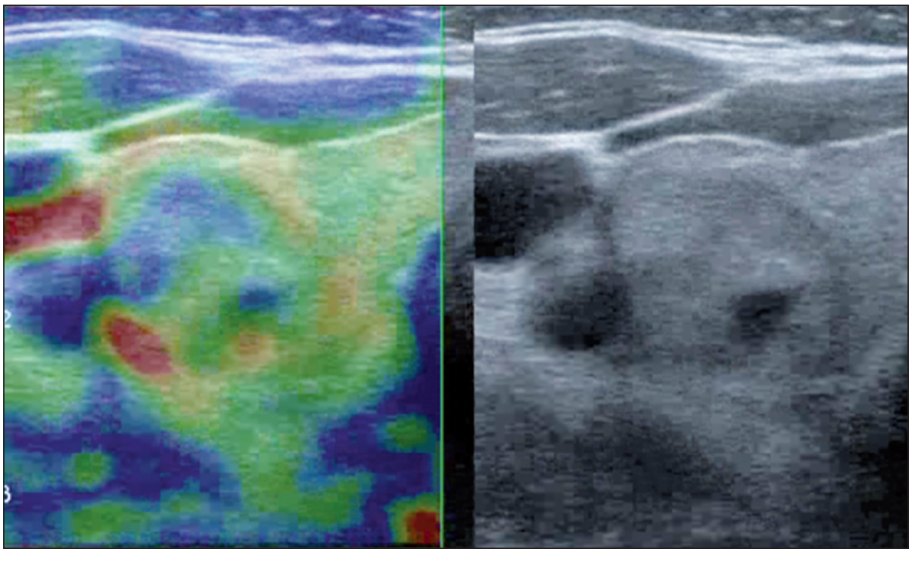


FIGURE 2: A 45-year-old female patient diagnosed with nodular goitre whose elastography score in the right thyroid lobe was 2 and the strain ratio was 2.2.

TABLE 1: Distribution of the elastography score in benign and malignant nodules (p< 0.05).

	Benign nodule, n (%)	Malignant nodule, n (%)	Total nodule, n (%)
Score 1- 2	172 (83.9%)	5 (17.2%)	177 (75%)
Score 3- 4	33 (16.09%)	24 (82.7%)	57 (25%)
Total n (%)	205 (87.6%)	29 (12.39%)	234

were determined as 3-4. Twenty-nine of the patients (12.3%) were diagnosed as malignant and were in the 2, 3 and 4 categories in the elasticity score. Five of the nodules (17.2%) that were diagnosed as malignant had an elasticity score of 2, whereas none of the nodules that were malignant had an elasticity score of 1 (Table 1).

The nodules were evaluated as score 1 and 2 and had benign cytology, which is statistically significant. The nodules that were categorised as score 3 and 4 had a malignant cytology, with sensitivity 85%, specificity 86.2%, PPV 70%, NPV 91% and accuracy 85.4%, which were statistically significant (p<0.05) (Figures 3, 4, 5).

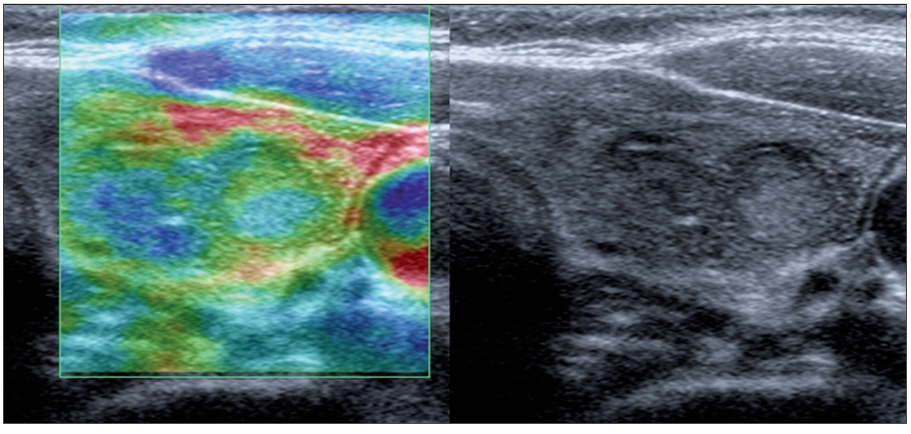


FIGURE 3: A 17-year-old female patient diagnosed with thyroid papillary carcinoma whose elastography score in the left thyroid lobe was 3 and the strain ratio was 4.3.

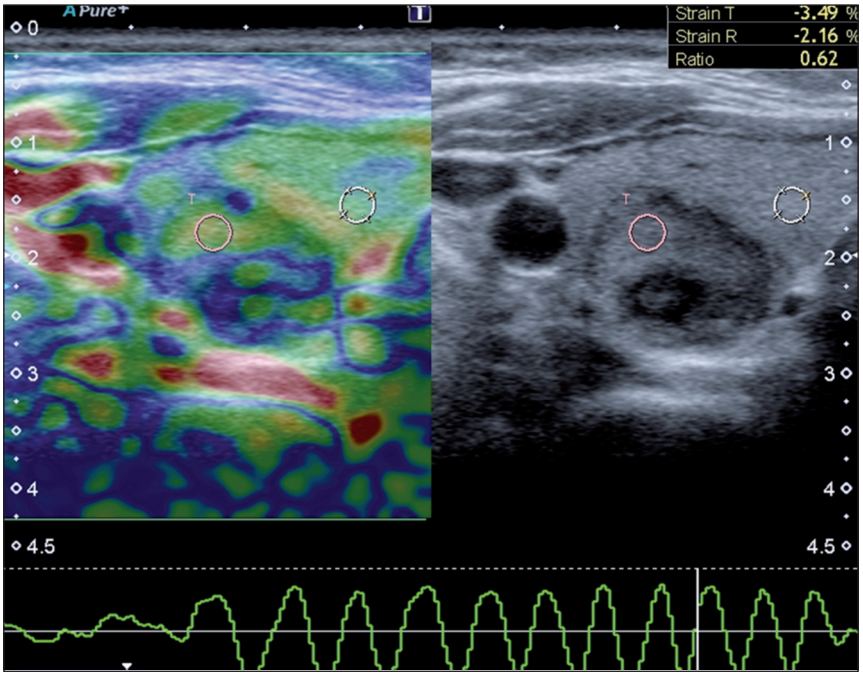


FIGURE 4: A 65-year-old male patient diagnosed with nodular goitre whose elastography score in the right thyroid lobe was 3 and the strain ratio was 0.6.

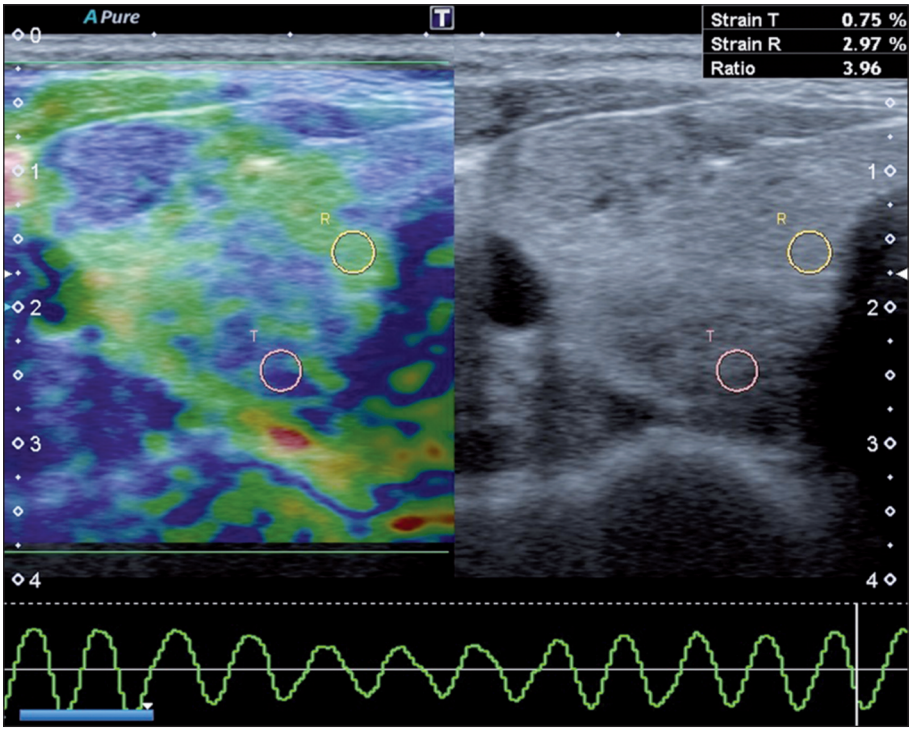


FIGURE 5: A 54-year-old male patient diagnosed with papillary carcinom whose elastography score in the right thyroid lobe was 3 and the strain ratio was 3.9.

TABLE 2: Distribution of strain ratio (SR) in benign and malignant nodules (p < 0.001).

	Benign nodule, n (%)	Malignant nodule, n (%)	Total nodule, n (%)
SR> 3. 4	29 (15%)	25 (87%)	54 (23.07%)
SR < 3. 4	176 (85%)	4 (13%)	180 (76.9%)
Total	205 (87.5%)	29 (12.5%)	234

TABLE 3: Diagnostic indices of elastography score and strain ratio.

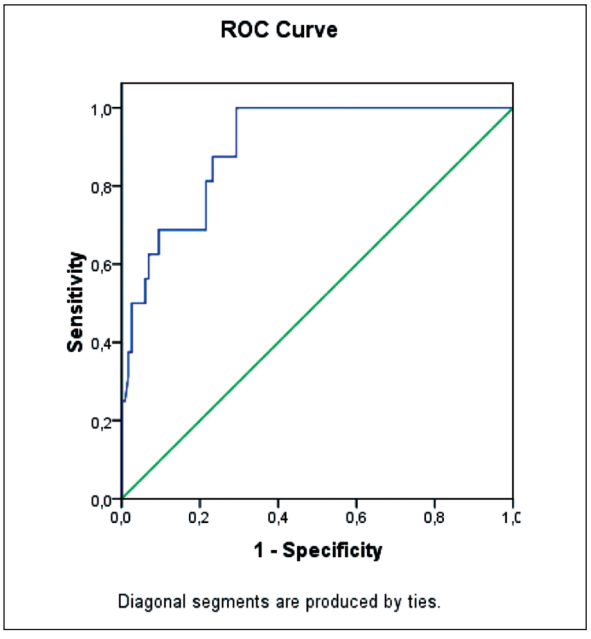
	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Elastography score	85	86.2	85.4	70	91
Strain ratio	88	89	89.8	73	93

The strain ratios for malignant (4.3±0.9) and benign (2.8±0.9) thyroid nodules were statistically different (p<0.001) (Table 2).

There were no significant differences between the strain ratio in patients who were diagnosed with thyroid papillary carcinoma and those who were diagnosed with follicular neoplasms. In the malignant and benign differential diagnosis using the strain ratio, the following values were found: sensitivity 88%, specificity 89%, PPV 73%, NPV 93% and accuracy 89.8% (Table 3). In the ROC analysis, the cut-off strain ratio point was 3.4 for both benign and malignant nodules (AUC: 0.903, p<0.05) (Graphic 1).

DISCUSSION

The FNAC technique has been accepted as the gold standard for the characterisation of thyroid nodules.[7] However, issues such as insufficient sampling and the need for repetition limit its use and renders it a minimally invasive process. Meanwhile, histology may not always differentiate adenoma from carcinoma. Elastography is a novel technique that is used for the characterisation of thyroid nodules. This technique is non-invasive and uses qualitative and semi-quantitative parameters that evaluate the elasticity of the tissues.[5,8,9] While the elasticity score evaluates the elasticity of the tissue in a qualitative manner, the strain ratio provides a



GRAPHIC 1: ROC for optimal cut- off strain ratio for distinguishing between benign and malign nodules. AUC was 0.903 (p<0.05).

semi-quantitative evaluation, according to the reference tissue.

These values, might contribute to the diagnosis of the malignancy in the thyroid nodules. In addition, the number of unnecessary biopsies and surgeries may also be reduced by using this technique. Meanwhile, they could also contribute to an accurate diagnosis in cases of insufficient cytology.

In our study, we examined the contribution of the elastography score and the strain ratio to the evaluation of malignant and benign nodules.

Nodules whose elasticity scores were evaluated as 1-2 were diagnosed as benign, and those whose elasticity scores were evaluated as 3- 4 were diagnosed as malignant, which was statistically significant. In this study, 12.5% of the patients received a malignant diagnosis, and 33 nodules were evaluated as score 3- 4 although being benign. The false- positive nodules, which received malignant scores although they are benign, might be due to the fibrotic tissue content. The reason for false-negative nodules (5 nodules out of 29 nodules) could be that nodules were localized in deeper areas of the tissue or the nodule was small in size (Table 1).

Unlütürk et al. was reported that the elastography score was superior to grayscale ultrasound findings in detecting malignancy.[10] In our study, the patients with 1 and 2 elasticity scores (83.9%) were benign. In none of the nodules diagnosed with malignant cytology in our study, the elasticity score was found to be 1. Therefore, the nodules whose scores are 1 may be followed up with sonographic findings rather than biopsy. Guazzaroni et al. conducted a study and reported similar results as ours and recommended not to apply biopsy in nodules whose scores were 1.[11] Patients with elastography score 3 and 4 received malignancy diagnosis, which was significant (sensitivity 85%, specificity 86.2%, PPV 70%, NPV 91% and accuracy 85.4%). Asteria et al. also reported similar results as ours (sensitivity 85%, specificity 81.2%, PPV 50%, NPV 91.2% and accuracy 83.7%).[12] Patients with elasticity scores 3 and 4 must definitely be evaluated with biopsy, and although a benign cytology is obtained, surgery must be definitely considered.

The strain ratio provides a semi-quantitative evaluation of the stiffness of the thyroid nodule. This ratio is calculated in the presence of a reference tissue.[13,14] For this reason, this value changes according to the reference tissue. In our study, we included patients with normal thyroid tissues, and used the normal thyroid tissue as the reference.

Deghi et al. conducted a study and demonstrated that the strain ratio was significantly higher in malignant nodules when compared with benign nodules. They also reported that this technique decreased the number of unnecessary FNAC procedures.[8]

The mean strain ratio in our study was found to be 2.8± 0.9 for benign nodules and as 4.3±0.9 for malignant nodules (p<0.001). The strain ratio was found to be statistically significantly higher in the malignant nodules than in the benign nodules.

Ning et al. reported that a strain ratio over 4, was beneficial in defining the malignancy in solid thyroid nodules (sensitivity 81%, specificity 83%).[15] In addition, Lyhchik et al. found a strong relationship between strain ratio of >4 and thyroid cancers (sensitivity 82%, specificity 96%)[5]. Wang

et al. conducted a study and reported the strain ratio for benign nodules to be 2.1±1.2 and 5.3± 2.5 for malignant nodules [13].The strain ratios in the present study were found to be lower than those in previous studies. In a study with a large sample size conducted by Çakır et al., the results were similar to those of our study.[16] Patients with a high strain ratio must definitely be evaluated in terms of biopsy and surgery.

In a recent study, Wang et al. reported that a cut- off value of 3.8 could differentiate between malignant and benign nodules with sensitivity 80.7%, specificity 91.3%, and accuracy 88.1%. The AUC with 0.907 was similar result as our study.[15] Ning et al. reported that a cut-off value of 4.2 could differentiate between malignant and benign nodules, with sensitivity 82.4%, specificity 71.6%, and accuracy 88.1% and the AUC was 0.88.[13]

In our study, we found that the optimal strain ratio cut-off 3.4, with the AUC of 0.903, sensitivity 88%, specificity 89%, and accuracy 88.8% in distinguishing between benign and malignant nodules.

Our results are similar to those of previous studies, which showed that the strain ratio has a higher diagnostic value than the elastography score for differentiating between benign and malignant thyroid nodules.

FNAC has been considered as the gold standard in the routine evaluation of patients with thyroid nodules, the technique also provides false negative results in nearly 15% of malignant patients.[18] There were non-diagnostic pathology reports in nearly 20% of patients who received biopsy.[19] Therefore, although it is a minimally invasive process, it is not desired for repetitions. In cases where the FNAC is false negative, elastography may contribute to the diagnosis. In addition to the grayscale findings, the patients may be evaluated using both the strain ratio and elastography score, and the follow-up scheme or the malignancy may be decided upon accurately.

Our study has some limitations. The first one is that the number of the patients diagnosed as malignant is lower, and the pathological cellular types of the patients with malignancy diagnosis were not discriminated but were evaluated only as follicular and papillary carcinomas. Another limitation is that our results are not independent from the users since our study was performed by only one operator. The nodules selected for elastography being deeply-located and small and not providing sufficient data in cystic nodules is the other limitation.

The strain ratio and elasticity score may provide information that may approve or exclude the biopsy decision or that can make distinction between benign and malignant tissues. Elastography is a non-invasive method that can contribute to clinical evaluations in cases with follicular diffusion and whose pathology results are insufficient. In addition, it may also decrease the unnecessary surgeries or may guide the surgeon.

The literature consists of several studies that have high sensitivity and specificity in ultrasound elastography[3]. In our study, only the elastography score and the strain ratio were evaluated. In a wider series, more accurate statistical data may be obtained using of grayscale findings, colour Doppler and elastography parameters. The strain ratio may be a powerful predictor of malignancy.

CONCLUSION

Both the elastography score and the strain ratio values are beneficial parameters for detecting the malignant thyroid nodules, and they contribute to the diagnostic process. They increase the diagnostic rate of malignancy together with other grayscale and colour Doppler findings and may reduce the number of unnecessary biopsies or false- negative results. Wider series of studies should be conducted to ensure that the strain ratio becomes more valuable.

REFERENCES

1. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011;99:39-51.
2. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 1993;118(4):282-9.
3. Moon HJ, Sung JM, Kim EK, Yoon JH, Youk JH, Kwak JY. Diagnostic Performance of gray-scale US and elastography in solid thyroid nodules. Radiology 2012;262(3):1002-13.
4. Khoo ML, Asa SL, Witterick IJ, Freeman JL. Thyroid calcification and its association with thyroid carcinoma. Head Neck 2002;24(7): 651-5.
5. Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, Mai JJ, et al. Thyroid gland tumor diagnosis at US elastography. Radiology 2005;237(1): 202-11.
6. Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, et al. Breast disease: clinical application of US elastography for diagnosis. Radiology 2006;239(2):341-50.
7. Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. Mayo Clin Proc 1994;69(1):44-9.
8. Dighe M, Kim J, Luo S, Kim Y. Utility of the ultrasound elastographic systolic thyroid stiffness index in reducing fine-needle aspirations. J Ultrasound Med 2010;29(4):565-74.
9. Wang HL, Zhang S, Xin XJ, Zhao LH, Li CX, Mu JL, et al. Application of Real-time Ultrasound Elastography in Diagnosing Benign and Malignant Thyroid Solid Nodules. Cancer Biol Med 2012;9(2):124-7.
10. Unlütürk U, Erdoğan MF, Demir O, Güllü S, Başkal N. Ultrasound elastography is not superior to grayscale ultrasound in predicting malignancy in thyroid nodules. Thyroid 2012;22(10):1031-8.
11. Guazzaroni M, Spinelli A, Coco I, Del Giudice C, Girardi V, Simonetti G. Value of strain-ratio on thyroid real-time sonoelastography. Radiol Med 2014;119(3):149-55.
12. Asteria C, Giovanardi A, Pizzocaro A, Cozzaglio L, Morabito A, Somalvico F, et al. US-elastography in the differential diagnosis of benign and malignant thyroid nodules. Thyroid 2008;18(5):523-31.
13. Wang H, Brylka D, Sun LN, Lin YQ, Sui GQ, Gao J. Comparison of strain ratio with elastography score system in differentiating malignant from benign thyroid nodules. Clin Imaging 2013;37(1):50-5.
14. Gungor G, Yurttutan N, Bilal N, Menzilcioglu MS, Duymus M, Avcu S, et al. Evaluation of Parotid Glands With Real-time Ultrasound Elastography in Children. J Ultrasound Med 2016;35(3):611-5.
15. Ning CP, Jiang SQ, Zhang T, Sun LT, Liu YJ, Tian JW. The value of strain ratio in differential diagnosis of thyroid solid nodules. Eur J Radiol 2012;81(2):286-91.
16. Cakir B, Aydin C, Korukluoğlu B, Ozdemir C, Sisman IC, Tüzün D, et al. Diagnostic value of elastosonographically determined strain index in the differential diagnosis of benign and malignant thyroid nodules. Endocrine 2011;39(1): 89-98.
17. Rago T, Scutari M, Santini F, Loiacono V, Piaggi P, Di Coscio G, et al. Real time elastosonography: useful tool for refining the presurgical diagnosis in thyroid nodules with indeterminate or nondiagnostic cytology. J Clin Endocrinol Metab 2010;95(12):5274-80.
18. Grant CS, Hay ID, Gough IR, McCharthy PM, Goellner JR. Long-term follow-up of patients with benign thyroid fine-needle aspiration cytologic diagnoses. Surgery 1989;106(6):980-5.
19. Meko JB, Norton JA. Large cystic/solid thyroid nodules: a potential false-negative fine-needle aspiration. Surgery 1995;118(6):996-1003.