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The importance of compression elastography in evaluation of thyroid nodule malignancy

Значај компресионе еластографије у процени могућности малигнитета нодуса штитасте жлезде

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SUMMARY

Introduction/Objective Compression, also called strain elastography imaging techniques, represent new echotomographic modality, which is a promising method in the differentiation of benign from malignant lesions, not only in the thyroid gland, but also in the other organs.

The aim of this study is to evaluate the importance of compression elastography in the differentiation of benign and malignant thyroid nodules.

Methods We performed echotomographic examinations in B mode, and examinations using compression elastography in total of 186 persons (152 females and 34 males, with average of 45.3±13.5 years of age), with 264 nodules in the thyroid gland. Elastography was done in two steps: first through scoring elastographic figures, and second through the determination of the resistance index (strain ratio).

Results Using elastography scores by Fukunari, 44 of 60 malignant nodules had a score of 3-4, while 152 of the 204 benign nodules had a score of 1-2. Using the ROC (Receiver operating characteristic) analysis, the best cut-off point obtained using elastography scores was 2, with sensitivity of 73.3% and specificity of 74.5%. Using the software calculated resistance index (SR), from 89 nodules with SR ≥ 2.5, 52 were malignant nodules, while from 175 nodules with SR <2.5, 167 were benign nodules. Using the ROC analysis, the best cut-off point obtained using SR was >2.5, with sensitivity of 86.7%, and specificity of 81.9%.

Conclusion As a follow of standard echotomographic examination in B mode, compression elastography is a newly developed and promising technique in the differentiation of benign from malignant lesions.

Keywords: compression elastography; nodule; thyroid gland; malignancy

САЖЕТАК

Увод/Циљ Компресиона еластографија је нов начин ултразвучног прегледа за који се очекује да са већом поузданошћу разликује доброћудне од злоћудних промена не само у штитастој жлезди него и другим органима.

Циљ овог истраживања је да проценимо значај ултразвучне еластографије у разликовању бенигних и малигних нодуса штитасте жлезде.

Методе Ултразвучне прегледе у Б моду и компресиону еластографију смо обавили код 186 особа (152 женског и 34 мушког пола; са 45,3±13,5 година живота), са 264 нодуса у штитастој жлезди. Еластографију смо радили у два корака. Најпре смо одредили степен растегљивости (еластичности) ткива приказано као колорна мапа а потом, упоређујући са околним ткивом, одредили индекс еластичности (ИЕ).

Резултати Користећи скорове еластографије према Фукунари, 44 од 60 малигних нодуса је имало скор 3–4, док је 152 од 204 бенигних нодуса имало скор 1–2. Анализом пријемних карактеристика најбоља гранична тачка добијена коришћењем скорова еластографије је 2, са сензитивношћу 73,3% и специчношћу 74,5%. Користећи софтверски израчунат индекс еластичности (ИЕ), од 89 нодуса са ИЕ≥2,5, било је 52 малигних нодуса, док од 175 нодуса са ИЕ<2,5 чак 167 је било бенигних нодуса. Користећи пријемну анализу, најбоља гранична тачка добијена коришћењем индекса отпора је >2,5 , са сензитивношћу од 86,7% и специчношћу 81,9%.

Закључак Придружено стандардном ултразвучном прегледу, компресиона еластографија пружа нову могућност која обећава поузданије разликовање бенигних од малигних промена.

Кључне речи: компресиона еластографија; нодус; штитаста жлезда; малигност

INTRODUCTION

Thyroid nodules are a very common in the general population, especially in iodine-deficient areas. It is estimated that the nodules are seen in 35-50% of people living in areas with deficiencies in iodine. However, the normal thyroid gland has some thyrocytes (follicular cells) with the tendency of autonomous growth. All of them can occur in nodules regardless of the amount of iodine, with increased frequency in the population [1]. Thyroid ultrasound is one of the very practical, easily manageable, accessible, and non-invasive method which can detect nodules. One of the most important assessment is to determine the nature of the nodules, or to differentiate benign from malignant thyroid nodules. Classical technique of echotomographic examination in B mode can`t differentiate benign from malignant nodules with great certainty. Hypoechoic changes, presence of microcalcifications, variable peripheral edge, intranodal hipervascularisation, and pathologically suspected lymph nodes in the neck are just some uncertain indicators of malignant nodules, but definitely insufficient to evaluate the nature of thyroid nodules. Today, thanks to the different software modes and modern ultrasound devices, it is possible to additionally assess the nature of the various nodules of the thyroid gland [2, 3].

Elastography is a new, non-invasive method, which estimates the elasticity of tissue by measuring the different degrees of distortion during the application of external force. The basic principle of ultrasound elastography is that tested tissue compression shows the resistance. As well as palpation, elastography can measure tissue deformation or strain which is caused by the external compression [4]. Nowadays, these methods for the assessment are promising in the differentiation of benign from malignant lesions, and not just in the thyroid gland, but also in the breast, liver, spleen, and prostate. Considering the fact that malignant lesions are characterized by a lower elasticity compared to the structure of a normal tissue, partly due to the uncontrolled proliferation of malignant cells, increased vascularization, and somewhat less frequently, due to the presence of fibrotic changes in them.

The aim of this study is to evaluate the importance of strain ultrasound elastography in the differentiation of benign from malignant thyroid nodules, especially when combined with standard echotomography examination in B mode.

METHODS

This cross sectional study included 186 patients with 264 thyroid nodules (152 females and 34 males, with the mean age of 45.3 ± 13.5 years). All patients had solid lesions (nodules), and presented in the Department of the radiological diagnostics in KBC "Dr. Dragiša Mišovic-Centar" in Belgrade, Serbia, in the period from March 2014 to June 2016. Patients with nodules over 3.5 cm, completely cystic, anechogenic without solid components, and nodules in close contact with the carotid artery, excluded from the study in order to increase the reliability of the findings. Echotomographic thyroid examinations were performed on an ultrasound device Toshiba brand Aplio XG, with linear transducer 10MHz.

All patients were examined by using three ultrasonic methods. The first step was a standard echotomographic examination in B mode, the second was to test a resistance of the tissue through elastography scores, and the third step was to measure SR as an indicator of semi-quantitative elastography method for tissue resistance.

In order to avoid potential differences in operation between different researchers, all examinations were performed by the same researcher with a long experience in dealing with different modalities of ultrasound equipment. Also in this way we standardize and equalize the compression on the tissue, during the elastography performance. Strain elastography was performed by repeated compressions (up to 7), with the same volume, and in the same time intervals (about 0.5 sec). All compressions based on the central positioned nodules in a region of interest, in the longitudinal view due enough of the surrounding normal thyroid tissue for elasticity comparison.

Based on the classification by Fukunari [5], each nodule is scored by the elastographic figure. Score of 1 means that the majority of nodule, or fully stained in green. Score 2 means that only the nodule center stained green, and the periphery was blue. Score 3 means that the nodule mixed discolored areas predominantly blue and green part, and the score of 4 means that the whole nodule was blue. Elastography scores represent different degrees of elasticity of the lesion, from the highest (score 1), to the smallest elasticity (score 4). Scores of 1 and 2 represent indicators of benign nodules, while scores of 3 and 4 represent indicators of malignant nodules. Then we recorded the resistance index (SR), which is the software calculated ratio of elasticity between the two regions of interest, in our case the nodule and the rest of the normal thyroid tissue. Each lesion we evaluated three times, using a variety of static images, and the average value was recorded as the final result.

After echotomographic examinations, all patients were sent to perform the ultrasound guided fine needle aspiration biopsy. The results are processed by a pathologist with a long experience. Fifty-two patients (52 nodules) with cytological findings suspicious for malignancy, and 36 patients (48 nodules) with cytological benign findings, were operated and histopathologic findings confirmed the earlier diagnosis. We compared cytological, and histopathological results with elastographic images, and evaluated the sensitivity, specificity, negative and positive predictive value, and accuracy of the techniques or methods. Quantitative data are presented in mean ± standard deviation (SD), and qualitative as frequencies. Receiver operating characteristic (ROC) curve was used to determine optimal cut-off values to differentiate benign and malignant nodules. For the statistical significance of differences was taken $p<0.05$. Data were statistically analyzed by the program MedCalc v.11.4.2.

RESULTS

Among186 patients who were included in the study, 152 female and 34 males with mean age of 45.3±13.5 years, it was obtained 264 nodules. Using classical echotomographic examination of the thyroid gland in the B mode, from 264 nodules that are discovered, 180 nodules were with homogeneous echostructure (68%), while 84 nodules (32%) had heterogeneous echostructure-partly cystic altered. The greatest number of nodules 120 (45%) were isoechogenic; hipoechogenic were 104 (40%); while the smallest number were hyperechogenic nodules, only 40 (15%). Proper edges had 192 nodules (73%), while the edges were irregular in 72 nodules (27%). Visible calcifications were present in 56 nodules (21%), while calcifications were not seen in 208 nodules (79%) (Table 1). Using elastography

Table 1. Number of nodules in each score by *Fukunari*.

Elasto score	*Malignant nodules*	*Benign nodules*	TOTAL
Scor 3-4	44	52	96
Scor 1-2	16	152	168
TOTAL	60	204	264

scores by Fukunari (5), from 204 benign nodules, 152 nodules (74%) belonged to the score 1–2 (60 nodules belonged to a score of 1, while 92 nodules belonged to a score of 2), and 52 nodules (26%) belonged to the score 3-4 (46 nodules score of 3, and 6 nodules score of 4). Of the 60 malignant nodules, 44 nodules (73%) belonged to the score 3-4 (14 nodules score of 3, and 30 nodules score of 4), while the 16 malignant nodules (27%) belonged to the score 1-2 (no one had score 1, and all belonged score of 2) (Figures 1–5). Sensitivity of elastography scores for getting positive results in malignant nodules was 73.3%. Specificity of elastography scores for the negative results in benign nodules was 74.5%. The positive predictive value was 45.8%. The negative predictive value was 90.4%. The accuracy in the differentiation of benign from malignant nodule was 74.2%

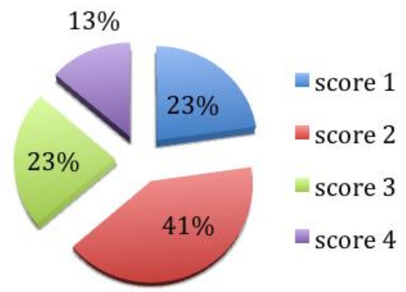

Figure 1. Total percentage of nodules in each score.

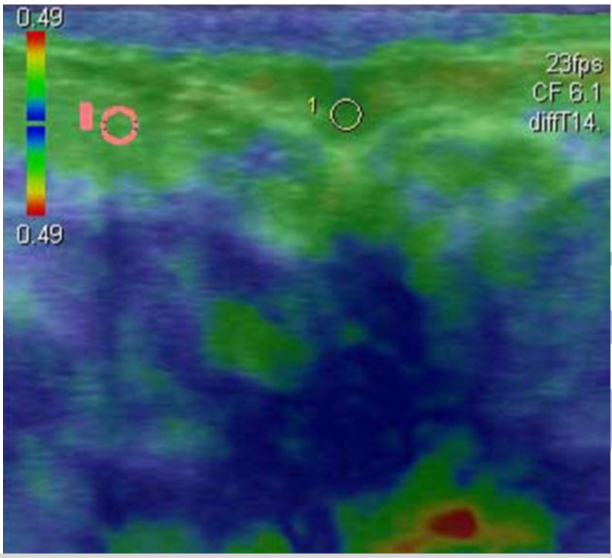

Figure 2. Score 1 by Fukunari – findings obtained by biopsy proving benign nodule.

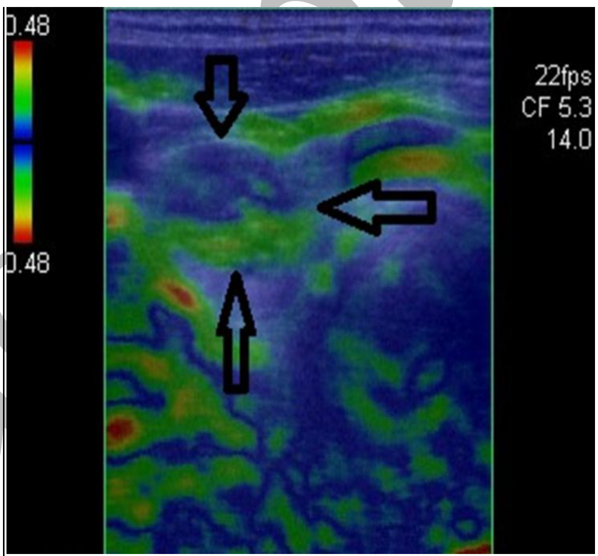

Figure 3. Score 2 by Fukunari – findings obtained by biopsy proving benign nodule.

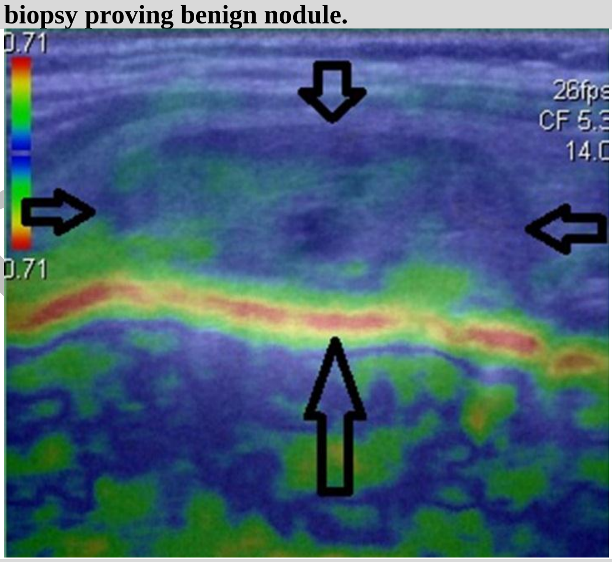

Figure 4. Score 3 by Fukunari – findings obtained by biopsy proving papillary carcinoma.

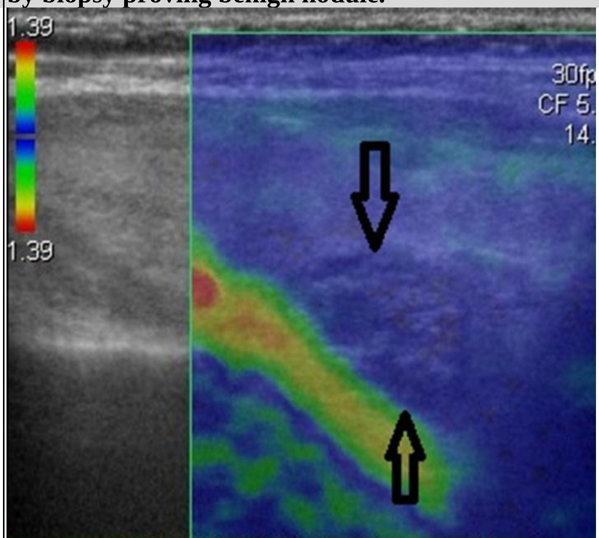

Figure 5. Score 4 by Fukunari – findings obtained by biopsy proving papillary carcinoma.

(Figure 6). Using the ROC analysis, the best cut-off point obtained using elastography scores to differentiate benign and malignant thyroid nodule was 2, with sensitivity of 73.3% and specificity of 74.5% (area under the ROC curve = 0.83, 95% confidence interval: 0.78–0.87, $p<0.0001$) (Figure 7).

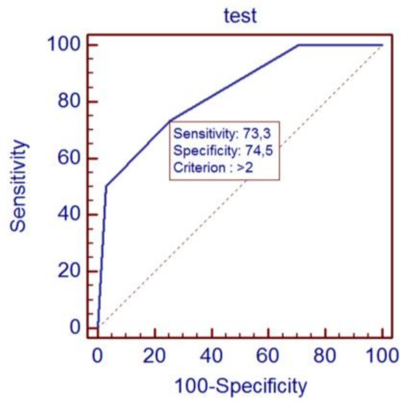

Figure 6. ROC analysis by using elastography scores.

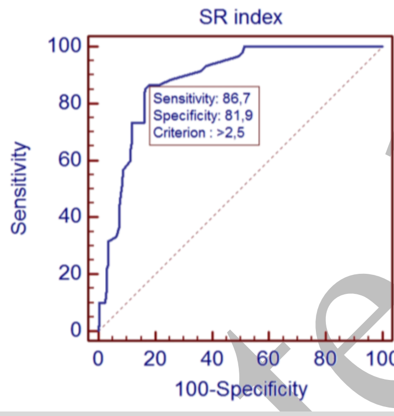

Figure 7. ROC analysis by using strain ratio.

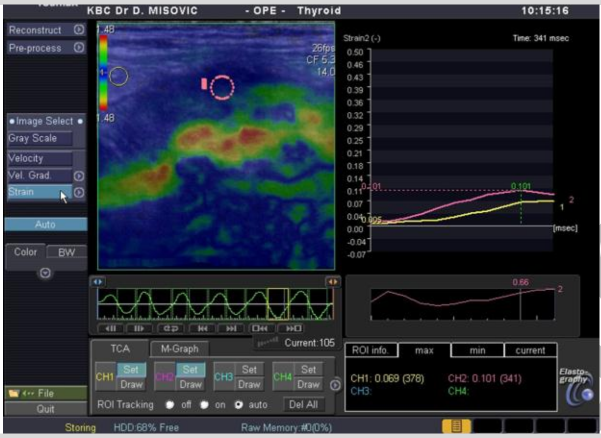

Figure 8. Nodule with elastography score 2, SR=0,66 – biopsy proven benign characteristics of thyroid adenoma.

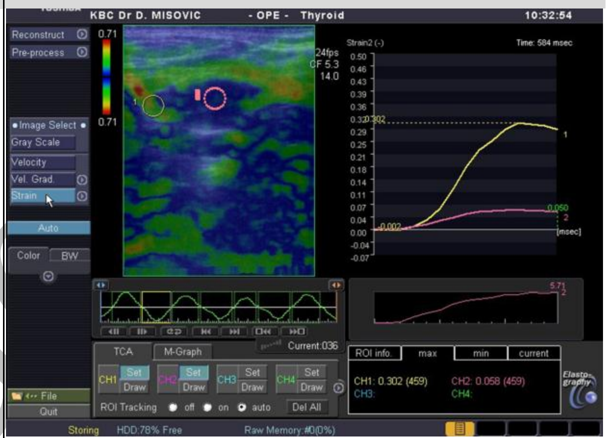

Figure 9. Nodule with elastography score 3–4, SR is 5.71, biopsy proven follicular carcinoma.

Using the ROC analysis, the best cut-off point obtained using SR to differentiate benign and malignant thyroid nodule was >2.5, with sensitivity of 86.7% and specificity of 81.9% (area under the ROC curve = 0.88, 95% confidence interval: 0.83–0.91, $P<0.0001$) (Table 2), (Figures 8–9). Using the software calculated resistance index (SR), while performing elastography, we took the criterion that SR ≥ 2.5 was an indicator of malignancy. From 89 nodules with SR≥2.5, 52 were malignant nodules. From 175 nodules with SR<2.5, as much as 167 were benign nodules. The sensitivity of SR for obtaining positive results in malignant nodules was 86.7%.The specificity of SR for obtaining negative results in benign nodules was 81.9%. The positive predictive value was 58.4%. The negative predictive value was 95.4%. The accuracy of SR in differentiating benign from malignant nodule was 82.9% (Table 3). The results obtained by fine needle aspiration biopsy (FNAB) showed that 204 nodules were benign (77%), while

Table 2. Number of nodules in each category by strain ratio (SR).

Strain ratio	*Malignant nodules*	*Benign nodules*	TOTAL
SR ≥ 2,5	52	37	89
SR < 2,5	8	167	175
TOTAL	60	204	264

Table 3. Histopathologic types of malignant nodules in each elasto score and SR category.

Type	Elasto score 3–4 (%)	Elasto score 1–2 (%)	SR ≥ 2,5 (%)	SR < 2,5 (%)	TOTAL (%)
Papillary carcinoma	33 (63.5)	7(13.5)	38 (73.1)	2 (3.8)	40 (76.9)
Follicular carcinoma	3 (5.8)	4 (7.7)	4 (7.7)	3 (5.8)	7 (13.5)
Anaplastic carcinoma	2 (3.8)	2 (3.8)	2 (3.8)	2 (3.8)	4 (7.7)
Primary thyroid lymphoma	0 (0)	1 (1.9)	1 (1.9)	0 (0)	1 (1.9)
TOTAL	**38 (73.1)**	**14 (26.9)**	**45 (86.5)**	**7 (13.5)**	**52 (100)**

60 nodules (23%) were malignant. Fifty-two patients (52 nodules) with malignant cells that are detected by FNAB, and 36 patients (48 nodules) with benign cells, were operated. Histopathologic findings for 52 patients (52 nodules) with malignant nodules were presented in Table 3.

DISCUSSION

One of the primary methods of clinical examination of the thyroid gland includes the palpation. Palpation gives us information about the shape, size, as well as hardness and elasticity of the thyroid gland. However, palpation is a subjective method of examination. Measurement of the elasticity and stiffness of soft tissue assessment are useful in the differentiation of tumor, inflammation, and normal thyroid tissue. It is generally accepted that the benign lesions showed less stiffness and greater elasticity as compared to malignant lesions, and a higher stiffness and lower elasticity as compared to normal tissue [4-7].

Classical echotomographic examination of the thyroid gland can detect characteristics of nodules that indicate malignancy. In addition to his looks, ranging from hypoechogenic to almost anechogenic, malignant nodules are echotomographically different, mostly by absent or incomplete (rarely closed) peripheral vascular edge. Microcalcifications are often present in the nodules, and it is almost always present an intense central vascularization. However, even at about 50% of benign nodules intranodal vascularization may be present. Approximately, the most accurate echotomographic diagnosis of thyroid cancer is only possible when the thyroid nodules have the simultaneous presence of all these above symptoms, with a high specificity, but a low sensitivity [8-9]. Therefore, in order to obtain the most reliable results, only with an unified and comprehensive informations obtained by classical echotomographic examination in B mode and color Doppler, it could be predictive for malignancy.

Fine needle aspiration biopsy under ultrasound control is still the most precise method for diagnosing cancer with high sensitivity and specificity, and a very small number of false-positive (2.3%) and false-negative (0.2%) results. The accuracy of the differentiation of benign from malignant lesions of the thyroid gland is more than 95% [10-11].

We examined a newly developed diagnostic method (ultrasound elastography), which estimates degree of distortion of the tissues when applying external force. In diagnostic algorithm, this method is placed between classical echotomographic examination in B mode, and FNAB, and has been introduced in order to further increase ultrasound accuracy. It is based on the principle that softer tissue and tissue parts are more easily deformed, and have greater elasticity than harder tissues. Some of the main benefits of elastography are its simple feasibility, non-invasivity, and its convenience during a routine echotomography performance. In addition, this technique enables the dynamic visualization of lesions in the region of interest during the compression. Elastography is performed in two steps: determine scoring nodules on elastography figure, and calculating the resistance index using the software. Scoring is a subjective estimate of the lesion of interest (nodule), classified into one of scores that there are, based on a color distribution in B mode. Different colors (green, red, blue) on echotomographicfigure represent different parts the elasticity of the tissues in the region of interest [12]. In our study we used scoring by Fukunara [5], where we have nodules that are the most elastic (score of 1; and they were mostly benign nodules), and nodules that are the least elastic (score of 4; and they were mostly malignant nodules). Using elastography scores by Fukunari we discovered malignant nodules with sensitivity of 73.3%. The same score system have used Wang et al. [12], while the score of the Ueno classification used by Ciledag et al. [4] and Itoh et al. [13]. Many studies indicate that this part of elastography is sufficient for the assessment of different tissue elasticity and for the differentiation of benign from malignant nodes [14-15]. Malignant thyroid nodules have less elasticity (score 3-4), while benign nodules have a higher elasticity (score 1-2), as shown by our results of sensitivity (73.3%) and specificity (74.5%); ($p < 0.05$), [14-18]. However, in determining the SR, we get even larger values of sensitivity (86.7%), specificity (81.9%), and the results pointed to increased reliability-accuracy of test (82.9%). We have demonstrated that malignant nodules had a significantly higher SR than benign nodules ($p < 0.001$). Determination of SR represent a software calculated quantitative measure of elasticity, which may provide more reliable information. In our study, all SR values ≥ 2.5 represent a predictor of malignant nodules, in accordance with the values that we got by ROC analysis. Lyshchik et al. [19] suggest SR> 4 as a strong predictor of malignant nodules, with a sensitivity of 82% and a specificity of 96%. However, Kagoyaet al. [7] used the SR> 1.5 as an indicator of malignancy nodules, with sensitivity 90%, and specificity 50%.

During the performance of this technique, the depth of the tissue should be taken into consideration when the comparison between the nodules and the normal tissues is performed, and it should be the same or similar when calculating the SR. The estimation should be performed on the longitudinal mode of the thyroid gland, because it shows sufficiently large fraction of the normal tissues that are used to compare and calculate the SR [12, 20]. Rago et al. [14] shows that the size of nodules does not affect the value of the SR and elastography predictability. However, other researchers have indicated that the size of the nodules may affect the SR, so that in some studies they include all the nodules to the maximum size up to 3cm [12], while some studies include all the nodules to a maximum size up to 4cm [4]. In our study, we included all nodules to a maximum size of 3cm. Nodules larger than 3cm, were not compressed by the same intensity in all parts of them, and the results of the index values of SR were inadequate. For now, there is no reliable information which indicates that minimal nodule size might be involved in this method. Researchers in some studies advise that, during the elastography procedure, nodules near the carotid artery must be treated with care due to the fact that pulsations of the carotid arteries can disrupt proper interpretation of elastography figure [4, 12]. Due to that, our study avoided patients whose nodules were near the carotid artery, and the method was performed by external compression. However, the study of Dighe et al. [21] showed that the pulsation of the carotid artery can be used, instead of external compressionby researchers, for the evaluation of elastography figures. Results that are obtained in this way by elastography analysis were similar to ours ($p < 0.05$). In our study, a small number of false-negative results inform us that elastography can reduce the number of patients which are sent to the surgeons for suspicion of malignancy, and therefore delay the eventual surgical intervention due to malignancy.

One of the biggest disadvantage of this method is subjectivity. Strain elastography in all its forms remains an examiner-dependent method, and require a trained and experienced operator to perform valid free-hand cyclic compressions that can yield reliable and reproducible readings. The free-hand probe pressure is difficult to standardize among different operators and strain variations due to changes in the amplitude and velocity of compression that cannot be avoided. Non-uniform compressions produce intra and inter observer variability [20]. For that reason, it was developed newer elastography technique called Shear Wave elastography (SWE). This method is designed to provide quantitative, more objective, information on elasticity in real time. SWE uses acoustic pressure from the probe for standardisation of compression. The tissue compression force does not depend on the skills of the person performing the examination, ensuring high reproducibility and objectivity of the results. SWE can produce quantitative and more precise results than strain elastography. Although SWE requires a more complex system to generate the shear waves, it allows visualization of smaller displacements compared to strain elastography [22].

Also, the histological features of the nodules themselves may lead to pitfalls. Fibrosis within a nodule, calcifications, partially cystic or colloid components, isthmus location, nodule size, and the multinodular nearness appearance are correlated to increased levels of stiffness [22-23]. Follicular carcinomas may lead to false negative results in strain elastography, as they may be soft and therefore may be missed [24].

CONCLUSION

Elastography is a newly developed and very promising technique in the differentiation of benign from malignant lesions, especially when combined with standard echotomography examination in B mode. However, it is important that all of these newly developed techniques are performed properly and with great attention because of their influence on the possible disposal or reduction of unnecessary surgical procedures.

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REFERENCES

1. Schmidt M, Schicha H. Thyroid disorders. Versicherungsmedizin. 2011; 63(4): 176–9. (German)
2. Wienke JR, Chong WK, Fielding JR, Zou KH, Mittelstaedt CA. Sonographic features of benign thyroid nodules: interobserver reliability and overlap with malignancy. J Ultrasound Med. 2003; 22(10): 1027–31.
3. Iannuccilli JD, Cronan JJ, Monchik JM. Risk for malignancy of thyroid nodules as assessed by sonographic criteria. J Ultrasound Med. 2004; 23(11): 1455–64.
4. Ciledag N, Arda K, Aribas BK, Aktas E, Köse SK. The utility of ultrasound elastography and MicroPure imaging in the differentiation of benign and malignant thyroid nodules. Am J Roentgenol. 2012; 198(3): W244–9.
5. Fukunari N. More accurate and sensitive diagnosis for thyroid tumors with elastography-detection and differential diagnosis of thyroid cancers. Medix. 2007; 05 Suppl; S16–9.
6. Menzilcioglu MS, Duymus M, Avcu S. Sonographic Elastography of the Thyroid Gland. Pol J Radiol. 2016; 81:152–6.
7. Kagoya R, Monobe H, Tojima H. Utility of elastography for differential diagnosis of benign and malignant thyroid nodules. Otolaryngol Head Neck Surg. 2010; 143(2): 230–4.
8. Becker D, Bair HJ, Becker W, Günter E, Lohner W, Lerch S, et al. Thyroid autonomy with color-coded image-directed Doppler sonography: internal hypervascularization for the recognition of autonomous adenomas. J Clin Ultrasound. 1997; 25(2): 63–9.
9. Woliński K, Szkudlarek M, Szczepanek-Parulska E, Ruchała M. Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta-analysis of prospective studies. Pol Arch Med Wewn. 2014; 124(3): 97–104.
10. Oertel YC, Miyahara-Felipe L, Mendoza MG, Yu K. Value of repeated fine needle aspirations of the thyroid: an analysis of over ten thousand FNAs. Thyroid. 2007; 17(11): 1061–6.
11. Hamburger JI. Diagnosis of thyroid nodules by fine needle biopsy: use and abuse. J Clin Endocrinol Metab. 1994; 79(2): 335–9.
12. 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.
13. 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.
14. Rago T, Santini F, Scutari M, Pinchera A, Vitti P. Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. J Clin Endocrinol Metab. 2007; 92(8): 2917–22.
15. 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.
16. Tranquart F, Bleuzen A, Pierre-Renoult P, Chabrolle C, Sam Giao M, Lecomte P. Elastosonography of thyroid lesions. J Radiol. 2008; 89(1 Pt 1): 35–9. (French)
17. Sun J, Cai J, Wang X. Real-time ultrasound elastography for differentiation of benign and malignant thyroid nodules: a meta-analysis. J Ultrasound Med. 2014; 33(3): 495–502.
18. Andrioli M, Scacchi M, Carzaniga C, Vitale G,Moro M, Poggi L, et al. Thyroid nodules in acromegaly: The role of elastography. J Ultrasound. 2010; 13(3): 90–97.
19. 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.
20. Park SH, Kim SJ, Kim EK, Kim MJ, Son EJ, Kwak JY. Interobserver agreement in assessing the sonographic and elastographic features of malignant thyroid nodules. AJR. 2009; 193(5): W416–23.
21. Dighe M, Bae U, Richardson ML, Dubinsky TJ, Minoshima S, Kim Y. Differential diagnosis of thyroid nodules with US elastography using carotid artery pulsation. Radiology. 2008; 248(2): 662–9.
22. Cantisani V, Grazhdani H, Ricci P, Mortele K, Di Segni M, D'Andrea V, et al. Q-elastosonography of solid thyroid nodules: assessment of diagnostic efficacy and interobserver variability in a large patient cohort. Eur Radiol. 2014; 24(1): 143-50.
23. Cantisani V, Lodise P, Grazhdani H, Mancuso E, Maggini E, Di Rocco G, et al. Ultrasound elastography in the evaluation of thyroid pathology. Current status. Eur J Radiol. 2014; 83(3): 420–8.

24. Bojunga J, Herrmann E, Meyer G, Weber S, Zeuzem S, Friedrich-Rust M.Real-time elastography for the differentiation of benign and malignant thyroid nodules: a meta-analysis. Thyroid. 2010; 20(10): 1145–50.