ORIGINAL ARTICLE

ROLE OF ELASTOGRAPHY IN DIFFERENTIATING MALIGNANT AND BENIGN THYROID NODULES USING FNAC AS A REFERENCE STANDARD

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PJR July - September 2017; 27(3): 200-206

ABSTRACT

BACKGROUND: Ultrasound elastography is a noninvasive technique for evaluating thyroid nodules that encompasses a variety of approaches such as supersonic shear imaging and acoustic radiation force impulse imaging as well as real-time tissue elastography. This technique is very useful in differentiating malignant thyroid nodules from benign ones. **OBJECTIVE:** To determine the diagnostic accuracy of ultrasound elastography in differentiating benign from malignant thyroid nodules by using FNAC as a reference standard. **METHODOLOGY:** 165 patients were selected for this study. The ultrasound examination including grey scale, doppler as well as elastography of thyroid nodules. Then ultrasound guided FNAC of selected nodule was performed and its result was obtained in order to compare diagnosis of ultrasound elastography and cytolology as operational definition. **RESULTS:** In our study, 42.42% (n=70) were males and 57.58% (n=95) were females,61.82% (n=102) were between 18-40 years of age while 38.18% (n=63) were between 41-60 years of age, Mean ± SD was calculated as 35.81 ± 9.03 years, frequency of malignant thyroid nodules on reference standard was recorded as 6.67% (n=11) while 93.33% (n=154) were benign, FNAC as reference standard shows that 81.82%, 95.45%, 56.25%, 98.65% and 98.09% had sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate. **CONCLUSION:** Elastography has great potential as an adjunctive tool with other ultrasound modalities in diagnosing benign and malignant thyroid lesions. It is easy and rapid to perform and reduces the burden of unnecessary invasive procedures.

Key words: Thyroid nodules, benign, malignant, elastography differentiating, FNAC

Introduction

Thyroid nodular disease is characterized by the presence of one or more palpable or non palpable nodules within the substance of the thyroid gland. A thyroid nodule is defined as a discrete lesion within the thyroid gland that is distinguishable from the adjacent parenchyma by ultrasonography.[1] Thyroid nodules occur with relatively high frequency in the general population with prevalence of 4-7% by palpation alone and 13% to 67% (average 40%) by sonographic evaluation.[2] However, less than 7% of thyroid nodules are malignant.[2] The prevalence of these nodules in a population depends on a number of predisposing factors like age, sex, diet, iodine deficiency and radiation exposure.[3] The incidence of all thyroid diseases is higher in females than in males.[4]

Nodular thyroid disease is the most common cause of thyroid enlargement. Majority of patients with thyroid disease present with midline neck swelling, occasionally causing dysphagia and hoarseness of voice. Broadly the thyroid diseases are classified into three categories: (i) benign thyroid masses (ii) malignant tumors of thyroid gland, and (iii) diffuse thyroid enlarge-

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Submitted 1 March 2017, Accepted 13 April 2017

ment.[4] Cytology of thyroid nodules remains as a reference standard has sensitivity and specificity of 100% and 98.7% respectively.[5]

It is of clinical importance to diagnose malignant nodules from benign ones which do not require surgery and the challenge is to evaluate the thyroid nodule and to decide which patient should undergo cytology.[6] Conventional ultrasound does not provide direct information corresponding to the hardness of a nodule. Hence, elastography is a newly developed dynamic technique that uses ultrasound to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. Ultrasound elastography is applied to study the hardness/elasticity of nodules to differentiate malignant from benign lesions.[7]

A recent study in 2014 reported that on real-time ultrasound elastography, 47 of 62 benign nodules (76%) had a score of 1 or 2, whereas 15 of 16 malignant nodules had a score of 3 to 5, with sensitivity of 93.7%, specificity of 90%, a positive predictive value of 71%, and a negative predictive value of 98%.6 Another study reported that Fifty-four of the 84 nodules had scores of 1 and 2, and 50 of these nodules were diagnosed at cytology as benign. Thirty of the 84 nodules had a score of 3 and 4, and 21 of these nodules were diagnosed at cytology as malignant. The scores of 1 and 2 with Itoh criteria were significantly seen in benign nodules, whereas, scores of 3 and 4 were significantly seen in malignant nodules ($p < 0.05$) with sensitivity 84%, specificity 84.7%, PPV 70%, NPV 92.6% and accuracy 84.5%.[8]

The rationale of this study is to confirm the role of diagnostic accuracy of ultrasound elastography in differentiating benign from malignant thyroid nodules by taking fine needle aspiration cytology as reference standard in our population. Globally a lot of researches have been published and they preferred ultrasound elastography in differentiating benign from malignant thyroid nodules,[6,8] however in our country larger prospective studies are needed to confirm these results and establish the role of this new technique. We still relay on cytology that is an invasive procedure and takes time for diagnosis. Ultrasound elastography is an easy and rapid imaging technique that is useful in differential diagnosis of thyroid cancer. Its use would definitely reduce the rate of unnecessary thyroid biopsies because of its high elasticity is being highly associated with benign cytology. Hence if we find similar diagnostic accuracy as reported in literature then in future ultrasound elastography can be used as a powerful adjunct tool with other ultrasound modalities for early detection of benign or malignant conditions and avoid unnecessary invasive workup and anxiety for patients.

OPERATIONAL DEFINITIONS:

Diagnosis on cytology: Malignant means atypical malignant cells seen in cytology and benign mean normal healthy thyroid tissue without any evidence of atypical cells on cytological examination.

Diagnosis of benign and malignant using ultrasound elastography and strain ratio: Each nodule is assigned an elastography score based on 4 point scale according to the classification. Patients were considered as benign if they got Score 1 or 2 and Strain Ratio < 3 while malignancy was labeled if we get score 3 or 4 and Strain Ratio > 3. Strain Ratio of each nodule is calculated by dividing the strain value of normal tissue by that of nodule. The border line of lesion is manually traced and the homogenous adjacent thyroid tissue is used as a reference to calculate the SR automatically by using a dedicated soft ware connected to ultrasound machine. Strain ratio is calculated by dividing the strain value of normal thyroid tissue by that of nodule.

DIAGNOSTIC ACCURACY

True Positive: If malignancy is diagnosed on ultrasound elastography + strain ratio and cytology shows malignancy

False Positive: If malignancy is diagnosed on ultrasound elastography + strain ratio and cytology shows benign lesion

False Negative: If benign is diagnosed on ultrasound elastography + strain ratio and cytology shows malignancy

True Negative: If benign is diagnosed on ultrasound elastography + strain ratio and cytology shows benign lesion.

1. Sensitivity = $\frac{a}{a + c}$ x 100

2. Specificity = $\frac{d}{b + d}$ x 100

3. Positive predictive value = $\frac{a}{a + b}$ x 100

4. Negative predictive value = $\frac{d}{c + d}$ x 100

Material and Methods

STUDY SETTING: This study was conducted at Diagnostic Radiology Department, CMH Lahore

DURATION OF STUDY: The study was of 6 months duration; From: 01-07-2016 to 31-12-2016

STUDY DESIGN: This is a "Cross-sectional study"

SAMPLING TECHNIQUE: This is a "Non-probability Consecutive Study"

SAMPLE SIZE: 165 cases were taken as sample size is calculated by using expected average percentage 40% prevalence of thyroid nodule and expected sensitivity of 93.7%, specificity of 90% of ultrasound elastography at 5% margin of error for sensitivity and 5% margin of error for specificity and 95% confidence level.

SAMPLE SELECTION:

Inclusion Criteria: Patients aged 18-60 years of either gender having solid nodule in thyroid lobe on conventional ultrasound examination included, solid nodule appears echogenic, having variable shapes, intrinsic vascularity and at least 08-15 mm in size underwent elastography/cytology.

Exclusion Criteria:

Uncooperative and non-willing patients

Cystic nodules without any solid component

Large nodules occupying >75% of thyroid lobe volume because insufficient surrounding normal thyroid tissue to be used as reference.(assessed on ultrasound)

On ultrasound thyroid nodules with peripheral calcification are excluded because posterior shadowing/ calcification produce artifacts (assessed on elastographic examination).

DATA COLLECTION PROCEDURE:

A total of 165 patients were taken from patients meeting inclusion criteria and permission from 'Hospital Ethical Committee' & informed consent was obtained before commencing the study. Patients basic demographic (age, gender) and clinical history were taken after an informed consent. All patients referred to diagnostic radiology department CMH Lahore to undergo ultrasound elastography, The ultrasound machine X TOUCH was used for all patients with a 7.5 (5-12 MHz) high frequency linear array transducer by using both conventional gray-scale and elastographic scanning. Ultrasound examination was done in a dim light room in a comfortable temperature (22°C - 24°C). All patients were examined in supine position with hyperextended neck. The ultrasound examination started with B mode imaging access thyroid nodular size, its solid nature, presence of sufficient surrounding reference tissue and internal vascularity on doppler and. The region of interest (ROI) is center on the lesion including sufficient surrounding thyroid tissue. The patient was asked to avoid swallowing and hold breath during examination to minimize motion of thyroid gland. By applying appropriate pressure elasticity images were obtained. The deformity was represented by colour scale over the B mode image that range from blue (softest component with greatest elastographic strain) to red (hardest component with no elastographic strain). The images were displayed on split-screen mode with ultrasound grey scale images on left and ultrasound elastography images on right. Strain ratio of each nodule was calculated by dividing the strain value of normal tissue by that of nodule. The border line of lesion was manually traced and the homogenous adjacent thyroid tissue was used as a reference to calculate the SR automatically by using a dedicated software connected to ultrasound machine. For ultrasound guided FNAC informed consent was taken from all patients, (22-25 guage) needle is selected and under aseptic conditions sample is collected and sent for evaluation at the main laboratory of CMH Lahore. The report of the cytology was obtained in order to compare diagnosis of ultrasound elastography and cytolology as operational definition.

DATA ANALYSIS:

Using SPSS version 22 data was entered and analyzed. All qualitative variables of Benign and malignant cases on cytology and ultrasound elastography were presented in the form of frequency and percentages. Mean and standard deviation was used to express the continuous variable such as age of the patients. 2 x 2 table was made to calculate Sensitivity, specificity, positive predictive value and negative predictive value of ultrasound elastography taking cytology as reference standard. Data was stratified for age and gender to address effect modifiers and post stratification chi-square test was used. P-value ≤ 0.05 was taken as significant.

Results

A total of 165 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the role of ultrasound elastography in differentiating benign from malignant thyroid nodules by using FNAC as reference standard.

Age distribution of the patients was done, it shows that 61.82% (n=102) were between 18-40 years of age while 38.18% (n=63) were between 41 - 60 years of age, Mean + SD was calculated as 35.81 ± 9.03 years. (Tab. 1)

Age (in years)	Number of patients	%
18-40	102	61.82
41-60	63	38.18
Total	165	100
Mean ± SD	35.81 ± 9.03	

Table 1: Age distribution (n = 165)

Gender distribution shows that 42.42% (n=70) were male and 57.58% (n=95) were females. (Tab. 2)

Gender	Number of patients	%
Male	70	42.42
Female	95	57.58
Total	165	100

Table 2: Gender distribution (n = 165)

Frequency of malignant thyroid nodules on reference standard was recorded as 6.67% (n=11) while 93.33% (n=154) were benign. (Tab. 3)

Thyroid nodules	Number of patients	%
Malignant	11	6.67
Benign	154	93.33
Total	165	100

Table 3: Frequency of malignant thyroid nodules on reference standard (n = 165)

Role of ultrasound elastography in differentiating benign from malignant thyroid nodules by keeping cytology as reference standard shows that 81.82%, 95.45%, 56.25%, 98.65% and 98.09% had sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate. (Tab. 4)

Ultrasound Elastography	Cytology		Total
	Malignant (Positive)	Malignant (Negative)	
Positive	True positive(a) 9 (5.45%)	False positive (b) 7 (4.24%)	a + b 16(9.70%)
Negative	False negative(c) 2 (1.21%)	True negative (d) 147 (89.09%)	c + d 149 (90.30%)
Total	a + c 11 (6.67%)	b + d 154 (93.33%)	165 (100%)

Sensitivity = a / (a + c) x 100 =81.82%
Specificity = d / (d + b) x 100 = 95.45%
Positive predictive value = a / (a + b) x 100 =56.25%
Negative predictive value = d / (d + c) x 100 =98.65%
Accuracy rate = a + d / (a + d + b + c) x 100 = 98.09%

Table 4: Role of ultrasound elastography in differentiating benign from malignant thyroid nodules by using FNAC as reference standard (n = 165)

The data was stratified for age and gender to address effect modifiers and post stratification chi-square test was used. P-value ≤ 0.05 was taken as significant. (Tab. 5-6)

Age: 18-40 years

Ultrasound Elastography	Cytology		P value
	Malignant (Positive)	Malignant (Negative)	
Positive	True positive(a) 6	False positive (b) 5	0.000
Negative	False negative(c) 2	True negative (d) 89	
Total	a + c 8	b + d 94	

Sensitivity = a / (a + c) x 100 =75%
Specificity = d / (d + b) x 100 = 94.69%
Positive predictive value = a / (a + b) x 100 =54.54%
Negative predictive value = d / (d + c) x 100 =97.82%
Accuracy rate = a + d / (a + d + b + c) x 100 = 93.25%

Age: 41-60 years

Ultrasound Elastography	Cytology		P value
	Malignant (Positive)	Malignant (Negative)	
Positive	True positive(a) 3	False positive (b) 2	0.000
Negative	False negative(c) 0	True negative (d) 58	
Total	a + c 3	b + d 60	

Sensitivity = a / (a + c) x 100 =100%
Specificity = d / (d + b) x 100 = 96.67%
Positive predictive value = a / (a + b) x 100 =60%
Negative predictive value = d / (d + c) x 100 =100%
Accuracy rate = a + d / (a + d + b + c) x 100 = 95.06%

Table 5: Stratification for age

MALE

Ultrasound Elastography	Cytology		P value
	Malignant (Positive)	Malignant (Negative)	
Positive	True positive(a) 4	False positive (b) 4	0.000
Negative	False negative(c) 0	True negative (d) 62	
Total	a + c 4	b + d 66	

Sensitivity = a / (a + c) x 100 =100%
Specificity = d / (d + b) x 100 = 93.94%
Positive predictive value = a / (a + b) x 100 =50%
Negative predictive value = d / (d + c) x 100 =100%
Accuracy rate = a + d / (a + d + b + c) x 100 = 92.57%

FEMALE

Ultrasound Elastography	Cytology		P value
	Malignant (Positive)	Malignant (Negative)	
Positive	True positive(a) 5	False positive (b) 3	6.97
Negative	False negative(c) 2	True negative (d) 85	
Total	a + c 7	b + d 88	

Sensitivity = a / (a + c) x 100 =71.42%
Specificity = d / (d + b) x 100 = 96.59%
Positive predictive value = a / (a + b) x 100 =62.5%
Negative predictive value = d / (d + c) x 100 =97.70%
Accuracy rate = a + d / (a + d + b + c) x 100 =94.47%

Table 6: Stratification for gender

Discussion

Ultrasound elastography has been introduced as a noninvasive technique for evaluating thyroid nodules that encompasses a variety of approaches such as supersonic shear imaging and acoustic radiation force impulse imaging as well as real-time tissue elastography.

This study was planned with the view to confirm the role of elastography in differentiating benign from malignant thyroid nodules by using fine needle aspiration cytology as reference standard in our population.

In our study, 42.42% (n=70) were male and 57.58% (n=95) were females, age distribution of the patients was done, it shows that 61.82% (n=102) were between 18-40 years of age while 38.18% (n=63) were between 41-60 years of age, mean ± SD was calculated as 35.81 ± 9.03 years, frequency of malignant thyroid nodules on reference standard was recorded as 6.67% (n=11) while 93.33% (n=154) were benign, diagnostic accuracy of ultrasound elastography in differentiating benign from malignant thyroid nodules by keeping FNAC as reference standard shows that 81.82%, 95.45%, 56.25%, 98.65% and 98.09% had sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate.

Cytology of thyroid nodules remains as a reference standard has sensitivity and specificity of 100% and 98.7% respectively.[5]

It is of clinical importance to diagnose malignant nodules from benign ones which do not require surgery and the challenge is to evaluate the thyroid nodule and to decide which patient should undergo biopsy.[6] Conventional ultrasound does not provide direct information corresponding to the hardness of a nodule. Hence, elastography is a newly developed dynamic technique that uses ultrasound to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. Ultrasound elastography is applied to study the hardness/elasticity of nodules to differentiate malignant from benign lesions.[7]

A recent study in 2014 reported that on real-time ultrasound elastography, 47 of 62 benign nodules (76%) had a score of 1 or 2, whereas 15 of 16 malignant nodules had a score of 3 to 5, with sensitivity of 93.7%, specificity of 90%, a positive predictive value of 71%, and a negative predictive value of 98%.[6] Another study reported that Fifty-four of the 84 nodules had scores of 1 and 2, and 50 of these nodules were diagnosed on cytology as benign. Thirty of the 84 nodules had a score of 3 and 4, and 21 of these nodules were diagnosed on cytology as malignant. The scores of 1 and 2 with Itoh criteria were significantly seen in benign nodules, whereas, scores of 3 and 4 were significantly seen in malignant nodules (p <0.05) with sensitivity 84%, specificity 84.7%, PPV 70%, NPV 92.6% and accuracy 84.5%.[8]

Several studies have evaluated the accuracy and role of SR for the detection of malignant thyroid nodules.

A recent study[9] involving 344 thyroid nodules evaluated the accuracy and inter operator agreement of SR for the detection of malignancy. The authors found a sensitivity of 93% and a specificity of 92% for the expert operator and excellent inter operator agreement. Data were unaffected by nodule size or thyroiditis. These findings were confirmed in multivariate analysis demonstrating a significant correlation of the SR with malignancy.

Chong et al.[10] found that although US elastography is helpful to predict malignant thyroid nodules, the addition of SR to color mapping does not improve performance compared to color mapping alone. They also found that a ratio higher than 1.21 may serve as the best cut-off value for predicting malignancy. However, according to the meta-analysis published in 2013, SR performed slightly better than qualitative USE and any other US features.

Another meta-analysis published in 2013[11] included 24 studies with 2624 patients and 3531 thyroid nodules (927 malignant and 2604 benign). Their statistical analysis yielded diagnostic performance measures which were better for SE than for US features. The sensitivities and specificities were, respectively, as follows: elasticity score, 82% and 82%; strain ratio, 89% and 82%; hypoechogenicity, 78% and 55%; microcalcifications, 50% and 80%; irregular margins, 66% and 81%; absent halo sign, 56% and 57%; nodule vertical development, 46% and 77%; and intranodular vascularization, 40% and 61%. They concluded that USE increased US accuracy. The differences in the results of the above studies are likely to result from differences in the frequency of malignancy within the study groups as well as the specific technology employed. The risk of malignancy in the study by Moon et al.[9] was 30%, while in the one by Azizi et al.[13] it was 11.40%, indicating that very different populations were being evaluated. Furthermore, Moon et al. excluded complex lesions with > 20% cystic component or lesions containing macrocalcifications.[9]

Globally a lot of researches have been published and they preferred ultrasound elastography in differentiating benign from malignant thyroid nodules[6,8] but large prospective studies needed in our country to confirm these results and establish diagnostic accuracy of this new technique elastography.

Conclusion

Elastography has great potential as an adjunctive tool with other ultrasound modalities in diagnosing benign and malignant thyroid lesions. It is easy and rapid to perform and reduces the burden of unnecessary invasive procedures.

References

1. Popli MB, Rastogi A, Bhalla P, Solanki Y. Utility of gray-scale ultrasound to differentiate benign from malignant thyroid nodules. Indian J Radiol Imag 2012; **22(1):** 63-8.

2. Yunus M, Ahmed Z. Significance of ultrasound features in predicting malignant solid thyroid nodules: need for fine-needle aspiration. J Pak Med Assoc 2010; **60(10):** 848-53.

3. Rani C, Lal P, Mahmood T. Comparative study for the evaluation of solitary thyroid nodule: ultrasonography versus fine needle aspiration cytology. Pak J Surg 2014; **30(1):** 14-7.

4. Chaudhary V, Bano S. Thyroid ultrasound. Indian J of endocrinol and metabol 2013; **17(2):** 219-27.

5. Sunita K, Shere, Anjali S. Kulkarni, Pragati P Phulgirkar. Correlation of fine needle aspiration cytology with histopathology in diagnosis of thyroid lesions. Journal of Evolution of Medical and Dental Sciences 2013; **(2):** 4826-31.

6. Eltyib HEH, Awad IA, Elsayed NM, Jastaniah SD. Real Time Ultrasound Elastography for the Differentiation of Benign and Malignant Thyroid Nodules. Open J Med Imag 2014; **4(1):** 38-47.

7. Bhargava S, Bhargava SK, Sharma S, Prakash M. Elastography: a new imaging technique and its application. JIMSA 2013; **(26):** 25-30.

8. EL-Hariri MA, Ali TFT, Tawab MA, Magid AM, Abdel-Fattah E-S. The clinical value of ultrasound

elastography in predicting malignant thyroid nodules. Egyp J Radiol and Nuclear Med 2014; **45(2):** 353-9.

9. Moon WJ, Baek JH, Jung SL, Kim DW, Kim EK, Kim JY. Ultrasonography and the ultrasound-based management of thyroid nodules: consensus statement and recommendations. Korean J Radiol 2011; **12:** 1-14.

10. Chong Y, Shin JH, Ko ES, Han BK. Ultrasonographic elastography of thyroid nodules: is adding strain ratio to colour mapping better? Clinical Radiology. 2013; **68(12):** 1241-6.

11. Razavi SA, Hadduck TA, Sadigh G, Dwamena BA. Comparative effectiveness of elastographic and b-mode ultrasound criteria for diagnostic discrimination of thyroid nodules: a meta-analysis. American Journal of Roentgenology. 2013; **200(6):** 1317-26.

12. Cantisani V, Grazhdani H, Ricci P. Q-elastosonography of solid thyroid nodules: assess-ment of diagnostic efficacy and interobserver variability in a large patient cohort. European Radiology. 2014; **24(1):** 143-50.

13. Azizi G, Keller J, Lewis M, Puett D, Rivenbark K, Malchoff C. Performance of elastography for the evaluation of thyroid nodules: a prospective study. Thyroid. 2013; **23(6):** 734-40.

14. 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 Am J Roentgenol 2009; **193:** W416-W423.

15. Asteria C, Giovanardi A, Pizzocaro A, Cozzaglio L, Morabito A, Somalvico F. US-elastography in the differential diagnosis of benign and malignant thyroid nodules. Thyroid 2008; **18:** 523-31.

16. Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T. Breast disease: clinical application of US elastography for diagnosis. Radiology 2006; **239:** 341-50.

17. Kim H, Kim JA, Son EJ, Youk JH. Quantitative assessment of shearwave ultrasound elastography in thyroid nodules: diagnostic performance for predicting malignancy. Eur Radiol 2013; **23:** 2532-7.

18. Bamber J, Cosgrove D, Dietrich CF. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1. Basic principles and technology. Ultraschall in der Medizin. 2013; **34(02):** 169-84.

19. Ueno E, Itoh A. Diagnosis of breast cancer by elasticity imaging. Eizo Joho Medical. 2004; **36(12):** 2-6.

20. Rago T, Santini F, Scutari M, Pinchera A, Vitti P. Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. Journal of Clinical Endocrinology and Metabolism. 2007; **92(8):** 2917-22

21. Rubaltelli L, Stramare R, Tregnaghi A. The role of sonoelastography in the differential diagnosis of neck nodules. Journal of Ultrasound. 2009; **12(3):** 93-100.

22. Bae U, Dighe M, Dubinsky T, Minoshima S, Shamdasani V, Kim Y. Ultrasound thyroid elastography using carotid artery pulsation: preliminary study. Journal of Ultrasound in Medicine. 2007; **26(6):** 797-805.

23. Cantisani V, Lodise P, di Rocco G. Diagnostic accuracy and interobserver agreement of quasistatic ultrasound elastography in the diagnosis of thyroid nodules. Ultraschall in der Medizin. 2014