Research Article   Open Access

Strain Elastosonography of Thyroid Nodules: A New Tool for Malignancy Prediction? Overview of Literature

Cannataro G*, Mastrodicasa D, Cotroneo AR and Caulo M

Department of Neurosciences, Imaging and Clinical Sciences, Section of Diagnostic Imaging and Therapy-Radiology Division, "G. d'Annunzio" University, Chieti, Italy

***Corresponding author:** Giovanni Cannataro MD, Department of Neurosciences, Imaging and Clinical Sciences, Section of Diagnostic Imaging and Therapy-Radiology Division, "G. d'Annunzio" University, Chieti, Italy, E-mail: cannatarogiovanni@gmail.com

Abstract

Ultrasound (US) elastography is a new non-invasive technique that uses ultrasounds to provide quantitative information about tissue stiffness. Two kinds of elastography (strain and shear wave elastography) are currently used in clinical practice. Although fine needle aspiration (FNA) is the most important procedure for the management of thyroid nodules, several studies have used US elastography as an adjunctive tool to conventional US, to differentiate malignant from benign nodules. In these studies malignant nodules are often associated with a greater elasticity scoring compared to benign. The conventional US plays an important role in defining which nodules are suitable for the US elastography because calcified and cystic nodules could be responsible for false positive and negative results respectively. On the other hand, follicular carcinoma gross anatomy and cellular pattern may resemble those of benign follicular adenoma. The histologic examination is often necessary to discover capsular or vascular invasion. Moreover, in contemporary literature there is disagreement about the role of US elastography in thyroid nodules with indeterminate or non-diagnostic cytology.

Keywords: Strain elastography; Thyroid nodule; Malignancy

Introduction

Elastosonography is a newly developed dynamic technique that provide an estimation of tissue stiffness via ultrasounds (US). This is achieved by measuring the degree of distortion under the application of an external force. This technique is based on the principle that when body tissues are compressed the softer parts deform more easily than the harder parts [1-2]. Strain US elastography technique is based on low-frequency compression of the tissue, which is usually applied manually via the hand-held ultrasound transducer (also known as free-hand EUS). The main principle of strain EUS is based on a compressive force applied to tissue causing axial tissue displacement (strain, Figure 1). Tissues' stiffness is calculated by comparing the echo sets before and after the compression. Ultrasound elastogram is displayed over a B-mode image in a color scale that ranges from red for components with the greatest elastic strain (i.e., softest components), to blue for those with no strain (i.e., hardest components) [3-5].

Analytical Discussion

Strain elastography is used to characterize thyroid nodules. They are very common in population and are found in 50% of ultrasound examinations Most nodules are benign, with approximately 5% to 10% of malignancy [6]. As reported by recent consensus, a firm or hard consistency upon palpation is associated with an increased risk of malignancy [7]. Fine needle aspiration cytology (FNAC) is the best single test for differentiating malignant from benign thyroid lesions. The major limitation of FNAC is that 10% to 15% of specimens are non-diagnostic or indeterminate [8].
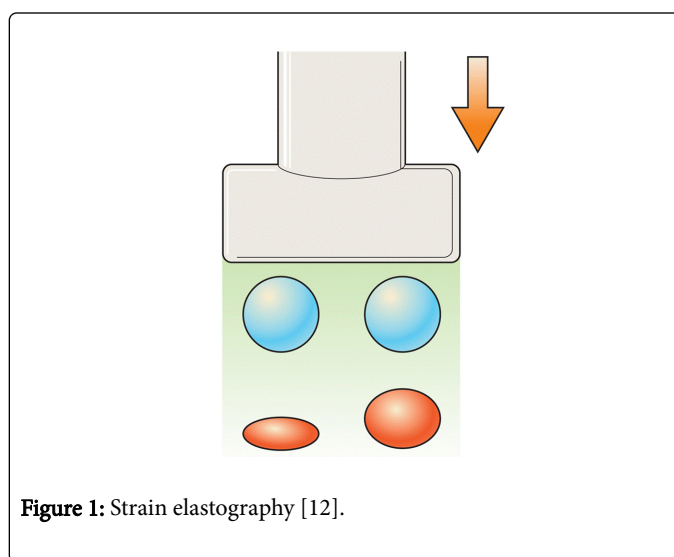

Figure 1: Strain elastography [12].

In Fukunari's study [9] strain elastography was used in order to characterize thyroid tumors such as papillary cancer, follicular cancer, and adenomatous goiter. Patients were studied first with conventional US and strain elastography, then diagnosed cytologically and finally surgically treated. Elastography images were also compared with CT images, cytological diagnosis, surgical specimen sections, and pathological findings. Strain elastography visualization is classified as pattern 1 (nodule is relatively homogeneous green and thus soft), pattern 2 (nodule has a soft green center and blue hard periphery), pattern 3 (nodule shows a mixture of soft and hard areas), and pattern 4 (the whole nodule is hard). Of the 72 benign thyroid nodules found, 83.3% showed pattern 1, 4.2% pattern 2 and 12.5% cases pattern 3 (Figure 2).
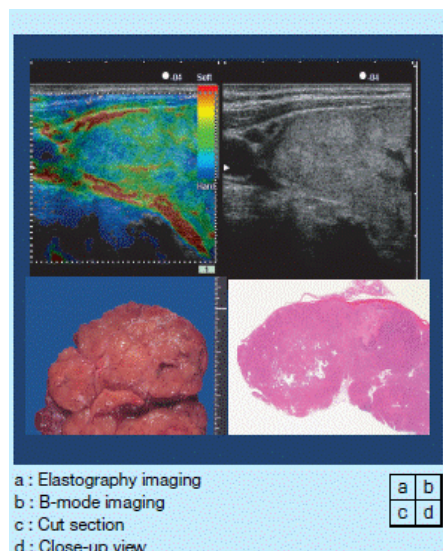
Figure 2: Adenomatous goiter. In elastographic image a, the whole tumor is displayed as light green up to the periphery, so it was classified as pattern 1. Figures c and d show respectively a cut section and a histologic specimen [9].

In cases of thyroid papillary cancer pattern 3 and 4 were obtained. They were thought to be characteristic findings for this condition (Figure 3).
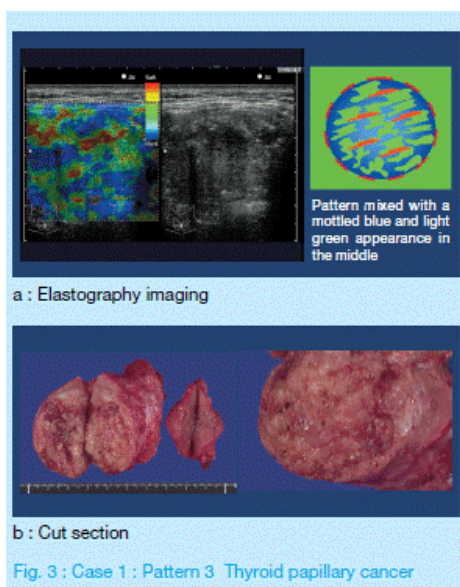

Figure 3: Papillary cancer with a typical pattern 3, a mix of soft and hard areas. Conventional-US image shows microcalcifications, hard at elastographic map [9].

Thyroid follicular cancer was found in sixteen cases. Fourteen of them showed elastosonographic pattern 2, 1 case pattern 1 and 1 case pattern 3 (Figure 4).
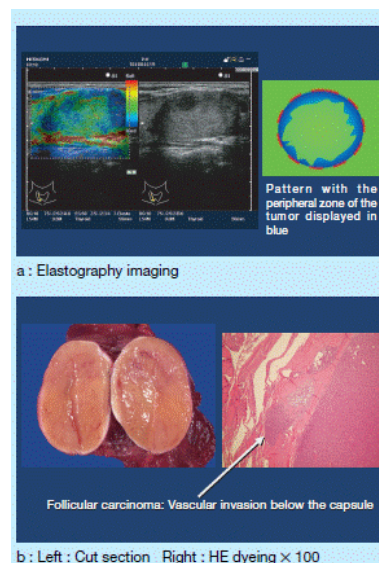

Figure 4: Follicular Carcinoma with type 2 elastosonographic map [9].

This study then observed a great overlap related to pattern 2 between benign nodules and follicular cancer. Thyroid follicular tumors tend to have a typical pattern 2, with peripheral blue hard zone and a green soft center. Clinical application of thyroid elastography was reported in 2007 by Rago and colleagues [10]. They studied the hardness/elasticity of nodules in 92 patients. They were then able to differentiate malignant from benign lesions, supported by FNAC and histology. All lesions were classified on a five-point scale, based on Ueno and Itoh's strain elastography study published on 2006 [11]. A score of 1 defines elasticity that is entirely soft in the nodule. Score 2 is mostly soft in the nodule with some internal spots of hard. Score 3 is peripherally soft and centrally hard. Score 4 is entirely hard in the nodule, and score 5 is hard in the entire nodule as well as the perilesional area (Figure 5).

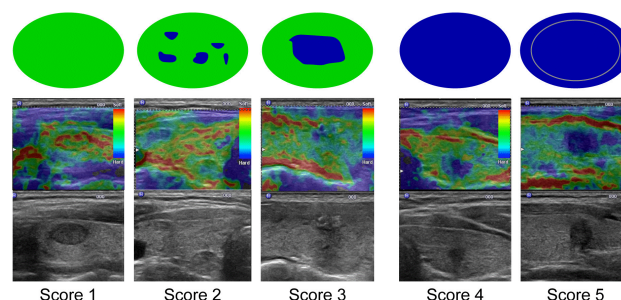**Figure 5:** Strain elastographic scores by Rago et al. [10].

Thyroid nodules with Rago's score 1 to 3 were found to be benign, while score 4 and 5 had an elastographic feature suggestive for malignancy (Table 1). US elastography score 1 was found in 41 cases, all benign lesions; score 2 in eight cases, all benign; score 3 in 13 cases, one of which carcinoma and 12 benign; score 4 in 16 cases, all

carcinomas; and score 5 in 14 cases, all carcinomas [12,13]. It showed a sensitivity of 97%, a specificity of 100%, a positive predictive value (PPV) of 100%, and a negative predictive value (NPV) of 98%.

	BN (n=BB)	CA (n=7)	P value
Hypoechogenicity on US			0.1
Present	14	6	
Absent	11	1	
Halo sign on US			0.6
Present	24	7	
Absent	1	0	
Spot microcalcifications on US			0.8
Present	6	2	
Absent	19	5	
Type IN vascularization on US			0.5
Present	1	0	
Absent	24	7	
Score 1-3 on US elastography	25	1	<0.0001
Score 4-5 on US elastography	0	6	
BN: Benign lesions; CA: Carcinoma.			

Table 1: Predictive values of US and US elastography in a subgroup of 32 patients with indeterminate nodule on FNA. There is a strong correspondence of score 4-5 with malignancy [10].

The statistical data of this study demonstrated that the overall values of sensitivity and specificity are respectively 97% and 100%, with PPV of 100% and NPV of 98%. The study concludes that US elastography has great potential as an adjunctive tool for the diagnosis of thyroid cancer, especially in indeterminate nodules on cytology. Larger prospective studies are needed to confirm these results and establish the diagnostic accuracy of this new technique.

In 2011 Lippolis and colleagues tried to verify the potential role of strain elastosonography in surgical selection of nodules with indeterminate or not diagnostic cytology [14]. 102 patients were studied with conventional ultrasonography and strain US elastography before being operated on for thyroid nodules with indeterminate cytology. All patients underwent surgical resection and nodular histology. Tissue stiffness was scored from 1 to 4 [15], where nodules with a score of 3 and score 4 had a prevalence of hardness and were suspicious for malignancy (Figure 6).

Results shows that elasticity was high in eight cases only (with score 1–2) although low in 94 (with score 3–4). Cancer was diagnosed in 35% of nodules, and associated with microcalcifications and inversely related to nodule diameter. Malignancy was detected in 50% of the nodules with a real-time elastography (RTE) score of 1–2 and in 34% of those with a score 3–4. Therefore, either the positive (34%) or the negative predictive value (50%) was clinically negligible. The study does not confirm the usefulness of strain elastography in pre-surgical selection of nodules with indeterminate cytology and suggests the need

for quantitative analytical assessment of nodule stiffness to improve EUS efficacy.
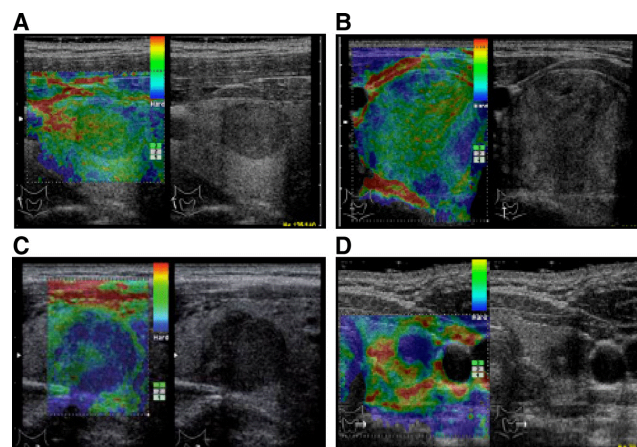

Figure 6: Tissue stiffness was scored from 1 to 4, where nodules with a score of 3 (showed in image C) and score 4 (showed in image D) had a prevalence of hardness and were suspicious for malignancy [14].

In another study, Eltyib and colleagues evaluate the predictive value of strain elastography in differentiating benign from malignant thyroid nodules, with FNAC as a reference standard [16].

A prospective evaluation was performed in 100 patients with thyroid nodules. All patients were evaluated by conventional-US imaging and strain elastography, followed by FNAC. Tissue stiffness on ultrasound elastography was scored by Ei Ueno and Itoh classification [11].

In this study, Strain elastography differentiated benign from malignant nodules with overall values of sensitivity, specificity, PPV and negative NPV of about 94%, 90%, 71% and 98% respectively. In particular, Score 4 and 5 were associated with malignancy with sensitivity of 87%, specificity of 90%, PPV of 68% and NPV of 90%.

In 2015, Sjoerd and colleagues published a systematic review and meta-analysis [17] on the possibility of replacing fine-needle aspiration (FNAB) of a soft thyroid nodule with qualitative elastography. All studies were supported by cytology and histology.

Two authors independently performed a selection of studies on Pubmed, Embase and Cochrane Library, reviewing about 4000 citations. After a quality assessment, 20 study were included in the meta-analysis. Because the included articles used several color classification systems and thresholds to distinguish between benign and malignant nodules, all nodules were classified according to the Asteria elastography (ES) classification. This classification is a 4-point scale. ES 1 is assigned to nodules with elasticity in the entire examined area, ES 2 for nodules with elasticity in a large portion of the examined area, ES 3 for nodules with stiffness in a large portion of the examined area, and ES 4 for hard nodules. The 4-point Asteria classification was used to generate 4 by 2 tables. A threshold between Asteria ES 2 and ES 3 was pre-specified and used during the statistical analysis to differentiate between potential malignant and benign nodules. Sensitivity, specificity, PPV, NPV, and corresponding 95% confidence intervals of the studies were pooled using methods that preserved the

2-dimensional nature of the data and accounted for variability within and between studies. A total of about 4000 nodules were analyzed, 62% of which were ES 1 or ES 2. The respective pooled sensitivity and specificity of elastography in differentiating between malignant and benign thyroid nodules were 85% and 80%. The respective pooled NPV and PPV were 97% and 40. 14% of nodules were ES 1. The pooled sensitivity and specificity of these studies for Asteria 1 nodules were 99% and 14% respectively. Only about 4% of the false negative nodules were found to be follicular carcinoma. From the conclusions of the meta-analysis, elastography seems to have a fair specificity and diagnostic accuracy in thyroid nodules' characterization. Its major strength entails the detection of benignity, especially when only completely soft nodules are qualified as benign. So, FNAC could be safely omitted in nodules with Asteria 1 elastosonographic pattern.

Conclusion

After this overview of literature we can conclude that strain elastosonography is a promising imaging technique. It demonstrated a significant accuracy in the differential diagnosis of thyroid cancer, in addition to conventional-US. It is useful for non-diagnostic nodules in a cytology evaluation. Since high elasticity has been highly associated with benign cytology, the use of US elastography could reduce the rate of thyroid biopsy and surgery. However, it is still a technique operator-dependent, since strain elastography reproducibility may vary according to the amount of externally applied pressure as well as the specific experience of operator. Diagnosis of follicular cancer is controversial, for the overlapping of its map with benign nodules (in particular, for Asteria's score 2) and consequently false negatives. Finally, the presence of coarse calcifications and cystic components, that are stiff, could cause false positives for thyroid cancer.

References

1. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X (1991) Elastography, a quantitative method for imaging the elasticity of biological tissues. Ultrason Imaging 13: 111-134.

2. Ophir J, Alam SK, Garra B, Kallel F, Konofagou E, et al. (1999) Elastography: Ultrasonic Estimation and Imaging of the Elastic Properties of Tissues. Proc Inst Mech Eng H 213: 203-233.

3. Hall TJ (2003) AAPM/RSNA physics tutorial for residents: topics in US: beyond the basics: elasticity imaging with US. Radiographics 23: 1657-1671.

4. Garra BS (2007) Imaging and estimation of tissue elasticity by ultrasound. Ultrasound Q 23: 255-268.

5. Garra BS (2011) Elastography: current status, future prospects, and making it work for you. Ultrasound Q 27: 177-186.

6. Gharib H, Papini E, Paschke R (2008) Thyroid nodules: a review of current guidelines, practices, and prospects. Eur J Endocrinol 159: 493-505.

7. American Association of Clinical Endocrinologists (2006) AACE/AME Task Force on Thyroid Nodules. Endocr Pract 12: 63-102.

8. Castro MR, Gharib H (2003) Endocrine Practice. 9: 128-136.

9. Fukunari N (2007) MEDIX Suppl.

10. Rago T, Santini F, Scutari M, Pinchera A, Vitti P (2007) Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. J Clin Endocrinol Metab 92: 2917-2922.

11. Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, et al. (2006) Breast disease: clinical application of US elastography for diagnosis. Radiology 239: 341-350.

12. Kwak JY, Kim EK (2014) Ultrasound elastography for thyroid nodules: recent advances. Ultrasonography 33: 75-82.

13. Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, et al. (2005) Thyroid gland tumor diagnosis at US elastosonography. Radiology 237: 202-211.

14. Lippolis PV, Tognini S, Materazzi G, Polini A, Mancini R, et al. (2011) Is elastography actually useful in the presurgical selection of thyroid nodules with indeterminate cytology? J Clin Endocrinol Metab 96: E1826-E1830.

15. Asteria C, Giovanardi A, Pizzocaro A, Cozzaglio L, Morabito A, et al. (2008) US-elastography in the differential diagnosis of benign and malignant thyroid nodules. Thyroid 18: 523-531.

16. Eltyib HEH, Awad IA, Elsayed NM, Jastaniah SD (2014) Real Time Ultrasound Elastogra- phy for the Differentiation of Benign and Malignant Thyroid Nodules. Open J Medical Imaging 4: 38-47.

17. Nell S, Kist JW, Debray TP, de Keizer B, van Oostenbrugge TJ, et al (2015) Qualitative elastography can replace thyroid nodule fine-needle aspiration in patients with soft thyroid nodules. A systematic review and meta-analysis. Eur J Radiol 84: 652-661.