Evaluation of Confounding Factors of Strain Sonoelastography in Patients With Thyroid Nodules

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Abstract- Thyroid nodule elastography has been exceedingly used for the differentiation of benign and malignant nodules. Determination of confounding factors of the results of sonoelastography in thyroid nodules when assessing the probability of malignancy is an issue of importance, and this matter needs further research. In this study, the contributing factors to the results of strain sonoelastography in cases of thyroid nodules were assessed in order to help the clinicians for better management and decision making. In this diagnostic study in Taleghani Hospital, Tehran, Iran, in 2018 and 2019, a total of 92 consecutive patients with thyroid nodules were assessed by grayscale ultrasound and strain sonoelastogaphy, and the contributing factors to the results of sonoelastography were determined according to low and high malignancy probability elasticity scores. The results in this study demonstrated that there were 57 cases (62%) with low probability scores and 35 patients (38%) with high probability scores according to strain sonoelastogaphy. The patient's age and nodule grayscale characteristics such as shape, echogenicity, margin, composition, size, and calcification were not related to sonoelastography results (P>0.05). This study showed that results of sonoelastography are not related to demographic factors and gray-scale sonographic features of the nodules.

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Keywords: Strain sonoelastography; Thyroid nodule; Elasticity score; Gray-scale sonography

Introduction

Thyroid disorders are common endocrinologic diseases, with hyperthyroidism, hypothyroidism, and goiter having prevalence rates of 2.5%, 4.8%, and 2.9%, respectively (1,2). Somatic and mental disorders are some adverse consequences in patients with thyroid diseases (3). Further clinical symptoms and adverse effects can affect the quality of life more prominently (3,4). Thyroid nodules are also well-recognized disorders of the gland, in which, despite the good diagnostic ability for total thyroidectomy (5), it may impose some complications and additional costs, and the use of fine-needle aspiration (FNA) and the frozen section as less invasive methods is popular (6). Determination of pathology results of thyroid nodules can be helpful for planning the treatment (7-11). In addition, besides less invasion of FNA, it is still an invasive diagnostic method, and the use of imaging techniques such as sonoelastography can help the clinician to access higher diagnostic thresholds (12). Also, the FNA sensitivity and specificity ranged from 60-98% and 54-90%, respectively (6). The nodule ultrasound characteristics such as size, echogenicity, calcification, margin, and vascularity are important indicators, but the results of sonoelastography can still improve the diagnostic capability of differentiating benign and malignant nodules (12,13). Sonoelastography applicability was initially done as static and free-hand (strain), which is related to pressure amount and also the operator skills (13). The introduction of shear wave elastography led to more accurate results since it is not pressure-dependent and has good reproducibility (13-18). The strain method can reflect the tissue deformity as color-coded elasticity scores, and higher scores are reflective of high malignancy probability. Determination of contributing factors can be helpful for better

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applicability and higher accuracy. Accordingly, in this study, we tried to search for the confounding and contributing factors to the results of stain sonoelastography with respect to the patients' demographics and grayscale ultrasound features. The endocrinologists should be aware of these limitations in elastography application in order to reduce the number of unnecessary FNA procedures.

Materials and Methods

In this diagnostic study in Taleghani Hospital, Tehran, Iran in 2018 and 2019, initially totally 92 consecutive patients with thyroid nodules were assessed and the contributing factors to the results of sonoelastography were determined with regard to low and high probability elasticity scores. The study was approved by local ethical committee in Shahid-Beheshti University of Medical Sciences. (Ethical code: IR.SBMU.MSP.REC.1397.419)

Data were collected by clinical assessment and interview, in addition to grayscale ultrasound and strain sonoelastography examination. The patients were referred for thyroid sonography by the hospital's endocrinology clinic based on nodule sensation on physical exam or for follow up of known thyroid nodule. They were provided by an informed consent. All included patients were going to perform an FNA of thyroid nodule based on clinical decision. Grayscale ultrasound and strain sonoelastography were done using a 7MHz linear array transducer of GE Voluson sonography device. The gathered data were recorded in checklist including patent's age and sex, grayscale nodule sonographic features (shape, margin, location, composition, size, echogenicity, calcification) and elasticity score of nodule. The elasticity scores are defined as color-coded patterns seen superimposed on nodules using strain elastography which most commonly are devided into 4 or 5 patterns(scores). In this study we used the 4-scores pattern described as below:

1-Elasticity score 1: the entire nodule is elastic.
2- Elasticity score 2: most of the nodule is elastic.
3-Elasticity score 3: most of the nodule is stiff.
4-Elasticity score 4: the entire nodule is stiff.

The patients then underwent FNA by their endocrinologist. After obtaining the FNA cytology results, we revised the demographic and grayscale sonographic features in patients whose nodules were reported as pathologically benign, in order to determine whether these features can act as confounding factors on elastography results (many of these benign nodules were labeled as malignant based on elastography results; the exact numbers are outlined in the rest of the paper).

Data analysis was done by SPSS (Statistical Package for Social Sciences) version 20.0 software. The utilized tests were chi-square, fisher, and Independent-Sample-T, and the *P* less than 0.05 were considered statistically significant.

Results

Among the initial 92 referred patients, 83 (90.2%) were female, and 9 (9.8%) were male. There were 57 nodules (62%) with low malignancy probability scores (elasticity scores 1 and 2) and 35 nodules (38%) with high malignancy probability scores (elasticity scores 3 and 4) according to strain elastography. After obtaining the FNA results, 57 nodules had benign cytology (62%), 3 were reported as PTC (3.3%), 1 MTC (1.1%), 19 nondiagnostic results (20.7%), 11 atypia of undetermined significance (12%), and 1 follicular neoplasm (1.1%). We excluded the nodules without obvious benign cytology. Among benign nodules, we had 38.6% high malignancy probability elasticity score (ES=3 or 4) and 61.4% low malignancy probability elasticity score (ES=1or 2). Due to this unacceptably high percentage of malignant estimation of true benign nodules by strain elastography, we tried to correlate grayscale sonographic features of nodules with elasticity score to see if there is any correlation between them and search for the possible confounding factors.

The patients had an average age of 49.4 years. The mean nodule size was 26.1mm (in the greatest dimension). 40.4% of nodules were mixed solid-cystic, and 59.6% were completely solid. 21.1% of nodules didn't have any calcification, 3.5% had macrocalcification, 1.8% had rim calcification, 68.4% had microcalcification, and 5.3% had both macro and microcalcification. 15.8% of nodules were hyperechoic, 52.6% were isoechoic, and 31.6% were hypoechoic. The grayscale sonographic features of these nodules are described in Table 1.

Also, among these benign nodules, 12 (21.1%) were reported as Hashimoto thyroiditis.

After statistical analysis, we found no significant correlation between nodule composition, calcification, echogenicity, shape, margin, and size and the result of strain elastography, using a confidence interval of 95% ($P>0.05$). Also, there was no correlation between Hashimoto pathology and elasticity score. The patient's age was not related to the elastography results.

Table 1. Frequency of grayscale ultrasound and elastographic features of benign nodules.

Composition	**Solid 34(59.6%)**			**Mixed solid-cystic 23(40.4%)**	
Calcification	None 12(21.1%)	Macrocalcification 2(3.5%)	Rim calcification 1(1.8%)	Microcalcification 39(68.4%)	Both micro and macrocalcification 3(5.3%)
Echogenicity	Hyperechoic 9(15.8%)		Isoechoic 30(52.6%)	Hypoechoic 18(31.6%)	
Shape	Wider than tall 55(96.5%)			Taller than wide 2(3.5%)	
Margin	Smooth 36(63.1%)		Ill-defined 3(5.3%)	Lobulated or irregular 18(31.6%)	
Size (greatest dimension)	Less than 15mm 11(19.3%)		15 to 24mm 17(29.8%)	25mm and more 29(50.9%)	
Elasticity score	High malignancy probability (ES=3,4) 22(38.6%)			Low malignancy probability (ES=1,2) 35(61.4%)	

Discussion

In this study, we tried to find the factors which can be confounding to the results of strain elastography. Interestingly, we found no related factors in this section. Plenty of studies have reported different ranges of accuracy for strain elastography of thyroid nodules up to now, and this emphasizes the need for searching for contributing factors, as well as the need for progression to more quantitative methods (such as available shear-wave elastography). The relatively low specificity of strain elastography described in some studies can lead to unnecessary invasive procedures. This matter shows the importance of higher clinical suspicion for cases without definite pathological findings. Since the invention of elastography techniques for medical imaging, many trials have taken place all around the world to assess the accuracy of this technique. The reported accuracies vary widely (12-18). Esfahanian *et al*., (12) reported the sensitivity of 61% and specificity of 78% for differentiating benign and malignant nodules when using an elasticity score of 2 as the cutoff. A systematic review by Ghajarzadeh *et al.*, (14) with the inclusion of 12 studies showed that strain sonoelastography has a sensitivity of 86% and specificity of 66%, and determination of related factors can help to better diagnosis. This matter again shows the importance of the study. Colakoglue *et al.*, (13) assessed 293 thyroid nodules and found a positive predictive value of 61.7% for strain elastography. It seems that elastography, although a useful adjunct for determining malignancy probability in thyroid nodules, has limitations and should be carefully interpreted as a malignancy indicator. Many studies have demonstrated high negative predictive values of elastography to rule out malignancy (18), But care should be taken when labeling a thyroid nodule as "malignant" based on elastography alone. It is necessary for the clinicians to be familiar with contributing factors that can affect the elastography result. A study by Wu *et al*., (19) assessed 244 patients and reported that margin status, microcalcification, and echogenicity were related to sonoelastography findings. But in our study with a smaller sample size, none of them were related to the elasticity score. In a study by Bhatia *et al*., (20), The ES was not significantly different between benign and malignant nodules (P=0.09) unless partially cystic nodules were excluded (P=0.005).; however, we didn't find any statistical difference between elasticity score of completely solid and mixed solid-cystic benign nodules. Strain elastography is a subjective method with visual assessment of color-coded patterns; Also, it is a free-hand technique with the need for manual compression of the ultrasound probe. These issues can suggest why there is a wide range of accuracy reported among different studies and also why there are different confounding factors reported. However, we found no confounding factors which can alter the diagnostic capability of strain elastography. In one study, ultrasound elastography did not show reliable inter-observer agreement for the diagnosis of malignant thyroid nodules (21). More extensive trials are needed to search for inter-observer agreement with regard to strain elastography. Also, future studies should search for possible confounding factors in more quantitative, shear-wave elastography to eliminate the inter-observer disagreement observed in strain elastography to some degree.

Totally, according to the obtained results and comparison to previous studies, it is necessary for the clinicians, especially referring endocrinologists, to be aware of limitations and inter-observer variability of strain elastography when planning the future treatment or surveillance of the patients based on the results of this technique. Although this study showed that results of sonoelastography are not related to demographic factors

and nodule-related grayscale characteristics, further studies with a larger sample size and multi-center samplings are required to attain more definite results.

We didn't find the grayscale sonographic features of the thyroid nodule and the patient's demographics to be confounding factors of the results of strain elastography when assessing the probability of malignancy. However, due to subjective nature of strain elastography and wide range of reported accuracies, it is recommended to assess the inter-observer variability of this technique in order to reassure the clinicians about the obtained results.

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