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Role of Sonoelastography in Differentiating Benign and Malignant Thyroid Nodules

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Abstract
Introduction: *Thyroid nodules are a common medical problem seen in about 8.5% of the population. It is of clinical importance to diagnose malignant nodules from benign which do not require surgery and decide which patient should proceed to biopsy. Ultra sound elastography is a noninvasive technique to evaluate the tissue stiffness of the lesion .The present study aims to assess the sensitivity, specificity, positive and negative predictive value of Strain Elastography in differentiating benign and malignant thyroid nodules by comparing with histo pathological analysis as the reference standard.*
Materials and Methods: *This study was a diagnostic test evaluation study involving 107 study subjects with palpable thyroid nodules who underwent ultrasound Strain elastography examination in Department of Radiodiagnosis for one year and six months.Strain elastography was performed and the nodules were classified into different elasticity scores according to the elasticity score developed by Itoh and Ueno. Scores 1,2&3 taken as benign and scores 4&5 were taken as malignant. Patients were followed up and their histopathological results after surgery were compared with the elastography findings. Sensitivity, specificity, positive predictive and negative predictive values were obtained. Also strain ratio was obtained for all lesions and a cut off value derived to aid in differentiating Malignant nodules from benign..*
Results & Conclusion: *Ultrasound strain elastography had a sensitivity of 90%, specificity of 94.3%, positive predictive value of 78.3% and negative predictive value of 97.6%.Strain ratio cut off of 3.96 derived which showed good diagnostic sensitivity, specificity and accuracy to differentiate malignant and benign nodules. Thus ultrasound Strain elastography scoring system and strain ratio found to be highly accurate in differentiating benign and malignant thyroid nodules.*
Keywords:*Thyroid; Thyroid nodules; Elastography; Strain Elastography; Strain ratio; Sonoelastography.*

Introduction

Thyroid cancer is the most common malignancy of the endocrine system. Definition of thyroid nodules have been given by the American Thyroid Association as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma."[1]. Thyroid nodules are seen in 8.5% of the population[2] and their prevalence depends on the diagnostic identification method

used. Even though most of the nodules found as palpable masses during neck examination in patients with or without suspected thyroid nodule, the prevalence of non-palpable thyroid nodules (*i.e.* <1 cm in diameter) in the general population has been recently increased, possibly as a result of the increasing application of ultrasound. In India the prevalence of palpable thyroid nodule in the community is about 12.2%.[3] But the percentage of malignancy generally accounts for 5% of thyroid nodules[4]. The ultrasonography is the most cost-effective imaging technique, and it is highly sensitive in assessing the nodule size and number[5]. No ultrasound feature has both high sensitivity and high specificity. The challenge of managing thyroid nodules is to reassure the majority of patients who have benign thyroid nodules and to diagnose the minority of patients who will prove to have malignant disease. FNAC is widely accepted as the most accurate, sensitive, specific, and cost-effective diagnostic procedure in the preoperative assessment of thyroid nodules. However false negative FNAC results may occur because of sampling error or misinterpretation of cytology and are of great concern because they indicate the potential to miss a malignant lesion[6]. FNAC has difficulty in distinguishing some benign cellular adenomas from their malignant counterparts and also it is an invasive procedure. It is of clinical importance to diagnose malignant nodules from benign which do not require surgery and the challenge in thyroid nodule evaluation is to decide which patient should proceed to biopsy**.**

Ultrasound elastography has been developed to noninvasively evaluate the tissue stiffness of the nodule by measuring its deformation degree in response to stress.[7] Elastography examines the mechanical and elastic properties of soft tissue, which rely on the composition and structural organization of the macromolecules. The core principle is that on application of compression, the softer parts of tissue deform easier than the harder ones and thus tissue stiffness can be determined objectively[8]. The American Thyroid Association guidelines in 2009 stated that USE is an emerging and promising technique that requires additional validation with prospective studies[9]. There are two kinds of elastography (strain and shear elastography) that are currently used in clinical practice.

The present study aims to assess the sensitivity, specificity, positive and negative predictive value of Strain elastography in differentiating benign and malignant thyroid nodules by comparing with histopathological analysis as the reference standard.

Material and Methods

The study was a diagnostic test evaluation study done in department of Radiodiagnosis for a period of one year and six months, from January 2016 to June 2017.Patients of all age groups who were clinically suspected to have palpable thyroid nodule and sent for performing ultrasound examination of neck and incidentally detected patients with thyroid nodules in routine ultrasound examination of neck within the study period were included in the study. Presence of cystic component in major part of the nodule and peripheral calcifications were excluded as they will interfere with the colour coding process. Also large nodules occupying >75% of thyroid lobe volume and patients not underwent histopathol-ogical analysis of the nodule on follow up are also excluded from the study.

A brief history and clinical examination done.Those confirmed to have a thyroid nodule by conventional B-mode USG were assessed with strain elastography. The patients were examined in the supine position, with the neck extended. Study was performed on GE LOGIQS8/v1 Ultrasound machine. The USG linear probe (ML6-15-D) (6-15 MHz), lubricated with gel was placed on the neck.The thyroid gland examined thoroughly in both transverse and longitudinal planes. The entire gland, including the isthmus, examined.The lesions were localized and studied to assess the size margin (regular or irregular),location within thyroid gland, echogenicity (nodule echogenicity compared with the normal thyroid parenchyma and graded as hypoechoic, hyperechoic, isoechoic or heterogeneous to normal thyroid tissue),presence of intra nodular, perinodular and normal thyroid

parenchymal vascularity, presence /absence of microcalcification, cystic areas, peripheral halo were also recorded. Cervical lymph nodes also studied to look for any features of malignancy. Subsequently ultrasound elastography was performed using freehand technique along with the B mode examination after switching the elastography mode on. Images were obtained by applying light compression repetitively on the targeted lesions .The images were presented in split screen mode with the conventional B mode images on the left hand side and the color scale elastograms superimposed on the grey scale image on the right hand side of the screen. A rectangular region of interest was set for elastography acquisition. The lateral margins were set to include more than 5mm of thyroid parenchyma adjacent to the nodule. Elastography strain images were scored according to the elasticity score developed by Itoh and Ueno[10].In patients with multiple nodules, all the lesions were studied, but the data entered only for the one lesion that had the highest elasticity score.Thus only one lesion per patient with highest elasticity score was finally compared with the histopathological analysis in cases with multiple nodules.

We used five scores for characterizing the lesions:

Score 1-Even strain throughout the lesion.Lesions have elasticity similar to the surrounding thyroid tissue, displayed in green colour on elastography.

Score 2 -Strain in most of the lesion with some areas of no strain. Lesions show inhomogeneous elasticity, with green and blue elastography appearance.

Score 3 –Strain at the periphery of the lesion with sparing of centre. Lesions show an elastic green periphery and a stiff blue centre.

Score 4 – No strain throughout the lesion. Lesions are entirely stiff, showing no deformation.

Score 5 –No strain throughout the entire lesion and surrounding area. The whole lesion and the adjacent tissue showed a blue appearance on the elasticity image.

Scores 1,2& 3 are taken as benign and scores 4 & 5 are taken as malignant .

For all lesions we calculated the strain ratio (SR).To obtain the strain ratio, a rectangular region of interest (ROI) box was first set to include the target mass. Then the target lesion was vertically compressed with very little pressure by transducer. On a representative static image, the relative strain values of mass and thyroid parenchyma were measured. The first ROI for the nodule strain was manually drawn and placed to be bounded by the inner margin of the thyroid lesion. The second ROI for the normal thyroid parenchyma strain was placed in the normal thyroid tissue at a depth similar to or as close as to the depth of the target mass to avoid the stress decay with depth. Strain ratio was obtained by dividing the 2 values.

Patients were then followed up and their surgical, biopsy details and histopathological analysis were collected and analysed. All the data collected were coded and entered in in Microsoft Office Excel 2013 which was rechecked and analysed using SPSS Statistical software version 18. Data were expressed as mean± standard deviation (SD) for quantitative parametric measures, quantitativenon-parametric measures and qualitative data were described using both number and percentages. Comparison between different groups regarding categorical variables was tested using Chi-square test.

The final histopathological diagnosis was used as the reference standard. The probability of error (p value) at 0.05 was considered significant. In addition, the diagnostic validity test was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy or efficacy. Strain ratio was obtained for all lesions and a cut off value also derived from ROC curve to aid in differentiating benign nodules from malignant. Positive Likelihood ratio of strain ratio also calculated from sensitivity and specificity of the cut off value.

A total of 228 nodules were studied from 107 patients out of which 50 were solitary nodules. All the lesions were studied, but the data entered only for the one lesion that had the highest Elastography score. Thus only one lesion per patient with highest

Elastography score was finally compared with the Histopathological analysis.

Results

The study sample had majority of female patients The females constituted 76% of the study population. The mean age of the study group were 47.87+/- 9.2 yrs. Most of the patients with thyroid nodules in our study were in the 41-60 years age group.Out of the 20 malignant lesions, females represented about 75% of cases.In our study of total 107 patients 20 cases (18.65%) proven to be malignant by HPR diagnosis. Most common malignancy in our study was papillary carcinoma (10 cases),rest of the thyroid malignancies in our study were 7 follicular carcinoma,2 anaplastic carcinomas and one case of medullary carcinoma.

Out of the 87 benign cases 61 cases were multinodular goitre with various histologic features like cystic changes, degenerative changes, with associated hyperplastic nodule, hashimotos thyroiditis and lymphocytic thyroiditis etc. Colloid nodule was the second most common lesion in our study was found to be colloid nodule which constituted about 16.1% of total cases followed by 7 cases of hyperplastic nodules and 5 cases of follicular adenomas.

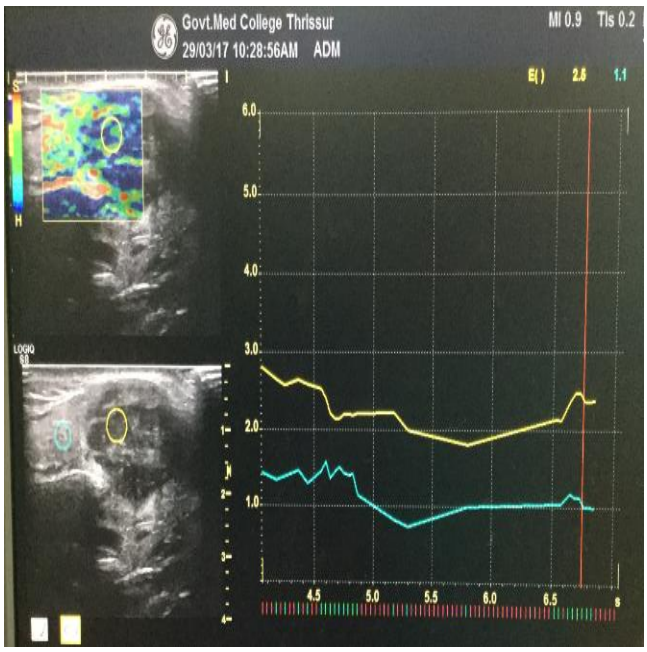

Figure 1:Thyroid nodule showing elasticity score 4 with strain valueswhich finally turned out to be a follicular carcinoma.

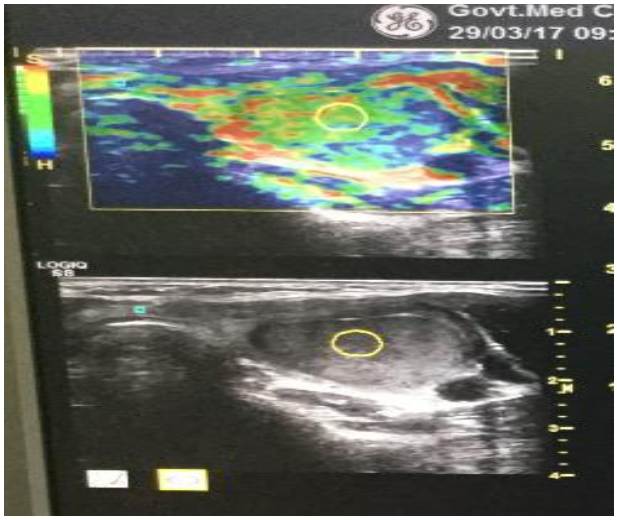

Figure 2: Thyroid nodule showing elasticity score 1which finally turned out to be a follicular adenoma.

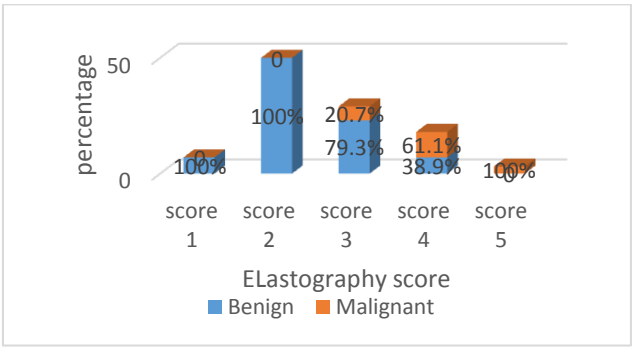

Figure 3: Chart showing percentage distribution of benign and malignant nodules in each elasto score category.

In our Elastography study 7 cases had elasto score 1(6.5%) and 50 cases had elasto score 2(46.2%).All of the cases with elasto score 1&2 were proven to be benign lesions .79.3% of cases with elasto score 3 turned out to be benign. 61.1% with elasticity score 4 were found out to be malignant. The remaining 38.9% cases which showed elasticity score 4 became benign. In our study 3 cases had elasticity score 5(2.8%), all of which were malignant with positive predictive value of 100%. Positive predictive values of elasticity score1,2,3&4 were 100%, 100%, 79.3% and 61.1% respectively.

Receiver operating characteristic curve for distinguishing malignant from benign nodules according to the elasticity score were plotted with the area under the receiver operating characteristic curve for diagnosing malignant thyroid nodules was 0.914 (95% confidence interval, 0.858–0.970).As a

cut off value, an elasticityscore of 4 corresponded to sensitivity of 70% and specificity of 92% for prediction of malignant thyroid nodules was derived. P value was highly significant (<0.001).

Table no 1: Contingency table showing relation between elastographic diagnosis and histopathological diagnosis.

		HPR Diagnosis		Total
		Malignant(n)	Benign (n)	
Elastography diagnosis	Malignant	18 (TP)	5(FP)	23
	Benign	2(FN)	82(TN)	84
Total		20	87	**107**

Discussion

Sonoelastography is a newly developed dynamic technique that provide an estimation of tissue stiffness via ultrasound. Studies on elastography have been done in recent years to differentiate between benign and malignant nodules in a non-invasive manner with higher sensitivity and specificity compared to conventional ultrasound. Sonoelastography improves the diagnostic performance of gray scale ultrasound as the gland is suitable technically for effective compression against underlying anatomic structures using ultrasound probe and therefore for adequate evaluation of the elastic nature of the thyroid nodules.

The sensitivity, specificity and accuracy of our study were obtained as 90%, 94.3% and 93.4% respectively using the 5 level elastography scoring system. We used the cut off value between score 3 and 4. The positive and negative predictive values of our study were 78.3 % and 97.6% respectively. P value was highly significant(<0.001).This is comparable with study done by Eltyib et al[11]) which predicted malignancy with 87.5% sensitivity,90% specificity,70% positive predictive value and 96.5% negative predictive value in 78 patients who underwent ultrasound elastography. This study reported that USE scores of 1 or 2 were found in 47 cases and 100% were diagnosed as benign lesions in histopathological analysis which is comparable to our study which had 57 cases with elasticity scores 1&2 and 100% of them turned out to be benign lesions. This means that nodules with high elasticity, which represent the largest proportion of nodules have no probability to bear malignancy according to our study result. The low number of false-negative results at USE, together with the low progression rate of differentiated thyroid cancer, may allow most patients to be placed in follow-up without significant costs in terms of prognosis. Rago et al[12] showed sensitivity and specificity as high as 97% and 100%, respectively for larger thyroid nodules using US elastography.

In our elastography study 7 cases had elasto score 1(6.5%) and 50 cases had elasto score 2(46.2%).All of the cases with elasto score 1&2were proven to be benign lesions.79.3% of cases with elasto score 3 turned out to be benign .61.1% with elasticity score 4 were found out to be malignant. The remaining cases which showed elasticity score 4 became benign were nodular colloid goitre with sub-acute thyroiditis and hyperplastic nodules. High tissue stiffness in these benign nodules in our study may be attributed to tissue composition in thyroiditis where normal tissue was replaced by a interstitial fibrosis and infiltration of lymphocytes, histiocytes and plasma cells. Concomitantly Hong et al[6] reported that two nodules in patients with sub-acute thyroiditis showed malignant ultrasound Elastography findings.

Mean strain ratio of benign lesions was 3.7 +/- 1.6.Mean strain ratio of malignant lesions was 5.7 +/- 1.2, which is significantly higher than that of benign nodules. Using numerical data analysis for the strain ratio to discriminate between benign and malignant solitary thyroid nodules, we found in the current study that the most accurate strain ratio cutoff value among studied cases was 3.96 from ROC curve with area under the curve 0.814 with 95% confidence interval 0.758 to 0.922, with p value <0.001,meaningthat a strain ratio >3.96 identified malignant nodules and a strain ratio <3.96 identified benign nodules having sensitivity of 90%, specificity of 81.6%**.** Study by Wang et al[13] showed similar results where the cut off strain ratio found out was 3.85 for differentiating benign and

malignant nodules. Various similar studies in literature detected a threshold between 1.8 and 4.5.[14]. When compared with the diagnostic indices of strain colour elasto score system versus strain ratio we found that the elasticity score overall accuracy was better than the strain ratio index which is comparable to the study done by Habib et al[15].

Conclusion

Ultrasound Elastography is a simple, rapid and non-invasive technique with high sensitivity and specificity. The combined use of elasticity scoring system and strain ratio increases the diagnostic performance of elastography in differentiating benign and malignant thyroid nodules and it is recommended to be routinely applied in evaluation of thyroid nodules. With its high accuracy it can decrease the rate of unnecessary biopsies. Cases that show elasto score 1 or 2 showed 100% sensitivity and they are not in need for further investigation, and only ultrasound follow up can be recommended thus can reduce unnecessary FNAC. Cases with score 5 are considered to be malignant soelastography scoring system can be used in combination with conventional ultrasound findings to predict the malignant nature of the nodules. FNAC can be advised in cases of elasto score 3 where malignancy can't be excluded using elastography criteria only. Cut off value of strain ratio of 3.96 in our study has 90% sensitivity in differentiating malignant nodules from benign nodules. Thus strain ratio proves to be a good quantitative indicator to predict malignant nature of thyroid nodules.

Conflict of Interest: No conflict of interest

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