International Journal of Research in Medical Sciences
Sachdev N et al. Int J Res Med Sci. 2019 Feb;7(2):328-333
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20190329

Original Research Article

Clinical utility of TIRADS and ultrasound elastography in characterization of thyroid nodules

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Received: 20 November 2018
Accepted: 29 December 2018

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ABSTRACT

Background: Thyroid nodules are a common entity in an iodine deficient population, however malignant nodules are relatively uncommon with excellent prognosis. Ultrasound elastography is a useful tool for characterization of nodules and allows selection of tumors for FNAC. This study aimed to evaluate the diagnostic value of strain elastography and acoustic radiation force impulse (ARFI) imaging in differentiating malignant from benign thyroid nodules.
Methods: This study included 100 thyroid nodules evaluated using ultrasound TIRADS classification. Strain elastography evaluated the nodules using the elasticity score and strain ratio followed by VTI and shear wave velocity generated from ARFI data to characterize the nodules. Final diagnoses were obtained from cytological and/or histological evaluation. The diagnostic performance of the two elastography methods was analyzed and compared by multiple receiver operating characteristic curve analysis.
Results: Of the 100 thyroid nodules observed in 100 patients (82 females and 18 males), 22% were malignant nodules and 78% were benign. The cut off values for elasticity scores, mean SR, VTI grade and mean SWV for predicting malignant thyroid nodules were greater than or equal to score 2, 2.4, grade 3, 2.5m/s respectively. The area under the receiver operating characteristic curve for elasticity score, mean SR, VTI grade and mean SWV was 0.79, 0.78, 0.89 and 0.84, respectively (P>0.05) and the accuracy was 74, 81.6, 88 and 87.5%, respectively (P>0.05). The accuracy of the combined use of conventional sonography, strain elastography and ARFI imaging was 85.6% respectively, which was higher than that of conventional sonography (P>0.05).
Conclusions: Strain elastography and ARFI imaging have high sensitivity and specificity for differentiating malignant from benign thyroid nodules and therefore have good clinical utility in evaluating these lesions.

Keywords: Acoustic radiation force impulse, Shear wave velocity, Strain elastography, Strain ratio, Thyroid nodule, Virtual touch tissue imaging

INTRODUCTION

Ultrasonography is generally the first choice and the most sensitive imaging modality for diagnosing intra-thyroid lesions.[1] For each thyroid nodule, gray-scale and color Doppler US are used to evaluate the US features, which include size, echogenicity (hypoechoic or hyperechoic) and composition (cystic, solid or mixed) as well as presence or absence of coarse or fine calcifications, a halo, irregular margins and internal blood flow but unfortunately, there is no single sonographic criterion that can reliably distinguish benign from malignant thyroid nodules. A classical criterion of malignancy is a hard or firm consistency upon palpation or ultrasound probe pressure.[2-7] With the introduction of ultrasound elastography, reproducible qualitative and quantitative assessment of tissue consistency became available. With strain elastography which qualitatively determines tissue elasticity by operator external compression of the lesion causing tissue deformation. Less displacement is seen on harder nodules (blue areas) than in softer lesions (red or green areas). Scoring system with 4-5 scales based on the predominant color pattern of the lesion are attributed. For quantitative analysis, strain ratio is obtained by dividing the mean strain within the lesion by the mean strain of the surrounding normal tissue. Stiff lesions (with low strain) tend to produce high strain ratios.[8-10]

Acoustic Radiation Force Impulse (ARFI) imaging utilizes an acoustic push pulse to generate shear waves through a user placed region of interest (ROI) for the quantification of tissue elasticity. It provides two modes for displaying the tissue elasticity-strain change under the push pulse is Virtual Touch Tissue Imaging (VTI) and is displayed as a gray scale image.[11] The second mode is Virtual Touch Tissue Quantification (VTQ) which represents a new technology for the quantification of tissue elasticity using ultrasound acoustic radiation force impulse (ARFI) imaging and allows calculation of the shear wave velocity. This numerical value is related to the stiffness of the tissue within the ROI. The stiffer the tissue the faster the shear wave propagates. Thus, Shear Wave Velocity (SWV) is the numerical value which provides differentiation between hard and soft tissue.[12,13]

METHODS

This study was approved by the ethics committee of this hospital and all the subjects provided informed consent. Hundred patients (age range 18-69years, mean age 37.8years, 82 females and 18 males) with 100 thyroid nodules who presented in the department from November 2017 to December 2018 were examined. All patients underwent strain elastography and ARFI imaging after conventional ultrasound examination.

The inclusion criterion was patients with nodular thyroid disease while the patients with diffuse thyroid swelling were excluded.

Patients were examined in a supine position with a fully exposed neck and the head in dorsal flexion by placing a 9L4-linear transducer lightly on the patient's neck.

The thyroid nodules were evaluated for attributing Thyroid Imaging and Data System (TIRADS) classification which included size and location, echo structure (cystic, predominantly cystic (>50% cystic), mixed, predominantly solid (>50% solid), solid, mixed echoic or spongy (microcystic components occupying more than half of the entire volume)), echogenicity comparing it with strap muscles or normal thyroid tissue (hypoechoic, isoechoic or hyperechoic), margin (well circumscribed or irregular), halo (no halo, thick or incomplete), calcifications (absence, macrocalcification (>1mm in size) or microcalcifications), color doppler features (absent, perinodular, intra-nodular or both).[14]

After TIRADS classification of thyroid nodules, strain elastography was performed with patient lying down same position with the same linear transducer. Using eSie Touch^{TM} elasticity imaging mode, gentle compression was applied to obtain high-resolution elastogram, depicting relative tissue stiffness. Author used light external compression ‘‘free hand” technique where elastographic image was created by a slight raising and lowering movement with the transducer and the elastogram was generated in real-time. The region of interest (ROI) used to obtain the elasticity image was set to include sufficient surrounding normal thyroid tissue. Elastogram and gray-scale US images were displayed simultaneously in dual mode. Next elasticity color maps were switched on, in which the nodule stiffness was displayed as an elastogram in color superimposed on B mode images. The elastogram in which high QF (Quality factor) value (55 or above) indicating minimal global motion artifacts was selected. Each color represents a certain level of elasticity. Elasticity was classified into four different patterns attributing an Elasticity Score (ES).

The strain ratio measurements on ultrasound elastography images were calculated by measuring the mean strain in a thyroid nodule (strain of the thyroid nodule) and comparing it to the mean strain of a similar-sized area of an adjacent thyroid tissue (strain of the thyroid tissue). The two ROI to be placed at equal depths since the elasticity may vary with distance from the surface. The strain ratio measurement was made according to the formula: strain ratio=strain of the thyroid tissue/strain of the thyroid nodule.

ARFI imaging with Virtual Touch^{TM} tissue imaging was conducted using same linear transducer (4-9MHz) while the patients were in the supine position. The probe was placed gently on the body surface with light pressure to the thyroid. The VTI image was visualized as a grayscale image in which dark indicated hard tissue and bright indicated soft tissue. The gray scale was based on the tissues in the field of view (FOV). In general, the FOV was adjusted to include the whole lesion (occupying ≈70% of the whole FOV) and some surrounding thyroid tissue (occupying ≈20%-30% of the whole FOV). In large nodules with dimensions exceeding the limit of the image, the FOV was placed on the connection between the nodule and the surrounding thyroid tissue. The patient was then asked to hold his or her breath and the VTI mode was initiated. The conventional sonographic and VTI images were displayed simultaneously on the same screen side by side. Elasticity was classified into six different patterns attributing VTI Elasticity Score. ARFI imaging with Virtual Touch^{TM} quantification was then conducted using same linear transducer (4-9MHz) while the patients were in the supine position. It was performed only on the nodules which were expected to undergo FNAC. The region of interest (ROI), which measures 0.5×0.6cm was placed in the solid components of the thyroid nodule at a depth of 1.5 and 2.0cm. The patients were asked to stop breathing for a moment, to achieve accurate and reproducible measurements. Six consecutive measurements were recorded for each nodule from the region identified with the ROI and three values were taken from healthy thyroid tissue and the mean of these measurements was recorded as the SWV value of the nodule. The SWV values were displayed on the screen as m/s (range from 0-9m/s). Only numerical results were taken into consideration. When stiffness of the tissue was beyond the limits of measurement, whether high or low, the SWV was displayed as “X.XX m/s”, these measurements were considered invalid.

All the nodules evaluated underwent pathological evaluation which was ultrasound guided fine needle aspiration cytology/histopathology to verify the diagnosis. FNAC was performed with a 25-gauge needle attached to a 10ml syringe.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric test was used. Quantitative variables were compared using Independent t test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-Square test/Fisher exact test. Diagnostic test was used to find out sensitivity, specificity, NPV and PPV. Receiver operating characteristic curve was used to find out cut off point of parameters for predicting malignancy. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

The pathological results revealed 78 of 100 (78%) benign nodules of which 74 cases were solitary colloid nodule (Figure 1) and 4 cases were benign adenomas (Figure 2).

Twenty-two nodules out of 100 (22%) were diagnosed as malignant. There were 10 cases of papillary carcinoma (Figure 3) and 10 cases of follicular carcinoma. 2 cases were diagnosed as medullary carcinoma (Figure 4).

TIRADS category 2 was assigned to 18% nodules in which 88% were benign. TIRADS category 3 was assigned to 62% nodules in which 90.3% were benign. TIRADS category 4 was assigned to 20% nodules in which 70% were found to be malignant. No nodule was given a category 5 or 6. The sensitivity, specificity and accuracy for TIRADS classification were calculated as 63. 64%, 92.31% and 81% respectively.

About 71.79% of benign and 18.18% of malignant nodules had elasticity score <2 while 81.81% malignant and 28.20% of benign nodules had Elasticity score >2.

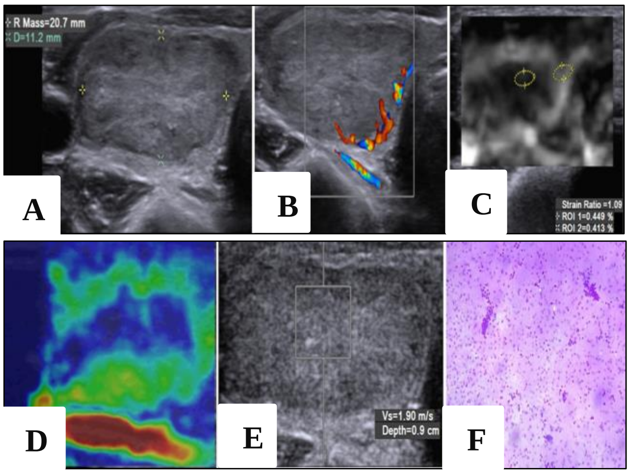

Figure 1: Colloid nodule. A) and B) Ultrasound: well circumscribed wider than taller hypoechoic nodule with incomplete halo and perinodular vascularity TIRADS 3. C) Mean strain ratio 1.09. D) Color coded elastogram: elasticity score 2. E) SWV 2.53m/s. F) Smear shows clusters of benign follicular epithelial cells in a background of thin colloid (Giemsa, 20X).

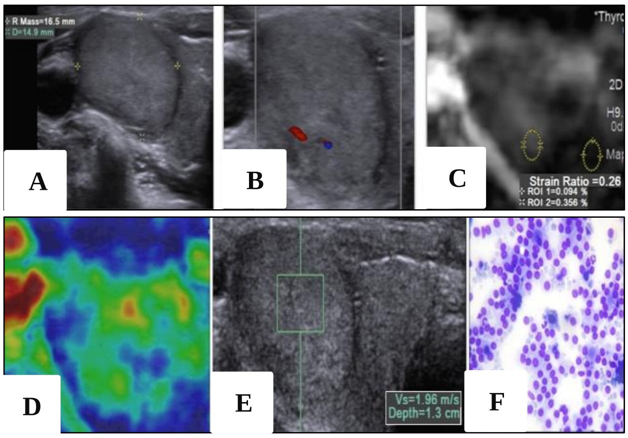

Figure 2: Follicular adenoma. A) and B) Ultrasound: solid isoechoic nodule with a complete fine halo and perinodular vascularity TIRADS 4A. C) Mean strain ratio 0.26. D) Color coded elastogram: elasticity score 2. E) SWV 1.96m/s. F) Cellular smear shows follicular cells in a repetitive microfollicular pattern (Giemsa, 40X).

The cut off for malignancy was calculated to be greater than 2 with a sensitivity, specificity and accuracy of 81.82%, 71.79% and 74 % respectively. The area under the curve (AUC) was 0.79 (95% CI, 0.66 to 0.89). The mean strain ratio for benign nodules and malignant ones was significantly different (1.71±1.47 vs. 2.92±1.92, p=0.004) and range was 0.1-6.9, 0.9-4.8 respectively. The cut off for malignancy was greater than 2.4 with a sensitivity, specificity and accuracy of 81.82%, 81.58% and 81.63% respectively. The area under the curve (AUC) was 0.78 (95% CI, 0.64 to 0.88). On VTI (Virtual Touch Tissue Imaging) of ARFI imaging, 92.30% of benign and 27.27% of malignant nodules had VTI elasticity score <3 while 72.72% malignant and 7.69% of benign nodules had VTI elasticity score >3. The cut off was calculated to be greater 3 with a sensitivity, specificity and accuracy of 72.73%, 92.31% and 88% respectively. The area under the curve (AUC) was 0.89 (95% CI, 0.77 to 0.96).

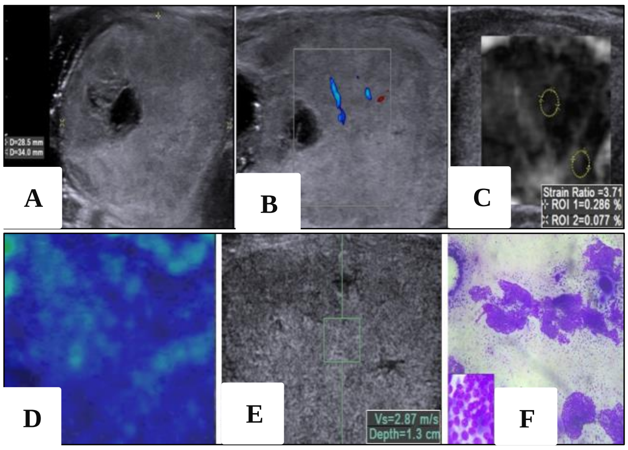

Figure 3: Papillary carcinoma. A) and B) Ultrasound: mixed encapsulated hypoechoic nodule with intra-nodular vascularity TIRADS 4B. C) Mean strain ratio 3.71. D) Color coded elastogram: elasticity score 4. E) SWV 2.87m/s. F) Cellular smear shows follicular epithelial cells in groups, papillaroid fragments, clusters and singly scattered (Giemsa, 20X), inset shows high power view of cells with prominent grooving (Giemsa, 40X).

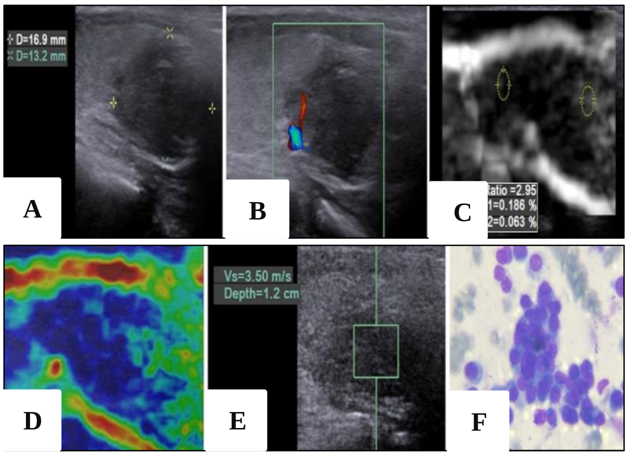

Figure 4: Medullary carcinoma. A) and B) Ultrasound: Solid irregular markedly hypoechoic nodule with perinodular vascularity TIRADS 4B. C) Mean strain ratio 2.95. D) Color coded elastogram: elasticity score 3. E) SWV 3.5m/s. F) Smear shows singly scattered follicular cells with plasmacytoid appearance (Giemsa, 40X).

On VTQ (Virtual Touch tissue Quantification) of ARFI imaging for normal thyroid gland, mean Shear Wave Velocity (SWV) value was 1.47±0.41m/s. The mean SWV value of the malignant nodules (3.08±0.63m/s) was significantly higher than that of the benign nodules (2.1±0.27m/s). A SWV cutoff value of greater than 2.5m/s yielded sensitivity, specificity and accuracy of 72.73%, 94.59% and 87.5% respectively for the diagnosis of malignant nodules. The area under the curve was 0.84 (95% CI, 0.74-0.92).

ROC curve analysis was done to obtain the combined diagnostic performance of ultrasound (TIRADS) and ultrasound elastography (strain elastography and ARFI imaging), it was observed that area under the curve was 0.84 (95%CI) with sensitivity and specificity of 81.8%, 90.9% respectively.

DISCUSSION

Although thyroid nodules are easily detectable on conventional ultrasound, this technique does not provide sufficient data for differentiating benign and malignant thyroid nodules. In recent years, ultrasound elastography has been introduced into clinical practice to evaluate the tissue elasticity of thyroid nodules, with an aim of enhancing the diagnostic ability to detect malignant thyroid diseases.

TIRADS given by Horvath E et al, defined 6 categories of which TIRADS-1 is a normal thyroid gland without nodules and TIRADS-6 is diagnosed by malignancy on FNAC. TIRADS 2-5 are based on different B-mode and doppler ultrasound criteria. The sensitivity and specificity for TIRADS classification were calculated as 63.64% and 92.31% respectively. The AUC was 0.78.[15]

Chandramohan A et al, in their study reported a sensitivity and specificity 72% and 68% with AUC 0.761, which was close to this result.[16] In present study, author only evaluated the TIRADS classification published by Horvath et al. Various other versions of TIRADS classification have been published. Kwak et al, used the sum of the number of suspicious US features. They reported that as the number of suspicious US features increased, the probability and risk of malignancy also increased. They also demonstrated that solid component, hypo-echogenicity, micro-lobulated or irregular margins, microcalcifications and taller-than-wide shape were associated with malignancy.[17]

Park JY et al, proposed an equation for predicting the probability of malignancy in thyroid nodules based on 12 ultrasound features.[18] Results for TIRADS are variable in different observers as it was not used in routine ultrasound practice thus, there was no prior training on the use of TIRADS terminologies.

On strain elastography with elasticity scores, author scored tissue stiffness from 1 to 4 on the basis of Asteria scoring for subjective analysis of the elastogram. Majority of the benign thyroid nodules had elasticity score of 1 and 2 while majority of malignant thyroid nodules had elasticity score of 3 and 4.[19] Bhatia KS et al, in their study reported that the difference was most statistically significant using an ES>2 to predict malignancy (p ¼ 0.0005), which achieved 75% accuracy (75% sensitivity, 74% specificity).[20] Rubaltelli L et al, in their study on 40 patients observed a sensitivity and specificity of 81.8% and 87.5% respectively slightly higher than that of this study while Rust FM et al, reported in their study a specificity of 91%.[21,22] Ultrasound Elastography cannot be done in completely cystic nodules as the results are misleading since, there was more liquid tissue elasticity and they mimic hard nodules hence, should be excluded.

For strain ratio, the results are variable. In a study by Cantisani V et al, a strain ratio greater than 2.31 predicted malignancy with a sensitivity of 86% and a specificity of 82%, whereas in another study by Ding J et al, gave cut off point of 2.73 with a sensitivity of 89.3%, specificity of 73.2% and AUC was 0.87 for strain ratio.[23,24]

In a study by Zhang Y et al, reported that with respect to differentiation between malignant and benign thyroid nodules using the VTI score, the corresponding sensitivity, specificity, PPV, NPV and accuracy were 87.0%, 95.8%, 91.8% and 93.1%, respectively.[25] Author also observed specificity for the diagnosis of malignant thyroid nodules using strain elastography elasticity scores rise from 71.7% to 92.3% when using VTI elasticity scores. The AUC was also observed to be higher for VTI elasticity scores (0.89) than elasticity scores used in strain elastography (0.79). The possible explanation is that in strain elastography, compression is continuously applied by a transducer and followed by decompression and tissue deformation from the mechanical stress by the operator is viewed as color coded elastogram while in VTI, the information is computed by examining the displacements of tissue elements in response to an acoustic push pulse (strain change under the push pulse).

In a study by Calvete et al, where used SWV greater than 2.50m/s for the diagnosis of malignant nodules and reported the sensitivity and specificity of ARFI imaging were 85.7% and 96.0%, respectively.[26] Present result corroborated well with their study. Zhang FJ et al, reported cut off value was 2.84m/s with sensitivity and specificity of 96.8% and 95.7% respectively and also higher VTQ values were observed in malignant nodules (6.34±2.58m/s) by them since all of them were papillary carcinoma. Papillary thyroid carcinoma usually includes microscopic psammoma bodies which show extensively punctuated calcifications on sonography. Sonographic calcifications result in higher SWV values.[27]

None of the studies are available which have combined ultrasonography based TIRADS classification with ultrasound elastography, to calculate overall diagnostic accuracy. Khurana T et al, combined diagnostic accuracy of TIRADS with ARFI: shear wave velocity and reported area under the curve of about 0.79.[28]

This study had few limitations. Firstly, ultrasound elastography cannot be performed in a completely cystic nodule in which no numeric value was obtained when the ROI box for SWV was placed. The probable reason was that the transverse waves of ARFI imaging used for measuring SWV cannot spread through fluid. Also, in the solid cystic nodule in which the size of the solid portion was less that the size of ROI (5x6mm), VTQ could not be measured. Thus, for calculating shear wave velocity the size of the solid portion of the nodule must be greater than size of ROI box. Secondly, additional studies with a greater variety of malignant nodules in a large series will be required to establish the strain elastography and ARFI imaging characteristics for different pathological types of thyroid carcinoma.

CONCLUSION

For characterization of thyroid nodules TIRADS can be used as a tool for selection of high-risk nodules. Ultrasound elastography has the potential for differentiating benign nodules from suspicious ones, thus aiding in the decision to proceed to FNAC with greater confidence and efficiency.

ACKNOWLEDGEMENTS

Authors would like to thank all the patients who participated in this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Sachdev N, Sana, Gupta S, Prasad A. Clinical utility of TIRADS and ultrasound elastography in characterization of thyroid nodules. Int J Res Med Sci 2019;7:328-33.