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DIAGNOSTIC UTILITY OF ACOUSTIC RADIATION FORCE IMPULSE IMAGING IN THE DISTINCTION OF BENIGN AND MALIGNANT THYROID NODULES.

Dr Swapnil Dhok*	DMRD, DNB Senior Resident in Radiology, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad. *Corresponding Author
Dr Amber Papalkar	Consultant Radiologist, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad.
DrAnant Ram Gudipati	Neurointerventional Radiologist, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad.
Dr Rupesh Mandava	Consultant Radiologist, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad.
Dr Chaithanya.I	Consultant Radiologist, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad.
Dr Amey Jaju	Senior Resident in Radiology, Krishna Institute of Medical Sciences, Secunderabad, Hyderabad.

ABSTRACT

INTRODUCTION: Ultrasound elastography using acoustic radiation force impulse (ARFI) is the novel technique used in oncology diagnosis.

AIM: The aim of the present study objective was to evaluate the role of ultrasound elastography using ARFI quantification in characterizing and differentiating malignant versus benign thyroid nodules.

METHODS: A total of 48 thyroid nodules were evaluated with conventional sonography and ultrasound elastography using ARFI quantification. The final diagnosis was obtained from histologic findings. A total of 31 benign and 17 malignant nodules were diagnosed on the basis of histologic examination.

RESULTS: On ARFI quantification, the mean shear wave speed (SWS) values (M ± SD) of malignant and benign thyroid nodules were 3.20±0.93 m/s and 1.66±0.50 m/s, respectively. The diagnostic accuracy of ARFI was found to be 93.75%.

CONCLUSION: ARFI as an effective diagnostic tool in characterizing and differentiating benign from malignant thyroid nodules.

KEYWORDS : Thyroid nodules, ultrasound, acoustic radiation force impulse.

INTRODUCTION

Globally due to westernization, sedentary life style and other factors the incidence of thyroid nodules has increased markedly. In India the prevalence of a palpable thyroid nodule is 12.2%. [1]Conventional ultrasonography is the prime imaging modality but its diagnostic accuracy is very low in differentiating the malignant nodules from benign nodules.[2]

Elastography is a novel sonographic method which elicits tissue elasticity information and assists the differential diagnosis of thyroid nodules according to the pathologic fact that malignant nodules tend to be much harder than benign.[3] Assisting stress elasticity imaging is used clinically and showed effective results in differentiating thyroid nodules. But there are some disadvantages which influence the results and induce the poor repeatability of this method. Array of factors like patient breath, the force given by the examiners and the experience of the examiners significantly affects the diagnostic outcome. The most prime disadvantage is the qualitative or semi-quantitative method.[4,5]

Acoustic radiation force impulse is a new elastic technique which is devoid of above mentioned limitations. [6, 7] The quantitative application of ARFI technology is called Virtual Touch tissue quantification (VTQ) technology. Generally the target tissue generates small (1 - 10 μm) localized displacements when it is mechanically "pushed" by short-duration acoustic radiation force transmitted from the transducer. The displacements of the target tissue generates the shear wave which is detected by sonographic detection pulses and numeric value of the shear wave velocity (SWV) is calculated and displayed on the monitor to estimate tissue stiffness. VTQ generates objective and reproducible data [8]. The stiffer a tissue is, the greater the shear wave velocity is [9] ARFI technology has been applied in the diagnosis of abdominal diseases and breast diseases.[10,11,12] Mounting reports highlights the application of ARFI technology in thyroid, especially using a linear array transducer.[13,14,15] In this backdrop, the present study was undertaken to investigate the diagnostic accuracy of ARFI elastography for evaluating focal thyroid nodules. Further, the thyroid nodules were evaluated using VTQ of ARFI imaging and cutoff value for the differentiation of malignant thyroid nodules was determined.

PATIENTS AND METHODS

This was a prospective study conducted among 50 patients who had one or more thyroid nodules on ultrasound and had normal serum thyroid stimulating hormone (TSH) levels, as well as no previous history of treatment were recruited from the period between May 2017 and June 2018. Further in this study out of 50 enrolled subjects, 2 patients were excluded due to absence of histopathological examination. The remaining patients (48 patients; 28 male and 20 female; age range, 20–70 years; mean age, 44 years ±14.9) with quantitatively assessed (VTQ) thyroid nodules were evaluated with ARFI imaging in this prospective study. The other exclusion criteria were patients with a nodule solid component less than 0.5 cm in diameter, a pure cystic nodule, thyroiditis, or a nodule close to the carotid artery were excluded from the study.

The study was carried out on Siemens Acuson S2000 sonography machine by using 9L4-linear array transducer (9 –18 MHz).The patients were examined in supine position with dorsal flexion of the head. Grey scale ultrasound was performed, followed by color Doppler.

Real-time US were performed by two radiologists with 8 - 10years of experience. The internal component of the nodules was classified as solid or mixed solid and cystic. Masses with mixed components were evaluated on the basis of the internal solid components. On the basis of echogenicity, nodules were classified as hyperechoic, isoechoic, hypoechoic and very hypoechoic. Nodule was classified as isoechoic, when the echogenicity of the nodule was similar to that of the thyroid parenchyma. When the echogenicity of the nodule was less than that of the thyroid parenchyma, it was classified as hypoechoic. The nodule was classified as very hypoechoic, if the echogenicity was less than that of the surrounding strap muscle. Margins were classified as smooth, lobulated or irregular.Then, switching to ARFI model, VTQ was used to measure the elasticity of nodules and normal thyroid tissues.

For VTQ examination, patients were asked to hold their breath. The region of interest (ROI) with fixed dimension of 5 mm × 6 mm was placed inside nodules when the nodules had similar size with ROI. The nodules were measured 5 times and the average value was calculated as SWV of nodules. The movement range of the ROI was small in the nodule when the size of the nodule was similar to the ROI. The repeatability of 5 times sampling was very high, and the measurements were in good agreement. The movement range of the ROI was bigger in the bigger nodule, the tissue could be completely different for each measurement, and measurements were not consistent. So the large nodule was divided into four parts, each part was measured 2 times, the average value of 8 measurements was more reliable than the average value of 5 measurements in bigger nodules. The surrounding thyroid parenchyma in the similar depth and 0.5 cm away from the nodule was measured 5 times in the same way and the average was calculated as SWV of surrounding thyroid parenchyma. The limits for measurement of the VTQ values (shear wave velocity) for this machine were 0–9 m/s. Values outside these limits were displayed as "X.XX m/s", the result was recorded as 9 m/s when the nodule was solid [4,16]. The average value of the nodules was defined as the value of the shear wave velocity (SWV) and the average value of the surrounding thyroid tissue was defined as V. The shear wave velocity ratio (SWR) was obtained for each nodule as SWV/V.

STATISTICAL ANALYSIS

All data were analyzed by SPSS version 19.0 software (SPSS Inc, Chicago IL) and a P value less than 0.05 was considered as statistically significant. Data were statistically described in terms of mean (±SD) and percentages when appropriate. For comparing categorical data, Chi square test was performed. Comparison of quantitative variables between the study groups was done using Student t test. Receiver operating characteristic (ROC) curve analysis was used to determine a cut-off value for the differentiation of malignant nodules. The characterization of the nodule by grey scale ultrasound was compared to the final diagnosis and the sensitivity, specificity, NPV, PPV and accuracy of ultrasonography were calculated. Similarly, the ARFI values of the nodules were taken and the sensitivity, specificity, NPV, PPV and accuracy were calculated. The accuracy of grey scale ultrasound was compared with that of ARFI. The sensitivity, specificity, NPV, PPV and accuracy of combined ultrasound and ARFI were also calculated.

RESULTS

In the present study, the age of the patients was ranged from 20- 70 years and out of 48 cases,28 were females and 20 were males. In the out of 48 nodules studied, 31 were benign (16 adenomas and 15 colloid nodules) and 17 were malignant (11 papillary carcinoma, 3 Medullary carcinoma and 3 Follicular carcinoma) on pathological diagnosis.

Further, based on morphological characters, margin regulalarity, pattern of echo, presence or absence of the halo sign, and presence or absence of microcalcifications on Ultrasonography, out of 48 nodules, 41 were found to be suspicious of malignancy and 7 were not suspicious of malignancy. The Sensitivity and specificity of US was found to be 94.12 and 19.35 %, respectively. The positive and negative predictive value for US was 39.02% and 85.71%.The diagnostic accuracy of US in the present study was found to be 45.83%.

In the present study, Acoustic radiation force impulse (ARFI) elastography technique shows that the ARFI value was significantly ($p<0.001$) higher in malignant cases compared to benign cases as per histopathology and cytological diagnosis. The mean ARFI values in benign and malignant were found to be 1.66± 0.50 and 3.20 ± 0.93 respectively. The data were shown in Table 1 and Fig 1.

Table 1: Mean ARFI value of benign and malignant thyroid nodules as per histological/cytological diagnosis.

Diagnosis by Cytology/Histopathology	ARFI value	p-value
	Mean±S.D	
Benign	1.66±0.50	< 0.001
Malignant	3.20±0.93	

The values are expressed as mean±S.D. The comparison were done using Chi square test. P value <0.05 was considered as statistically significant.

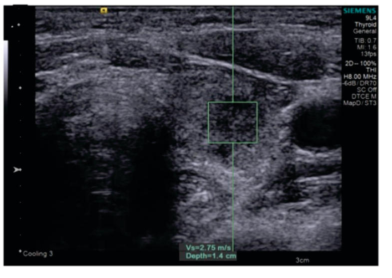

Figure 1: VTQ images, mean ARFI value of the lesion was 2.75 m/s

Further, the area under the receiver operating characteristic (ROC) curve for the differentiation of malignant and benign thyroid nodules using ARFI (VTQ) imaging was found to be 0.940 (95 % CI: 0.839–1.000, $p < 0.001$) with shear wave velocity cut off value 2.545 m/s. The ROC curve was displayed in Fig 2.

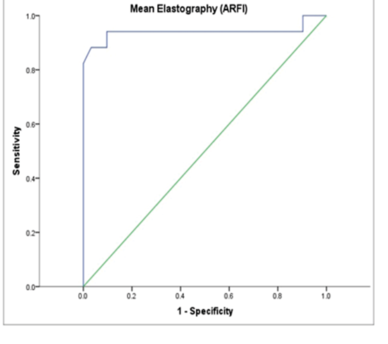

Figure 2: The ROC curve of ARFI in differentiating benign and malignant thyroid nodules

The ARFI cut off value in the present study was found to be 2.545 m/s. Based on this cut-off value the thyroid nodules were classified into benign and malignant. Histopathology diagnosis revealed 31 benign cases and in this 30 cases had ARFI value <2.545 and 1 cases had ARFI value ≥ 2.545. Out of 17 malignant 15 cases had ARFI value ≥2.545 and 2 cases had ARFI value < 2.545. The values was found to be statistically significant ($p < 0.05$). The data were shown in Table 2.

In the present study, the ARFI value higher than 2.545 m/s predicted malignancy with a sensitivity of 88.24%, specificity of 96.77%, positive predictive value of 93.75%, negative predictive value of 93.75% and diagnostic accuracy of 93.75%.

Table 2:Distribution of thyroid nodules by considering 2.545 m/s as ARFI cut-off value for malignant thyroid nodule.

Thyroid Nodules	Histopathology Diagnosis		Total	P value
	Benign	Malignant		
Benign (<2.545)	30	2	32	<0.001
	93.75%	6.25%	100.0%	
Malignant (≥ 2.545)	1	15	16	<0.001
	6.25%	93.75%	100.0%	
Total	31	17	48	<0.001
	64.58%	35.42%	100%	

Furthermore, in our study on combining USG and ARFI, they displayed a sensitivity of 88.24%, sensitivity of 100%, positive predictive value of 100%, and negative predictive value of 93.94% and diagnostic accuracy of 95.83%. The data were shown in Table 3.

Table 3: Sensitivity, Specificity, PPV, NPV and Accuracy of USG, ARFI and in combination in differentiating between benign and malignant thyroid nodules.

Diagnostic outcome	USG	ARFI	Combined USG and ARFI
Sensitivity	94.12%	88.24%	88.24%
Specificity	19.35%	96.77%	100%
PPV	39.02%	93.75%	100%
NPV	85.71%	93.75%	93.94%
Accuracy	45.83%	93.75%	95.83%

DISCUSSION

Thyroid nodules are highly prevalent and have a low but not insignificant risk of malignancy. The oncologists have a high challenge in the diagnosis and management of benign nodules and accurate diagnosis and treatment of malignant thyroid at early stage in huge patient population. The current management criteria is mainly depend on clinical data, TSH values, and thyroid B-mode US as preliminary screening and the secondary screening involves US guided FNAC whenever feasible and cost effective.[17,18] However in majority of the cases, where there is lack of clinical history, symptoms showing presence of cancer the decision to undertake thyroid biopsy predominantly depends of nodule appearance during sonography.[19,20] Hence, US techniques with a high sensitivity for malignancy are highly essential to reduce the risk of undetected malignant nodules.

Ultrasonographic elastic technology is based on the principle of tissue elasticity which is a vital reference index used in the differentiation of malignant and benign nodules. [21] During disease conditions the tissue elasticity or hardness undergoes a deformation and it differs from one tissue to another. It will change when pathological change occurs in tissue. Also tissue elasticity differs in different tissues or different pathological status of the same construction.[22] Tissue stiffness is significantly correlated with malignancy whilst the benign lesions are reported to be soft.[21] ARFI, a novel ultrasound based procedure, elicits a valid quantitative information about the tissue hardness over artificial compression and it is a functional complement for routine ultrasonography.[23]

Virtual Touch Tissue Quantification (VTQ) of ARFI gives shear wave velocity (SWV) value depending on the stiffness of the tissue. Most of the malignant lesions have higher stiffness due to malignant cells and surrounding desmoplastic reaction.[4] In our study, mean ARFI value of benign and malignant nodules was found to be 1.66 ± 0.508 m/s and 3.20 ± 0.932 m/s respectively. Our results showed significantly higher stiffness in malignant nodules compared to benign nodules. Mounting studies showed the usefulness of differentiating the benign and malignant thyroid nodules. In a study done by Zhang et al. the malignant nodules had a higher mean SWV value than benign nodules [6.34 ± 2.58 m/s vs 2.15 ± 0.59 m/s, respectively].[24] In another study reported by Hou et al a higher mean SWV value for malignant nodules was observed as compared to benign nodules [3.10 ± 1.08 m/s vs 2.03 ± 0.42 m/s].[25] Gu et al. reported a higher SWV values for the malignant as compared to benign nodules [3.941 ± 1.393 m/s vs2.005 ± 0.485 m/s].[15]

In the present study, receiver operating characteristic (ROC) curve analysis was employed to determine a cut-off value for the differentiation of malignant nodules and the value was found to be 0.94 with 95 % confidence interval of 0.839 – 1.000. In this study, the cut-off value for differentiating between benign and malignant thyroid nodules was 2.545 m/s. Our results are in corroboration with the study done by Bojunga et al. and Zhuo et al. where the cut off value of 2.57 m/s and 2.545 m/s with highest sensitivity and specificity are employed for the differentiation of malignant from benign nodules. [26,27] In Hamidi et al. study the area under the ROC curve was found to be 0.964 with cut-off point of ARFI at 2.66 m/s.[28]

In our study, the sensitivity and specificity of ARFI was 88.24 % and 96.77 % respectively based on ARFI cut off point as 2.545 m/s. Further, the positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of ARFI was found to be 93.75 %, 93.75 % and 93.75 % respectively.

Our results are in line with the previous study done by Zhuo J et al. where the sensitivity and specificity of ARFI was 96.3% and 96.2% using 2.545 m/s as a cut-off value. Further in another study done by Zhang et al. on 155 thyroid nodules cases the sensitivity, specificity, PPV, NPV and accuracy was found to be 96.80%, 95.70%, 93.75%, 97.80% and 96.13% respectively with the cut-off value of 2.84 m/s.

Further, in our study we had compared the sensitivity, specificity, PPV, NPV and accuracy of ARFI alone and in combination with ARFI and Ultrasonography in characterizing thyroid nodules. The present study showed 100% specificity, 100% PPV and 95.83 % accuracy of combined ARFI and USG as compared to ARFI alone with specificity 96.77%, PPV 93.75%, Accuracy 93.75%). However, there is no significant difference in the sensitivity (88.24%) and Negative predictive value (93.94%) whether ARFI is used or both ARFI and USG are employed. Corroboration with the present study report, in Zhang et al. study the accuracy of ARFI alone was 81.58 % and the accuracy of the combined use of conventional sonography and ARFI was 95.39%.[29]

CONCLUSION

VTQ of ARFI imaging discriminates between benign and malignant nodules with high sensitivity and specificity and may positively contribute to clinical evaluation of thyroid nodules.

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Nil.

Conflicts of interest

None to Declare

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