Diagnostic accuracy of Acoustic Radiation Forced Impulse (ARFI) for differentiating between benign and malignant thyroid nodules

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Aims and objectives

AIM:
Diagnostic accuracy of Acoustic Radiation Force Impulse (ARFI) for differentiating between benign and malignant thyroid nodules in patients with solitary thyroid nodules and comparison with histopathology.

OBJECTIVES:

1. To obtain the best fit ARFI values to differentiate benign and malignant thyroid nodules
2. To assess diagnostic accuracy of virtual touch imaging (VTI) and VTQ (Virtual touch Quantification) in differentiating benign and malignant thyroid nodules when compared to ultrasound TIRADS(4) for thyroid nodules and histopathology.

RATIONALE BEHIND THE STUDY:

Thyroid nodules are common in Indian population with a prevalence of 12.2 % (1) and the incidence of malignancy is 8.6 in 100000, (2). The single most important factor in deciding the management of a thyroid nodule is to determine if the nodule is benign or malignant. (3) Malignant thyroid nodules are stiffer than the benign nodules; this forms the basis of elastography which reflects the stiffness of the nodule. Acoustic radiation force impulse imaging is a new sonographic technique which is more objective and less operator dependent than conventional elastography.(14) ARFI assigns a numerical value to the nodules on the basis of their stiffness(9). These numerical values holds potential promise in differentiating benign and malignant thyroid nodules.

The two kinds of imaging method available using ARFI technology include Virtual touch imaging (VTI) and Virtual tissue quantification (VTQ) by SEIMENS medical systems and can be used to determine the lesion stiffness qualitatively and quantitatively.(6)(9-11)
Methods and materials

MATERIALS AND METHODS:

Prospective IRB approved study carried out from September 2012-August 2013 in Christian Medical College (CMC) Vellore, a 3000 bedded tertiary care teaching hospital in South India. Informed consent was obtained from all participants.

INCLUSION CRITERIA:

a) Patients with solitary thyroid nodules or dominant nodule of MNG being referred for ultrasound.

b) Patients with a conclusive FNAC

c) Patients who undergo surgical resection with a valid histopathology report.

EXCLUSION CRITERIA:

a) Purely cystic nodules

b) Nodules < 1 cm

c) Nodules with gross macrocalcification where the ARFI box cannot avoid areas of macrocalcification

d) Patients who do not undergo FNAC / surgery or if the FNAC is inadequate

Sample size calculated was 165 nodules with a precision of 5% and an anticipated prevalence of nodules of 12.2% with alpha level of significance 95%. Fig. 1 on page 5

The period between the ultrasound and FNAC was 1-2 days and time period between ultrasound and surgery was 1-6 months. Ultrasound was performed prior to FNAC / surgery. The observer was blinded to the results of FNAC. All the scans were performed on (ACUSON S2000™, Siemens) using a high frequency linear probe (4-9 MHz).

Conventional sonography, colour Doppler and ARFI was performed in all patients. ARFI -Imaging (Virtual-Touch Quantification™ and Virtual-Touch Imaging™, Siemens-ACUSON-S2000), VTQ Fig. 2 on page 5 Fig. 3 on page 6 were performed in all the patients. The values exceeding 8.4m/s were displayed as x.xx m/s Fig. 4 on page 7. VTI was performed and classified as category 1-4 Fig. 5 on page 7 Fig. 6 on page 8 Fig. 8 on page 10 in all the patients(2). ARFI imaging was performed using
a 9 MHz L4 - linear ultrasound probe and five successful measurements were recorded with the ROI placed in thyroid nodule. In patients without valid numeric values and more x.xx m/s measurements, x.xx m/s was allocated to 8.4 m/s (6). In nodules with mixed echogenicity ROI placed in the suspicious (hypoechoic, irregular) part of the nodule.

FNAC was performed after thyroid ultrasound by the surgeon for solid palpable thyroid nodules whereas radiologists performed ultrasound guided FNAC for cystic, mixed solid and cystic nodules, non-palpable nodules with suspicious ultrasound features and palpable thyroid nodule in which part of the nodule had features suspicious for malignancy. Bethesda system for reporting thyroid cytology was followed and Bethesda class II (benign) and Bethesda class VI (malignant) were considered as diagnostic cytology reports. Rest of the categories was considered non-diagnostic (7)(13)

STATISTICAL ANALYSIS:

Statistical analyses were performed using SPSS software version 16. Receiver operating characteristic (ROC) curves were employed to compare the diagnostic performance of TIRADS, ARFI- both VTQ and VTI and combined ultrasound and ARFI. P < 0.05 was considered statistically significant.
Fig. 1: Study population

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Fig. 2: VTQ measurement of the nodule at a depth of 9mm, VTQ-0.97 m/s

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**Fig. 3:** VTQ measurement of the nodule at a depth of 10mm, VTQ-8.03 m/s

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**Fig. 4:** VTQ values were x.xx m/s from this hypoechoic, ill-defined nodule with multiple microcalcification.

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**Fig. 5:** Nodule that is softer than thyroid

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Fig. 6: Nodule that is as stiff as thyroid

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Fig. 7: Ultrasound of the nodule showed few illdefined hypoechoic areas in the peripheray of the nodule. VTI of the same nodule shows that the peripheral part of the nodule is harder than thyroid gland. Histopathology revealed follicular variant of papillary carcinoma.

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Fig. 8: Honeycomb appearance indicating a highly cellular lesion. This nodule was papillary carcinoma on histopathology.

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Results

Fig. 9 on page shows the histopathology of thyroid nodules which were subjected to surgery.

Performance of TIRADS:

Receiver-operating characteristic (ROC) curve depicting accuracy of TIRADS in predicting malignancy. (Fig. 11 on page 15)

The area under the curve was 0.682.

Sensitivity = 82.8%
Specificity = 58.9%
Diagnostic accuracy = 72.7%.

Results of thyroid ARFI:

I. VIRTUAL TOUCH IMAGING (VTI):

<table>
<thead>
<tr>
<th>VTI</th>
<th>BENIGN (%)</th>
<th>MALIGNANT (%)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41 (83.7)</td>
<td>8 (16.3)</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>16 (64%)</td>
<td>9 (36%)</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>15 (19.7)</td>
<td>61 (80.2)</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>21 (100)</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>99</td>
<td>171</td>
</tr>
</tbody>
</table>

Category 3 and 4 of VTI predicted malignancy, Pearson chi-square test value =70.522, p < 0.001. All the nodules showing a VTI category 4 i.e. Honeycombing were found to be malignant while 80% of nodules with category 3 (hypoechoic to thyroid gland) appearance on VTI were malignant. 16.3% and 36% of thyroid nodules with category 1 and 2 appearance on VTI were malignant.
Of a total of 97 nodules which were classified as category 3 and 4 (Stiffer than thyroid) on VTI, 82 (84.5%) were malignant. Of the 74 nodules which were classified as category 1 or 2 on VTI, 17 (22.9%) were malignant.

II) RECODED VTI RESULTS:

Category 1 - including VTI-1(Softer than thyroid), VTI-2(As stiff as thyroid)

Category 2 - including VTI-3(Stiffer than thyroid gland) and VTI-4(Honeycomb appearance)

<table>
<thead>
<tr>
<th>VTI CODE</th>
<th>BENIGN</th>
<th>MALIGNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTI 1 and 2(Softer)</td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>VTI 3 and 4(Stiffer)</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>TOTAL</td>
<td>72</td>
<td>99</td>
</tr>
</tbody>
</table>

Fig. 12 on page 16 shows receiver-operating characteristic (ROC) curve depicting accuracy of VTI in predicting malignancy.

The area under the curve was 0.849.

Diagnostic performance of VTI:

Sensitivity - 82.8%

Specificity - 79.17%

Positive predictive value - 84.5%

Negative Predictive value - 77%

Diagnostic accuracy - 81.2%

III) ARFI - virtual touch quantification (VTQ):

<table>
<thead>
<tr>
<th>Number</th>
<th>Mean VTQ (m/s)</th>
<th>Standard deviation (m/s)</th>
<th>95% CI (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENIGN</td>
<td>71</td>
<td>2.18</td>
<td>1.35</td>
</tr>
</tbody>
</table>
There was significant difference in the mean SWV between benign (2.18 +/- 1.35 [95% CI=1.874-2.512] m/s) and malignant (3.97 +/- 2.65 [95% CI=3.43-4.503] m/s) thyroid nodules, p<0.001.

Box plot (Fig. 10 on page 15) depicting the median and range of shear wave velocity measurements in benign and malignant thyroid nodules, p<0.001.

Receiver operating curve (Fig. 13 on page 17) demonstrating accuracy of ARFI -mean VTQ on predicting malignancy.

Area under the curve was 0.6988

Diagnostic performance of VTQ:

Sensitivity-57.1%
Specificity-82.5%
Positive predictive value -53.6%
Negative predictive value -84.5%
Diagnostic accuracy -65.5%

IV) Combined criteria:

Receiver operator curves (ROC) (Fig. 14 on page 18) demonstrating the diagnostic performance of VTI, VTQ measured using ARFI technology compared with conventional ultrasound (TIRADS) and combined criteria (VTI+VTQ+TIRADS)

Diagnostic performance of VTI (AUC = 0.849) and combined VTI+VTQ (AUC= 0.791) was better than VTQ alone (AUC=0.699), conventional ultrasound (AUC = 0.682) and combined criteria (conventional ultrasound + VTI + VTQ) with AUC = 0.727.
**Fig. 10:** Box plot depicting the median and range of shear wave velocity measurements in benign and malignant thyroid nodules, p<0.001

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**Fig. 11:** Receiver-operating characteristic (ROC) curve depicting accuracy of TIRADS in predicting malignancy. The area under the curve was 0.682

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**Fig. 12:** Receiver-operating characteristic (ROC) curve depicting accuracy of VTI (virtual touch imaging) in predicting malignancy. The area under the curve was 0.8490.

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Fig. 13: ROC demonstrating accuracy of ARFI - VTQ (virtual touch quantification) on predicting malignancy. Area under the curve was 0.699.

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**Fig. 14:** Receiver operator curves (ROC) demonstrating the diagnostic performance of VTI, VTQ measured using ARFI technology compared with conventional ultrasound (TIRADS) and combined criteria (VTI+VTQ+TIRADS).

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Conclusion

CONCLUSIONS:

1. Diagnostic performance of VTI (virtual touch imaging) was better than conventional ultrasound alone and combined ARFI and conventional thyroid ultrasound.

2. There was a considerable overlap in the VTQ values for benign and malignant thyroid nodules and the cut off values obtained for benign nodules was 2.19 +/- 1.35 m/s and for malignant nodules was 3.97 +/- 2.65 m/s.

Thus in conclusion, VTI of ARFI technology is a useful tool for evaluating thyroid nodules.

LIMITATIONS

1. There were more number of malignant thyroid nodules in our study because this study was conducted in a tertiary care referral center.

2. Second FNAC was not performed on nodules with inadequate or indeterminate initial FNAC as recommended in literature and were excluded from the study.

TECHNICAL LIMITATIONS

1. Thyroid gland is a superficial organ, in few cases with large nodules it was not possible to keep the face of the transducer in close contact with the nodule.

2. VTQ values which were displayed x.xx m/sec were considered as greater than 8.4 m/sec and the real stiffness of the nodule could not be determined.

3. The ROI box while performing VTQ could not be altered in size.

4. Transmitted pulsations from common carotid artery could have led to erroneous values.

5. Random placement of ROI box in homogeneous nodules
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