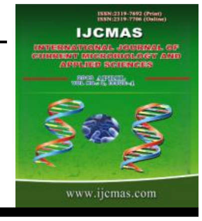
International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 2 Number 4 (2013) pp. 92-99**
http://www.ijcmas.com



Original Research Article

Acoustic Radiation Forced Impulse (ARFI) for Differentiating between Benign and Malignant Thyroid Nodules in Patients with Solitary Thyroid Nodules

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Keywords

Acoustic radiation forced impulse, Thyroid nodules, Sonographic features

A B S T R A C T

The modality of choice for imaging of the thyroid gland is high resolution sonography. Although no single ultrasound feature is diagnostic for malignancy, a combination of ultrasound features of malignancy enables an accurate prediction of malignancy in any given nodule. A thyroid nodule with multiple sonographic features of malignancy will then have to be assessed with fine needle aspiration cytology to establish a possible diagnosis. The prospective study patients were referred from the department of Endocrinology and Endocrine surgery. All patients who fulfilled the inclusion criteria were included in the study. The selection of the study population was independent of the reference standard (histopathology). Personal data and ultrasound findings were entered into a coded – numbered proforma . 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) nodules, p<0.001.

Introduction

Thyroid nodules are a relatively common occurrence and are detected in approximately 50% adults. Thyroid nodules may be benign or malignant. Malignancy of the thyroid gland is rare, in contrast benign thyroid nodules are common, nodular hyperplasia being the commonest of the benign nodules. The percentage of malignant thyroid nodules is quoted to be less than 7%. Although the percentage of malignancy in thyroid nodules is considerably low, it is critical to identify these lesions accurately (Juan *et al.,* 2008).

The modality of choice for imaging of the thyroid gland is high resolution sonography. Although no single ultrasound feature is diagnostic for malignancy, a combination of ultrasound features of malignancy enables an accurate prediction of malignancy in any given nodule (Gharib *et al.,* 2007). A thyroid nodule with multiple sonographic features of malignancy will then have to be assessed with fine needle aspiration cytology to establish a possible diagnosis. Thyroid malignancy: The major histopathological types of thyroid malignancy include papillary, follicular, medullary and anaplastic types. Of the above types, papillary and follicular types are associated with a favourable prognosis with 20 year survival rates of 95-96 % and 75 % respectively Medullary and anaplastic thyroid cancers are aggressive lesions and are generally associated with a poorer prognosis, literature quotes reveal an approximate 10 year survival of 42-90 % for medullary carcinoma of the thyroid. Anaplastic cancer of the thyroid gland is associated with the poorest survival rates with 5 years survival rates of approximately 5%. Thyroid lymphomas are not common, the lymphomas that do involve the thyroid gland are of the non-Hodgkin's type and occur as a Part of a systemic disease, isolated thyroid lymphoma can occur in a gland with background thyroiditis (Hashimoto's thyroiditis). Patients with non-thyroid malignancies can occasionally have metastatic disease which involves the thyroid gland (Cooper *et al.,* 2006). The current recommendations for management of palpable thyroid nodules is that they be subjected to FNAC with the thyroid function tests, clinical features, sonographic characteristics and risk factors for carcinoma of thyroid all being considered in totality while making the decision to subject a given nodule to a Fine needle aspiration cytology. There is however considerable controversy regarding the management of the incidentally detected thyroid nodule which are asymptomatic (Edmund *et al.,* 2009). The issues that are in play include a need to avoid burdening the health care system with unnecessary invasive evaluation of benign nodules and at the same time achieve timely detection of malignancy. In the attempt to achieve this fine balance, ultrasound has a role to play in the choice of lesion where FNAC is mandatory and determine those nodules that can be followed up.

To this end, Horvath *et al.,* and Park *et al.,* have played a major role in developing a thyroid nodule imaging and reporting data system (TIRADS) with the aim of standardising thyroid imaging and reporting terminology which will attain universal acceptance similar to the BIRADS system.

Horvath *et al.,* aimed to categorise thyroid nodules into sub-sets and a percentage of malignancy risk to each of the categories in a fashion similar to BIRADS.

They conducted the study in three stages over a period of 8 years, the first stage involved sonographically guided FNAC of thyroid nodules (Hamberger *et al.,* 1982). The FNACs were performed by a group of five radiologists with sufficient experience in image guided procedures. FNACs were performed with a 19 / 21 Gauge needle attached to a 10 cc syringe. The samples obtained were studied by 2 experienced pathologists (Yassa *et al.,* 2007).

During stage 1 of the study, sonographic characteristics of362 thyroid nodules were reviewed in an attempt to define and specify lesion characteristics. They reviewed the nodule characteristics with regards to certain features such as echogenicity, shape, orientation, acoustic enhancement / shadow, lesion margins, presence / absence of pseudo-capsule, presence of calcifications and Doppler detectable vascularity of the nodule (Goellner *et al*., 1987).

In the stage 2 of the study another 500 thyroid nodules were prospectively studied and characterised based on the abovementioned sonographic characteristics which were then correlated with the FNAC results, at this stage a TIRADS group classification was generated and the nodules studied were categorised accordingly.

Materials and Methods

Study design: Study of diagnostic test accuracy

Study type: Prospective

Inclusion criteria:

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

- Patients with a conclusive FNAC
- Patients who undergo surgical resection with a valid histopathology report.

Exclusion criteria

- Purely cystic nodules
- Nodules < 1 cm
- Nodules with gross macrocalcification where the ARFI box cannot avoid areas of macrocalcification.
- Patients who do not undergo FNAC / surgery or if the FNAC is inadequate

The prospective study patients were referred from the department of Endocrinology and Endocrine surgery. All patients who fulfilled the inclusion criteria were included in the study. The selection of the study population was independent of the reference standard (histopathology). Personal data and ultrasound findings were entered into a coded – numbered proforma. Informed consent was obtained from the patient / patient`s relative prior to ultrasound in accordance with the ethical guidelines of Helsinki declaration and approved by the Institutional review board of the hospital.

Results and Discussion

There is very strong statistical correlation between VTI category 3 and 4.Outcome Pearson chi-square test value =70.522, DF=3, $p < 0.001$ ($p<0.05$)

All the nodules showing a VTI category 4 i.e. Honeycombing were found to be malignant whereas 16.3% and 36% of VTI category 1 and 2 were malignant. In VTI category 3 80% of the nodules were malignant. Total 97 nodules were classified in category 3 and 4 (Stiffer than thyroid) – 82 (84.5%) proved to be malignant. For the nodules classified as VTI softer and as stiff as thyroid 17 (22.9%) out of the 74 turned out to be malignant. This formed the basis of recoding our VTI results

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

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

There is no evidence of significant statistical correlation between the presence of background thyroiditis and VTI observations. The Pearson chi square test value=5.432, DF=3, P=0.143 ($P>0.05$). VTI of the thyroid nodules was not statistically different among patients with background changes of thyroiditis

There is significant statistical correlation between the ARFI values, t value – 5 and, $p<0.001$

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) nodules, $p<0.001$.

Mean VTQ of the thyroid nodules was not statistically different among patients with background changes of thyroiditis and without thyroiditis, Pearson chi-square teat value is =0.928, DF=210, p=0.354

The Interobserver agreement was using interpreted according to guidelines laid by Landis and Koch 1977.

The Interobserver agreement was substantial for presence of calcification and moderate for halo, composition, margins and shape and a fair Interobserver agreement for echogenicity.

Overall Interobserver agreement for TIRADS was Moderate.

Table.1 Virtual touch imaging –VTI

p	BENIGN (%)	MALIGNANT (%)	TOTAL
1	41 (83.7)	8 (16.3)	49 (100)
2	16 (64%)	9 (36%)	25 (100)
3	15 (19.7)	61 (80.2)	76 (100)
4	0 (0)	21 (100)	21 (100)
Total	72	99	171

Table.2 VTI CODE

VTI CODE	BENIGN	MALIGNANT
VTI 1 and 2(Softer)	57	17
VTI 3 and 4(Stiffer)	15	82
TOTAL	72	99

Table.3 Tirads

TIRADS	RECODED VTI CATEGORY	BENIGN	MALIGNANT	TOTAL
TIRADS-2	0	3	0	3
TIRADS-3	0	33	9	42
	1	6	8	14
TIRADS-4	0	6	3	9
	1	1	6	7
TIRADS-4b	0	6	3	9
	1	3	11	14
TIRADS-4c	0	5	2	7
	1	3	19	22
TIRADS-5	0	4	0	4
	1	2	38	40

Table.4 Thyroiditis

Thyroiditis	VTI-1	VTI-2	VTI-3	VTI-4
Present	3	5	13	2
Absent	69	27	77	20
Total	72	32	90	22

Table.5 ARFI – VTQ

	Number	Mean VTQ	Standard deviation	95% CI
BENIGN	71	2.18	1.35	1.874-2.512
MALIGNANT	97	3.9	2.65	3.43-4.503
TOTAL	168			

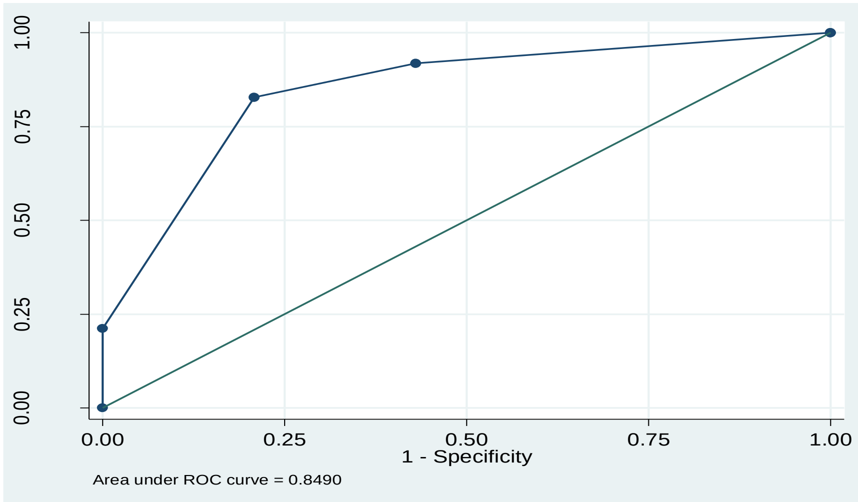
Table.6 Background thyroiditis and relation to mean VTQ values

Thyroiditis	Number	Mean VTQ	Standard deviation
Present	22	3.412	2.2413
Absent	190	2.949	2.2445
Total	212		

Table.7 Inter-observer agreement between observers for ultrasound findings:
Linear weighted kappa coefficients and p value

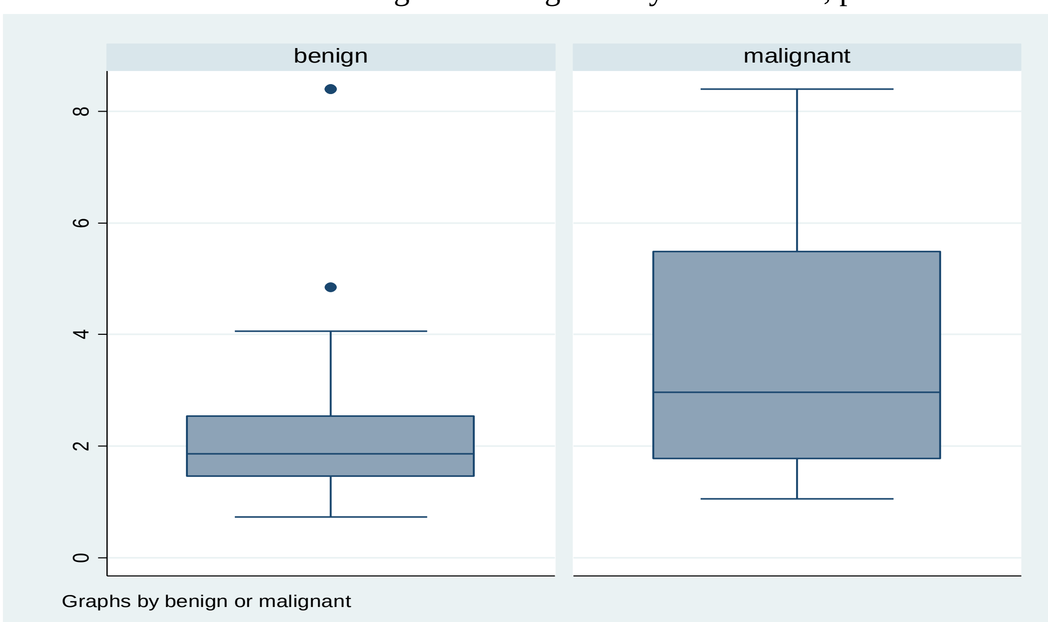
p	N	Kappa	P value	Interobserver Agreement
Halo	211	0.459	$p < 0.001$	Moderate
Composition	217	0.478	$p < 0.001$	Moderate
Echogenicity	217	0.291	$p < 0.001$	Fair
Margin	217	0.462	$p < 0.001$	Moderate
Calcification	217	0.626	$p < 0.001$	Substantial
Shape	216	0.519	$p < 0.001$	Moderate
TIRADS	217	0.438	$p < 0.001$	Moderate

Fig.1 Receiver-operating characteristic (ROC) curve depicting accuracy of VTI in predicting malignancy. The area under the curve is 0.8490



Performance of the VTI
Sensitivity – 82.8
Specificity – 79.17%
Positive predictive value – 84.5%
Negative predictive value – 77%
Diagnostic accuracy – 81.2%
Likelihood ratio – 3.97

Figure.2 Box plot depicting the mean, median and range of shear wave velocity measurements in benign and malignant thyroid nodules, $p<0.001$



According to the study conducted by Gu *et al,,* 77.6 % of the benign nodules showed softer images on the VTI, 77.3% of the nodules showed stiffer images ($P<0.001$) (Jiying Gu *et al.,* 2012).

The current study showed that of the 97 nodules classified as category 3 and 4 (Stiffer than thyroid) 82 (84.5%) proved to be malignant. For the nodules classified as VTI softer and as stiff as thyroid 17 (22.9%) out of 74 turned out to be malignant whereas 77.1% nodules were benign ($p<0.001$).

The Sensitivity, specificity, PPV, NPV and diagnostic accuracy were 82.8%, 79.19%, and 84.5%, 77% and 81.2% respectively

According to Gu *et al.*, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accordance rate were 86.36%, 93.42%, 79.17%, 95.95% and 91.84% based on the standard VTQ value of 2.555m/s. Benign nodules had VTQ values with a mean of 2.005 ± 0.485 m/s, lower than the malignant subgroup and the VTQ values in malignant nodules had a mean of 3.941± 1.393 m/s, higher than the benign nodules, $P <.001$. The area under the receiver operating characteristic curve was 0.954 (Jiying Gu *et al.,* 2012)

At a mean VTQ of 3.450 for the malignant nodules, the sensitivity, specificity, positive predictive value and negative predictive value and diagnostic accuracy were 63.6%, 100%,100%, 90.48%, and 91.84% respectively

According to another study conducted by Bojunga *et al*., (1), the sensitivity, specificity, Positive predictive value and negative predictive value and likelihood ratios were 57%, 85%, 38%, 93% and 3.91 respectively (Bojunga *et al.,* 2010).

The current study showed that mean VTQ values for the benign nodules was 2.18(±1.35) and 95 CI (1.874-2.512) whereas the mean VTQ for malignant nodules was 3.9(±2.65) and 95 CI (3.43-4.50) $p<0.001$. The area under the receiver operating curve –ROC 0.6988. The sensitivity, specificity, positive predictive value, Negative predictive value and accuracy were 57.1, 82.5%, 53.6%, 84.5% and 65.5% respectively and the likelihood ratio was 3.65 at a cut off value suggested by ROC curve of 2.958 m/s. At a cut off of 3.502 the sensitivity, specificity, diagnostic accuracy and likelihood ratios were 42.3%, 90.14%, 62.50% and 4.28 respectively

The current study showed similar results to the two studies available in literature on ARFI in thyroid nodules. Combining VTI with VTQ and TIRADS to determine if there is increase in the diagnostic accuracy

In conclusion, the Inter-observer agreement was substantial for presence of calcification and moderate for halo, composition, margins and shape and a fair Inter-observer agreement for echogenicity.

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