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

A dissertation submitted in partial fulfilment of MD Radiodiagnosis (Branch VIII) examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2014

CERTIFICATE

This is to certify that the dissertation entitled “Diagnostic accuracy of Acoustic Radiation Forced Impulse (ARFI) in differentiating benign from malignant thyroid nodules in patients with solitary thyroid nodules and comparison with histopathology” is the bonafide original work of Dr. Abhishek Khurana submitted in partial fulfilment of the requirement for MD Radiodiagnosis (Branch VIII) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2014.

Guide:

Dr Elizabeth Joseph

Professor

Department of Radiology

Christian Medical College

Vellore .

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Head of the department

Dr Shyam kumar NK
Professor
Department of Radiology
Christian Medical College
Vellore

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Department of Radiology
Christian Medical College
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Dear Dr. Abhishek Khurana,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed the following request to include additional co investigators - Dr. Deepak Abraham. Endocrine surgery and Dr. Dukhabandhu Naik, Endocrine surgery for the study titled "Diagnostic accuracy of Acoustic Radiation Forced Impulse (ARFI) for differentiating between benign and malignant thyroid nodules in patients with solitary thyroid nodules in comparison with histopathology" on December 5, 2012.

Name	Qualification	Designation	Other Affiliations
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Clinician
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Clinician
Dr. Bobby John	MBBS, MD, DM, PHD, MAMS	Cardiology, CMC	Clinician
Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	Pharmacologist

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

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We approve the above request as presented.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Elizabeth Joseph, Department of Radiology

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ABSTRACT

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

Aims and objectives: To assess the value of shear wave elastography (SWE) using ARFI technology in differentiating benign and malignant thyroid nodules

Materials and methods: IRB approved prospective study in a 2800 bedded tertiary care teaching hospital. Ultrasound, shear wave velocity (SWV) measurements were obtaining by virtual touch quantification (VTQ) and virtual touch imaging (VTI) using ARFI technology on patients with solitary thyroid nodule, one or two dominant nodule of multinodular goitre >1cm. These were compared with cytology and surgical histopathology. Diagnostic performance of SWV measurement, VTI and conventional ultrasound were compared

Results:

Of 193 patients with 217 thyroid nodules, 153 patients (37 males, 166 females; age 16-82 years) with 172 nodules were included. 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, $p<0.001$. There is significant difference in the elasticity score obtained by VTI between benign and malignant nodules (chi-square =70.522, $p < 0.001$). Sensitivity, specificity, PPV, NPV, accuracy of VTI was 82.8%, 79.0%, 84.5%, 77%, and 81.2% respectively and that of VTQ at a cut off SWV of 2.87 m/s was 82.5%, 57.1%, 53.6%, 84.5% and 65.5% respectively. Diagnostic performance of VTI (AUC = 0.849) and combined VTI+VTQ (AUC= 0.831) was better than VTQ alone, conventional ultrasound and combined criteria (conventional ultrasound + VT I + VTQ); AUC was 0.699, 0.682 and 0.727 respectively

Conclusion: ARFI –VTI is highly sensitive and specific modality for differentiation of benign and malignant thyroid nodules

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AIMS

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 evaluate thyroid nodules using ultrasound and score the likelihood of malignancy according to TIRADS
2. To assess pattern of ARFI values in various types of solitary thyroid nodules.
3. To obtain the best fit ARFI values to differentiate benign and malignant thyroid nodules.
4. To assess accuracy of virtual touch imaging (VTI) and VTQ (Virtual touch Quantification) in differentiating benign and malignant thyroid nodules

LITERATURE REVIEW

The thyroid gland is an endocrine gland situated in the lower neck extending from the fifth cervical vertebra to the first thoracic vertebra. The thyroid gland is enveloped by the pre-tracheal fascia. The thyroid gland is a midline structure and consists of a right and left lobe connected across the midline by a narrow isthmus (1). The lobes of the thyroid gland conform to the shape of a cone. The medial or deep aspect of the thyroid gland is closely applied to the larynx and the upper part of the trachea. The recurrent laryngeal nerve and the oesophagus are located deep to the gland, the left lobe of the thyroid gland is more closely related to the oesophagus. The thyroid gland occasionally has a pyramidal lobe which usually arises from the isthmus and connects to the hyoid bone. (1)

Vascular supply of the thyroid gland: the vascular supply of the thyroid gland is via the superior and inferior thyroid arteries with occasional contribution form the arteria thyroidea ima which is a branch of the brachio-cephalic trunk or the arch of aorta (1). The superior thyroid artery is a branch of the external carotid artery, the inferior thyroid artery arises as a branch from the thyrocervical trunk which is in turn a branch of the first part of the subclavian artery.

Nerve supply of the thyroid gland: the superior, inferior and middle cervical sympathetic ganglia supply the thyroid gland.

Ultrastructure of the thyroid gland: the gland is enveloped by connective tissue with septations which extend into the substance of the gland resulting in the formation of lobules. The basic functional unit of the thyroid gland consists of follicles. The follicle has a core of colloid with a layer of epithelial cells which rest on a basal membrane. The colloid consists of inactive form of thyroid hormone in the form of a glycoprotein which is iodinated. (1)

The epithelial cells lining the follicles are influenced by TSH levels and change in morphology (squamous, low cuboidal or columnar) under the influence of TSH levels (1). Follicular cells are responsible for conversion of the inactive colloid to active T3 and T4. The other significant cells seen in the thyroid gland are the C-cells which are responsible for production of calcitonin, a hormone which regulates calcium homeostasis. (1)

Pathology of the thyroid gland:

Pathological processes that involve the thyroid gland can be broadly divided into diffuse and focal diseases.

Diffuse thyroid disease can be the result of

1. Hyper functioning or hypo functioning thyroid gland in terms of hormone production
2. Infections and infiltrative disorders including auto-immune diseases form the rest of the spectrum of diffuse thyroid disease

Goitre: diffuse or focal enlargement of the thyroid gland is termed goitre. (2)

Goitre is the most common form of thyroid pathology. Goitre can be broadly classified as

1. Diffuse Goitre: the thyroid gland is enlarged without the presence of nodularity
2. Nodular goitre: characterised by the presence nodules in the thyroid gland, which may be solitary or multiple, multi-nodular goitre is self-explanatory and is characterised by the presence of multiple nodules.

Of the nodular forms of goitre, multinodular goitre is the result of essentially the same pathological process as diffuse simple goitre (2). Over time, multiple episodes of glandular hyperplasia and involution result in a more nodular, irregular form of thyroid gland enlargement which is termed multinodular goitre (2).

Multinodular goitre: multinodular goitres are thought to arise due to differences in response of follicular cells to stimuli such as trophic hormones which in turn result in proliferation of follicular cells which are genetically more sensitive to the effects of trophic hormones. Non-uniform hyperplasia of certain subsets of follicular cells, production of new follicles, non-uniform accumulation of colloid result in stress within the thyroid gland, the end result of increased stress within the thyroid gland results in bleeding into the gland, scar tissue formation and calcifications within the gland. The stromal network of the thyroid gland restricts the hyperplastic follicles and results in the nodular appearance (2).

Neoplasms of the thyroid gland: neoplasms of the thyroid gland can be broadly classified into benign and malignant neoplasms.

The most common benign neoplasm of the thyroid gland is the adenoma. Adenomas of the thyroid gland are usually single and discrete (2). Adenomas usually consist of cells of follicular origin and are also referred to as follicular adenomas. Thyroid adenomas take up less radio-iodine when compared to the rest of the thyroid parenchyma and appear “cold” on thyroid scintigraphy. Upto 10% of cold thyroid nodules may harbour malignancy (2). Occasionally, an adenoma may be hyperfunctioning and result in the presence of a hot nodule on thyroid scintigraphy.

Thyroid carcinomas: thyroid malignancies are classified into the following subtypes

1. Papillary

2. Follicular

3. Medullary and

4. Anaplastic

The cell of origin in most thyroid carcinomas is the follicular cell, the exception being medullary carcinomas. The cell of origin for medullary carcinomas is the C-cell which is responsible for secreting calcitonin (2).

Papillary carcinoma is the commonest form of thyroid malignancy, are common between the ages of 20 and 40 and is the most common form of thyroid carcinoma associated with exposure to ionising radiation. Thyroid lesions can be solitary or multifocal in case of papillary carcinomas. They may be well circumscribed, surrounded by a capsule or can have infiltration into the adjacent parenchyma (2). Pathologic characteristics of papillary carcinomas include the following

1. Single layer / multiple layers of cuboidal epithelium over a fibro-vascular stalk or core.

2. Finely dispersed chromatin in the nuclei with “orphan Annie appearance” of the nuclei.

3. Cytoplasmic invaginations into the nucleus giving a “pseudo-inclusion” appearance.

4. Concentric calcifications which are termed “psammoma” bodies.

Variants of papillary carcinoma include

a. Encapsulated papillary carcinoma

b. Follicular

c. Tall cell

d. Diffuse sclerosing

e. Hyalinizing trabecular variants

Follicular carcinomas form the next most common histological subtype of form of thyroid malignancies and account for ~ 10-20 % of thyroid malignancies. The microscopic

appearance of follicular carcinomas consist of uniform sized cells arranged in a follicular pattern with central colloid material. Capsular and vascular invasion is necessary to make a diagnosis of follicular carcinoma (2).

Medullary carcinomas are essentially tumours of a neuro-endocrine nature and arise from the C-cells which are responsible for calcitonin secretion. The histology of medullary carcinomas reveals the presence of polygonal or spindle shaped cells. Acellular Amyloid deposits which are derived from calcitonin are seen on microscopy, the calcitonin can be demonstrated by employing immunohistochemistry (2).

Anaplastic carcinoma of the thyroid gland are undifferentiated neoplasms of follicular origin. They are characterised by their clinical aggressiveness, the mortality rates are in the region of ~ 100%. Less than 5% of thyroid malignancies are of the anaplastic subtype and tend to occur in an older age group. (2).

Thyroid nodules are a common reason for patient referral to endocrine surgery (3). By 80 years of age, 80 % of the population are likely to have one or more thyroid nodules (4).

The classical description used to describe a thyroid nodule in the past has been to describe it as a hot / cold nodule base on the nodule's uptake of radioactive iodine, this system of classification has now been discarded (3). Prevalence of thyroid nodules on physical examination ranges from 5-10% (3). This number has been found to be a gross underestimation of the actual prevalence of thyroid nodules in the adult population with the advent of high resolution imaging of the thyroid using ultrasound (3). Clinical and sonographic evaluation of the thyroid nodule is aimed at detecting the functioning thyroid nodules which result in toxic symptoms and in detection of the nodules that harbour malignancy. It is to achieve this end that the efforts of clinicians and sonographers are directed. A hyperfunctioning thyroid nodule is detected by either palpation or sonography

and thyroid function tests will reveal the activity which is then confirmed with radionuclide scintigraphy. Thus diagnosing a hyperfunctioning thyroid nodule is fairly straight forward.

On the other hand, detection of malignancy within a thyroid nodule is a complex process involves biochemical lab evaluation of thyroid function, clinical assessment, sonographic assessment which is then followed by a FNAC and or surgery.

Thyroid nodules may be palpable or asymptomatic and are detected on thyroid sonography.

Biochemical evaluation is the next logical step following detection of a thyroid nodule. Hyperfunctioning nodules are rarely malignant and once a hyperfuctioning nodule is detected by assessing the TSH, further evaluation at this juncture would include a radionuclide scan.

A thyroid nodule with euthyroid status as determined by the TSH levels is then subjected to FNAC based on the sonographic features. General recommendations state that a thyroid nodule with suspicious sonographic characteristics be subjected to a thyroid FNAC. Cytological diagnosis is the most accurate diagnostic tool available at present to determine whether or not a thyroid lesion is malignant or benign (5).

FNAC has a critical role to play in the assessment of euthyroid individuals with a thyroid lesion. Cytology smears which are diagnostic will result in a reduction in the rate of unnecessary thyroid surgery in patients with cytopathologically proven benign lesions (6). Prior to routine FNAC for thyroid nodules, the percentage of malignancy in resected surgical specimens was 14% (7), by incorporating FNAC of thyroid nodules into routine practice, the percentage of malignancy in resected surgical specimens has gone upto 50% (8). In view of the confusion regarding cytopathology reporting terminology, the NCI has come up with the

"Bethesda system" in reporting of thyroid cytopathology smears (6). The Bethesda system recommends that each thyroid cytopathology report have 6 general diagnostic categories, each of these categories has an implied risk of malignancy

The following are the general categories under which cytopathology reports are grouped.

1. Non-diagnostic or unsatisfactory

2. Benign

3. Atypia of undetermined significance or follicular lesion of undetermined significance

4. Follicular lesion or suspicious for a follicular neoplasm

5. Suspicious for malignancy

6. Malignant

The implied risk of malignancy for each of the above categories varies from 1-4 % for non-diagnostic to 97-99 % for the malignant category (6). Of the above general categories the subcategory of non-diagnostic or unsatisfactory necessitates further explanation.

An FNAC smear is considered adequate if there are at least 6 groups of follicular cells, each group with a minimum of 10 cells. Smears which may considered inadequate include air dried alcohol fixed smears and thick smears (6). In the presence of colloid, a smear may be judged adequate for evaluation even if the numerical criteria regarding number of follicular cells is not met (6). Non-diagnostic or unsatisfactory smears must ideally represent ~ 10 % of thyroid FNAC smears, in practice however, the percentage number of non-diagnostic or unsatisfactory cytopathology smears encompasses a wide range – ranging from 2-20 %. (11, 12,13). Some cytopathology smears may contain only macrophages – in these instances, macrophages are present and sonographic appearances may prompt the clinician to seek a

repeat FNAC if sonographic features are of concern for malignancy. In the absence of sonographic features that raise suspicion for malignancy, the clinician may interpret a cyst fluid only result as benign. Cyst fluid only cases were analysed separately in a study which reported a malignancy rate of 4% (12).

The case of the inadequate / non-diagnostic / unsatisfactory thyroid FNAC smear:

Sonography aided FNAC of thyroid lesions is a proven method for increasing the yield of thyroid FNAC accuracy with the rate of non-diagnostic smears reported to have reduced from 15 % to 3 % (14). Non diagnostic cytology smears require a repeat FNAC or if clinical and sonographic features are suspicious for malignancy surgery is recommended.(3)

Management of a patient with a thyroid nodule:

The management of a euthyroid patient with a thyroid nodule is based on the FNAC result. Recommendations regarding a benign FNAC smear result include repeat FNAC until 3 successive FNAC smears have been reported as benign or follow up with biochemical analysis of thyroid function tests and repeat FNAC after a one year interval. (15, 16)

The algorithm for management of thyroid lesions wherein cytology smears have been reported as follicular neoplasm require to be considered separately as the diagnosis of benign vs malignant follicular neoplasm cannot be made on cytology – it is essential to demonstrate capsular invasion and vascular invasion to diagnose follicular carcinomas. Approximately 15% of thyroid nodules fall into the category of follicular neoplasm following

cytopathological examination (17). The presence of vascular or capsular invasion can be diagnosed only by histopathological examination of the surgically excised nodule. (3). the further management of such nodules is controversial and the clinician may decide to follow

up or excise the nodule, the decision being based on clinical assessment and sonographic features of the thyroid lesion in question. (3)

Sonography of thyroid nodule:

Thyroid nodules are a relatively common occurrence and are detected in approximately 50% adults (18). Thyroid nodules may be benign or malignant. Malignancy of the thyroid gland is rare (19), in contrast benign thyroid nodules are common, nodular hyperplasia being the commonest of the benign nodules (20). The percentage of malignant thyroid nodules is quoted to be less than 7% (20). Although the percentage of malignancy in thyroid nodules is considerably low, it is critical to identify these lesions accurately.

The modality of choice for imaging of the thyroid gland is high resolution sonography (18). 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 (18). 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. (18)

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 (21-23) 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 % (22,23) 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% (22, 23). 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) (22, 23). Patients with non-thyroid malignancies can occasionally have metastatic disease which involves the thyroid gland. (18)

Sonographic features of malignancy in the thyroid gland:

1. Calcifications: calcifications in the thyroid gland are classified as micro-calcifications, coarse calcifications and peripheral calcification. Micro-calcifications appear as punctate Hyperechoic foci with no posterior acoustic shadowing (18). Presence of micro-calcifications is considered to be one of the specific features of thyroid malignancy, they are the sonographic equivalent of "psammoma bodies" (10-100 micron size calcific deposits). The specificity and positive predictive values for micro-calcifications in predicting malignancy are 85-95% and 41.8- 94 % respectively (20, 22-24). Microcalcifcations are distinguished from colloid calcifications (benign) by observing the lack of ring down /reverberation artefact seen in inspissated colloid material (26). Coarse calcification can be diffusely distributed in multi-nodular goitres, however, when they are associated with a solitary nodule, they are suspicious for malignancy with malignancy being diagnosed in ~ 75 % of cases with coarse calcifications (25). Peripheral calcifications are usually seen with multi-nodular goitre but can be seen occasionally in malignant thyroid nodules (27).

2. Margins, Contour, and Shape: Presence of an uninterrupted, complete hypoechoic halo surrounding a thyroid nodule is indicative of benignity, the specificity of this sign being ~ 95%. (29). The Hypoechoic halo represents a combination of compressed thyroid tissue, inflammatory infiltrates and a pseudo-capsule of fibrous tissue (28). A thyroid nodule is considered ill-defined if more than 50% of the margins cannot be clearly defined at sonography. Margins of a thyroid can be described as smooth and rounded or irregular with jagged edges. The sensitivity and specificity of smooth margin versus an ill-defined, irregular

margin varies widely in literature reports and papillary carcinoma can have deceptively smooth margins (30). Sonographic appearance of the nodule is thus unreliable for determining the malignant or benign nature of the lesion (1). The shape of the nodule has been reported to be a useful feature to distinguish between benign and malignant thyroid nodules, a lesion that is taller than wide (AP diameter greater than transverse diameter has a reported specificity of 93% for being malignant(23). This appearance is due differential growth of the tumour. (18)

3. Lesion vascularity: The commonest pattern of vascularity within a malignant thyroid nodule is reported to be marked intrinsic hyper-vascularity which is said to occur in 69-74% of malignant thyroid lesions (20, 30). Marked intrinsic hypervascularity is however, not a specific sign and can occur in benign thyroid lesions (31). Peripheral flow was defined by Chan et al as vascularity around the nodule, the vascularity being present along a minimum of 25 % of the lesion circumference (30). Chan et al further opined that intrinsic vascularity was a common feature in papillary carcinomas and a nodule with absence of intrinsic vascularity was likely to be benign (30). Nodule vascularity can be utilised in two ways for thyroid nodule imaging, the first being to determine which nodule to biopsy in a patient with multiple thyroid nodules, the presence of intrinsic vascularity and other features of malignancy directing the nodule to be targeted for image guided FNAC, the other being that the solid component with vascularity can be preferentially targeted during image guided FNAC. (19, 26)

4. Echotexture of the nodule: Hypoechoic and solid appearance of a thyroid nodule in combination is reported to have a sensitivity of 87% in determining thyroid malignancy, the above features are however associated with a low specificity and positive predictive value (19). The nodule echotexture is compared to that of the adjacent strap muscles and if the nodule echotexture is markedly lower than that of the strap muscles, the specificity for

determining malignancy approaches 94 %, this is however at an expense of the sensitivity which becomes lower (20). A markedly hypoechoic thyroid nodule is highly suspicious for malignancy (18).

5. Nodule size: presence or absence of malignancy in any given thyroid nodule is not related to nodule size (18). It is recommended that the basis for selection of a nodule for FNAC in a multi-nodular goitre be determined by ultrasound characteristics of the nodule rather than depending solely on the size of the nodule (19).

6. Number of nodules: risk of malignancy in a gland with multiple nodules is almost the same as the risk of detection of malignancy in a gland with solitary nodule (20). Follicular carcinoma of the thyroid is the commonest malignancy to be detected in multinodular goitre, multifocality is seen in 12% of papillary carcinomas (32). In multinodular goitre, the choice of lesion / lesions to be sampled by FNAC should be entirely directed by the presence of suspicious ultrasound characteristics and compelling clinical examination findings (18). A diffusely enlarged gland with multiple sonologically benign appearing nodules with no normal intervening thyroid parenchyma is unlikely to be harbouring foci of carcinoma and need not be subjected to FNAC (19).

7. Change in size on serial follow up: a change in size of nodule on follow up sonography is not reliable in distinguishing benign and malignant lesions as benign lesions also tend to exhibit interval growth (33, 34)

8. Local invasion and lymph node metastases: involvement of adjacent soft tissues and nodal disease are highly indicative of malignancy (24). On sonography, invasion of adjoining tissues can be subtle – ie, lesion extension beyond the contours of the thyroid gland, at times, the invasion is unequivocally evident (18). Lymph nodal disease spread has been reported to

be present in 19.4 % of thyroid malignancies (20). Nodal metastases occurs most commonly in papillary carcinoma (21) and approximately 50% of patients with medullary carcinoma are reported to have early nodal metastases (21). Sonographic assessment of nodal disease must be included in the imaging protocol for thyroid nodule imaging (18). The internal jugular nodal chain on the same side as the nodule has to be carefully assessed (18). Sonographic features that are suspicious for nodal metastatic disease include a rounded, bulging contour, increase in size, obliteration of normally present central fatty hilum, margin irregularity, heterogeneity of the nodal echotexture, presence of nodal calcifications and vascularity that is present throughout the node (19,36,37). The nodal group involved by metastatic disease was used as a factor for prognostication. Nodal disease in thyroid carcinoma can be divided into disease involving the central or lateral compartment. The central compartment is anatomically defined to lie between the carotid arteries and comprise the pre-tracheal and para-tracheal nodes, the thymic and pre-thymic nodes. The lateral compartment is defined as internal jugular chain of nodes, the posterior triangle and supra-clavicular group of lymph nodes (18). Local disease recurrence was reported to be higher in the presence of lateral compartment nodal disease as opposed to central compartment nodal disease in cases of microcarcinoma (38, 39).

Thus high frequency sonography of the thyroid gland has contributed to

a. Increased detection of non-palpable thyroid nodules

b. Characterise the nodule (palpable and non-palpable) to enable informed clinical decision making

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. (18)

There is however considerable controversy regarding the management of the incidentally detected thyroid nodule which are asymptomatic. 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 JY 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. 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 (40)

During stage 1 of the study, sonographic characteristics of362 thyroid nodules were reviewed in an attempt to define and specify lesion characteristics (40). 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.

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.

The TIRADS group classification that was generated included the following groups.

TIRADS 1 – normal thyroid gland

TIRADS 2 – benign conditions with zero malignancy risk

TIRADS 3 – probably benign (< five percent risk of malignancy)

TIRADS 4 – suspicious nodule (5- 80 % risk of malignancy)

TIRADS 4 group was further subdivided into

4a (malignancy risk in the range of 5 to 10 %) and 4b (malignancy risk in the range of 10 to 80 %)

TIRADS 5 – more than 80% risk of malignancy

TIRADS 6 – biopsy proven thyroid malignancy

The third stage of the study was the period during which the TIRADS system of reporting was validated by evaluating 1097 other additional nodules (40)

The sonographic descriptors used to categorise the nodules detected at sonography by Horvath et al with correlation with FNAC results are given below.

Table 1. (40)

Sonographic description	Sonographic patterns	Malignancy	TIRADS
Anechoic with echogenic foci, no vascularity	Colloid pattern 1	0%	TIRADS 2
No capsule, mixed echogenicity, nonexpansile, with echogenic foci, vascularity present lesion, lacy appearance (spongiform nodule)	Colloid pattern 2	0%	”
No capsule, mixed echogenicity with solid component, isoechoic, expansile, Vascular nodule with echogenic foci	Colloid pattern 3	0%	”
Hyper, iso, or hypoechoic, partially encapsulated nodule with peripheral Vascularization, in Hashimoto’s thyroiditis.	Hashimoto’s pseudo-nodule	< 5%	TIRADS 3 probably benign
Solid or mixed hyper, iso, or hypoechoic nodule, with a thin capsule	Simple neoplastic pattern	5-10%	TIRADS 4a, indeterminate
Hypoechoic lesion with ill-defined borders, without calcifications	De Quervain’s pattern	”	”
Hyper, iso, or hypoechoic, hypervascularized, encapsulated nodule with a thick capsule, containing calcifications (coarse or microcalcifcations)	Suspicious neoplastic pattern	”	”
Hypoechoic, not encapsulated, with irregular shape and margins, Central vascularity, with or without calcifications	Malignant pattern A	10-80%	TIRADS 4B: suspicious
Iso or hypo-echoic, not encapsulated nodule with multiple peripheral Micro-calcifications and increased vascularity	Malignant pattern B	>80%	TIRADS 5: consistent with malignancy
No capsule, Isoechoic, mixed nodule with increased vascularity with or without calcifications, without hyperechoic spots.	Malignant pattern C, cancer, confirmed by previous biopsy	100%	TIRADS 6, malignant

The probability of detecting a follicular lesion on the FNAC of nodules categorized as TIRADS 2, 3, 4 and 5 was 0, 10.7, 31 and 3.1%, respectively.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 88, 49, 49, 88, and 94%, respectively (40).

Based on the above findings, Horvath et al have concluded that TIRADS 2 category lesions need not be subjected to FNAC as they are invariably benign, TIRADS 3 lesions may be subjected to follow up, FNAC may be done for TIRADS 3 lesions under circumstances like – patient unable to come for follow up, follow up sonography reveals increase in lesion size, presence of family history of thyroid malignancies and history of radiation to the neck.

Patients with TIRADS 4 and 5 category thyroid lesions must be subjected to an FNAC and most of them surgically excised if FNAC proves inconclusive. (40)

The authors have concluded that application of the TIRADS criteria in sonographic assessment has resulted in reduction in the number of unnecessary thyroid nodule FNACs,

(40) And TIRADS system for thyroid lesion categorization is a useful tool in selection of those lesions that require to be subjected to FNAC (40).

Although the TIRADS reporting system for thyroid nodules has achieved some success, the studies published were from single institutions and reproducibility is an issue. The factors that influence reproducibility include the quality of the ultrasound machine used, differences in the ultrasound criteria used and inter-observer variability which created issues related to reproducibility. E.g.the above quoted study uses fairly elaborate sonographic descriptors to enable nodule categorisation and inter-observer variability became a major issue. Other studies have attempted to streamline TIRADS system to minimise issues related to inter-observer variability.

Moon et al in another study attempted to retrospectively evaluate individual sonographic characteristics and their individual sensitivity, specificity, PPV and NPV in predicting lesion malignancy or benignancy (42).

They (Moon et al) retrospectively analysed 831 patients with 849 nodules detected at sonography of the thyroid gland who then had undergone either surgery / trucut biopsy / fine needle aspiration cytology which yielded benign result at least twice within a one year interval. (42)

The authors (Moon et al) aimed to evaluate the diagnostic accuracy of sonographic criteria for delineating malignant and benign lesions. Three head and neck radiologists with more than 6 years' experience retrospectively analysed static DICOM images obtained at thyroid sonography. The reviewers retrospectively analysed the imaged thyroid lesions based on predetermined criteria. The criteria included lesion size, internal architecture, presence of a spongiform appearance, shape of lesion, margins, overall echogenicity, echogenicity of solid components and presence of calcifications (42).

Statistical analysis of the thyroid lesions included in the study were as follows.

1. The mean largest dimension of cancer nodules were statistically lower than that of benign nodules (p-value less than 0.001)

2. Presence of solid component – no statistically significant difference was found in the presence of solid component between cancerous thyroid lesions and benign thyroid lesions

3. Sonographic features which indicated lesion benignancy which were of statistical significance included ovoid – round shape, well defined smooth margin, lesions which were isoechoic to surrounding normal thyroid parenchyma and the presence of a fine lacy internal architecture (spongiform)

4. Sonographic features which were statistically significant in indicating cancerous lesions included taller than wide lesions, presence of margin spiculations, markedly Hypoechoic internal echotexture, Hypoechoic internal echotexture, micro and macrocalcifications.

The authors concluded in their report that there was no single sonographically suspicious feature had an overall diagnostic accuracy of more than 75%. Markedly hypoechogenic lesion echotexture was a highly sensitive sonographic feature in predicting malignancy but this feature has a poor specificity (42).

The rest of the sonographic features which were indicative of malignancy were highly specific but had relatively low sensitivities. (42)

Jin Young Kwak et al in an attempt to achieve wider acceptance have attempted to simplify the sonographic criteria used to the TIRADS reporting system.

They retrospectively analysed data from various individual studies in an attempt to develop and validate a simple diagnostic prediction model. (41)

The sonographic criteria used in the study by Jin et al are as follows:

1. Size – size equal to or larger than 5 mm

2. Lesion composition – the nodules were characterised as solid (<10 % cystic component), predominantly solid (10-50% cystic component) and predominantly cystic (> 50% cystic component) and spongiform appearance (defined as aggregate of micro-cysts forming >50 % of lesion volume

3. Lesion echotexture: Hyper/Isoechoic (Hyperechoic - echotexture more than that of the surrounding normal thyroid parenchyma, isoechoic when the echotexture of the nodule was similar to that of the surrounding normal thyroid parenchyma) Hypoechoic when the

echotexture of the lesion was lower than the surrounding normal thyroid parenchyma and markedly Hypoechoic when the lesion was of an echogenicity lower than that of the strap muscles)

4. Lesion orientation: non-parallel (AP dimension of the lesion being greater than the transverse dimension) vs. parallel (AP dimension lesser than the transverse dimension)

5. Lesion shape: ovoid to round when the AP dimension of the lesion was less than or equal to the transverse dimension vs. irregular when lesion was neither ovoid or round

6. Lesion margin: the lesion margins were categorised as well-defined and smooth, or micro-lobulated / spiculated and ill-defined

7. Calcifications: calcifications were defined as micro-calcifications if they were tiny

</= 1 mm with or without posterior acoustic shadowing, presence of comet-tail / reverberation artefact posterior to echogenic foci resulted in the lesion being considered to be of colloid nature, calcifications were denoted as macrocalcifications if the calcific foci were > 1 mm in size, macro-calcifications included ring and egg-shell calcifications, in case of nodules with micro and macrocalcifications, the lesion was considered to contain micro-calcifications.

Consensus criteria were thus established with regards to various sonographic features to be assessed in the study.

Eighteen ultrasound features were considered while formulating a prediction model (41), the ultrasound features considered were based on a study by Moon et al (42).

In an attempt of stratify risk of malignancy in thyroid lesions, Jin Young et al

An assumption was made that the prevalence of malignancy on FNAC was 16%.

A training set which included 70% of data was used for formulation of the prediction model and 30% of data was used for validation of the prediction model (41).

Nodules which were included in the study were larger than 5 mm and had been subjected to ultrasound guided FNAC.

Further criteria for nodule inclusion were one or more of the following criteria

1. Undergone thyroid surgery
2. At least 2 benign FNAC results
3. One benign FNAC result with no change or reduction in lesion size on follow up sonography

Results of multiple regression analysis of the training data set (randomly selected 1402 nodule) and odds ratio calculation showed the following sonographic features had statistical significance in predicting presence of malignancy.

1. Lesion echotexture – Hypoechoic and markedly Hypoechoic lesions were more likely to be malignant

2. Non-parallel orientation

3. Margin spiculations

4. Poorly delineated lesion margins

5. Presence of micro-calcifications

Of the above features, odds ratio of more than 5 were seen for micro-lobulated or spiculated lesions and lesions with markedly hypoechoic echotexture. Risk scores were assigned to each suspicious ultrasound characteristic based on the odds ratio for each sonographic

characteristic which was in turn calculated by logistic regression analysis. (41). The odds ratios were rounded off to the closest integer and denoted as the risk score, the lowest risk score was 0 and maximum risk score was 6.

Risk scores for suspicious ultrasound features were assigned as follows.

1 –Non parallel orientation

2 –Hypoechogenecity and microcalcifcations

5 –Microlobulated or spiculated margins

6 –Markedly Hypoechoic

The total risk score for a particular lesion was the sum of the risk score of individual risk scores for each suspicious sonographic feature the nodule possessed (42)

Malignancy rates were 59.1 in microlobulated / spiculated lesions and 43.6 in lesions which were markedly hypoechoic.

The malignancy rate was found to be the maximum (95.2) in lesions which had a combination of findings such as being markedly Hypoechoic, of non-parallel orientation with microlobulations / spiculated borders and micro-calcifications (42).

Validation of the prediction model was then performed by analysing 598 thyroid lesions in 536 individuals (24). The results obtained during the validation phase of the prediction model showed a 6.2 cancer rate in thyroid lesions with no suspicious sonographic features. Lesions which were of non-parallel orientation and lesions with ill-defined borders had a cancer rate of 8.6, lesions with micro-lobulations or spiculations had a cancer rate of 33.3, lesions which were markedly Hypoechoic had a cancer rate of 34.5 (42).

The authors concluded that the above prediction model which uses suspicious sonographic characteristics may be useful in risk stratification of thyroid lesions (42).

Jin Young et al thus concluded that a malignancy risk similar to that in BIRADS cannot be assigned to a nodule based on a TIRADS system, on the other hand, calculating the overall risk scores for a thyroid lesion may be more accurate than the TIRADS system in assigning malignancy risk to each individual thyroid lesion. They further concluded that a predictor model which assigns risk scores to thyroid lesions may be contributory in the risk stratification of thyroid lesions (42).

Real time high resolution sonography of thyroid lesions have been reported in multiple studies to be highly predictive of malignancy only if multiple suspicious sonographic features are present simultaneously, the predictive value of sonography in the diagnosis of cancer in thyroid nodules improves at the expense of its sensitivity and malignancy is predicted in only ~ 20 % of case with a high degree of specificity (43)

Clinicians have however, long relied on palpatory findings in clinical evaluation of thyroid lesions, a hard thyroid nodule being more likely to be malignant as opposed to soft nodules being likely benign (44).

Lesion texture on palpation is however subjective and palpation findings vary with the examiner. The palpatory findings are variable depending on the size of the thyroid lesion and the depth at which it is located (45-47).

Elastography is a relatively new diagnostic modality that has been recently introduced.

It is a modality by which hardness of a lesion can be analysed with greater objectivity when compared to palpation. (48, 49)

Elastography is an advanced imaging technique which enables the sonographer to objectively assess the visco-elasticity of tissues. The image displayed as a result of applying elastography technique to a particular organ is essentially similar to the information obtained by palpation.

The basic concepts involved in Elastography are

1. Stress

2. Strain

3. Elastic modulus (50)

The physical principles and basis of Elastography: modern Elastography techniques rely on stress, strain or shear modulus or shear wave velocity imaging. Elastography images are generated by an ultrasound machine along with a simultaneous acquisition of grey scale images enabling comparison between the appearance of a lesion on grey scale and appearance on application of Elastography. (50)

Techniques for Elastography vary depending on

1. The mode of tissue excitation (tissue excitation can be achieved by using mechanical force or ultrasound force)

2. The method of measuring the response of tissue to compression (static or quasi-static where single compression is applied and the tissue response is imaged or dynamic systems in which rapid compression or vibration is measured.) (50)

3. The mechanical parameters measured i.e. Stress, strain or modulus (34)

Stress and strain are mutually dependent quantities (51)

Stress is defined as force per unit area, the SI unit for stress is Pascal = Newton /m2

When an object is subjected to stress, the object undergoes deformation, the amount of deformation is known as strain – strain can be longitudinal (change in length of object) or shear where there is change in the angles / shape of the object. (50)

Strain is a unit less quantity and is expressed as $\Delta l / l$. (50)

Strain imaging is more widely used in the clinical setting.

The information derived from strain imaging is a measure of tissue displacement in response to an externally applied force. (51)

The ultrasound machine obtains a map (information related to the tissue prior to application of a compression force) which is in essence a grey scale image of the anatomy being scanned.

Following this, an external compression force is applied via the ultrasound transducer following which a second map is obtained. The displacement of the tissue in response to the external compression is measured by comparing the pre-compression and post –compression map. (50)

Elastography imaging that is based on strain imaging is qualitative, it can be made semi-quantitative by calculating the strain ratio = ratio of strain within the lesion and the strain in the surrounding normal tissue. (49)

Another development is the ability to quantitatively measure tissue deformation using shear wave propagation. (49)

When an external compressive force is applied to tissue, the tissue deforms generating shear waves which travel perpendicular to the direction of the applied force.

An ROI placed along the direction of shear wave propagation measures the shear wave velocity which result in a quantitative measurement of tissue stiffness.

Harder tissues generate shear waves with faster velocities, the harder the tissue, the faster the shear wave velocity. (50)

Elastography and ARFI are emerging techniques in the imaging evaluation of thyroid nodules. Elastography and ARFI are in essence methods of virtual palpation and as clinicians rely on palpation for clinical assessment of a lesion's potential for harbouring malignancy (harder lesions are more likely to be malignant – (50, 51, 52) it makes eminent sense to add Elastography and ARFI to the existing methods of grey-scale B-mode sonography in an effort to objectively quantify and qualify a lesion's hardness.

Utilisation of Elastography in combination with real time sonography in thyroid nodules was pioneered by Rago et al.

Elastography technique has been used to assess a nodule's hardness or elastic properties to differentiate cancerous lesions from non- cancerous lesions (53-56). They had used as a basis for their study a prior report which indicated that off line processed elastograms may predict cancer with a high degree of specificity and moderately high sensitivity (57).

Rago et al performed real time sonographic examination and simultaneous Elastography (on the same ultrasound machine) of 92 consecutive thyroid nodules in patients who underwent thyroid surgery for compressive symptoms or suspected malignancy based on FNAC results.

Elastography images were acquired before and after application of compression, the elastogram image was displayed over the grey scale image in colour, the colour scale ranging from red (soft lesions) to blue (stiff / hard lesions). The Elastography image was classified according to the Ueno and Ito grading for elasticity (58). Elastography scores were assigned as follows: (32)

Score

1 Elasticity in the whole nodule

2 Elasticity in a large part of the nodule

3 Elasticity only at the peripheral part of the nodule

4 No elasticity in the nodule

5 No elasticity in the nodule and in the posterior shadowing

The 92 nodules that were evaluated by Elastography eventually underwent surgery, of these 31 nodules were found to be malignant on HPE (histopathological examination). 30 of these 31 malignant nodules had a score of 4-5 (p-value < 0.001). The sensitivity and specificity of the test 97% and 100% respectively with a NPV of 98% and PPV of 100%.

The authors found that Elastography was unreliable in completely cystic nodules and nodules with a peripheral rim of calcification.

Tran quart et al studied 96 patients with 106 nodules. Their results are as follows – of the 95 lesions categorised as ES 1 and 2, none were malignant, of the lesions categorized as ES 3 and 4, six lesions were malignant and 2 were indeterminate on FNAC.

Another study by Asteria et al 16 out of 17 nodules with ES score 3 and 4 were malignant, 50 out of 69 benign nodules has ES of 1 and 2 whereas 13 benign nodules had an elasticity score of 3/4.

The value of Elastography has thus been studied in small numbers by various groups with promising results and may prove of value in cases of indeterminate cytology by influencing the decision to resect lesions which are indeterminate on cytology but have high elasticity scores on Elastography. (59)

Elastography is promising technique which studies the elastic properties of tissue and is proven to be of some value as quoted in literature. The major limitation of the Elastography technique is that is a subjective phenomenon (a qualitative diagnostic test) (60).

To evaluate tissue elasticity with more objectivity, a reliable quantitative measure of the tissue elasticity is desirable. Acoustic radiation force impulse (ARFI) is a quantitative technique which can be employed to study the elastic properties of tissues (60)

There are two methods of imaging in ARFI, they are virtual touch imaging (VTI) and virtual touch quantification (VTQ)

Virtual touch quantification (VTQ):

Technique: thyroid gland is imaged with grey scale sonography, the lesion is identified on grey scale imaging, a region of interest box (ROI) is placed at the required location.

Following placement of ROI, an ultra-short duration “pushing pulse” is generated.

The “pushing pulse” results in localised tissue displacement which in turn results in the generation of a “shear wave”– the direction of the shear wave is perpendicular to the direction in which the “pushing pulse” is applied. The shear wave thus generated is “tracked” by multiple “ultrasound tracking” beams, these “tracking beams” are positioned laterally.

At each lateral location, the time to peak displacement is measured and using the time to peak at various lateral locations, the velocity of the shear wave can be calculated. (60) the speed

with which the shear wave travels is related to the square root of the tissue elasticity (61-63). The speed of the shear wave is expressed as a number (the unit for shear wave velocity is meters / second). VTQ is thus a purely quantitative, indirect measure of the tissue elasticity

Virtual touch imaging (VTI): on the other hand is a semi-quantitative measure of the tissue stiffness. In VTI, the elasticity of a nodule is compared with that of the surrounding stroma.

Technique: the ROI box encircles the nodule completely, when the VTI button is then pressed, the resultant black and white image is displayed along with the corresponding grey scale image on a dual screen. Lesions are categorised as

a. Softer than the surrounding stroma

b. Equal in stiffness to the surrounding stroma

c. Stiffer than the surrounding stroma and

d. Cellular sample – which means a nodule showing black and white areas in a honeycomb pattern. (64)

Lesion categorization on VTQ as given above was proposed by Tian et al in their study on differentiating benign and malignant liver lesion using ARFI.

Jiying Gu et al studied 72 individuals with thyroid nodules who subsequently underwent thyroidectomy with grey scale sonography and ARFI VTI and VTQ imaging. They excluded individuals with anatomical abnormalities of the neck, cystic thyroid lesions and lesion that were of a size smaller than 6 mm. all the patients underwent subsequent thyroidectomies and the final diagnosis was established by histopathological examination which is considered the gold standard.

They used an Acuson S2000 diagnostic ultrasound system (Siemens Medical Solutions) with ARFI imaging software and linear high-frequency probes (9 Mega Hertz).

The patients were examined in supine with necks extended.

Initial examination was performed with grey scale sonography and the lesion characteristics with regard to size, shape, composition, micro-calcification, echotexture, margins and nodule vascularity were studied. VTI and VTQ imaging were then performed in the same sitting.

VTI and VTQ were performed for each nodule as described above. Nodules with VTQ values of x.xx were excluded as invalid. The reasons for obtaining velocity measurement of x.xx were patient movement, respiration, wrong ROI positioning and very hard tissue with high shear wave velocities that were not recordable by the machine due to hardware and software limitations.

A total of 98 nodules were studied, of which 76 nodules were proven to be benign by histopathological examination. 22 nodules proved to be malignant.

59 of the 76 benign nodules were softer than or as stiff as the surrounding thyroid parenchyma on VTI. 17 of 22 malignant nodules were stiffer than the surrounding thyroid parenchyma and 4 of the malignant lesions had a honeycomb pattern. (60) When compared to benign nodules, malignant nodules were stiffer on Virtual Touch Imaging with a statistically significant difference (p value < 0.001)

Virtual touch quantification imaging: benign lesions demonstrated lower shear wave velocities with a mean velocity of 2.005 +/- 0.485 metres / sec. there was no statistically significant discrepancy between benign nodules and the surrounding normal thyroid parenchyma, nor was a statistically significant discrepancy between the various histopathologically benign nodules. The mean VTQ values for malignant lesions on the other hand was 3.941 +/- 1.393 metres / sec. The difference between the VTQ values for benign lesions and malignant lesions was statistically significant with a p-value < 0.001. VTQ value of 2.555 was noted to be an accurate cut-off for differentiating benign from malignant thyroid lesions.

The sensitivity, specificity, PPV, NPV and diagnostic accuracy were 86.36%, 93.42%, 79.17%, 95.95%, and 91.84%, respectively. (60)

VTQ (shear wave velocity) values were more than 3.450 metres / sec for the diagnosis of malignant nodules, with sensitivity, specificity, PPV, NPV and diagnostic accuracy of 63.6%, 100%, 100%, 90.48%, and 91.84%. (60)

Imaging for the thyroid has evolved by leaps and bound in the past 2 decades with technical advances in grey scale imaging and other sonographic techniques like Elastography. Ultrasound thus plays a critical role in thyroid lesion evaluation and is one of the few areas where advanced imaging like CT and MR are unlikely to have an advantage over USG by virtue of easy accessibility and cost effectiveness as well as high resolution imaging with which are as of now achievable by CT and MRI.

The value of USG in imaging thyroid lesions is thus emphasised.

MATERIALS AND METHODS:

STUDY DESIGN: Study of diagnostic test accuracy

STUDY TYPE –Prospective

SETTING: Christian Medical College (CMC) Vellore is a tertiary care centre in northern Tamil Nadu. The institution was established in 1900 and is now a 2700 bedded hospital. The annual outpatient visits is around 1.9 million with inpatient admissions of ~ 120,000. The Department of Radiology in CMC, Vellore was established in 1936. Digitalization of the system and introduction of PACS (Picture Archival and Communication System) was done in the year 2000. The Department functions independently with around 70 radiologists. The radiological investigations routinely performed are radiographs, IVU, barium studies, ultrasonography and Doppler studies, mammograms, CT and MRI.

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

METHODOLOGY:

SAMPLING AND CONSENT:

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 (Appendix I). 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. The consent form and the patients information sheet is attached in Appendix 2

TIMING: The study period was from September 2012-August 2013. The time 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.

PERFORMING THE ULTRASOUND EXAMINATION

a) Ultrasound scanner:

Ultrasound of the neck and thyroid gland was performed using (ACUSON S2000^{TM}, Siemens) using a high frequency linear probe (4-9 MHz). Conventional sonography was performed in all patients. The patients were examined in supine position with extension of neck by placing a pillow under the upper back. The images were sent to PACS where another radiologist with 8 years of experience interpreted the findings and was blinded to findings of other radiologist.

Gray scale imaging of the thyroid gland was done in both transverse and longitudinal planes and Colour Doppler evaluation of the nodule was done.

Each thyroid nodule was examined for Site (Right lobe, Isthmus, Left lobe), composition (solid, cystic, mixed), Halo (present, absent), echogenicity (hyperechoic, isoechoic, hypoechoic, markedly hypoechoic), margins (well defined, microlobulated, ill-defined, irregular), presence of calcification (microcalcification, macrocalcification), shape of the nodule (wider than tall, taller than wide), vascularity of the nodule (central or peripheral), Presence of background changes of diffuse thyroiditis and lymph nodes.

Nodule with solid component >2/3rd were labelled as solid; cystic nodules had no solid components, mixed nodules had both solid and cystic areas with solid component constituting <2/3rd of the size of the lesion. For mixed lesions echogenicity, margin, shape and presence of calcification was assessed for the solid component. Echogenicity was described in comparison with the thyroid gland and strap muscles.

1. **Composition of the nodule: The nodules were classified as solid, cystic and mixed. Cystic nodules were excluded from this study**

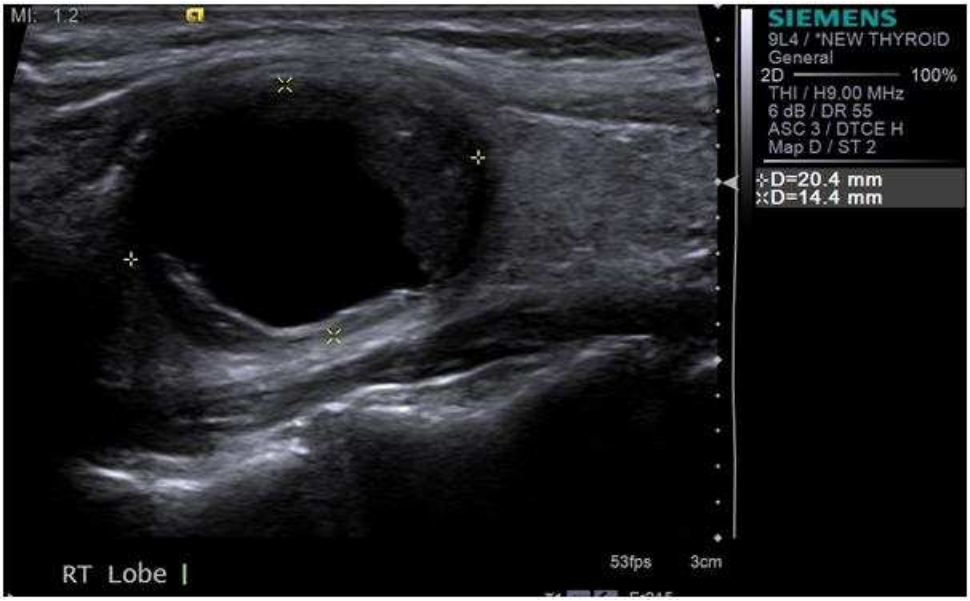


Fig 1.shows a well-defined mixed lesion with a predominantly cystic component

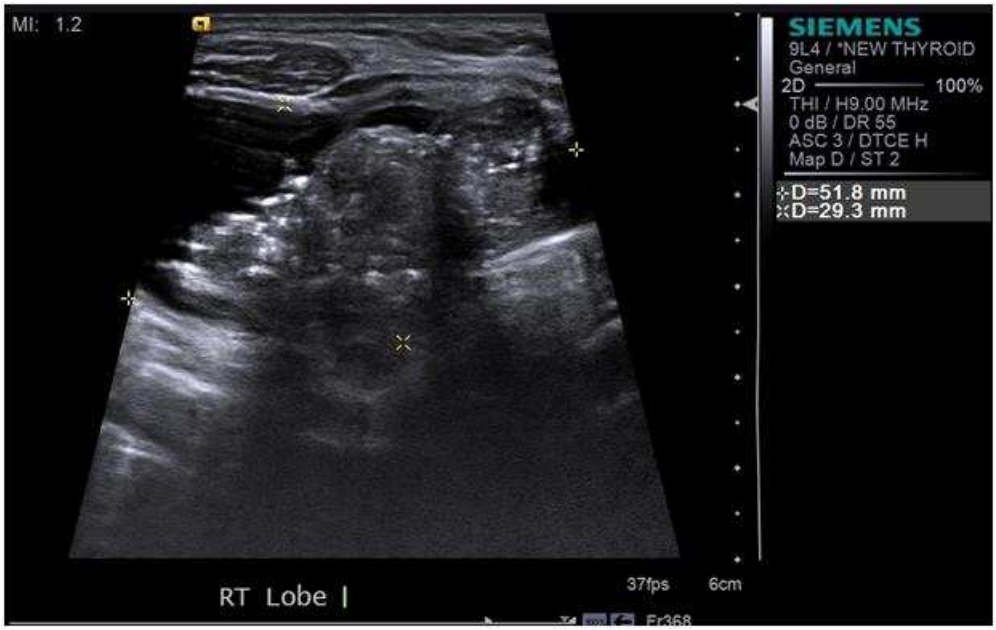


Fig 2. Shows a mixed solid-cystic nodule, the solid component of the nodule was more than 2/3rd

2. Halo sign:

Hypoechoic smooth rim around the nodule was considered as halo

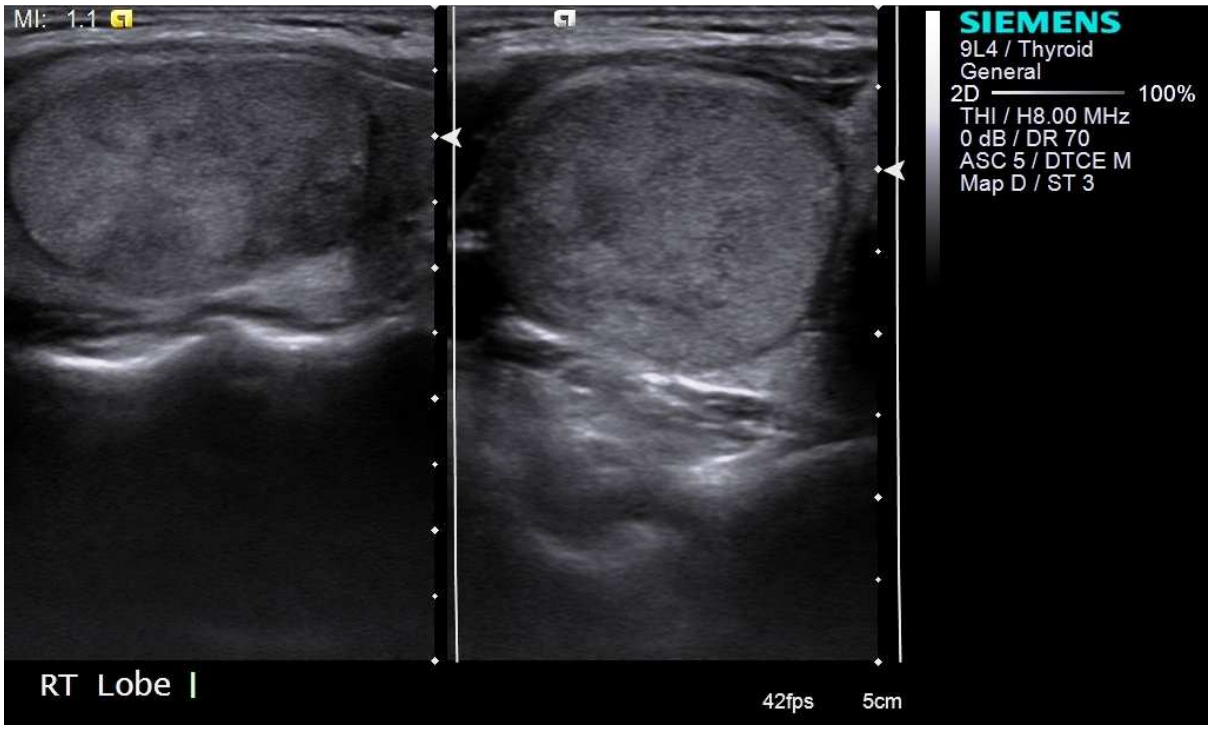


Fig.4 shows a smooth, well defined, hypoechoic, complete halo around the lesion

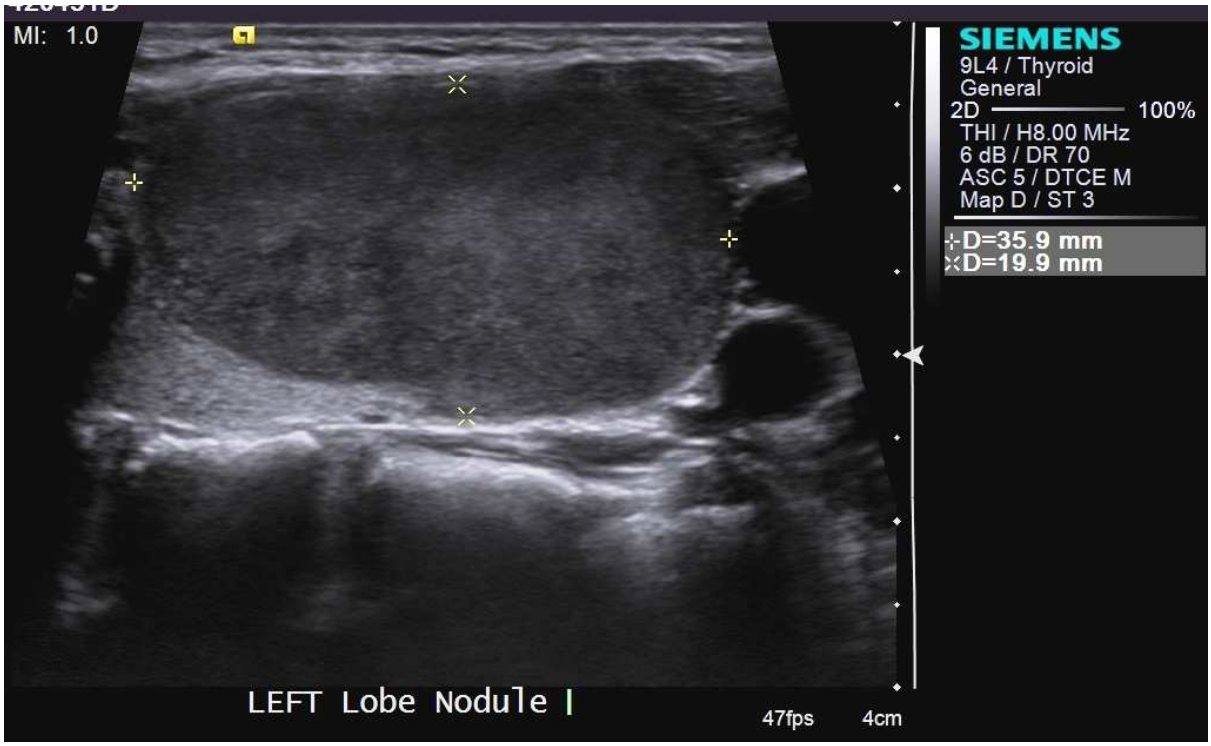


Fig.5 shows negative halo sign

3. Echogenicity: On the basis of echogenicity the nodules were classified into four categories, hyperechoic, isoechoic, hypoechoic and markedly hypoechoic

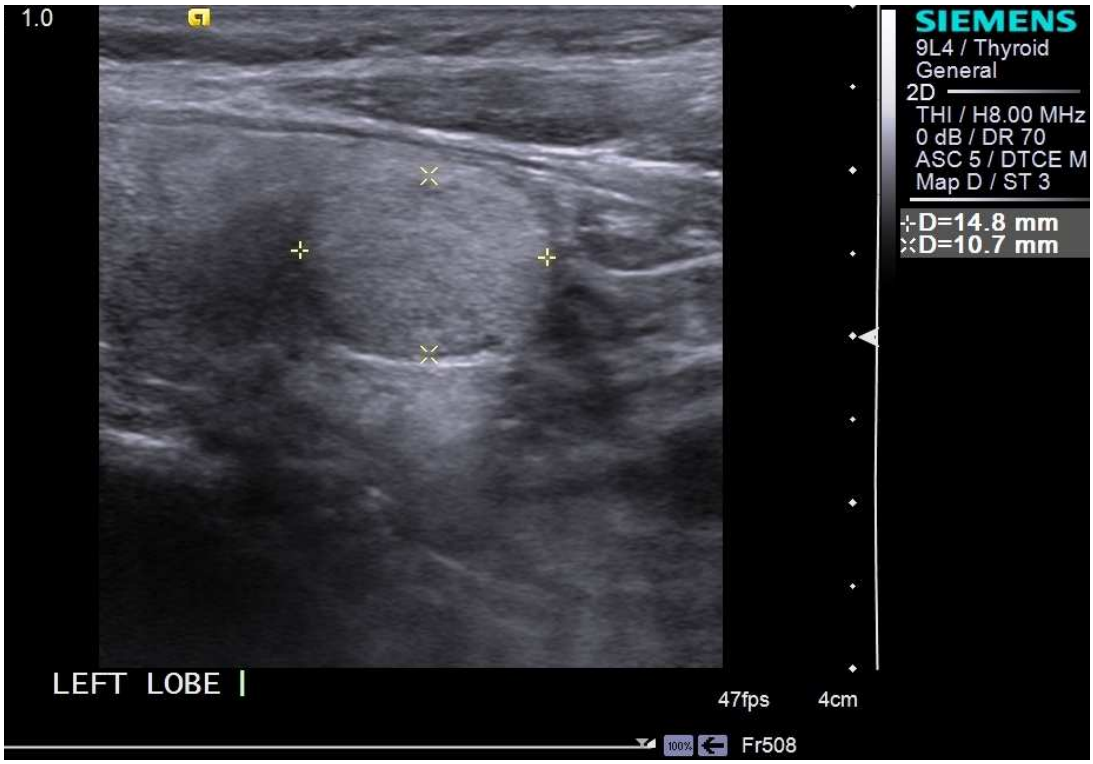


Fig. 6 shows a left lobe nodule with echogenicity more than that of thyroid gland

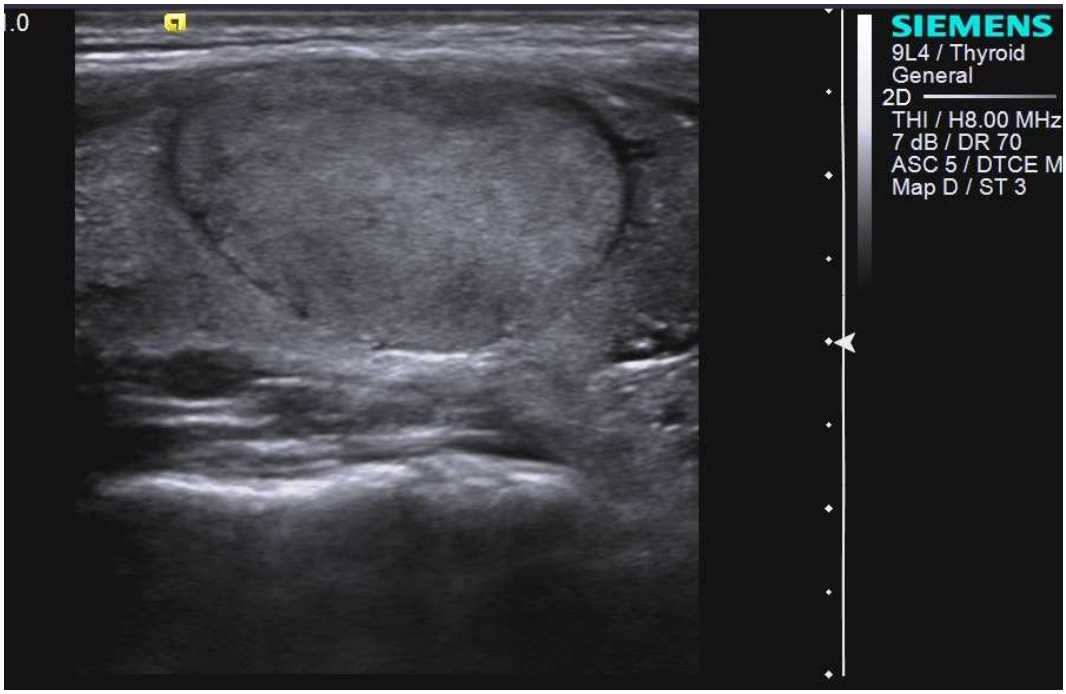


Fig 7 shows a well-defined nodule that is isoechoic to thyroid gland

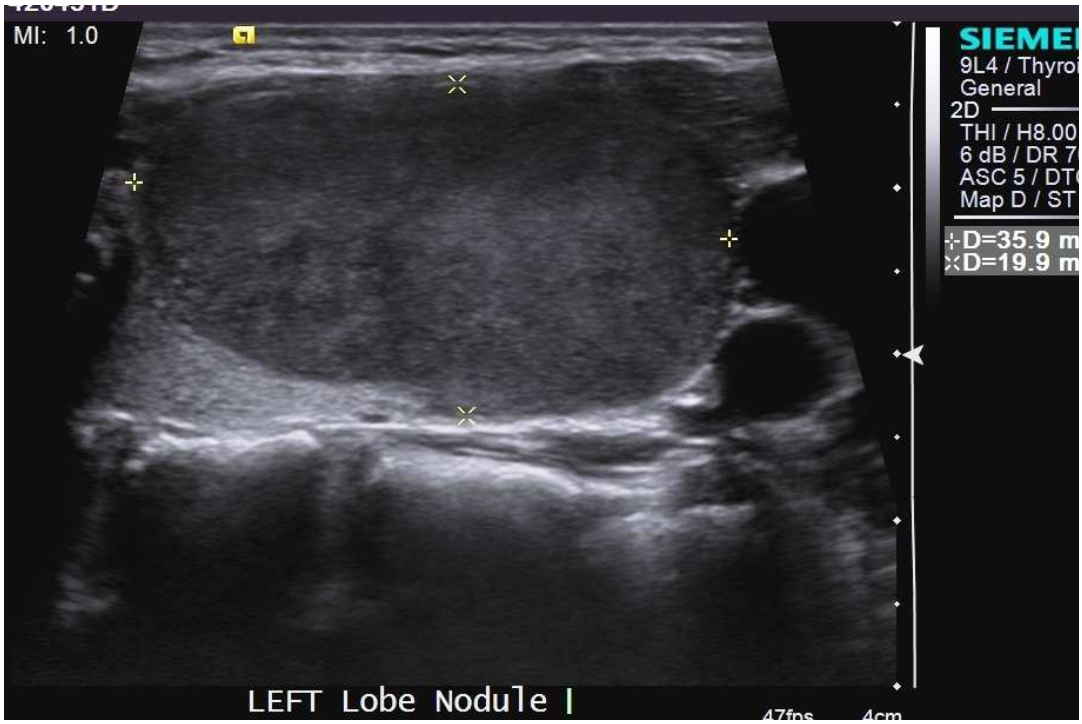


Fig. 8 shows a hypoechoic nodule

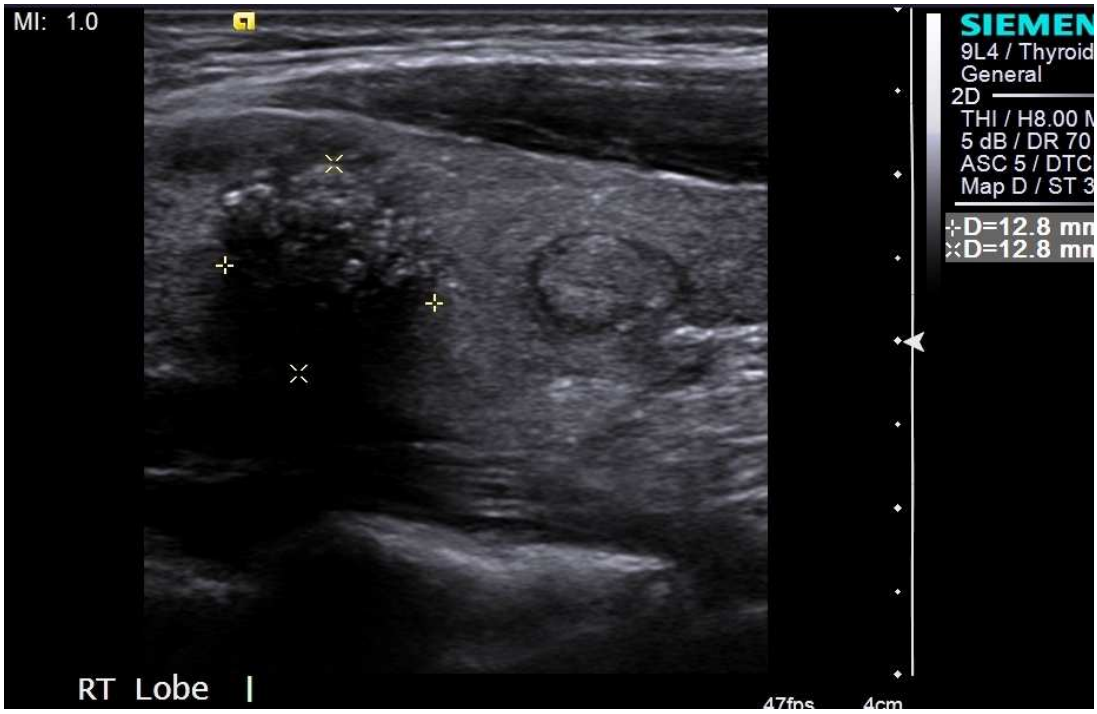


Fig. 9 shows markedly hypoechoic nodule with reduced through transmission of sound and is hypoechoic when compared to strap muscle.

4. Calcification: A calcification greater than 1mm in size was considered as macrocalcification and less than 1 mm was considered as microcalcification

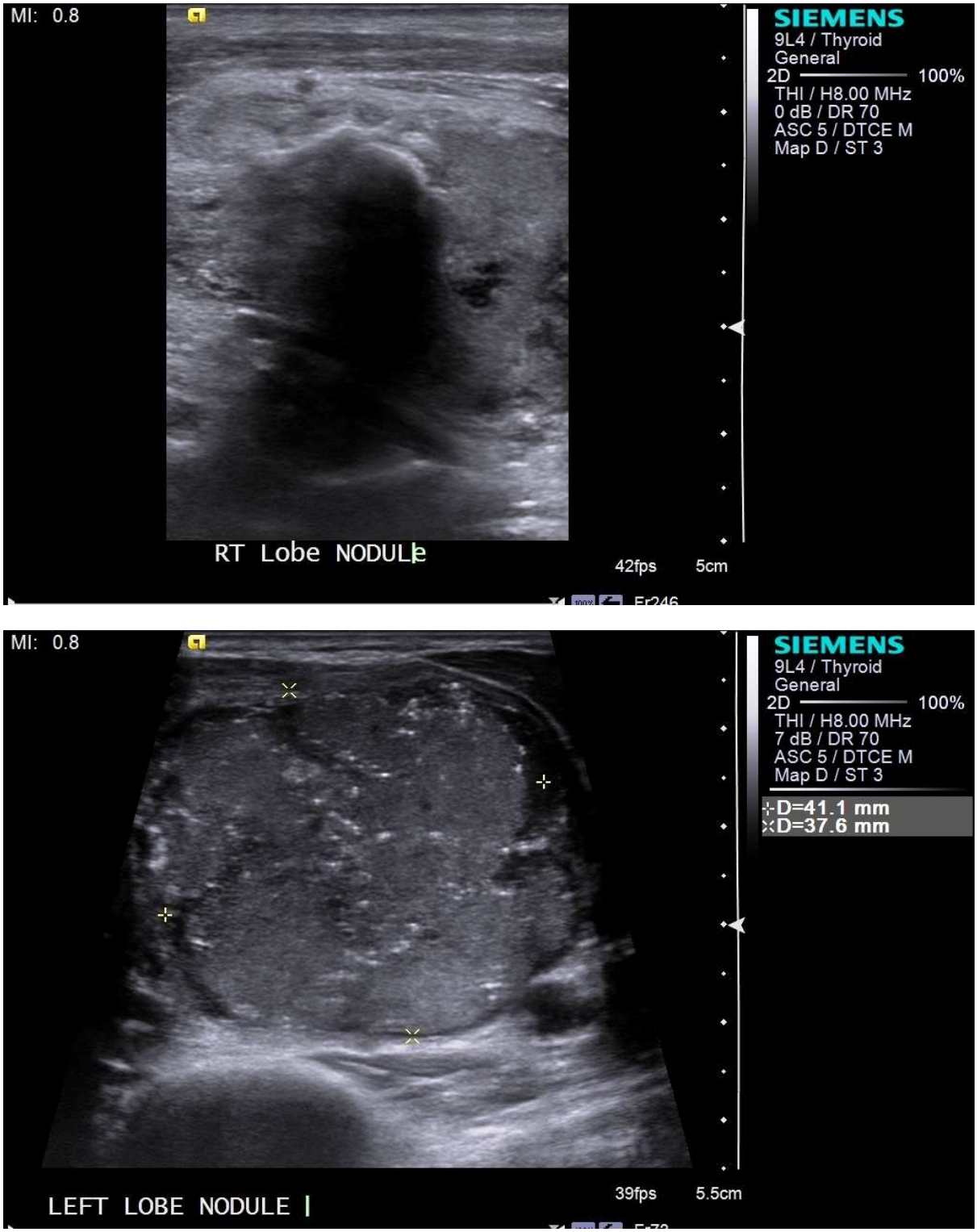


Fig.10 and 11 showing macrocalcification and microcalcification respectively

5. Shape: Shape was described as taller than wide if anterio-posterior dimension was equal to greater than transverse dimension and nodule which was wider than tall was described as oval nodule**.**

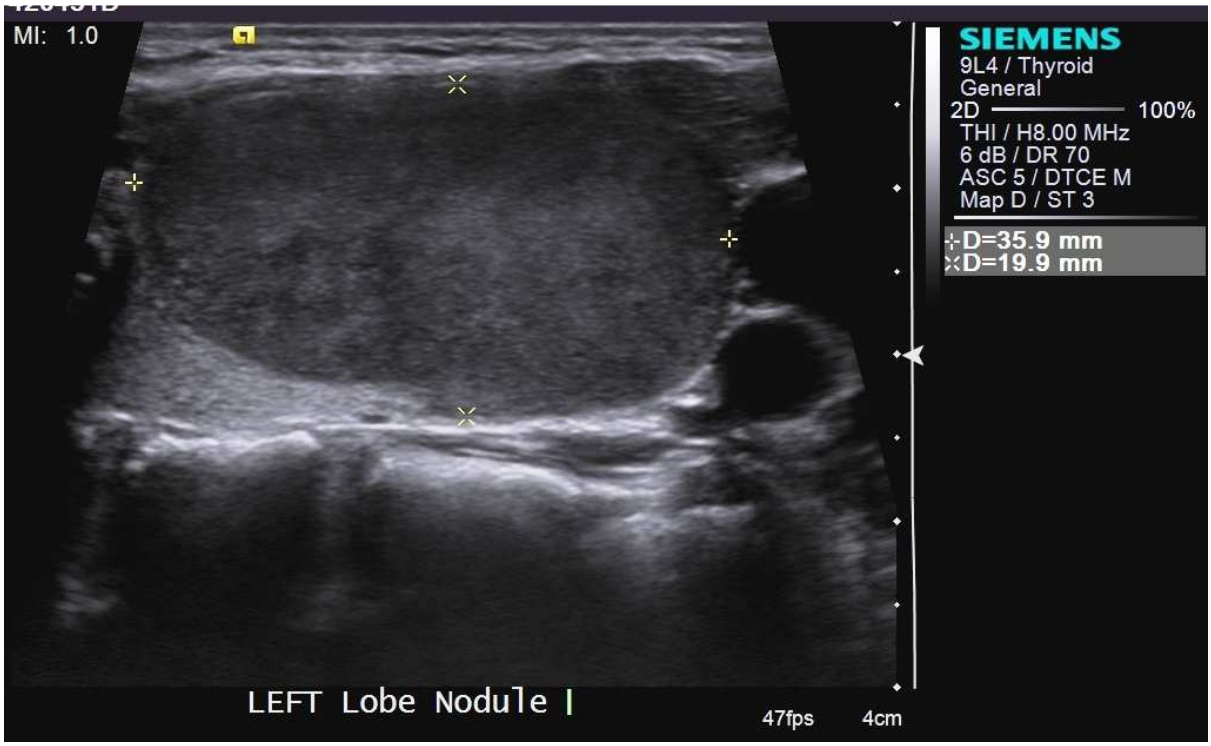


Fig. 12 showing a wider than tall nodule in the left lobe

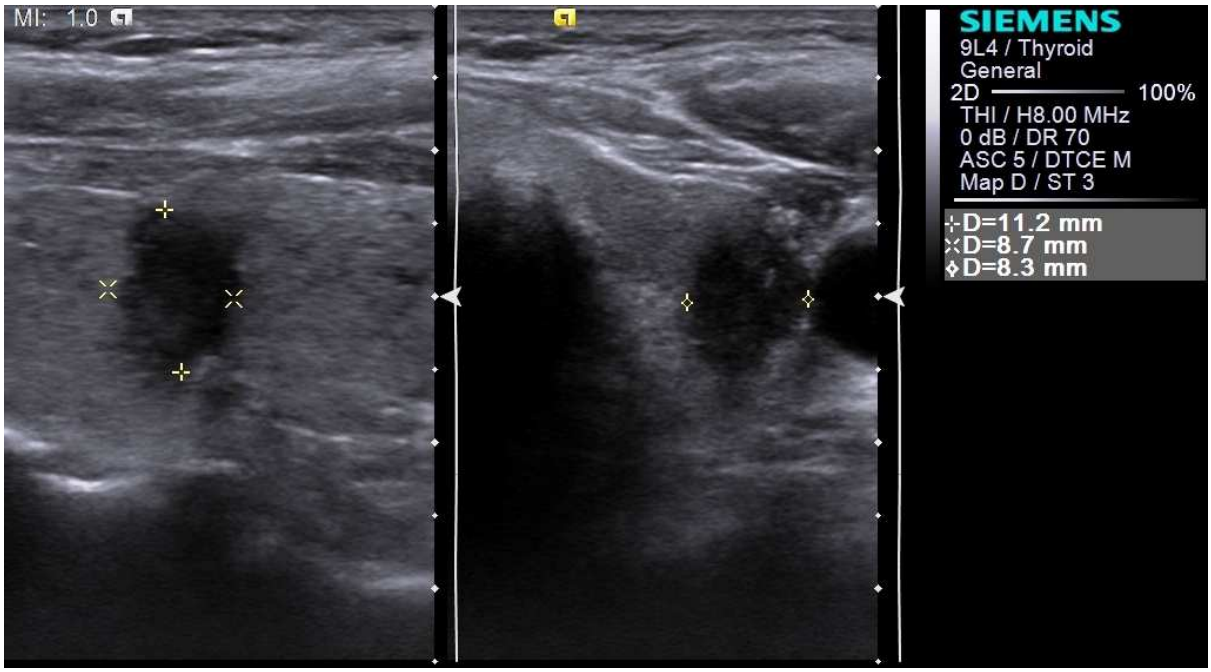


Fig. 13 showing a taller than wide nodule

6. Vascularity: Vascularity was classified as central and peripheral

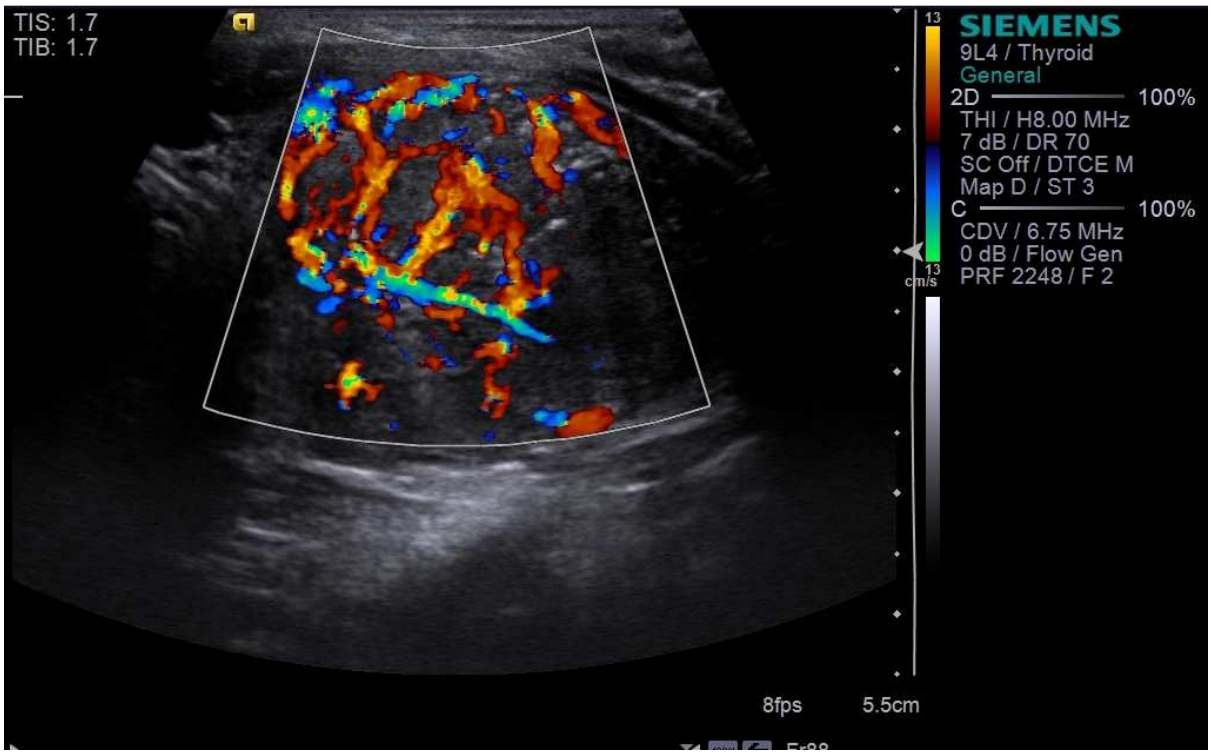


Fig 14. Showing intranodular vascularity

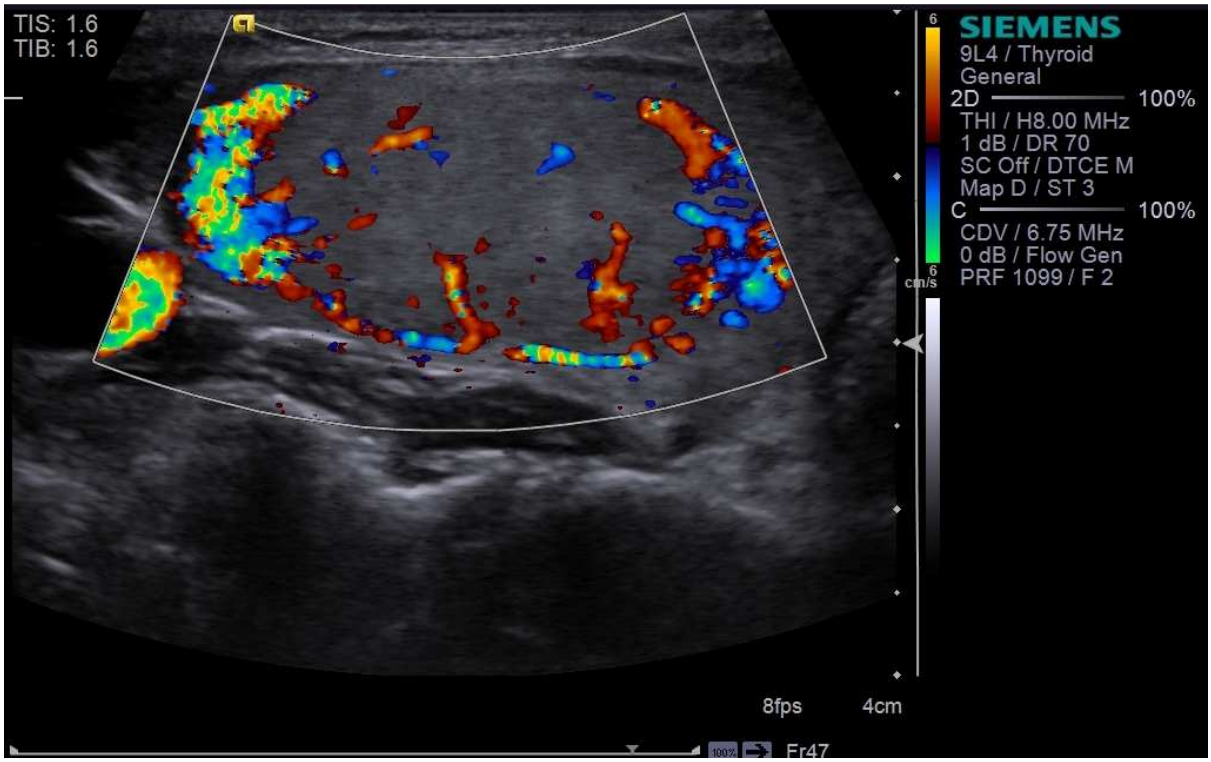


Fig. 15 shows Perinodular vascularity

Findings that were considered to be favour malignancy were hypoechoic or markedly hypoechogenecity; irregular, microlobulated or ill-defined margins; presence of microcalcification and round shape. In addition to describing the ultrasound features, a TIRADS category was assigned to the thyroid nodule as described by Kwak JY et al (41).

Another radiologist with 8 years' experience (A.C – reader 2) retrospectively reviewed the images of the thyroid stored in picture archiving and communication system (PACS) and documented ultrasound features and TIRADS final assessment category for each thyroid nodule blind to the findings of other radiologists, FNAC and histopathology reports. A common consensus was arrived after discussion among each other for nodules with discrepancy in the interpretation of the findings or assigned TIRADS category.

ACOUSTIC RADIATION FORCE IMPULSE IMAGING:

ARFI –Imaging (Virtual-Touch Quantification^{TM} and Virtual-Touch Imaging$^{TM),}$ Siemens-ACUSON-S2000) involves targeting of an anatomic region whose elastic properties are to be evaluated with a Region of interest (ROI) cursor while the B mode imaging is being performed. The tissue in ROI is mechanically excited using acoustic pulses to generate localized displacements. The displacements cause a shear-wave propagation away from the region of excitation and are tracked using ultrasonic, correlation based methods. The maximum displacement is estimated from many ultrasound tracking beams and shear wave propagation of the tissue can be reconstructed.

By using a 9L4-Linear ultrasound probe, the shear velocity is estimated within a ROI graphically displaying a size of 5 x 5 mm. The Shear wave velocity is proportional to the square root of elasticity. Results are expressed in m/sec (Range 0.7-8.4m/sec).The values exceeding 8.4m/s were displayed as x.xx m/s. ARFI imaging was performed using a 9L4 – 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. In nodules with mixed echogenicity ROI placed in the suspicious (hypoechoic, irregular) part of the nodule.

The patients was asked not to move and hold breath during image acquisition. Care was taken so that the ultrasound transducer does not move during the examination. The ROI box was kept away from the vascular structures and liberal amount of gel was applied to avoid false positive observations. In each nodule five valid measurements were taken and images were stores and sent to PACS. All the ultrasound findings were recorded in the proforma (Appendix 2) and a mean value of the VTQ was calculated.

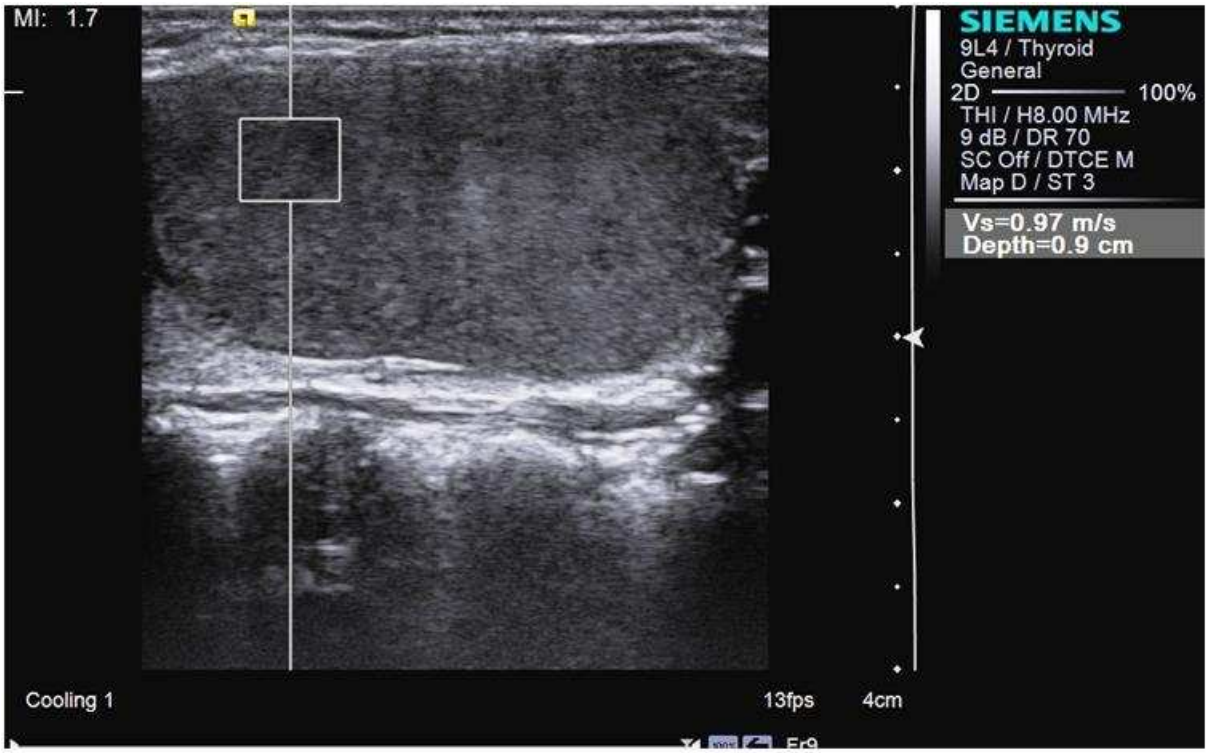


Fig.16 showing VTQ measurement of the nodule at a depth of 9mm, VTQ-0.97 m/s

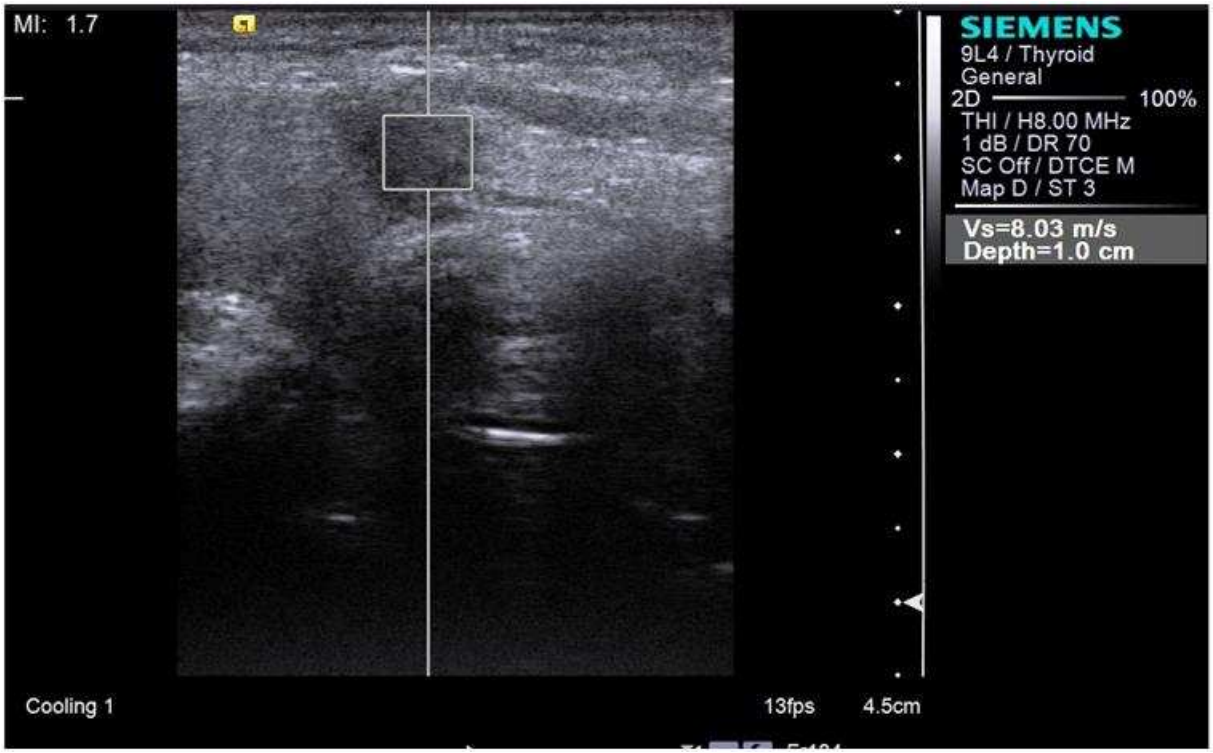


Fig.17 showing VTQ measurement of the nodule at a depth of 10mm, VTQ-8.03 m/s

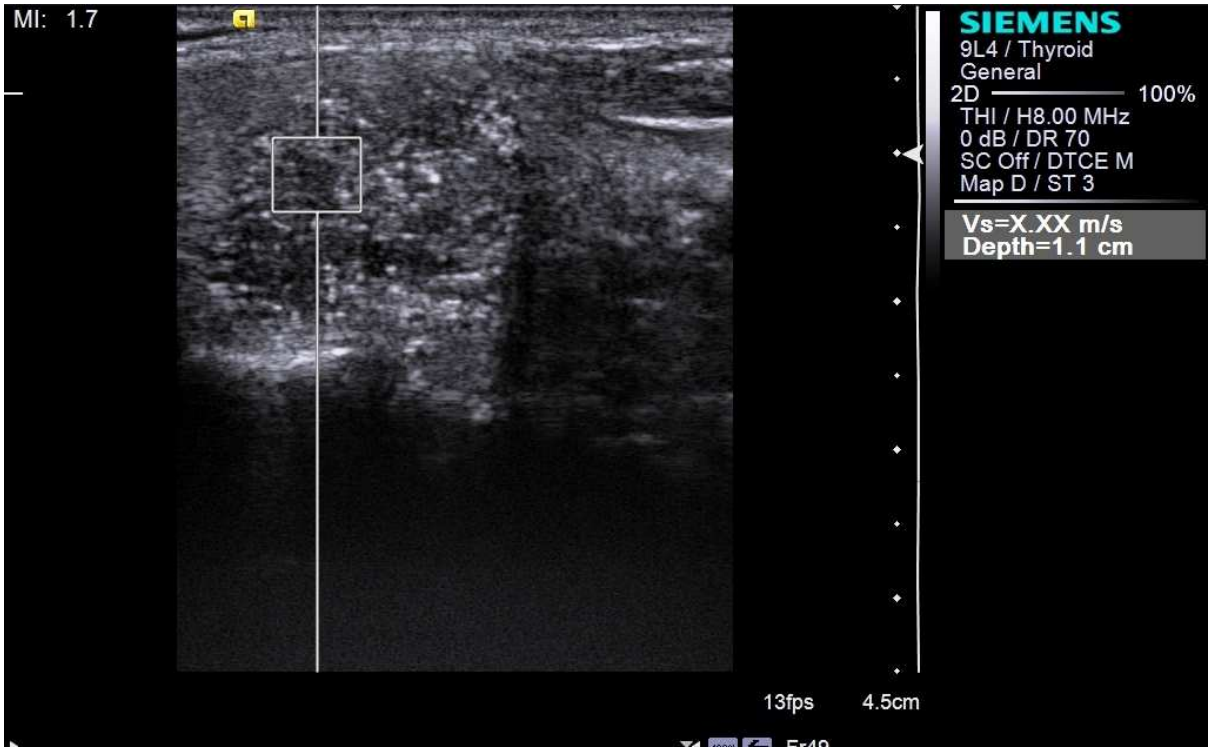


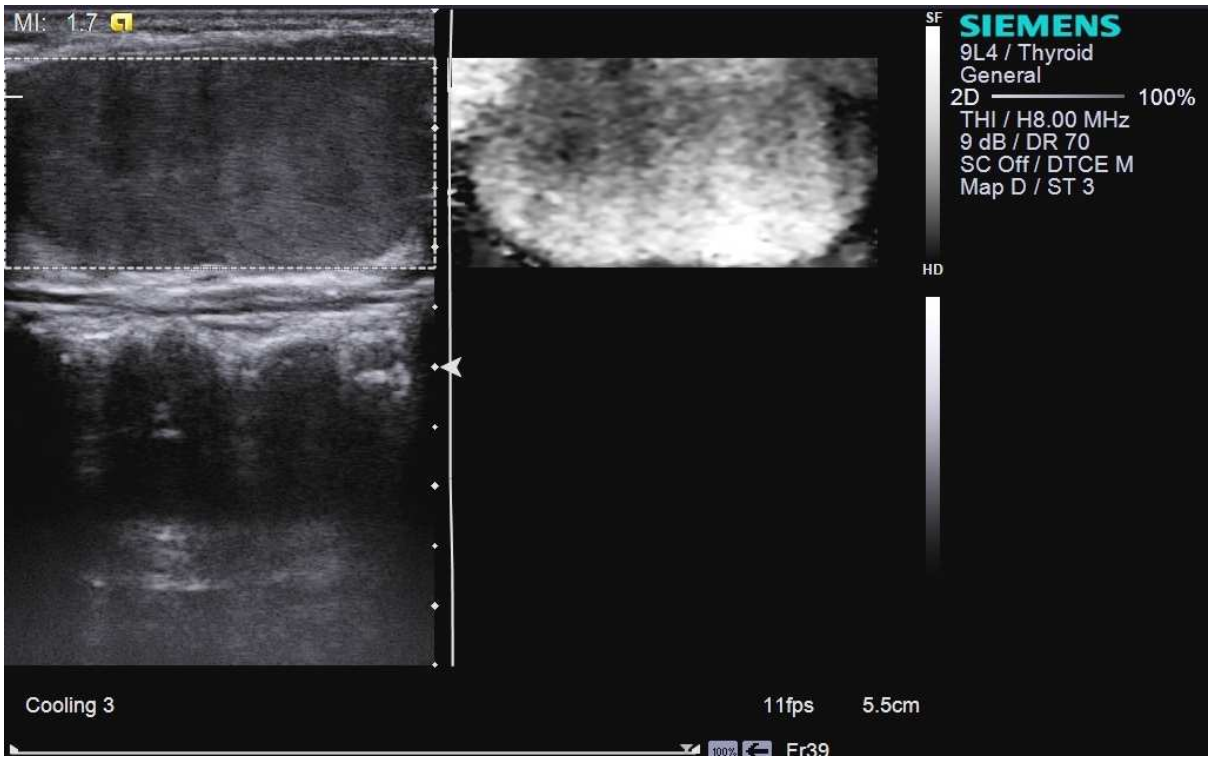
Fig.18 showing VTQ values from a hypoechoic, ill-defined nodule with multiple microcalcification being expressed as x.xx m/s

Virtual touch imaging –VTI

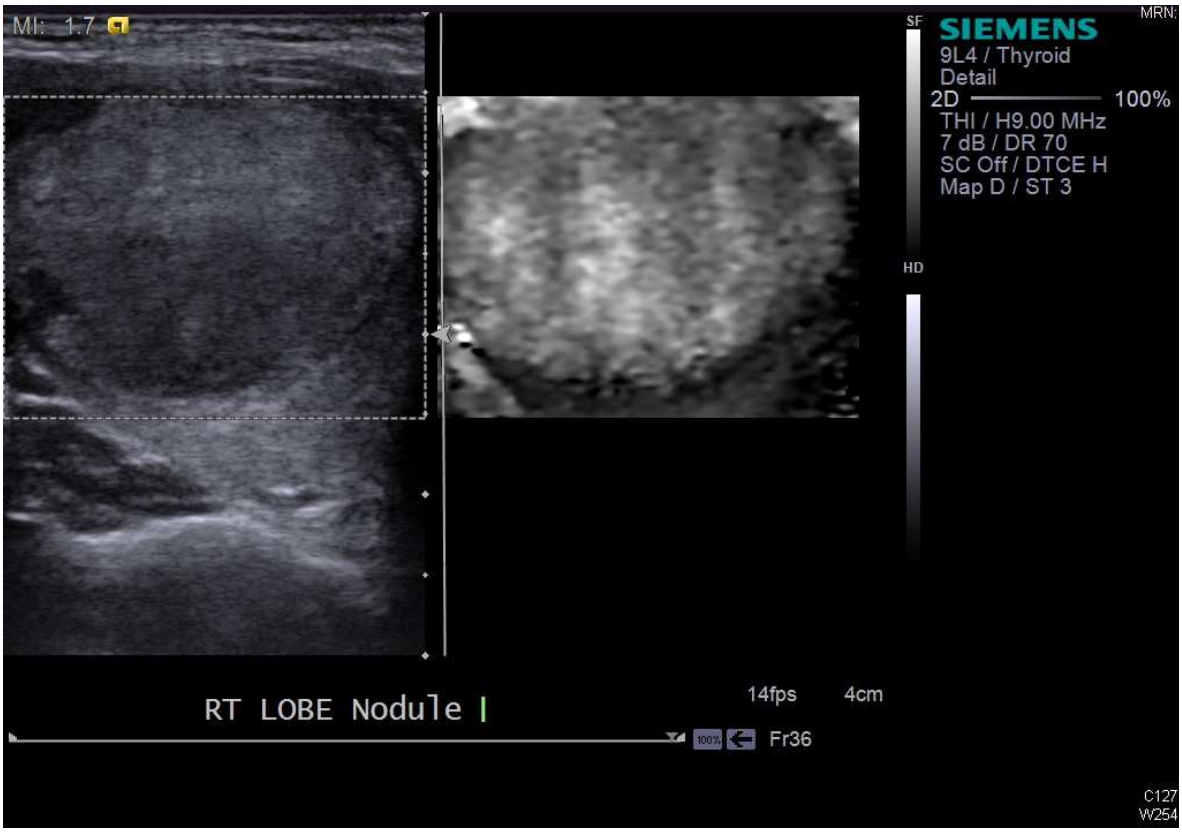
Virtual touch imaging was performed in a way that the ROI completely circles the nodule and the patient was asked not to move and hold breath. The probe was applied in such a way that there was complete contact with the patient`s thyroid without compressing the gland. After this a black and white image was achieved by pressing the key designated for VTI.

The display of VTI result is in B mode image in split screen format. The left side shows the gray scale picture of the nodule with VTI ROI placed over it whereas the right side demonstrates the actual elastic property if the nodule. The images were based on the classification method suggested by Tian et al (64). The images were classified into four types described on the next page.

Fig 19 and 20 showing category 1 – softer than thyroid and 2- as stiff as thyroid respectively



2-As stiff as thyroid gland



3-Stiffer than thyroid gland

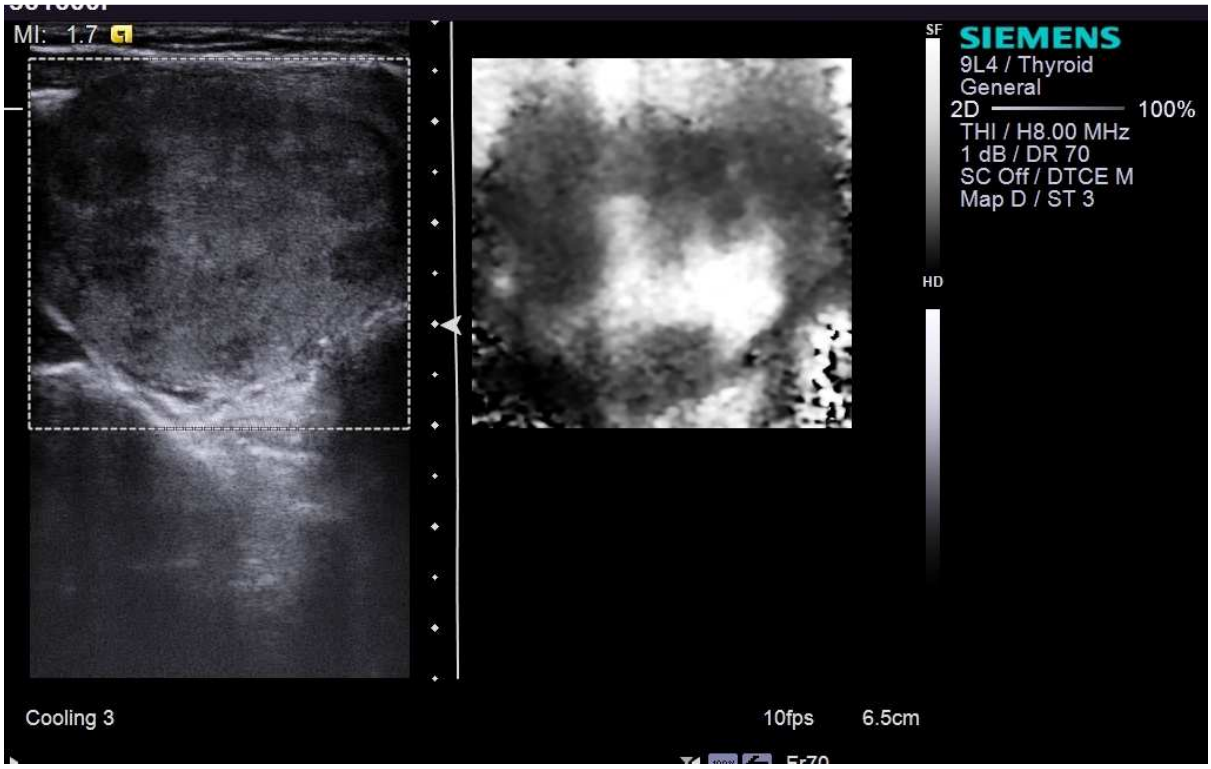


Fig.21 Shows nodule in the left lobe of thyroid, the left gray scale image shows that the peripheral part of the nodule is hypoechoic and central part is relatively echogenic. The VTI image shows the hypoechoic areas are darker than the centre suggesting the peripheral part of the lesion is stiffer than thyroid gland.

4. Honeycomb appearance

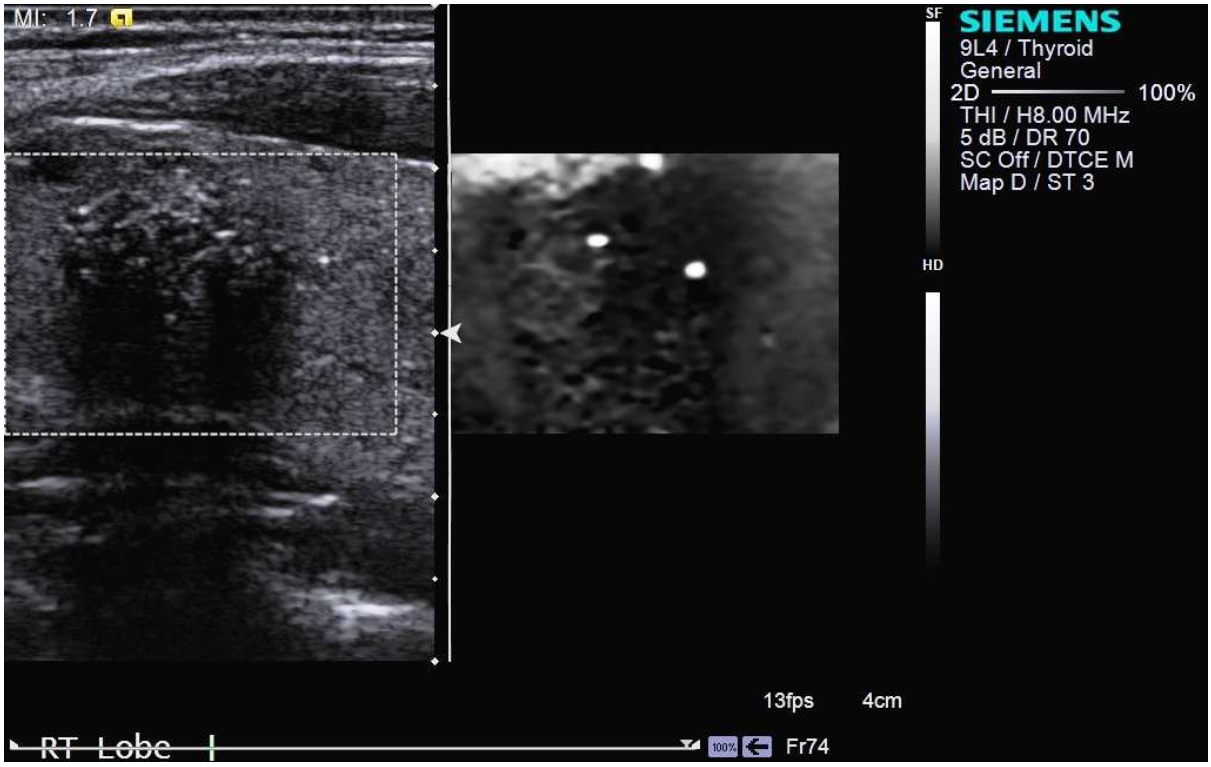


Fig. 22 shows a nodule in the right lobe of thyroid in the right lobe of thyroid, the nodule is markedly hypoechoic and shows multiple microcalcification, the VTI image shows that that the nodule is extremely cellular and shows alternating areas of white and black giving the honeycombed appearance

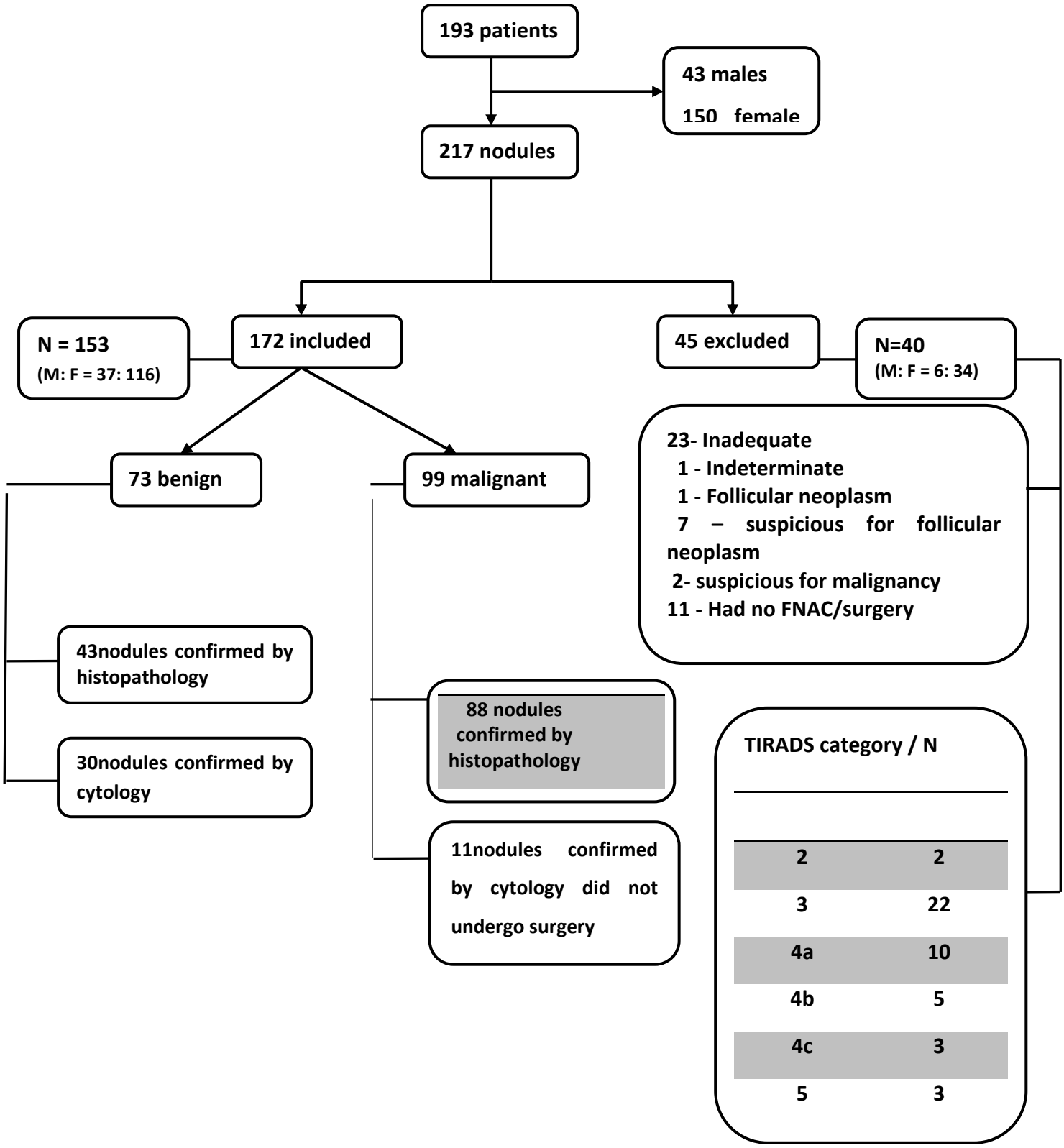
FNAC:

FNAC was performed after thyroid ultrasound and time period between the ultrasound and the FNAC was 12 hours to 2 days. FNAC was performed by the surgeon for solid palpable thyroid nodules. In patients with dominant nodule of multi-nodular goitre, nodules to be subjected for FNAC were marked by the radiologist. 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. Aspiration was performed using 23 gauge needle attached to 5 ml syringe. Two to three aspirations were performed on each nodule. Cytology smears were prepared on three to six slides. Slides were fixed immediately in 95% alcohol and stained with Papinicolaou stain. Cytology technician was available on site to prepare the slides and to confirm adequacy of specimen. The remainder of the aspirated material was rinsed in saline for cell block processing. Cytology was reported by cytopathologists according to Bethesda system for reporting thyroid cytology. (6) Bethesda class II (benign) and Bethesda class VI (malignant) were considered as diagnostic cytology reports. Rest of the categories was considered non-diagnostic. Cytology was reported inadequate (Bethesda class I) if there were less than six clusters of cells with each cluster comprising of less than 10 cells. Cytology reported as atypical cells or follicular cells of indeterminate significance was classified as indeterminate cytology (Bethesda class III). Specimen rich in follicular cells or hurthle cells were classified as follicular neoplasm.

(Bethesda class IV). FNAC of nodules showing few abnormalities of carcinoma however did not fulfil criteria for diagnosis of carcinoma were classified as suspicious for malignancy (Bethesda class V).

Imaging findings, TIRADS category and ARFI observations were compared with FNAC and surgical histopathology when available. Patients whose FNAC smears were non-diagnostic FNAC and were not being planned for surgery were excluded.

Flow chart of the progress of the study



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. $P < 0.05$ was considered statistically significant. The positive predictive value, likelihood ratio and odds ratio for malignancy for ultrasound features of thyroid nodules, ARFI including both VTI and VTQ was determined by using data from assessments of both the observers. Inter-observer reliability was measured using the Kappa coefficient. Kappa is scaled such that zero is the amount of agreement that would be expected by chance and one is perfect agreement. Kappa was interpreted according to guidelines laid by Landis and Koch.

A) STUDY DESIGN

(i) Duration of the study:

The study was done in prospective manner over a period of one year from September 2012 to August

(ii)Sample size:

In order to differentiate between benign and malignant nodules the sample size calculated was found to be 165 nodules with a precision of 5% and an anticipated prevalence of nodules of 12.2% with alpha level of significance of 95%.

B) PATIENT DEMOGRAPHICS

(i) Age distribution:

The mean age of the patient population was 42.14 years (range 15-82 years)

(II) Sex distribution:

Of the 193 patients examined 43 were male (22.2%) and 150 were female (77.8%)

C) TUMOUR CHARACTERISTICS:

(I) Location distribution:

Of the 217 nodules examined 105 nodules were located in the right lobe (48.4%), 14 nodules were located in Isthmus (6.5%) and 98 nodules were located in the left lobe (45.2%). There was no significant statistical correlation between nodule location and incidence of malignancy $p>0.05$ (Pearson chi square test – 0.302, DF-2, $p = 0.862$)

(II) Type of tumour

BENIGN TUMOURS:

HISTOPATHOLOGY	NUMBER OF NODULES 42 (%)
Adenomatous hyperplasia	5 (11.9)
Follicular Adenoma	1 (2.4)
Hurthle cell adenoma	2 (4.8)
Cyst with haemorrhage	2 (4.8)
Nodular hyperplasia	31 (73.8)
Hashimoto`s thyroiditis	1 (2.4)

Nodular hyperplasia was noted to be the most common benign nodule in this study

MALIGNANT TUMOURS:

HISTOPATHOLOGY	NUMBER OF NODULES n=89 (%)
Papillary carcinoma	46 (51.7)
Follicular variant of papillary carcinoma	32 (36.0)
Medullary carcinoma	2 (2.2)
Poorly differentiated carcinoma	1 (1.1)
Micropapillary carcinoma	6 (6.7)
Thyroid tumours of uncertain malignant potential	2 (2.2)

Papillary carcinoma of thyroid was the most common histopathological subtype followed by follicular variant of papillary carcinoma.

III) ULTRASOUND CHARACTERISTICS OF NODULES

(i) Size of the nodule:

Size	Benign (%)	Malignant (%)
< 1 cm	1	3
>1cm	72	96
Total	73	99

There is no significant correlation between the size of the nodule and presence of malignancy; Pearson Chi-square value = 0.510, DF =1 and p = 0.475 (p>0.05).

(ii) Halo sign:

Halo	Benign (%)	Malignant (%)
Present	37(55.2)	30(44.8)
Absent	33(33)	67(67)
Total	70	97

Strong correlation was present between the absent halo sign and outcome Pearson Chi-square value= 8.139, DF=1 and p=0.004($p < 0.05$).

There is strong evidence that the absent halo sign is associated with malignancy. The sensitivity, specificity, PPV and NPV of the absent halo sign is -69%, 52%, 67% and 55% respectively. In this study 67% of the nodules with an absent halo sign were found to be malignant.

(iii) Composition:

Composition	Benign	Malignant
Solid	54(38.2)	87(61.8)
Mixed	18(66.7)	9(33.3)
Total	72	96

There was moderate correlation between the composition of the nodule and malignancy Pearson Chi-square value=7.975, DF=2, p=0.019($p < 0.05$)

(iv) Calcification:

Calcification	Benign (%)	Malignant (%)
Microcalcification	7(11.8)	52(88.1)
Macrocalcification	8(72.7)	3(27.3)
Both	3(60)	2(40)
No calcification	55(56.7)	42(43.2)
Total	**73**	**99**

There is very strong correlation between the calcification in the nodule and outcome, Pearson Chi -square value- 35.416, DF=3, and $p < 0.001$ ($p < 0.05$).

The sensitivity, specificity, PPV and NPV for the presence of calcification were 57%, 75%, 76% and 56 % respectively. In this study 88% of the nodules with microcalcification were malignant. The presence of macrocalcification was not associated with malignancy with 72.7% of the nodules were found to be benign.

(v) Echogenicity:

Echogenicity	Benign	Malignant
Hyperechoic	5(55.6)	4(44.4)
Isoechoic	46(78)	13(22)
Hypoechoic	15 (26.8)	41(73.2)
Markedly hypoechoic	7(14.5)	41(85.5)
Total	**73**	**99**

There is very strong correlation between the hypoechogenecity of the nodule and presence of malignancy. Pearson Chi-square value = 27.747, DF=3 and p<0.001(p < 0.05).

The sensitivity, specificity, PPV and NPV for hypoechogenecity of the nodule were -82.8%, 69%, 78%, and 75% respectively. In this study 85.5% of the markedly hypoechoic nodules were malignant and 73.2% of the hypoechoic nodules were found to be malignant and 78.9 % of combined hypoechoic and markedly hypoechoic nodules were malignant

(vi) Margins of the nodule:

Margins	**Benign**	**Malignant**
Well defined	52(59.1)	36(40.9)
Microlobulated	2(40)	3(60)
Ill defined	14(27)	38(73)
Irregular	5(18.5)	22(81.5)
Total	**73**	**99**

There is very strong correlation between absence of a well-defined margin and malignancy. Pearson Chi-square value = 21.450, DF=3 and p <0.001

The sensitivity, specificity, PPV and NPV were 63.6%, 71%, 75% and 59% respectively. 81.5% of the nodules with irregular margins and 73% of nodules with ill-defined margins were malignant.

(vii) Shape of the nodule:

Shape	Benign	Malignant
Wider than tall	62 (56.9)	47 (43.1)
Tall than wide	11(17.4)	52 (82.6)
Total	**73**	**99**

There is very strong correlation between the shape of the nodule and malignancy. Pearson Chi-square value- 25.4, DF=1, $p < 0.001$

The sensitivity, specificity, PPV and NPV of a nodule being taller than wide were 52.5%, 84%, 82% and 56% respectively. In this study 82.6% of taller than wide nodules were malignant compared to only 43% of the wider than tall nodules.

(viii) Background features of thyroiditis:

Background thyroiditis	Benign	Malignant
Present	5 (25)	15 (75)
Absent	68 (44.7)	84 (55.3)
Total	**73**	**99**

There is weak statistical correlation between presence of background thyroiditis and the malignancy Pearson Chi-square value= 2.818, DF=1, and $p = 0.093$ ($p > 0.05$)

(ix) Nodule Vascularity:

Vascularity	Benign	Malignant
Central	11(16.2)	57 (83.8)
Peripheral	62 (59.6)	42 (40.4)
Total	**73**	**99**

There is very strong statistical correlation between presence of central vascularity and malignancy. Pearson Chi-square value= 31.759, DF=1, and p <0.001 ($p < 0.05$). The sensitivity, specificity, PPV and NPV for central vascularity were 57.5%, 84%, 83.8% and 59.6% respectively. In this study 83.8% of the nodules with central vascularity were found to be malignant.

(x) Lymphadenopathy:

Lymph nodes	Benign	Malignant
Present	4 (11.1)	32 (88.9)
Absent	69 (50.7)	67 (49.3)
Total	**73**	**99**

There is very strong statistically significant correlation between presence of lymphadenopathy and the outcome Pearson Chi-square value= 31.759, DF=1, and $p < 0.001$ ($p < 0.05$).

The sensitivity, specificity, PPV and NPV for presence of cervical lymphadenopathy were 32.3%, 94%, 88.9% and 50% respectively. In this study 83.8% of the nodules associated with lymphadenopathy were found to be malignant.

D) FNAC ACCORDING TO BETHESDA CLASSIFICATION:

CATEGORY	NUMBER	PERCENTAGE
I – Non diagnostic	65	30
II- Benign	65	30
III – AOUS	8	3.7
IV-Follicular neoplasm	13	6.0
V-Suspicious for malignancy	11	5.1
VI- Malignant	38	17.5
TOTAL	200	100

E) FNAC (BETHESDA) – PERFORMANCE IN BENIGN and MALIGNANT

CATEGORY	EXCLUDED	BENIGN	MALIGNANT
I –Non diagnostic	23	18	24
II- Benign	1	47	17
III- AOUS	1	1	6
IV- Follicular neoplasm	7	2	4
V- Suspicious for malignancy	2	0	9
VI- Malignant	0	1	37
NOT DONE	11	4	2
TOTAL	45	73	99

F) Frequency of ultrasound features of thyroid nodules according to TIRADS descriptors

Ultrasound Features	Total 217	Included 173	Benign N= 73	Malignant N= 99
Composition:				
Solid	162	125	45	80
Mixed	55	47	28	19
Echogenicity:				
Hyperechoic	25	19	15	4
Isoechoic	63	50	37	13
Hypoechoic	80	57	16	41
Markedly hypoechoic	49	46	5	41
Margins:				
Well-defined	129	93	63	30
Microlobulated	19	19	3	16
Ill-defined	52	44	6	38
Irregular	17	16	1	15
Halo sign				
Positive	80	56	41	15
Negative	137	116	32	84
Calcification:				
Micro-calcification	4	59	7	52
Macro-calcification	2	11	8	3
Micro- and macro-calcification	1	5	3	2
No calcification	38	97	55	42
Shape:				
Round	169	132	67	65
Oval	48	40	6	34
Vascularity				
Central	75	68	11	57
Peripheral	142	104	62	42
Lymph nodes				
Present	37	36	4	32
Absent	180	136	69	67
Thyroiditis				
Present	23	20	5	15
Absent	194	152	68	84

G) TIRADS category:

TIRADS category	Benign	Malignant	Total
TIRADS-2	4 (100)	0 (0.00)	4 (100)
TIRADS-3	39 (69.7)	17 (30.3)	56 (100)
TIRADS-4a	7(43.7)	9 (56.3)	16 (100)
TIRADS-4b	9 (39.1)	14 (60.9)	23 (100)
TIRADS-4c	8 (27.5)	21(72.5)	29 (100)
TIRADS-5	6 (13.6)	38 (86.4)	44 (100)
TOTAL	**73 (42.44)**	**99 (57.5)**	**172 (100)**

There is very strong statistical correlation between TIRADS category and outcome Pearson chi-square test value =40.065, DF=5, $p<0.001$ ($p<0.05$)

TIRADS 2 – None of the nodules classified as TIRADS 2 were found to be malignant

TIRADS 3- Of the nodules classified as TIRADS 3, 30.3% were found to be malignant

TIRADS 4- Of the nodules classified as TIRADS 4 64% of the nodules were found to be malignant, the individual break up

TIRADS 4a – 9 out of 16 – 56.3%

TIRADS 4b– 14 out of 23 – 60.9 5%

TIRADS 4c – 21 out of 29-72.5%

TIRADS 5 – 38 of 44 nodules – 86.4% were malignant.

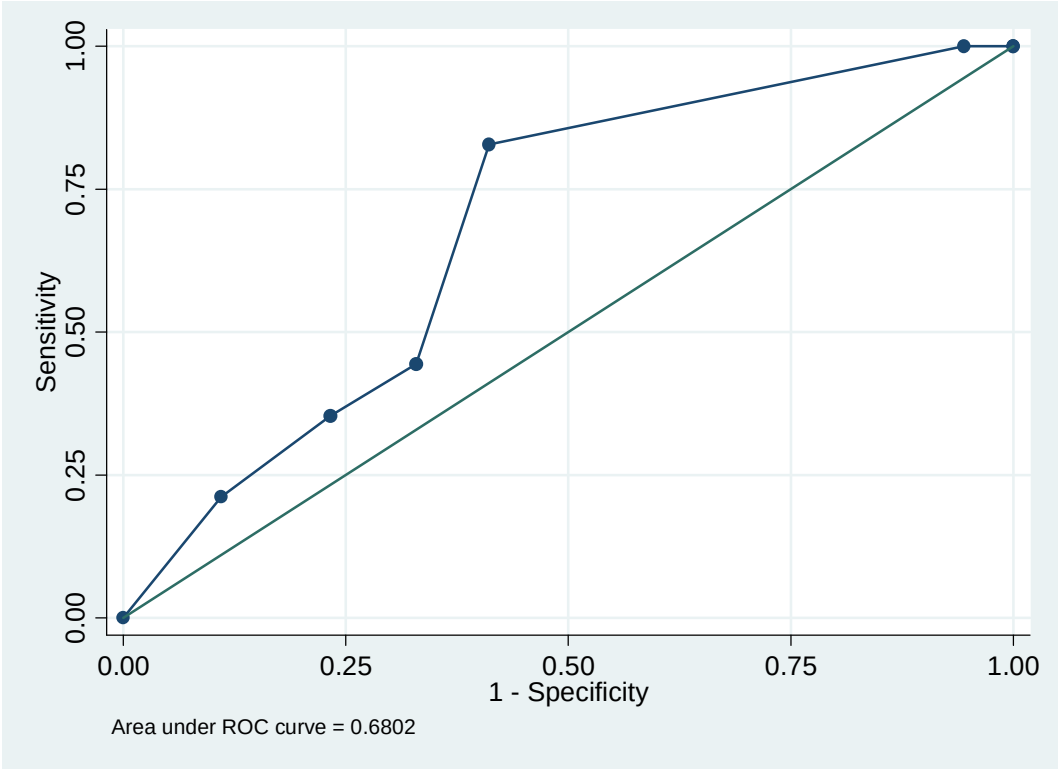


Fig.1 Receiver-operating characteristic (ROC) curve depicting accuracy of TIRADS in predicting malignancy. The area under the curve is 0.682

TIRADS categorization

Sensitivity–82.8%

Specificity – 58.9%

Diagnostic accuracy – 72.7%

Likelihood ratio–2.01

ARFI OBSERVATIONS

I. VIRTUAL TOUCH IMAGING –VTI

VTI	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**

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.

II) RECODED 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)

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

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

BACKGROUND CHANGES OF THYROIDITIS AND VTI OBSERVATIONS

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

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

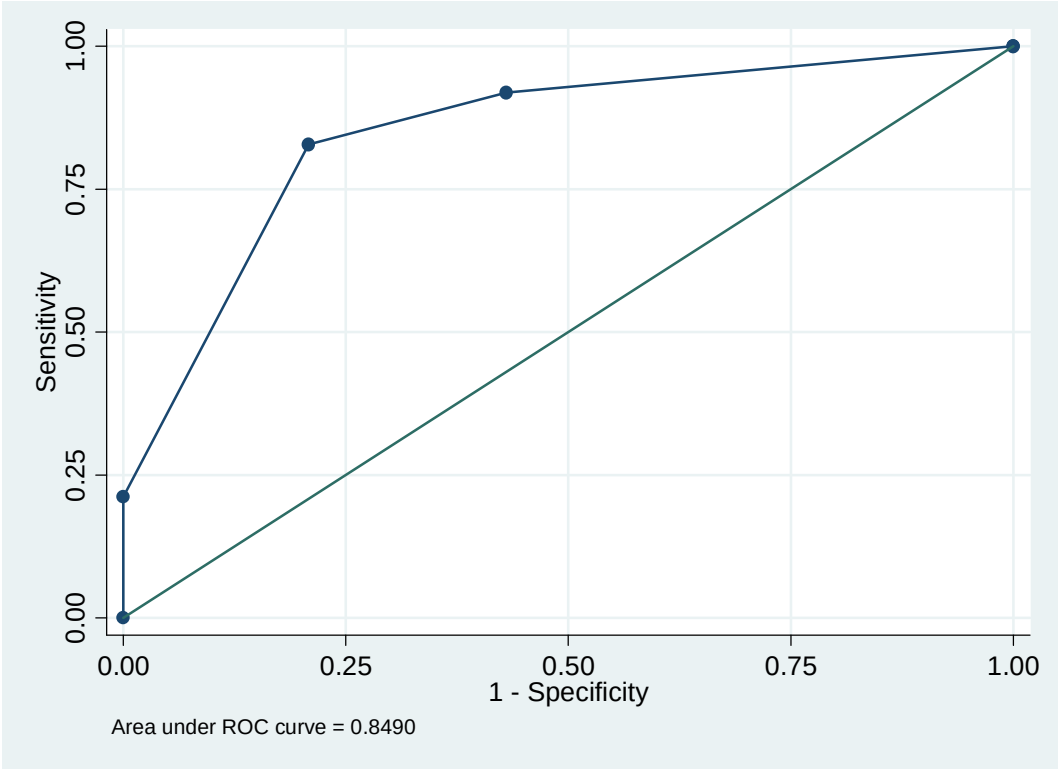


Fig. 2 Receiver-operating characteristic (ROC) curve depicting accuracy of VTI in predicting malignancy. The area under the curve is 0.8490

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

III) 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**			

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, $p<0.001$.

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**		

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.

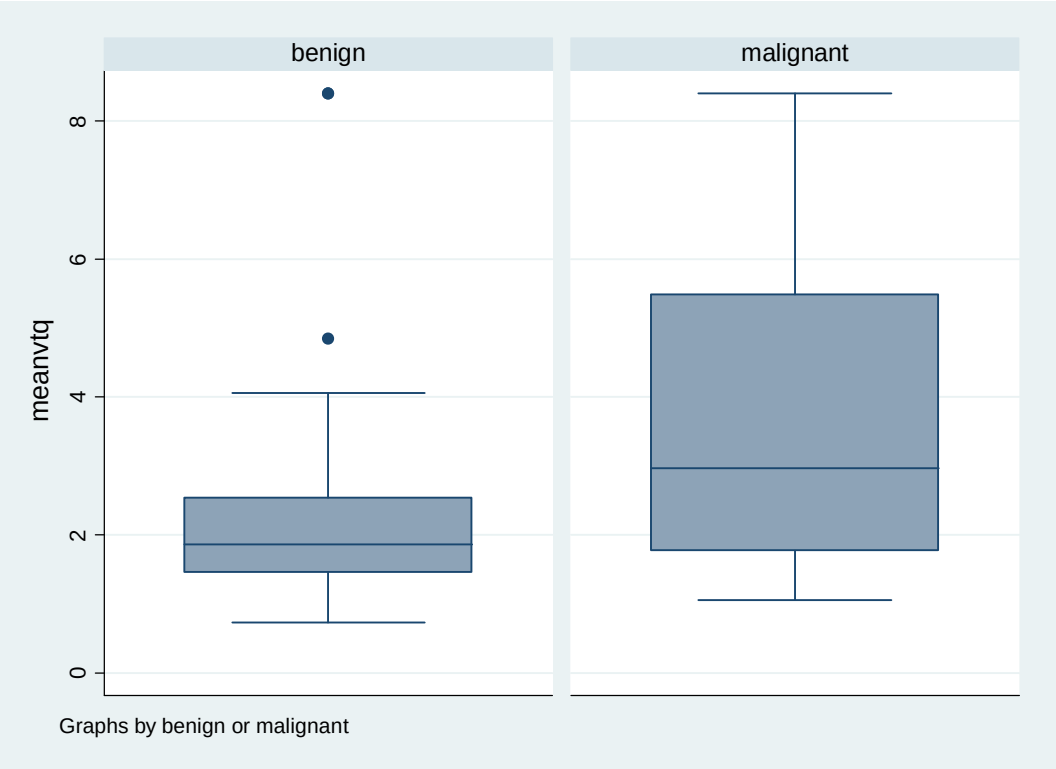
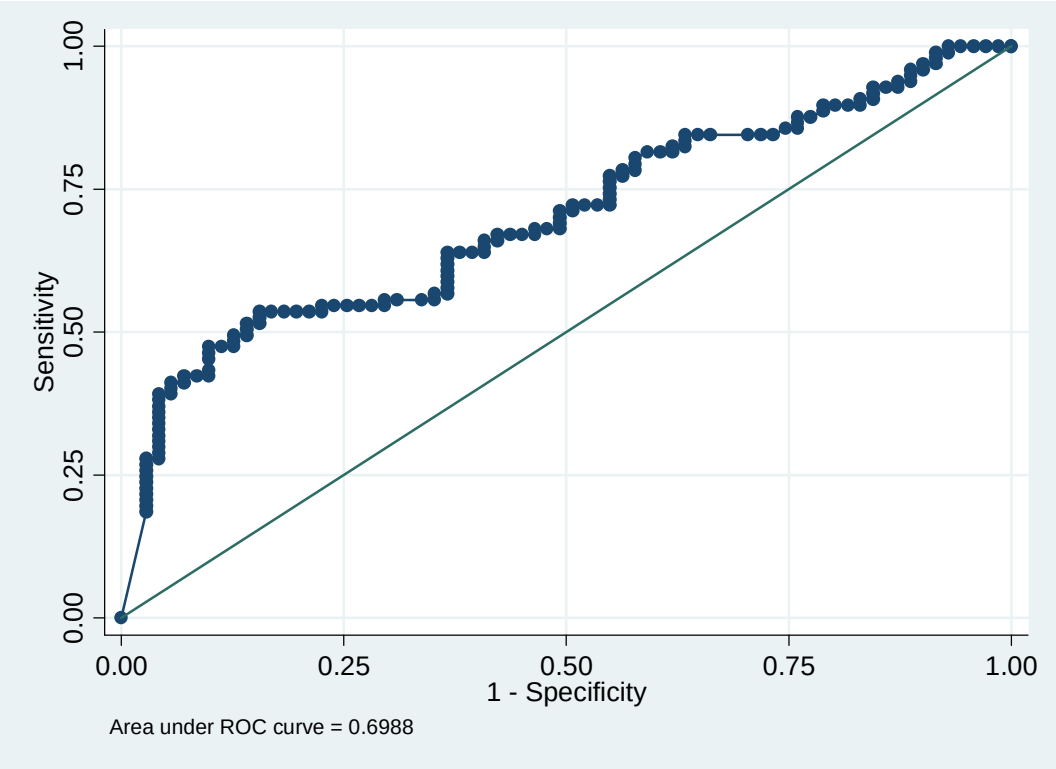


Figure 2: Box plot depicting the mean, median and range of shear wave velocity measurements in benign and malignant thyroid nodules, $p<0.001$.



Receiver operating curve –ROC demonstrating accuracy of ARFI –mean VTQ on predicting malignancy. Area under the curve is 0.6988

The mean VTQ value for benign and malignant nodules is as follows

Benign nodules- 2.19 m/s

Malignant nodules – 3.97 m/s

Sensitivity-57.1%

Specificity- 82.5%

Positive predictive value -53.6%

Negative predictive value -84.5%

Accuracy - 65.5%

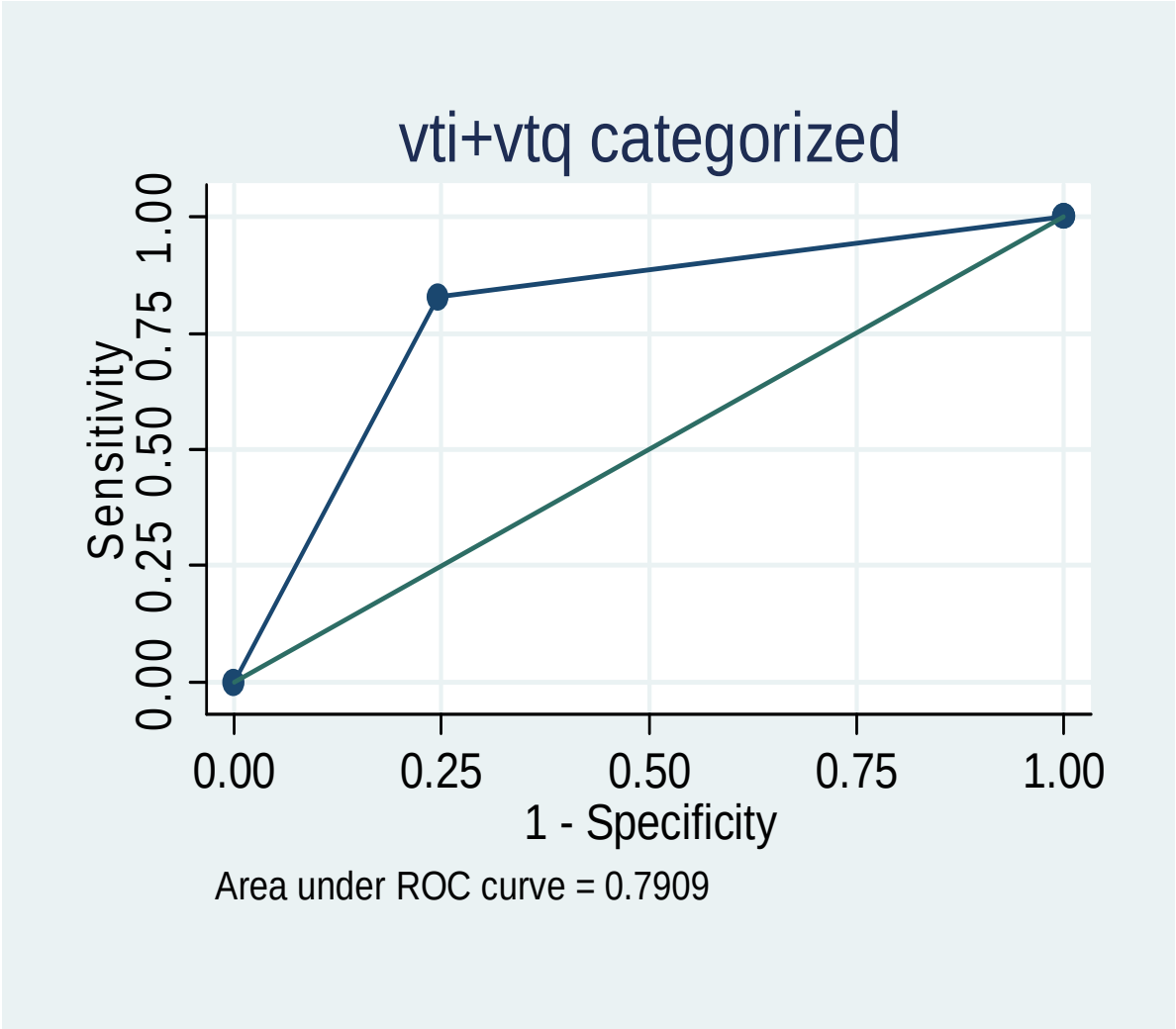


Fig showing combined ROC curves when VTI and VTQ are combined together

The combined performance is as follows

Sensitivity–82%

Specificity–75.3%

Diagnostic accuracy – 82%

Likelihood ratio – 3.36

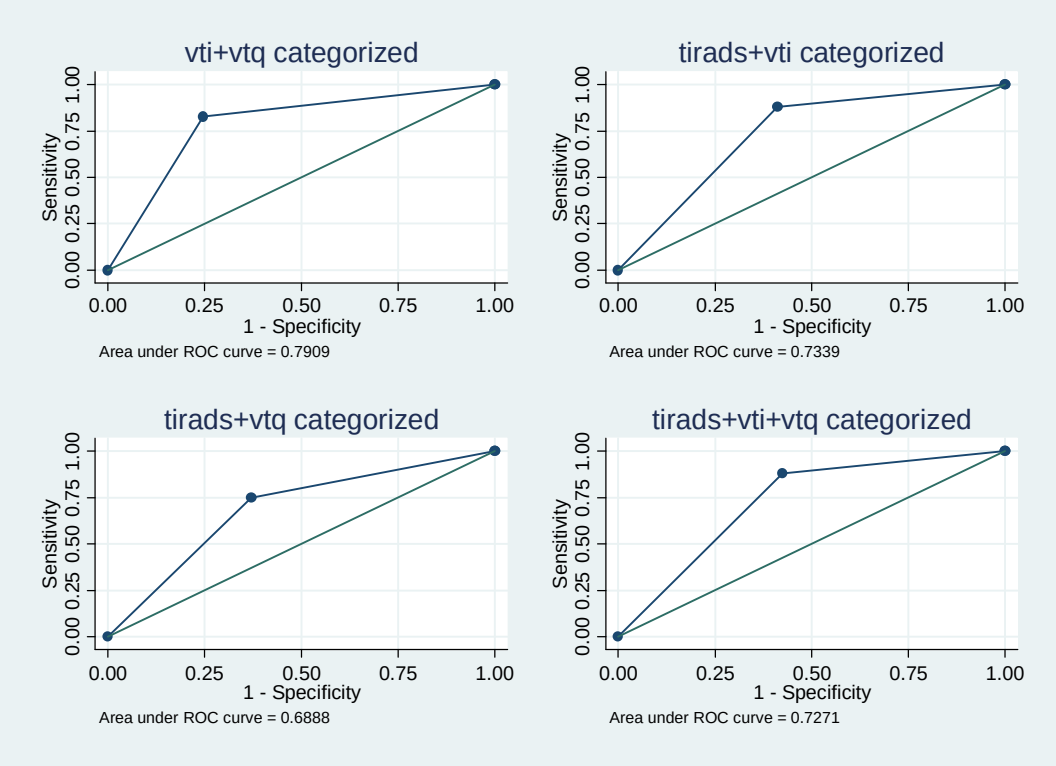


Figure 3: Receiver operator curves (ROC) demonstrating the diagnostic performance of VTI, VTQ measured using ARFI technology compared with conventional ultrasound (TIRADS) and combined criteria (VTI+VTQ+TIRADS)

Diagnostic performance of VTI (AUC = 0.849) and combined VTI+VTQ (AUC= 0.791) was better than VTQ alone, conventional ultrasound and combined criteria (conventional ultrasound + VT I + VTQ); AUC was 0.699, 0.682 and 0.727 respectively.

Table 6: Inter-observer agreement between observers for ultrasound findings:

Linear weighted kappa coefficients and p value

Characteristics	**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

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 .

DISCUSSION OF THE RESULTS

ULTRASOUND EVALUATION AND TIRDS

All the nodules were evaluated using ultrasound and graded for a risk of malignancy according to TIRADS. There was no evidence to suggest that sex of the patient and site of the nodule (right lobe, left lobe and isthmus) had an effect on the nodule outcome. The most helpful features in predicting malignancy were

1. Absence of a well-defined halo around the lesion

2. Presence of microcalcification

3. Hypoechogenecity of the nodule – both when the nodule was hypoechoic compared to thyroid parenchyma but more echogenic than the strap muscles and more so when more hypoechoic than the strap muscles

4. Taller than wide nodule

5. Presence of irregular or Ill-defined margins of the nodule

6. Presence of central vascularity

7. Presence of lymphadenopathy

These features have already been described in literature and the current study also found similar results

The Ultrasound features that suggested benign nature of the lesion were

1. Presence of a complete hypoechoic halo around the lesion

2. Absence of calcification

3. Nodule echogenicity more than that of thyroid parenchyma

4. A nodule with well-defined margins

5. Perinodular vascularity

6. Absence of lymphadenopathy

TIRADS CATEGORIZATION OF THE NODULES

TIRADS 2 – None of the nodules characterized as TIRADS 2 were found to be malignant

TIRADS 3- Of the nodules characterized as TIRADS 3, 30.3% were found to be malignant

TIRADS 4- Of the nodules classified as TIRADS 4 64% of the nodules were found to be malignant, the individual break up

TIRADS 4a – 9 out of 16 – 56.3%

TIRADS4b - 14 out of 23 – 60.9 5%

TIRADS4c -21out of 29-72.5%

TIRADS-5 – 38 of 44 nodules – 86.4% were malignant.

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.

ARFI- ACOUSTIC RADIATION FORCE IMPULSE IMAGING

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).

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.

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.

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.

CONCLUSIONS

1. TIRADS characterization of the thyroid nodules is helpful in guiding FNAC and surgery decisions

2. Application of TIRADS criteria brings uniformity in reporting and can be performed with moderate to fair Interobserver agreement.

3. Addition of the absent halo sign to TIRADS algorithm may lead to increased diagnostic performance

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

4. Overall Interobserver agreement for TIRADS was Moderate

5. VTI is an additional imaging tool that can increase the diagnostic accuracy of Ultrasound examination as a whole.

6. The sensitivity, specificity and diagnostic accuracy of VTI was higher than that of TIRADS and VTQ separately and also when combined together

7. There was a considerable overlap in the VTQ values for benign and malignant thyroid nodules, the cut off value was difficult to choose

8. In future more number of cases can be evaluated by VTQ to establish their usefulness in diagnosis and avoiding unnecessary FNAC

LIMITATIONS

LIMITATIONS OF THE STUDY

1. There was a selection bias owing to the fact that the study was conducted in a tertiary care centre and most of the referrals were from endocrine surgery which resulted in increased number of clinically aggressive lesions being referred for Ultrasound and ARFI.

2. Lesions which were studied and subsequently underwent FNAC and were reported as inconclusive or indeterminate, did not undergo a second FNAC as recommended in literature and thus had to be excluded from the study.

3. Interobserver bias for TIRADS categorization

4. Inspite of having conducted a pilot study, there was a learning curve during which interpretation of TIRADS and ARFI became more compatible with the clinical impression as the study progressed.

TECHNICAL LIMITATIONS

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

2. VTQ values which were displayed x.xx m/sec were considered as higher 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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APPENDIX I

PROFORMA FOR ULTRASOUND and ARFI ELASTOGRAPHY

Name: _____ **Age:** _____ **Date:** _____

Hospital No: _____ **Sex**: Male -1, Female -2

USG Findings:

Site:

1. Right
2. Isthmus
3. Left

Size:

1. <1cm --1
2. >1 cm --2

Halo:

1. Present
2. Absent

Composition:

1. Cystic
2. Solid
3. Mixed

Echogenicity:

1. Hyperechoic to thyroid
2. Isoechoic to thyroid
3. Hypoechoic to thyroid and iso to strap muscle
4. Markedly Hypoechoic compared to strap muscle

Margins:

1. Well Circumscribed
2. Microlobulated
3. Ill-defined
4. Irregular

Calcification: should have no comet tail artefact

1. Micro calcification (< 1mm)
2. Macro calcification (> 1 mm)
3. Micro and macro calcification
4. No calcification

Shape:

1. wider than tall
2. Taller than wide

Vascularity:

1. Central
2. Peripheral

Lymph nodes

1. Present
2. Absent

TIRADS category

TIRADS 2-2

TIRADS 3-3

TIRADS 4a-41

TIRADS 4b-42

TIRADS 4c-43

TIRADS 5-5

BACKGROUND THYROIDITIS CHANGES

Present -1

Absent -2

FOLLOW UP AT 6 months

FNAC

Write in words

1. benign
2. Indeterminate
3. suspicious for papillary thyroid carcinoma
4. malignant
5. Inadequate

HISTOPATHOLOGY:

In words

HISTOPATHOLOGY CODE

Benign

Malignant

MALIGNANCY CODE

1. Papillary carcinoma
2. Follicular variant
3. Medullary carcinoma
4. Minimally invasive follicular carcinoma
5. Widely aggressive follicular carcinoma
6. Poorly differentiated
7. Anaplastic carcinoma
8. Micropapillary carcinoma
9. Lymphoma

BENIGN CODE

1. Adenomatous hyperplasia
2. Follicular adenoma
3. Hurthle cell adenoma
4. Hyalinised Trabecular tumour
5. Cyst with he
6. Nodular hyperplasia
7. Hashimoto thyroiditis

Overall

1. Benign
2. Malignant

ARFI modality	*Results*
VTI	
VTQ-1	
VTQ-2	
VTQ-3	
VTQ-4	
VTQ-5	
Mean VTQ	

APPENDIX II

INFORMED CONSENT

Department of Radiology, Christian Medical College, Vellore

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

Information sheet

You are being requested to participate in a study where ARFI Elastography of thyroid nodules will be performed and compared with fine needle aspiration cytology and histopathology

How is it different from the usual ultrasonography of neck?

There is no difference in the scan procedure, but the scan takes about five minutes more than the routine ultrasound scan.

Does ultrasonography have any side effects? There are no side effects.

If you take part what will you have to do?

If you agree to participate in this study, your ultrasound scan will be done in Room no 19 of the radiology department at 4 O clock on Mondays and Thursdays

You may be expected to come for a review to the hospital 6 months after the scan and may require a follow up scan after 6 months.

Do you have to pay for these tests? Yes, because these tests are a part of your disease management and will be required anyway whether you participate in this study or otherwise.

Will this study affect your treatment? No

Will treatment for other unrelated conditions be affected? All other treatments that you are already on will be continued and your regular treatment will not be changed during this study.

Can you withdraw from this study after it starts? Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr. Abhishek (tel: 0416 2283012 ext 114 or email: drabhishekkhurana@gmail.com)

CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: Role of ARFI and Elastography in predicting benign vs. Malignant lesions in patient with solitary thyroid nodules

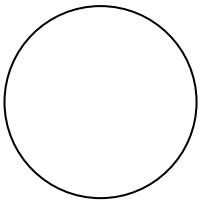
Study Number:
Participant's name:
Date of Birth / Age (in years):

I_____,
Son/daughter of _____

(Please tick boxes)
Declare that I have read the information sheet / the information sheet provided was read to me, provided to me regarding this study and have clarified any doubts that I had. [ ]
I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access
[ ]
I understand that my identity will not be revealed in any information released to third parties or published [ ]
I voluntarily agree to take part in this study [ ]

Name:
Signature:
Date:

Left thumb impression



Name of witness:
Relation to participant:
Date: