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ORIGINAL ARTICLE

CORRELATION OF HIGH RESOLUTION ULTRASOUND AND COLOR DOPPLER FINDINGS OF THYROID NODULES WITH FINE NEEDLE ASPIRATION CYTOLOGY

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ABSTRACT: The objective of this study was to assess the utility of gray scale and color Doppler Ultrasonographic (US) findings in characterization of benign and malignant thyroid nodules in correlation with the pathological diagnosis. **METHODS:** From January 2013 through December 2013, a total of 70 patients with solitary thyroid nodule underwent thyroid US with 7.5–12 MHz, linear array transducer of ESOATE MYLAB 40. The following characteristics of each nodule were determined: Nodule diameter, Shape, Margins, Internal Contents, Echo texture, Halo, Presence and pattern of calcification, Pattern of vascularity, resistive index (RI) of Intranodular/Peripheral vessels, and Association of cervical lymphadenopathy. Sensitivity, specificity, and positive and negative predictive values were obtained. The results were then compared to the fine needle aspiration (FNA)/Histopathological diagnosis. Diagnostic accuracy of US was determined using multiple logistic regression analysis. **RESULTS:** Statistically significant (P<.05) findings of malignancy were: taller than- wide shape, lobulated/poorly defined margins, hypoechogenicity and marked hypoechogenicity, thick incomplete/absent halo, microcalcification, central/ central >peripheral pattern of vascularity and associated cervical lymphadenopathy. The overall diagnostic accuracy of thyroid US for differentiating a malignant lesion from a benign one was found to be 84.3%. **CONCLUSION:** Taller-than-wide shape, Lobulated/poorly defined margins, Hypoechogenicity and Marked hypoechogenicity, Microcalcifications and Central/central >peripheral pattern of vascularity are helpful criteria for the discrimination of malignant from benign nodules. Thyroid US achieved a good overall diagnostic accuracy in the categorization of benign and malignant thyroid nodules.

KEYWORDS: Thyroid, Nodules, Malignant.

INTRODUCTION: Thyroid nodules are common occurring in up to 50% of the adults and higher in females as compared to males. However, less than 10% of thyroid nodules are malignant. High-resolution ultrasonography (US) is commonly used to evaluate the thyroid gland, but US is frequently misperceived as unhelpful for identifying features that distinguish benign from malignant nodules.

At ultrasonography (US), 10%–67% of adults have thyroid nodules. Thyroid US has been widely used to differentiate benign from malignant nodules and to guide fine-needle aspiration cytology for nodules suspected of being malignant.

A combination of the US findings provides better diagnostic accuracy than only one of these findings. However, considerable overlap between benign and malignant characteristics has been found in results of some studies. Sensitivity and specificity of the US findings for malignant thyroid nodules are also variable.

Fine-needle aspiration cytology is considered a sensitive, specific, and accurate diagnostic test in the evaluation of patients with thyroid swellings.

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Thus this study aims to assess the sensitivity and specificity of high resolution ultra-sonography and color Doppler in characterization of thyroid nodules in correlation with fine needle aspiration cytology findings.

MATERIALS AND METHODS: The study was performed in the Department of Radio-diagnosis, Mysore medical college and research institute, Mysore on patients referred for ultrasound with clinically detected thyroid nodule/s.

Sample Size: Seventy cases.

Type of Study: Prospective study.

Study Period: One year from January 2013 to December 2013.

METHOD OF COLLECTION OF DATA: A structured pre- prepared case proforma was used to enter the patient details, clinical history, and physical examination including thyroid profile of patients who met the inclusion criteria. The ultrasound examination of the thyroid gland was performed in gray scale and color Doppler modes using a high resolution, 7.5–12 MHz, linear array transducer of Esoate Mylab 40 prior to the FNA.

These lesions will be then characterized into benign or malignant lesion considering the following gray scale and color Doppler findings: Nodule diameter, Shape, Margins, Internal Contents, Echo texture, Halo, Presence and pattern of calcification, Pattern of vascularity, RI of Intranodular/ Peripheral vessels, Association of cervical lymphadenopathy and Characteristics of lymph nodes (Loss of fatty hilum, Cystic change, Calcification, Hyperechogenicity, Round Shape and Abnormal vascularity).

The shape was determined by measuring the antero-posterior diameter to transverse diameter ratio on transverse US images. A taller-than-wide shape was defined as a nodule having a greater anteroposterior diameter than its transverse diameter. The margins were assessed as well defined, lobulated or poorly defined and whether surrounded by a peripheral halo or not. The halo around the nodules (peripheral halo), when present, is classified by its thickness. A thin halo is <2 mm and a thick halo > 2 mm. The halo thickness was included in the nodule measurements. The echogenicity was assessed as hypoechoic, hyperechoic, and isoechoic or anechoic in comparison to normal thyroid parenchyma. The hypoechoic nodules were further sub classified as markedly hypoechoic if less echogenic than strap muscles. The nodules were also categorized as solid, predominantly solid (<50% cystic), predominantly cystic (>50%) or cystic based on their composition. The presence of calcification as well as type of calcification whether micro or macro calcification was noted. Microcalcifications were defined as tiny, hyperechoic foci (<1 to 2mm in size) with or without posterior shadowing and no posterior reverberation. Macro-calcifications were defined as >2mm in diameter with posterior shadowing. The pattern of vascularity was assessed with calculation of RI.

Pathologic Evaluation: All the nodules underwent either palpation guided FNA or US guided FNA, regardless of their size. The histopathological results were considered as the final diagnosis. Tissue diagnosis was available in 34 of the surgically resected nodules. The US diagnoses were compared with cytopathology results. The overall diagnostic accuracy of thyroid US in differentiation of benign and malignant nodules was assessed using logistic regression analysis.

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RESULTS: Out of 70 nodules, 42 were benign and 28 were malignant. The median patient age in the benign and malignant groups was 40 years and 42.5 years respectively. There were 62(88.6%) females and 8(11.4 %) males in this study with a male to female ratio of 1:7.7. Right lobe of thyroid was the most common location for both benign and malignant thyroid nodules. Most of the patients were euthyroid in both benign and malignant categories. Of the 42 benign nodules, 39 were more than 2cms in diameter and of the 28 malignant nodules 19 were more than 2cms in diameter.

In the benign group, colloid/adenomatoid nodule was the most common (n=24) followed by follicular adenoma (09) and colloid cyst (08). Diagnoses of malignancy included papillary thyroid carcinoma (n=15), follicular carcinoma (n=9), medullary thyroid carcinoma (n=2), anaplastic thyroid carcinoma (n = 1), and lymphoma (n=1).

The significance of US characteristics in differentiation of benign and malignant thyroid nodules is presented in Table 1, Table 2 depicts the diagnostic accuracy of us findings for malignant nodules. Table 3 shows the results of multiple logistic regression analysis for overall diagnostic accuracy of ultrasound diagnosis.

DISCUSSION: Thyroid pathologies are classifiable into two groups: nodular and diffuse diseases.

All diffuse thyroid diseases (with the exception of rare diffuse thyroid lymphoma) and approximately 90 to 92 % of nodular pathologies are benign.[1]

Thyroid nodules occur in up to 50% of adults, whereas palpable thyroid nodules occur in only 3%–7%. Malignancy occurs in 5%–7% of all thyroid nodules.[2] Thyroid nodules and thyroid malignancy have a female predilection of 4:1 and 2–3:1, respectively.[3] In general, the probability of malignancy in a nodule is higher for men and for patients under 15 years or over 45 years of age.

Nodular diseases of thyroid can be classified as in table 4.[4]

Thyroid ultrasound (US) is the major imaging modality for evaluating thyroid nodules. Using US, a thyroid nodule appears as a nodular lesion within the thyroid gland that is distinguishable from the adjacent parenchyma. Several gray scale and Doppler US features are evaluated as potential predictors for the presence of thyroid malignancies. However, there is a considerable overlap in the appearance for distinction between benign and malignant thyroid nodules, regardless of whether it has a solid or cystic US configuration.

Once a thyroid nodule has been detected with sonography, the fundamental problem is to determine whether it is benign or malignant. Current management guidelines recommend sonography and FNA for management of thyroid nodules, because no single noninvasive test can reliably distinguish benign from malignant nodules.

Numerous sonographic features of thyroid nodules have been described and studied as a means of triaging nodules for FNA. These include size, multiplicity, and echogenicity, presence of calcifications, margins, contour, shape, internal architecture, and vascularity.

The size of a thyroid nodule is not helpful for distinguishing a malignant nodule from a benign nodule. The nodule size should be precisely documented for the purpose of follow-up.[5]

Kwak et al in 2013 conducted a retrospective study to develop and validate a simple diagnostic prediction model by using ultrasound (US) features of thyroid nodules obtained from multicenter retrospective data. US features that were statistically significant for malignant nodules were hypoechogenicity, marked hypoechogenicity, non-parallel orientation, microlobulated or spiculated margin, ill-defined margins, and microcalcifications.

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They concluded that the predictor model using suspicious malignant US features may be helpful in risk stratification of thyroid nodules.[6]

Popli et al in 2012 conducted a prospective study to assess the utility of gray scale US to identify patterns of thyroid nodules and correlate characteristics of benign and malignant nodules with pathological diagnosis. They concluded that gray-scale US features of thyroid nodules are useful to identify patients with clinically significant thyroid nodules from those with innocuous nodules. US features of poorly defined margins, marked hypoechogenicity, and taller-than-wide shape were found to have high diagnostic accuracy for identifying malignant thyroid nodules.[7]

Algin et al in 2010 conducted a prospective study to evaluate the usage of duplex power Doppler ultrasound for the differentiation of benign and malignant thyroid nodules. They concluded that vascularity is not a useful parameter for distinguishing malignant from benign thyroid nodules. However, RI and PI values are useful in distinguishing malignant from benign thyroid nodules.[8]

Moon et al in 2010 conducted a retrospective study to evaluate the diagnostic performance of power Doppler ultrasonography (US) in depicting vascularity and to determine whether the combination of vascularity and suspicious gray-scale US features is more useful in predicting thyroid malignancy than are gray-scale features alone. They concluded that vascularity itself or a combination of vascularity and grayscale US features was not as useful as the use of suspicious gray-scale US features alone for predicting thyroid malignancy.[9]

Moon et al in 2008 conducted a multicenter retrospective study on ultrasound differentiation of benign and malignant thyroid nodules using tissue diagnosis as reference standard. They concluded that shape, margin, echogenicity and presence of calcifications are helpful criteria for discrimination of malignant from benign nodules and diagnostic accuracy is dependent on the tumor size.[10]

Chammas et al in 2008 conducted a prospective study to determine the predictive value for malignancy of microcalcifications determined by ultrasonography in thyroid nodules. They concluded that that microcalcifications were highly specific for malignancy and were present in 61% of the malignant nodules.[11]

Chammas et al in 2005 conducted a retrospective evaluation of thyroid nodules with power Doppler and duplex Doppler and concluded that Doppler is helpful in screening of thyroid nodules at high risk for malignancy. Power Doppler and RI have a diagnostic sensitivity and specificity of 92.3% and 88%, respectively, in the detection of malignant nodules.[12]

In an incidentally detected thyroid nodule, the goal should be to avoid extensive and costly evaluations in the majority of patients with benign disease, without missing the minority of patients who have clinically significant thyroid cancer.[13]

PRESENT STUDY: The US features of Taller-than-wide, Lobulated/poorly defined margins, Hypoechogenicity and Marked hypoechogenicity, Thick incomplete/absent halo, Microcalcifications, Central/central > peripheral pattern of vascularity and associated cervical lymphadenopathy were individually statistically significant for depiction of a malignant nodule. This correlated well with the study done by Moon et al who found that Taller than wide shape, A spiculated margin, Marked hypoechogenicity, Hypoechogenicity, and Microcalcification as features statistically significant for the depiction of a malignant nodule.

The US features of Wider than tall, Well defined margins, and Thin halo were individually statistically significant for depiction of a benign nodule. This again correlated well with the study of

Moon et al who found that Wider than tall and Well defined margins are significant to depict benignity. However present study found that hyperechogenicity to be significantly associated with benignity, which is in contradiction to the study of Moon et al.

Internal contents of nodules were found to be statistically significant in the present study and this correlated well with the study of Moon et al.

The US finding of solid/predominantly solid nodule was found almost in equal incidence in benign and malignant groups and was not statistically significant.

Moon et al found macrocalcification to be statistically significant in prediction of malignancy, but it was not found to be significant in the present study. In the present study, presence of any of these features - taller than-wide shape, lobulated/poorly defined margins, hypoechoic and marked hypoechogenicity and microcalcification was very specific in the range of 92.8%–100%. These findings are comparable to studies done by Popli et al who found specificity range of 80.1% -97.9% and that of Moon et al in which it ranged 90.8%-92.8%.

When the presence any of the above malignant findings was chosen as a criterion for malignancy, the overall accuracy ranged 74.0% -85.7 %. This correlated well with study done by Popli et al in which diagnostic accuracy ranged 79.5%-92%.

Solid/predominantly solid composition of the nodule with thick incomplete or absent halo had a high sensitivity in the range of 89.3%– 100%. These findings are comparable to study done by Popli et al who found sensitivity range of 70.4% -88.6%.

Presence of calcifications had a low sensitivity (50%) and specificity (57%) in characterization of malignant nodules. This is not in correlation with study done by Popli et al who found higher sensitivity (86.3%) and specificity (76%) for presence of calcifications in malignant nodules.

Central/central >peripheral pattern of vascularity was found to be statistically significant for depiction of a malignant nodule. This can compared to the previous studies done by Chammas et al and Moon et al. who also found that Central/ central > peripheral pattern of vascularity was more frequently seen in malignant nodules and was statistically significant.

RI of >0.7 in intranodular/perinodular vessels was seen almost equally in both benign and malignant categories and was found not statistically significant. This does not correlate to the study done by Algin et al who found that a RI of >0.7 is statistically significant in depiction of malignancy in thyroid nodule.

OVERALL DIAGNOSTIC ACCURACY THYROID US: Using multiple logistic regressions, the diagnostic accuracy of thyroid US for differentiating a malignant lesion from a benign one in the present study was found to be 84.3 %. This is in correlation with study by Lee et al.[14] who found overall diagnostic accuracy of 92%.

There were several limitations to the present study, first the sample size was small compared to the previous studies. Secondly RI of >0.7 in the intranodular or perinodular vessels was not found to be statistically significant which is in contradiction to the previous studies. This can be attributed to technical limitations.

CONCLUSION: The presence of gray scale US features - Taller-than-wide shape, Lobulated/poorly defined margins, Hypoechogenicity and Marked hypoechogenicity, Thick incomplete/absent halo, Microcalcifications, Central/central >peripheral pattern of vascularity and associated cervical

lymphadenopathy suggests malignancy. The risk of malignancy increases as intranodular blood flow becomes more dominant. Likewise the presence of Wider than tall shape, Well defined margins, Hyperechogenicity, and Thin halo suggests benignity.

Thyroid US achieved a good overall diagnostic accuracy for differentiating benign and malignant nodules.

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CHARACTERISTIC	BENIGN (42)	MALIGNANT (28)	P VALUE
SHAPE			< .001
WIDER THAN TALL	41	06	< .001
TALLER THAN WIDE	01	22	< .001
MARGINS			< .001
WELL DEFINED	40	09	< .001
LOBULATED/POORLY DEFINED	02	26	< .001
INTERNAL CONTENTS			< .001
CYSTIC/PREDOMINANTLY CYSTIC	16	00	
SOLID/PREDOMINANTLY SOLID	26	28	0.785
ECHOTEXTURE			
HYPERECHOIC	28	07	< .001
HYPOECHOIC/MARKEDLY HYPOECHOIC	03	28	0.001
HALO			< .001
THIN	31	03	< .001
THICK INCOMPLETE AND ABSENT	09	25	0.006
CALCIFICATION			0.557
MICROCALCIFICATION	01	07	0.034
MACROCALCIFICATION	16	07	0.061
VASCULARITY			
CENTRAL AND CENTRAL > PERINODULAR	09	20	0.041
PERINODULAR>CENTRAL	33	08	
RI > 0.7	20	18	0.746
ASSOCIATED CERVICAL LYMPHADENOPATHY	02	08	0.058

TABLE 1: SIGNIFICANCE OF US CHARACTERISTICS IN DIFFERENTIATION OF BENIGN AND MALIGNANT THYROID NODULES

	Sensitivity	Specificity	PPV	NPV	Accuracy
TALLER THAN WIDE	20/28 (71.4%)	40/42 (95.2%)	20/22 (90.9%)	40/48 (83.3%)	60/70 (85.7%)
LOBULATED/POORLY DEFINED MARGINS	18/28 (64.3%)	40/42 (95.2%)	18/20 (90 %)	40/50 (80 %)	58/70 (82.9%)
SOLID/PREDOMINANTLY SOLID	28/28 (100%)	16/42 (38.1%)	28/54 (51.9 %)	16/16 (100 %)	44/70 (48.6%)

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HYPOECHOIC	19/28 (67.8%)	39/42(92. 8%)	19/22 (86.4%)	39/48 (81.3%)	58/70 (82.8%)
MARKEDLY HYPOECHOIC	10/28 (35.7%)	42/42 (100%)	10/10 (100%)	42/60 (70%)	52/70 (74.3%)
THICK INCOMPLETE HALO/ ABSENT	25/28 (89.3%)	31/40 (77.5%)	25/34 (73.5 %)	31/34 (91.2 %)	56/68 (80 %)
CALCIFICATIONS	14/28 (50%)	24/42 (57%)	14/32 (43%)	24/38 (63 %)	38/70 (54.3%)
MICROCALCIFICATIONS	7/14 (50 %)	16/17 (94 %)	7/8 (87.5 %)	16/23 (69.5 %)	23/31 (74.2%)
CENTRAL AND CENTRAL > PERINODULAR	20/28 (71.4%)	33/42 (78.6 %)	20/29 (69%)	33/41 (80.5 %)	53/70 (75.7%)
RI > 0.7	18/28 (64.3%)	22/42 (52%)	18/38 (47%)	22/32 (68.75%)	40/70 (57.1%)

TABLE 2: DIAGNOSTIC ACCURACY OF US FINDINGS FOR MALIGNANT NODULES

OBSERVED		Predicted		
		FNA DIAGNOSIS GROUP		Percentage Correct
		BEN	MAL	
US DIAGNOSIS GROUP	BEN	38	7	84.4
	MAL	4	21	84.0
Overall Percentage				84.3

TABLE 3: RESULTS OF MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR OVERALL DIAGNOSTIC ACCURACY OF US DIAGNOSIS

The overall diagnostic accuracy of thyroid US in differentiation of benign and malignant nodules is 84.3%.

BENIGN	MALIGNANT
Benign follicular nodules: Hyperplastic/adenomatoid nodule Colloid nodule.	Papillary carcinoma
	Follicular carcinoma Hürthle cell variant Poorly differentiated carcinoma.
Cysts : simple, colloid and hemorrhagic	Medullary carcinoma
Follicular adenoma Hürthle cell variant	Anaplastic carcinoma
Chronic lymphocytic thyroiditis (Hashimotos)	Primary thyroid lymphoma
	Metastatic carcinoma (breast, renal cell, Others)

TABLE 4: NODULAR DISEASES OF THYROID

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CASE 1: ADENOMATOID NODULE.

Fig. 1A-D: Longitudinal images showing a well-defined ovoid shaped solid nodule in right lobe of the thyroid with hypoechoic halo, biopsy proved it to represent a hyperplastic nodule.

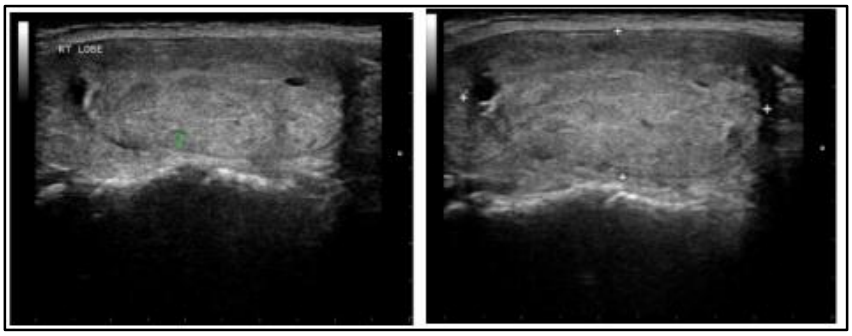

Fig. 1A **Fig. 1B**

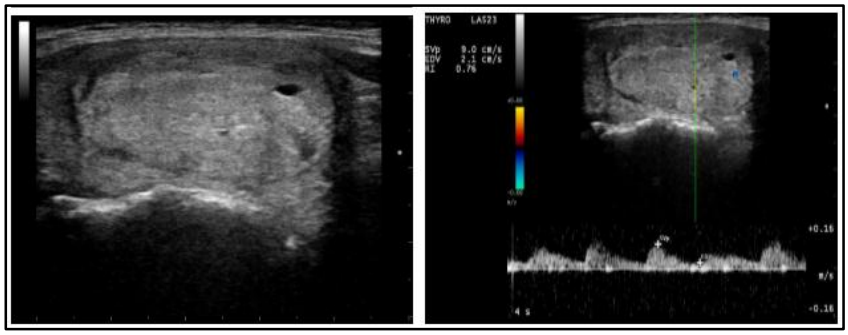

Fig. 1C **Fig. 1D**

CASE 2: FOLLICULAR CARCINOMA WITH SKULL METASTASIS.

Fig. 2A-F: Longitudinal and transverse gray-scale images shows a taller than wide, lobulated isoechoic nodule with hypoechoic areas in the left lobe. The nodule has a thick incomplete halo with speck of calcification within. On color Doppler, central vascularity was noted with an RI of 0.68. CT axial images of the brain in head and bone windows showing expansile lytic lesion with enhancing soft tissue component suggestive of metastasis.

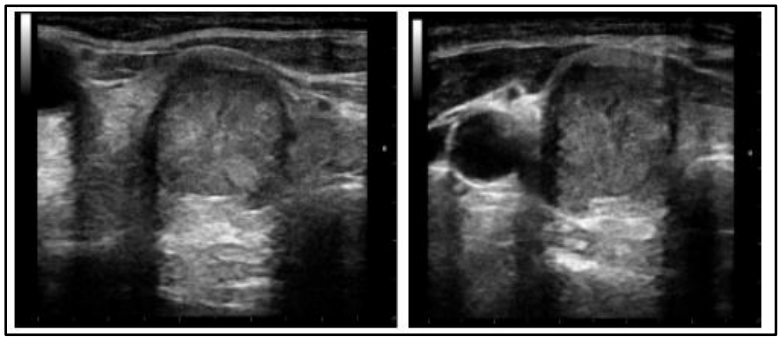

Fig. 2A **Fig. 2B**

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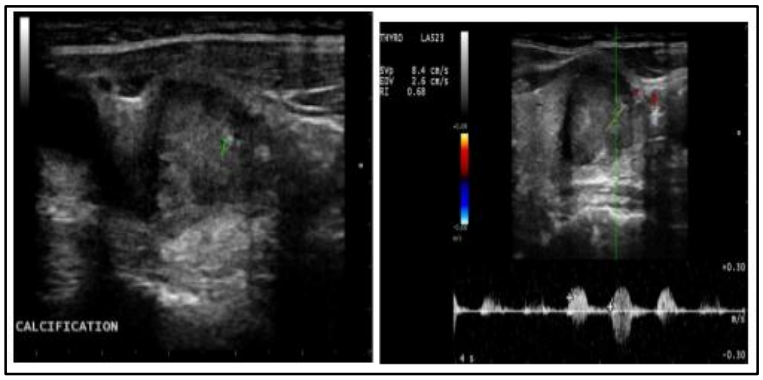

Fig. 2C Fig. 2D

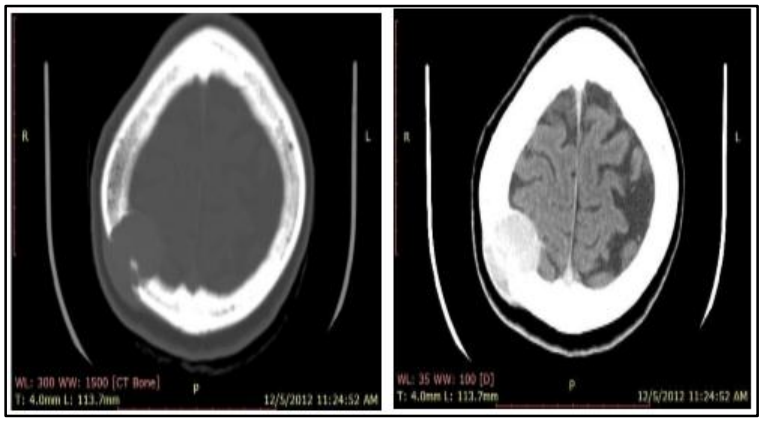

Fig. 2E Fig. 2F

CASE 3: PAPILLARY CARCINOMA OF THYROID WITH LYMPH NODE METASTASIS.

Fig. 3A-D: Longitudinal gray-scale images showing an ill-defined hypoechoic nodule with no peripheral halo in right lobe of thyroid. Transverse images showing cystic changes in Level III cervical lymph nodes on right side. FNAC proved to be papillary carcinoma of thyroid with lymph node metastasis.

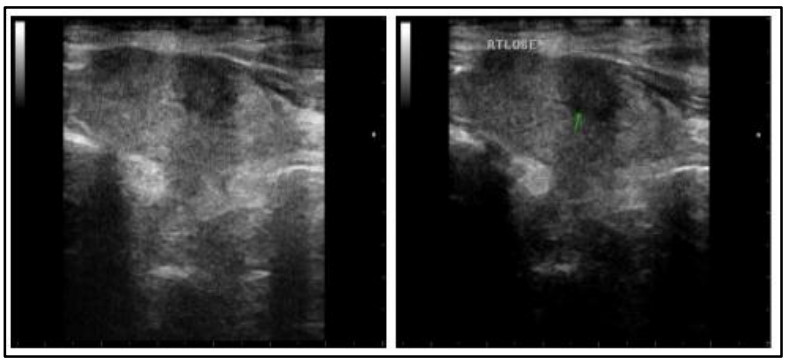

Fig. 3A Fig. 3B

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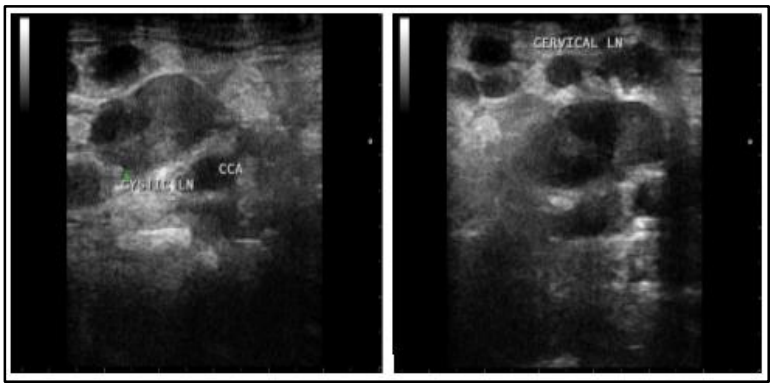

Fig. 3C **Fig. 3D**

CASE 4:

Fig. 4A-F: Papillary carcinoma in male patient with lymph node metastasis and ijv thrombus.

Longitudinal and transverse images showing a hypoechoic nodule with taller than wide shape and absent halo in right lobe of thyroid. On pulsed Doppler RI was found to be 0.59. Multiple enlarged hypoechoic rounded lymph nodes noted in level II and III bilaterally. Also note the presence of thrombus in right internal jugular vein. FNA of the lesion proved papillary carcinoma with lymph node metastasis.

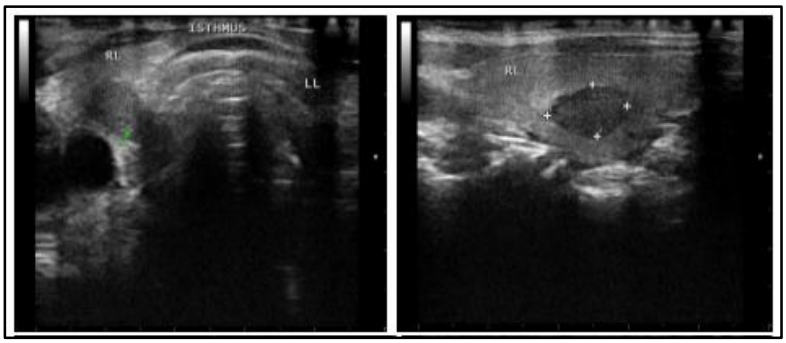

Fig. 4A **Fig. 4B**

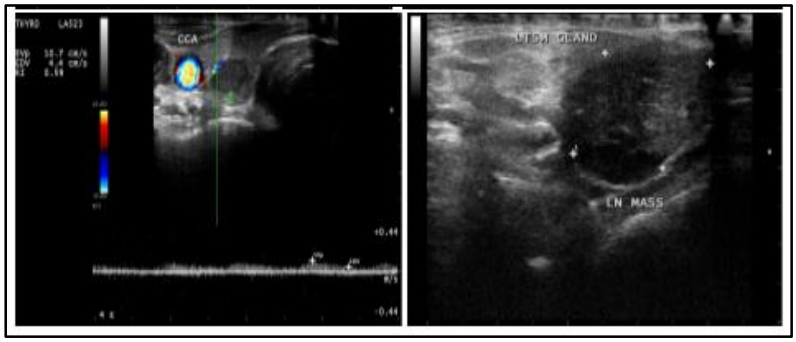

Fig. 4C **Fig. 4D**

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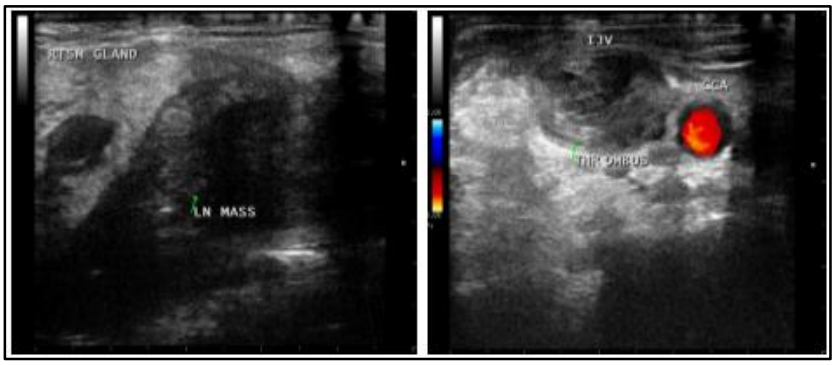

Fig. 4E **Fig. 4F**

CASE 5: ANAPLASTIC CARCINOMA:

Fig. 5A-D: Transverse and longitudinal gray-scale image showing an enlarged, irregular, heterogeneous thyroid mass with coarse internal calcifications involving right lobe. Color Doppler images showing central vascularity with high RI (0.89). Histopathology proved to be anaplastic carcinoma of thyroid.

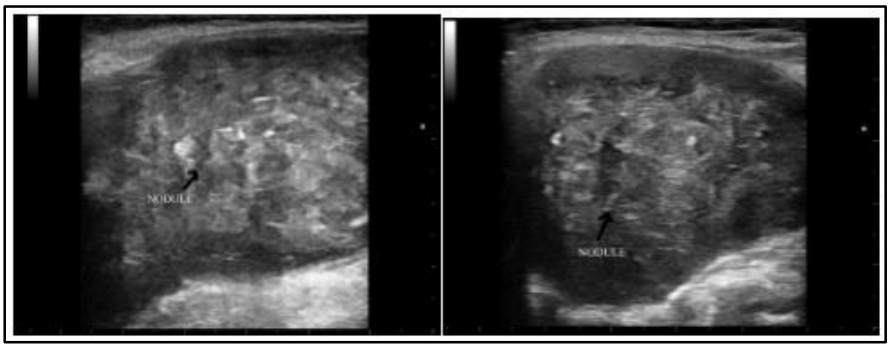

Fig. 5A **Fig. 5B**

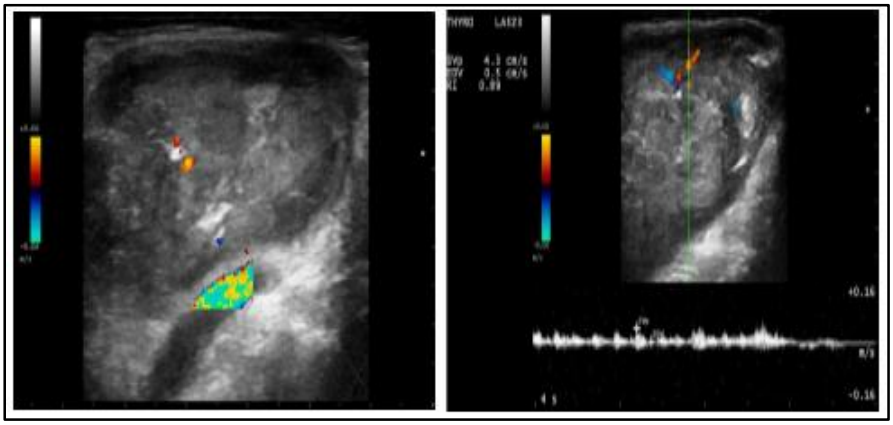

Fig. 5C **Fig. 5D**

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CASE 6: MEDULLARY CARCINOMA OF THYROID:

Fig. 6A-D: Longitudinal images showing hypoechoic nodule in the right lobe of thyroid with specks of calcifications. Color Doppler images showing central vascularity with an RI of 0.63. Histopathological examination proved it to be medullary carcinoma of thyroid.

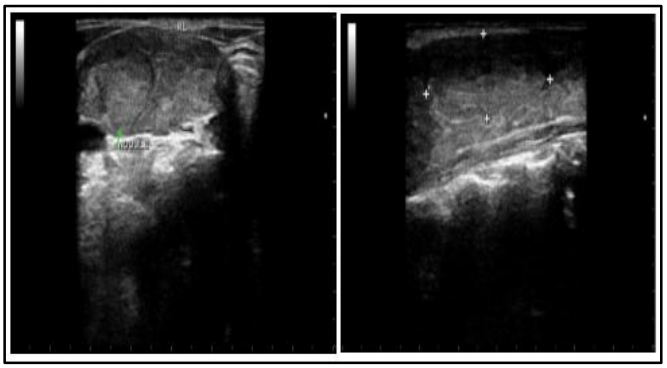

Fig. 6A **Fig. 6B**

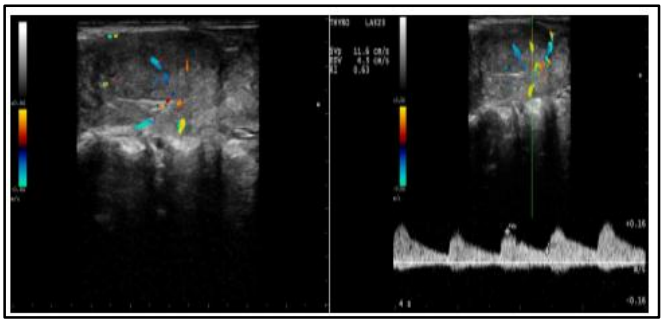

Fig. 6C **Fig. 6D**

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