

Gray Scale and Colour Doppler Sonography in the Evaluation of Follicular Neoplasms of Thyroid

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ABSTRACT

Introduction: Follicular neoplasms of the thyroid gland include benign follicular adenoma and follicular carcinoma. Currently, a follicular carcinoma cannot be distinguished from a follicular adenoma based on cytologic, sonographic, or clinical features alone.

Aim: To evaluate the gray scale and colour Doppler findings in differentiation of follicular carcinoma from follicular adenoma of thyroid.

Materials and Methods: From January 2013 through December 2013, ultrasound images of 40 patients with histopathologically proven diagnosis of follicular carcinoma and follicular adenoma were studied retrospectively. The following characteristics of each nodule were evaluated: margins, internal contents, echo texture, halo, presence and pattern of calcification, pattern of vascularity, Resistive Index (RI) of intranodular/ perinodular vessels. The frequencies of the ultrasound features were compared

by χ^2 tests. The relative risk of malignancy was determined using logistic regression analysis.

Results: Lobulated/poorly defined margins, predominantly solid composition, hypoechoic echotexture and thick incomplete or absent halo were associated with follicular carcinoma ($p < 0.05$). On colour Doppler presence of predominantly central pattern of vascularity with an RI of > 0.7 were more frequently observed in follicular carcinoma subgroup. Logistic regression analysis demonstrated that lobulated/poorly defined margins, predominantly solid contents, thick incomplete or absent halo, Central/central $>$ peripheral pattern of vascularity and Resistive Index (RI) of > 0.7 in intranodular/perinodular vessels were associated with significant increase in the relative risk of follicular carcinoma.

Conclusion: Gray scale and colour Doppler sonographic characteristics provide useful information for differentiating follicular carcinoma from follicular adenoma of thyroid.

Keywords: Cytology, Follicular adenoma, Follicular carcinoma, Imaging features

INTRODUCTION

Follicular adenoma and follicular carcinoma of the thyroid gland consists of microfollicular architecture and are tumours of follicular cell differentiation. The follicles are lined by cuboidal epithelial cells. A follicular adenoma is a benign encapsulated tumour of the thyroid gland and follicular carcinoma is the malignant counterpart of the same [1]. Adenomas represent only 5% to 10% of all nodular disease of the thyroid and are seven times more common in women than men [2]. Most adenomas are solitary, but may also develop as part of a multinodular process. Follicular carcinoma accounts for 5% to 15% of all cases of thyroid cancer, affecting women more often than men. There are two main variants—minimally invasive and widely invasive [3].

The cytologic features of follicular adenomas are generally

indistinguishable from those of follicular carcinoma. Vascular and capsular invasion are the hallmarks of follicular carcinoma, identified by histologic rather than cytologic analysis. Needle biopsy is therefore not a reliable method to distinguish between follicular carcinoma and follicular adenoma.

On sonography, to our knowledge and search of literature no unique ultrasound feature allow differentiation of follicular carcinoma from adenoma. Thus, this study aims to evaluate the role of gray scale and colour Doppler ultrasound findings in the differentiation of follicular carcinoma from follicular adenoma of thyroid.

MATERIALS AND METHODS

This retrospective study was performed in the Department of Radio-diagnosis, Mysore Medical College and Research

Institute, Mysore, India for the duration of one year between the period of January 2013 to December 2013. Total 40 patients who were referred for ultrasound with clinically detected thyroid solitary nodule were considered for the study.

Inclusion Criteria

- Adult female and male patients with clinically palpable solitary thyroid nodule.

Exclusion Criteria

- Neck swelling other than thyroid.
- Patients who don't give consent for fine needle aspiration cytology.
- Patients with bleeding diathesis.

The study was performed with the approval of our institutional review board. Fine Needle Aspiration (FNA) and histopathological examinations were performed with informed consent of the patient.

A structured pre-prepared case proforma was used to enter the relevant patient details, clinical history and physical examination findings. The ultrasound examination of the thyroid gland was performed in gray scale and colour Doppler modes using a high resolution, 7.5 – 12 MHz, linear array transducer of GE VOLUSON and ESOATE MYLAB 40 ultrasound scanners.

The lesions were characterized into follicular adenoma or carcinoma considering the following gray scale and colour Doppler findings: margins, internal contents, echotexture, halo, presence and pattern of calcification, pattern of vascularity, RI of intranodular/perinodular vessels.

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, was classified by its thickness. Halo thickness of < 2mm is considered as thin hallow and thickness > 2mm has thick halo. The halo thickness was included in the measurement of nodules. The echogenicity was assessed as hypoechoic, hyperechoic, and isoechoic in comparison to normal thyroid parenchyma. Based on their composition the nodules were categorized as solid, predominantly solid (<50% cystic), predominantly cystic (>50%) or cystic. The presence of calcification, as well as type of calcification whether micro or macro calcification was noted. Micro-calcifications were defined as tiny, hyperechoic foci (<1 to 2 mm in size) with or without posterior shadowing and no posterior reverberation. Macro-calcifications were defined as >2 mm in diameter with posterior shadowing. The pattern of vascularity was assessed with calculation of RI. A cut off value of 0.7 was used for RI of intranodular/perinodular vessels to discriminate between follicular neoplasms.

Histopathologic Evaluation: All the nodules had undergone ultrasound guided FNA followed by surgical excision. Tissue diagnosis by histopathological examination was made in all the forty cases. The histopathological results were considered as the final diagnosis. The ultrasound diagnoses were then compared with the histopathological results.

STATISTICAL ANALYSIS

The frequencies of the sonographic features were compared by χ^2 tests. The relative risk of malignancy was determined using logistic regression analysis. All the above analysis was performed with the use of SPSS v 12 software (SPSS for windows, USA).

RESULTS

In this study, 8 patients (20%) were male and 32 patients [80%] were females (p value >0.05). The maximum number of patients were in the age group of 41-60 years (62%) and the least were in the age group of 61-80 years (8%) (p value < 0.05).

Out of the 40 nodules, 22 were follicular adenoma and 18 were follicular carcinoma on histopathological examination. No case of Hurthle cell variant of follicular carcinoma was encountered. The median patient age in the adenoma and carcinoma groups were 40 years and 42.5 years respectively.

The significance of ultrasound characteristics in the differentiation of follicular adenomas from follicular carcinomas is presented in [Table/Fig-1].

[Table/Fig-2] depicts the diagnostic accuracy of ultrasound findings for follicular carcinomas.

[Table/Fig-3] shows the results of univariate logistic regression analysis for prediction of follicular carcinoma.

The ultrasound features of lobulated/poorly defined margins, predominantly solid composition, hypoechoic echotexture, thick incomplete/absent halo, central/central >peripheral pattern of vascularity and RI of > 0.7 in intranodular/perinodular vessels were more frequently seen in follicular carcinoma group than adenoma and were individually statistically significant (p value < 0.05) for detection of carcinoma. The presence and pattern of calcifications was not found to be statistically significant in the present study (p-value >0.05) [Table/Fig-1].

The ultrasound findings of lobulated/poorly defined margins and hypoechoic echotexture had high specificities of 95.4% and 100% respectively. The positive predictive values (PPV) were 88.8 % and 100% respectively. The diagnostic accuracy was 75%. A predominantly solid composition of the nodule and thick incomplete or absent halo, had high sensitivities of 77.7% and 88.8% respectively. Diagnostic accuracies were 65% and 85% respectively. The pattern of colour Doppler finding of central/ central > peripheral pattern of vascularity

Characteristics	Follicular Adenoma (22)	Follicular Carcinoma (18)	p Value
Age			< 0.05
< 45 Yrs	16(72.7)	06(33.3)	
>45 Yrs	06(27.3)	12(66.6)	
Sex			> 0.05
Female	16(72.7)	16(88.8)	
Male	06(27.3)	02(11.2)	
Margins			< 0.05
Well Defined	21(100)	10(55.5)	
Lobulated/Poorly Defined	01(2.5)	08(44.4)	
Internal Contents			< 0.05
Solid	10(45.4)	14(77.7)	
Predominantly Solid	12(54.5)	04(22.2)	
Echotexture			< 0.05
Hyperechoic	18(81.8)	-	
Hypoechoic	-	12(66.6)	
Heterogenous	04(18.2)	06(33.3)	> 0.05
Halo			< 0.05
Thin	14(63.6)	02(11.2)	
Thick Incomplete and Absent	08(36.3)	16(88.8)	
Calcification			> 0.05
Absent	16(72.7)	12(66.6%)	
Microcalcification	-	06(33.3%)	
Macrocalcification	06(27.3)	-	
Vascularity			< 0.05
Central	08(36.3)	14(77.7)	
Peripheral	14(63.6)	04(22.2)	
RI			< 0.05
<0.7	12(54.5)	04(22.2)	
>0.7	10(45.4)	14(77.7)	

[Table/Fig-1]: Significance of ultrasound and colour doppler characteristics in differentiation of follicular adenomas from carcinomas.

Note:-Numbers in parentheses indicates percentages.
The p value of < 0.05 indicates significance.

had a specificity of 77.7% with a diagnostic accuracy of 75%. Considering a cut off value of 0.7 for RI of intranodular /perinodular vessels to discriminate between follicular neoplasms, specificity was 77.7% with diagnostic accuracy of 65% [Table/Fig-2].

Using univariate logistic regression analysis, the ultrasound features of lobulated/poorly defined margins, predominantly solid contents, thick incomplete or absent halo, central/central > peripheral pattern of vascularity and RI of > 0.7 in intranodular /perinodular vessels were individually associated with significant increase in the relative risk of follicular carcinoma (odds ratios, 17.6, 4.2, 14, 6.1 and 4.2 respectively; p < 0.05) [Table/Fig-3].

Predictor	Odds Ratio
Margins	17.6 (1.84-153.3)
Internal Contents	4.2 (1.04-16.9)
Echogenicity	2.2 (0.5 -9.7)
Halo	14 (2.5 -77.2)
Calcifications	1.3 (0.3 -5.2)
Pattern Of Vascularity	6.1 (1.5 -25.1)
RI > 0.7	4.2 (1.04 -16.9)

[Table/Fig-3]: Results of univariate logistic regression analysis for prediction of follicular carcinoma.

Note:-Numbers in parentheses indicates range of odds ratio.

DISCUSSION

The diagnostic evaluation of a patient who presents with a thyroid nodule consists of a fine needle aspiration biopsy, ultrasound examination of the neck, and a screening serum TSH level. Fine needle aspiration biopsy remains the most important diagnostic modality for the evaluation of thyroid nodules. However, inability to distinguish a follicular adenoma from a follicular carcinoma is a major limitation of fine needle aspiration biopsy.

Thyroid adenomatous nodule, follicular adenoma, follicular carcinoma, and follicular variant of papillary thyroid carcinoma show follicular morphologic features [4]. The benign follicular adenoma is a true thyroid neoplasm, characterized by a fibrous encapsulation and compression of adjacent tissues. Various subtypes of follicular adenoma include the foetal

	Sensitivity	Specificity	PPV	NPV	Accuracy
Lobulated/Poorly Defined Margins	08/18 (44.4%)	21/22 (95.4%)	08/09 (88.8%)	22/31 (70.9%)	30/40 (75%)
Predominant Solid Composition	14/18 (77.7%)	12/22 (54.5%)	14/24 (58.3%)	12/16 (75%)	26/40 (65%)
Thick Incomplete Halo/ Absent	16/18 (88.8%)	14/22 (63.6%)	16 /24 (66.5%)	14/16 (87.5%)	34/40 (85%)
Hypoechoic Echotexture	12/18 (66.6%)	22/22 (100%)	12/12 (100%)	22/28 (78.5%)	30/40 (75%)
Central and Central > Perinodular Vascularity	14/18 (77.7%)	14/22 (63.6%)	14/22 (63.6%)	14/18 (77.7%)	28/40 (70.0%)
RI > 0.7	14/18 (77.7%)	12/22 (54.5%)	14 /24 (58.33%)	12/16 (75%)	26/40 (65%)

[Table/Fig-2]: Diagnostic accuracy of ultrasound and colour doppler findings for diagnosis of follicular carcinoma.

adenoma, Hürthle cell adenoma, and embryonal adenoma, each distinguished according to the type of cell proliferation.

A follicular carcinoma cannot be distinguished from a follicular adenoma based on cytologic features alone. It is distinguished from a follicular adenoma on the basis of capsular invasion, vascular invasion, extra thyroidal tumour extension, lymph node metastases, or systemic metastases [5].

Fine needle aspiration biopsy in patients with a follicular adenoma and patients with a follicular carcinoma is characterized by abundant follicular epithelial cells in sheets with crowding and overlapping of cells, microfollicle formation, and scant or no colloid [6]. According to the Bethesda system for reporting thyroid cytopathology, this cytologic appearance is classified as follicular neoplasm or suspicious for follicular neoplasm and has a 15%–30% risk of malignancy [7].

All patients with nodular thyroid disease should have a serum TSH level measured to evaluate the functional status of the thyroid gland. "Toxic adenoma" may have a low serum TSH level. In patients with a fine needle aspiration biopsy consistent with a follicular neoplasm, the incidence of malignancy with hypo functioning nodule is 20% compared with 1% with a hyper functioning nodule [8].

An ultrasound examination of the thyroid gland is recommended in all patients with a thyroid nodule to help characterize the nodule as well as to examine the rest of the thyroid gland for other nodules. On sonography, several gray scale and colour Doppler features have been described to distinguish follicular adenomas from carcinomas. However none of the ultrasound features can serve as an absolute criterion of the benign character of a thyroid nodule.

Sillery et al., retrospectively evaluated sonography of thyroid follicular neoplasms for features that would aid in distinguishing follicular adenoma from follicular carcinoma and for any imaging features that distinguish the classic follicular carcinoma from Hürthle cell variant of follicular carcinoma. They concluded that larger lesion size, lack of a sonographic halo, hypoechoic appearance, and absence of cystic change favoured a follicular carcinoma diagnosis but the sonographic features of follicular adenoma and follicular carcinoma are very similar. Malignancy is associated with increased patient age and male sex. Within the follicular carcinoma subgroup, nodules having a heterogeneous appearance and lacking internal calcifications is more often seen in older patients with Hürthle cell variant of follicular carcinoma [9].

In the present study, 40 nodules were studied out of which 22 were follicular adenoma and 18 were follicular carcinoma on histopathological examination. There was female preponderance in both the groups which was in good correlation with previous studies. The ultrasound features of lobulated/poorly defined margins, predominantly solid

composition, hypoechoic echotexture and thick incomplete /absent halo were individually statistically significant for depiction of a follicular carcinoma.

The present study correlated well with the study of Sillery et al., who found that hypoechoic appearance, absence of halo, absence of cystic change, greater patient age, size and male sex were more frequently associated with follicular thyroid cancer than with benign adenoma [9].

Zhang and Hu conducted a retrospective study to determine the sonographic features of thyroid follicular carcinoma in comparison with thyroid follicular adenoma. They found that nodules of follicular carcinoma were associated with predominantly solid contents, hypoechoic echogenicity, a heterogeneous echo texture, presence of calcifications and an absent or irregular thick halo ($p < 0.05$). Logistic regression analysis demonstrated significant increase in the relative risk of follicular carcinoma in nodules with predominantly solid contents, a heterogeneous echotexture, and the presence of calcifications. They concluded that sonography could provide useful information for differentiating follicular carcinoma from follicular adenoma [10].

Zhang et al., study was in good correlation with the present study in which the ultrasound features of lobulated/poorly defined margins, predominantly solid composition, hypoechoic echotexture and thick incomplete /absent halo were found to be individually statistically significant for depiction of a follicular carcinoma [10].

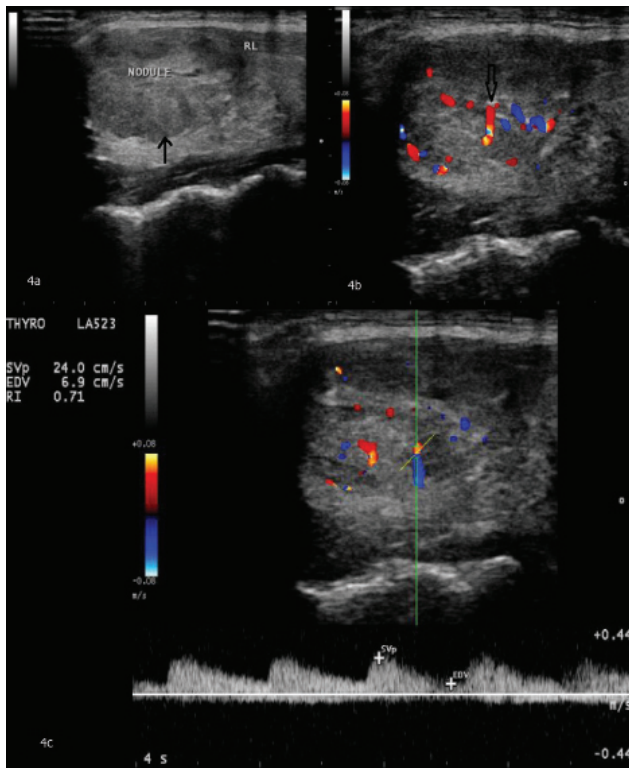
However, Zhang and Hu also found a heterogeneous echo texture and the presence of calcifications were also associated with follicular carcinoma ($p < 0.05$), which were not found to be significant in our study [10].

In the present study, lobulated/poorly defined margins and hypoechoic echotexture had high specificity and PPV which correlated with the study by Zhang and Hu. Likewise predominantly solid composition and thick incomplete /absent halo had high sensitivity which again correlated well with study by Zhang and Hu. The combined overall diagnostic accuracy of these four ultrasound features was found to be in the range of 65 to 85 %. This again correlated well with study of Zhang and Hu who found the diagnostic accuracy in the range of 80.4 to 100% [10].

Seo et al., conducted retrospective study to differentiate thyroid follicular adenoma and follicular carcinoma using ultrasound. They found that follicular carcinoma was associated with iso- to hypo-echoic echogenicity, predominantly solid or mixed echotexture, and presence of micro calcifications or rim calcifications ($p < 0.05$). Logistic regression analysis demonstrated significant increases in relative risk for follicular carcinoma in nodules with predominantly solid or mixed echotexture and micro calcifications or rim calcifications (odds

ratio 8.1 and odds ratio 13.5, respectively, $p < 0.01$). They concluded that the ultrasound features of iso- to hypo-echoic echogenicity, predominantly solid or mixed echotexture, and microcalcifications or rim calcifications are more common in follicular carcinoma than in follicular adenoma [11].

These findings were in good correlation with present study in which the ultrasound features of predominantly solid composition and hypoechoic echotexture were more commonly seen in follicular carcinoma. However presence of microcalcifications was not found to be associated with follicular carcinoma as was noted in study by Seo et al., [11] [Table/Fig-4a-c].



[Table/Fig-4a-c]: Longitudinal and transverse gray-scale images showing a solid hypoechoic nodule with incomplete peripheral halo (4a) in the right lobe of thyroid. No evidence of cystic areas. On colour Doppler, the lesion shows central > peripheral flow pattern of vascularity (4b). RI of intranodular vessel was found to be 0.71 (4c). The lesion was excised and histopathological examination confirmed the diagnosis of follicular carcinoma.

Gulcelik et al., in 2008 conducted prospective study to identify clinical and ultrasonographic features that may help in predicting malignant tumours in patients with a diagnosis of follicular neoplasm on findings from fine-needle aspiration cytology. They found that ultrasound features of solid echotexture, microcalcifications, and a hypoechoic pattern were predictive for malignant neoplasms. The highest sensitivity was associated with the presence of a solid nodule

variable (88.5%), and the highest specificity was the presence of microcalcifications (94.4%). The combination of the three ultrasonographic features (solid echotexture, hypoechoic pattern, and microcalcifications) resulted in a sensitivity of 95.0% and a specificity of 98.6%. In patients with follicular neoplasm cytologic findings, older age, male sex, solitary nodule, and larger nodule size were not predictive for malignant neoplasms [12].

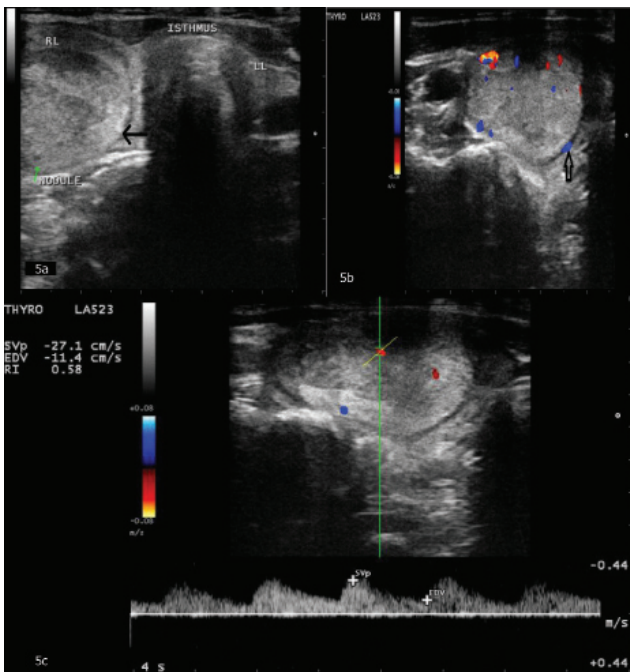
This again correlated well with the present study in which specificity for predominantly solid composition was 77.7% and specificity for hypoechoic pattern was 100%. However presence of microcalcifications was not found to be predictive for malignant neoplasms in our study.

lared et al., in 2010 conducted a systematic review and meta-analysis in predicting malignancy in thyroid follicular neoplasms using the diagnostic accuracy of colour Doppler ultrasound. They concluded that malignancy of thyroid follicular neoplasms is associated with a predominant internal flow seen on colour Doppler ultrasound. A low probability of thyroid follicular malignancy is associated with absence of internal flow or predominantly peripheral flow [13].

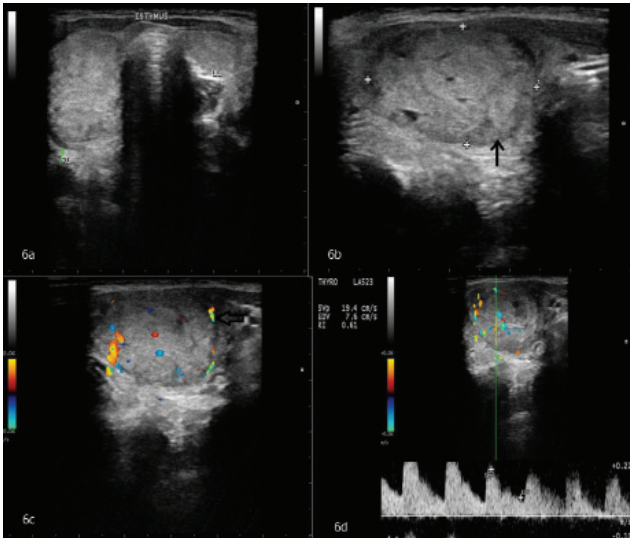
De Nicola et al., in 2005 evaluated to distinguish benign from malignant thyroid follicular neoplasms using flow pattern and RI as parameters. They concluded that in follicular neoplasms, there were significant positive associations between predominantly peripheral flow and benign disease and between predominantly central flow and malignancy ($p < .0001$, Fisher exact test). However, 20% of malignant nodules had predominantly peripheral flow and power Doppler characteristics could not be used to rule out malignancy. For predicting malignancy, an RI cut off of 0.75 had good accuracy, specificity, and negative predictive value but had low sensitivity and positive predictive value (respectively, 91%, 97%, 92%, 40%, and 67%). Malignant nodules and adenomas had higher resistive index values than non-neoplastic nodules ($p < 0.001$, χ^2 test) [14] [Table/Fig-5,6].

In the present study, central/ central > peripheral pattern of vascularity and RI of > 0.7 in intranodular /perinodular vessels were more frequently seen in follicular carcinoma group than adenoma and were individually statistically significant for detection of carcinoma. This correlated well with the study by De Nicola et al., who found that there were significant positive associations between predominantly peripheral flow and benign disease and between predominantly central flow and malignancy ($p < 0.0001$ Fisher exact test).

In the present study, a cut off value of 0.7 was used for RI of intranodular /perinodular vessels to discriminate between follicular neoplasms. This achieved a good specificity and diagnostic accuracy which correlated well with the study of De Nicola et al., [14].



[Table/Fig-5a-c]: Longitudinal and transverse gray-scale images showing a well-defined solid hyperechoic nodule with thin peripheral halo (5a) in right lobe of thyroid. Transverse colour Doppler image shows predominantly peripheral vascularity (5b) with an RI of 0.58 (5c). Histopathological examination confirmed follicular adenoma.



[Table/Fig-6a-d]: Longitudinal and transverse gray-scale images showing a solid hyperechoic nodule with thin peripheral halo in the right lobe of thyroid (6a,6b). Few cystic areas noted within. On colour Doppler, the lesion shows peripheral > central flow pattern of vascularity (6c). RI of perinodular vessel was found to be 0.61 (6d). All the features were consistent with follicular adenoma. The lesion was excised and histopathological examination revealed micro invasive follicular carcinoma.

However, there are a few limitations in our study. First, this study was in a retrospective design. Selection bias may have existed in patient inclusion. Secondly presence of

microcalcifications was not found to be statistically significant which is in contradiction to the previous studies. This can be attributed to small sample size. Large scale prospective study on a large number of patients is required to strengthen the current criteria of follicular malignancy.

CONCLUSION

The presence of gray scale ultrasound features of lobulated/poorly defined margins, predominantly solid composition, hypoechoic echotexture and thick incomplete /absent halo were individually statistically significant for depiction of a follicular carcinoma. On colour Doppler, central/central > peripheral pattern of vascularity and RI of > 0.7 in intranodular/perinodular vessels were more frequently seen in follicular carcinoma group than adenoma and were individually statistically significant for carcinoma. Thyroid ultrasound achieves a good overall diagnostic accuracy for differentiating follicular adenoma from carcinoma.

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