Section: Radiology

Original Research Article

ROLE OF GRAY SCALE, COLOR DOPPLER AND SPECTRAL DOPPLER IN DIFFERENTIATION BETWEEN MALIGNANT AND BENIGN THYROID NODULES

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Abstract

Background: Thyroid nodules are common and occur in up to 50% of the normal adult population. Ultrasound evaluation has the advantages of being able to characterize the presenting nodule, evaluate the rest of the thyroid for other non palpable nodules (often multiple) and can be used to guide percutaneous biopsies. Present study was aimed to establish the specific gray scale and doppler characteristics in differentiating malignant from benign thyroid nodules. **Material and Methods:** Present study was single-center, prospective case control study, conducted patients with clinically palpable / nonpalpable thyroid nodules irrespective of size, had either ultrasound guided fine needle aspiration cytology (FNAC) or surgico pathological confirmation. **Results:** In present study mean patient age was 41.5 ± 9.65 and 49.3 ± 10.4 years in patients with benign and malignant nodules, respectively. Majority were females (n=147) as compared to males (n=47). A solitary nodule was found in 90 and multi-nodular goiter was found in 104 of 194 cases. Majority of malignant lesions were correctly diagnosed by gray scale characteristics (n=36). Majority of malignant lesions were correctly diagnosed by color doppler ultrasonography (n=41). Among the RI values > 0.73, seen in malignant thyroid nodules. (76.77 %) **Conclusion:** The specific malignant features on ultrasound include microcalcifications, hypoechogenicity, taller than wide, irregular thick halo, lymphadenopathy and local extra thyroidal invasion.

INTRODUCTION

Thyroid nodules are common and occur in up to 50% of the normal adult population.[1]Thyroid nodules are more prevalent with increasing age, but the majority of these nodules are undetectable by physical examination.[2]However, only 7% of the thyroid nodules are malignant, it is critical that they are accurately identified.[3] Palpable nodules occur in 4% to 7% of the population; however, high-resolution ultrasonography (US) reveals nodules as small as 2 mm in 35% to 67% of the general population.[4,5,6]

High resolution ultrasound (US) is the most sensitive imaging test available for the examination of the thyroid gland, to detect the thyroid lesions, accurately calculate their dimensions, identify the internal structure and vascularization and evaluate diffuse changes in thyroid parenchyma which could not be evaluated with CT or MRI. CT and MRI are more helpful for extra thyroid lymphadenopathy, local infiltration, mediastinal extension and retro tracheal extension.

Ultrasound evaluation has the advantages of being able to characterize the presenting nodule, evaluate the rest of the thyroid for other non palpable nodules (often multiple) and can be used to guide percutaneous biopsies.[7,8]US is also important in preoperative planning, being able to provide an early demonstration of local invasion and lymph node involvement. Present study was aimed to establish the specific gray scale and doppler characteristics in differentiating malignant from benign thyroid nodules.

MATERIAL AND METHODS

Present study was single-centre, prospective case control study, conducted in department of Radiodiagnosis and Imaging, K J Somaiya Medical

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College, Mumbai, India. Study duration was of 2 years. Study approval was obtained from institutional ethical committee.

Inclusion Criteria

- Patients with clinically palpable / nonpalpable thyroid nodules irrespective of size, had either ultrasound guided fine needle aspiration cytology (FNAC) or surgicopathological confirmation, willing to participate in present study

Exclusion Criteria

- Patients received any treatment which affect thyroid status (like antithyroid drugs),
- Patients with undetermined, inadequate, or suspicious malignant cytology from FNAC
- Patients underwent FNAC before ultrasound

Study was explained to patients in local language & written consent was taken for participation & study. Information regarding name, age, sex, inpatient number, associated risk factors like family history and h/o irradiation, clinical symptoms of the patients and clinical diagnosis were obtained from all subjects by standard questionnaire and medical records. After collecting the above data, patients were subjected to both gray scale and doppler imaging of the thyroid lesions after obtaining the informed consent.

The equipments used were: HS 70 with probe frequency 6-12 MHz. Both lobes of thyroid with isthmus were evaluated in succession for thyroid nodules, initially with gray scale and then color and spectral Doppler. RI and pulsatility index (PI) values were calculated from the arteries of thyroid nodules (either central or peripheral) by standard software of equipment.

US-Guided Fine Needle Aspiration was performed & slides were interpreted by an experienced cyto-pathologist who was blinded to the USG findings. The final pathological diagnosis for each nodule was made by reports of US-guided FNAC or surgical pathological examination (if available) to categorize all nodules as benign or malignant.

Ultrasound criteria were divided into major and minor criteria for the diagnosis of malignant nodules. The major criterias were hypoechoic nodule, solid nodule, incomplete halo, illdefined borders, microcalcifications, lymphnode enlargement with loss of fatty hilum, local infiltration, intranodular vascularity and high RI and PI (>0.73 and 1.3). The minor criteria were taller than wide nodule, no halo, mixed echogenicity, macrocalcifications and mixed vascularity. Finally, a radiologist without knowledge of the clinical outcome independently reviewed each set of US images. The contribution of the physical examination, US findings, and FNAC results of all nodules to the final diagnoses were evaluated statistically.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.05 was considered as statistically significant.

RESULTS

In present study mean patient age was 41.5 ± 9.65 and 49.3 ± 10.4 years in patients with benign and malignant nodules, respectively. Majority were females (n=147) as compared to males (n=47) Overall nodule diameter ranged from 4-67 mm in the greatest dimension (mean: 27.04 ± 11.5 mm). Cyto-pathological results were similar in both sexes and different age groups ($p > 0.05$).

Table 1: Demographic details (age and sex) of the thyroid nodules in current study.

Cytology	Number of nodules	Sex ratio (Female / Male)	Mean age ± SD
Benign	151	118/33	41 ± 9.65
Malignant	43	29/14	49 ± 10.4
Total	194	147/47	45.78 ± 9.9

A solitary nodule was found in 90 and multi-nodular goiter was found in 104 of 194 cases. No correlation was found between the cyto-pathological results and the number of nodules ($p > 0.05$). Mean nodule diameter was 25.7 +/- 6.5mm in benign nodules and 33.6+/- 4.8 mm in malignant nodules. Significant relationship was observed between malignancy and irregular margins, microcalcifications, hypoechogenicity, taller than wide, lymphnode enlargement with loss of fatty hilum and local infiltration ($P < 0.05$). Most of the thyroid nodules had solid contents which were seen in both benign and malignant nodules with insignificant p value. Majority of the cystic thyroid nodules were benign in nature(Fig 1). Most of the isoechoic and hyperechoic nodules were seen in benign thyroid nodules. Hypoechoic nodules were most commonly seen in malignant nodules with a six-fold increase for malignancy than iso-hyperechoic nodules (Fig 2 and 3).

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Table 2: Comparison of B mode ultrasonographic findings of benign and malignant study:

Nodule features	Benign (151)	Malignant (43)	P value
Solitary nodule	90(46.39%)	103(53.61%)	0.0766
Mean diameter	25.7+/-11.06	33.6+/-9.09	0.0455
Solid nodule	93(67%)	31(33%)	0.172
Hypoechogenicity	31(45.58%)	37(54.42%)	0.0001
Incomplete halo	6(31.68%)	13(68.42%)	0.001
Irregular borders	26(49.06%)	27(50.94%)	0.012
Taller than wide	61(61%)	39(39%)	0.003
Microcalcifications	0	12%(100%)	<0.05
Lymphadenopathy with loss of fatty hilum	0	17(100%)	<0.05
Local invasion	0	1(100%)	<0.05

Figure 1: shows a well-defined anechoic cystic nodule in the left lobe of the thyroid gland. On FNAC, it was confirmed to be adenomatous goitre with secondary colloid degeneration.

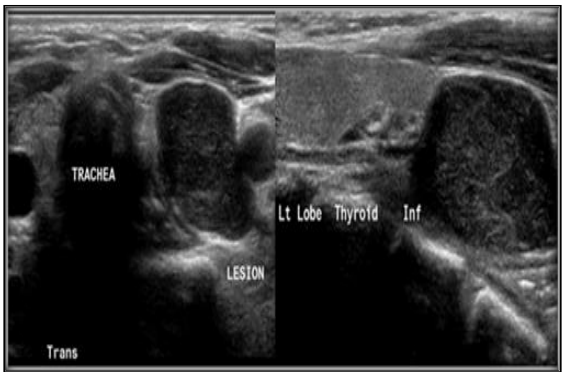

Figure 2: shows a well defined hypoechoic solid nodule in the left lobe of the thyroid gland. On FNAC, it was confirmed to be medullary carcinoma.

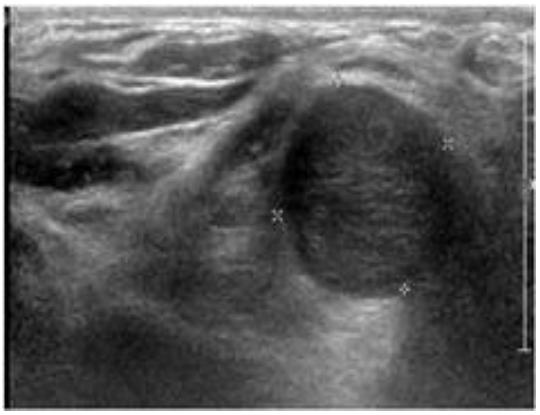

Figure 3: shows a well defined hypoechoic nodule in the right lobe of the thyroid gland. On FNAC, it was confirmed to be medullary carcinoma.

Absence of halo was seen in both malignant and benign thyroid nodules with insignificant p value. Presence of halo was seen in majority of the benign nodules which showed a significant p value in differentiating benign malignant nodules(Fig 4). Thick irregular halo was one of the specific features of malignant nodules which were not mentioned elaborately on literature(Fig 5). Significant numbers of the malignant nodules were taller than wide due to increase in the nutrient supply to tumor tissue which was a significant criterion in differentiating malignant from benign nodules. All cases of microcalcifications were seen in papillary carcinoma with 100% specificity(Fig 6). Barring few cases of papillary and medullary carcinoma, majority of the macrocalcifications were seen in benign thyroid nodules (Adenomatous nodules) and showed insignificant p value(Fig 7). Local invasion was a very specific ancillary criterion of malignant thyroid lesions in differentiating benign and malignant thyroid nodules, but the incidence was very less. Lymphadenopathy with loss of fatty hilum was seen only in malignant thyroid nodules majority of them are seen in papillary carcinoma (Fig 8).

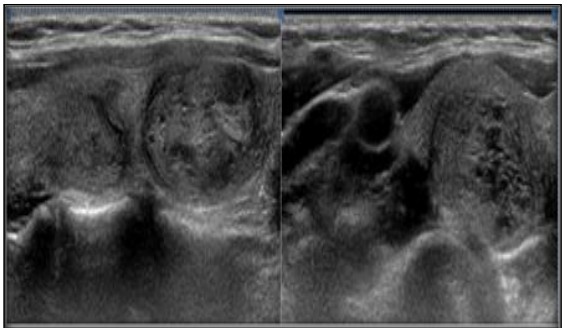

Figure 4: shows a well defined isoechoic nodule with smooth complete halo in the right lobe of the thyroid gland. On FNAC, it was confirmed to be adenomatous goitre with secondary spongiform type of degeneration.

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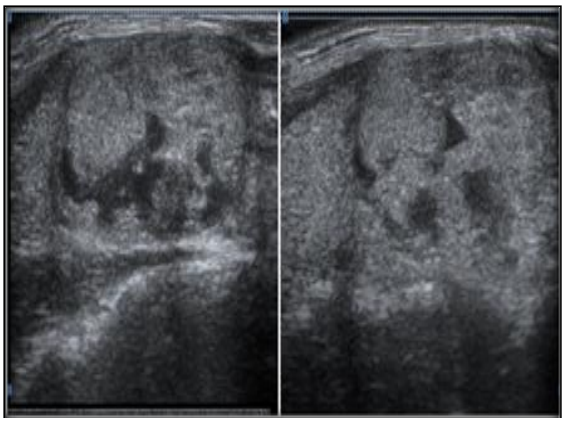

Figure 5: shows ill defined isoechoic nodule with thick irregular halo in the right lobe of the thyroid gland. On FNAC, it was confirmed to be follicular carcinoma

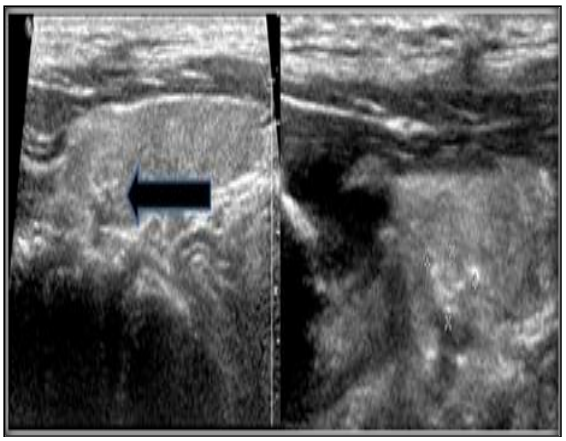

Figure 6: shows multiple ill defined foci of microcalcifications (black arrow) and the patient presented with neck swelling. FNAC was confirmed as an occult papillary carcinoma where lymphadenopathy and microcalcifications are the only findings.

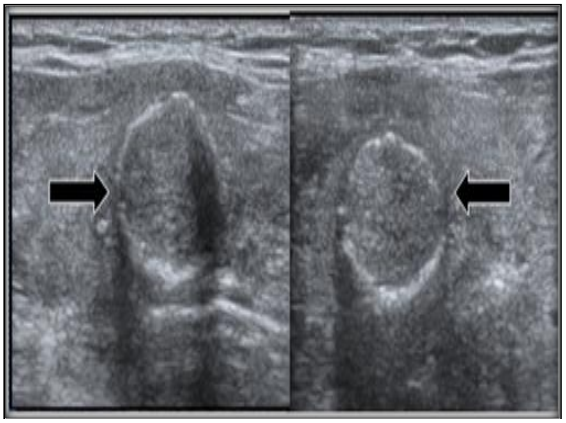

Figure 7: Shows well defined isoechoic nodule with peripheral egg shell type of macrocalcifications (black arrows). FNAC was confirmed as adenomatous goitre

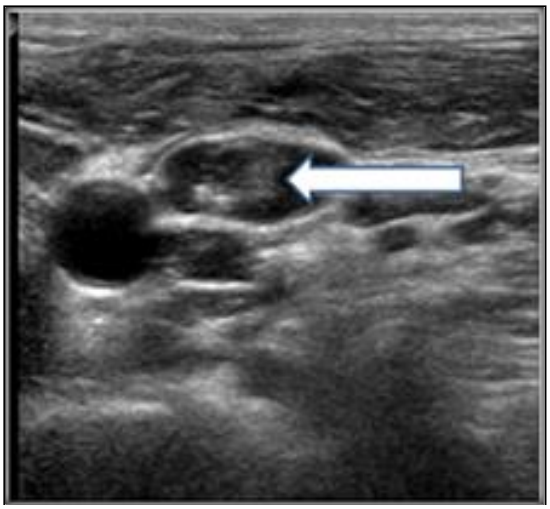

Figure 8: shows well defined hypoechoic enlarged lymphnode with loss of fatty hilum and foci of microcalcifications. FNAC of the lymphnode was considered to be a metastatic deposit from the papillary carcinoma with cystic degeneration.

Based upon the gray scale characteristics, the nodules were classified into benign and malignant. Majority of malignant lesions were correctly diagnosed by gray scale characteristics (n=36).

Table 3: Comparison of the gray scale USG with histopathology confirmed nodules (HX)

Gray Scale Characteristics	HX confirmed Malignant	HX confirmed Benign	Total
Malignant	36	20	56
Benign	7	131	138

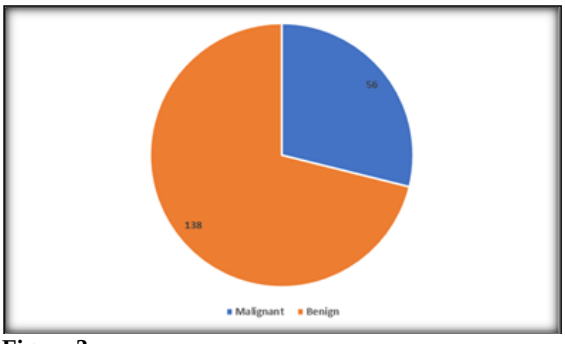

Figure 3

Of the 194 nodules, 121 nodules showed perinodular flow, 37 nodules showed intranodular flow and 33 cases showed both intranodular and perinodular flow. 3 nodules showed no vascularity. Of the 33 nodules with both intranodular and perinodular flow, 28 nodules were benign and 5 nodules were malignant. Of the 36 malignant nodules with intranodular vascularity, 19 nodules were papillary carcinoma, 9 nodules were follicular carcinoma, 7 nodules were medullary carcinoma and 1 nodule was metastases. Only one benign nodule showed intranodular vascularity. Intranodular vascularity was one of the specific

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finding for malignant nodules in differentiating benign and malignant thyroid nodules(Fig 9).

Table 4: Distribution of vascular patterns among benign and malignant thyroid nodules

Flow type	Benign	Malignant	Total
Central	1(0.66%)	36 (83.72%)	37
Peripheral	119 (78.83%)	2 (4.65%)	121
Mixed	28 (18.5%)	5 (11.62%)	33
No flow	3 (1.9%)	0	3
Total	151	43	194

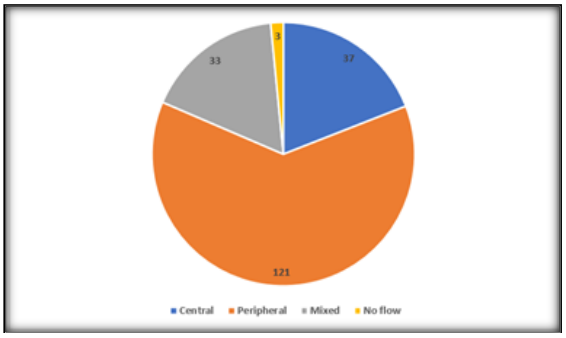

Figure 4

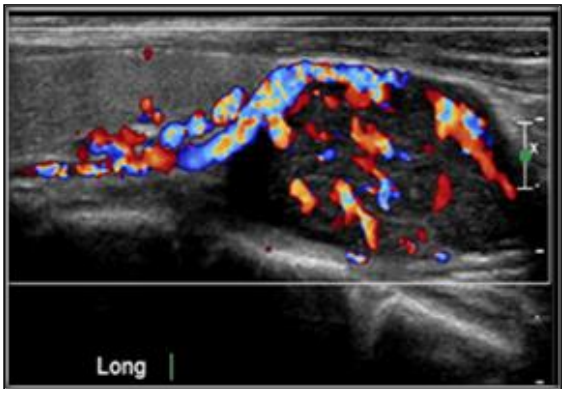

Figure 9: On color doppler shows a well defined hypoechoic nodule showing internal vascularity. On FNAC, it was malignant thyroid nodule (medullary carcinoma).

Based upon the color doppler characteristics, the nodules were classified into benign and malignant. Majority of malignant lesions were correctly diagnosed by color doppler ultrasonography (n=41).

Table 5: Comparison of color doppler ultrasonography with histopathology confirmed nodules.

Color doppler	Malignant (HX)	Benign (HX)	Total
Malignant	41 (TP)	29 (FP)	70
Benign	2 (FN)	119(TN)	121
Total	43	148	191

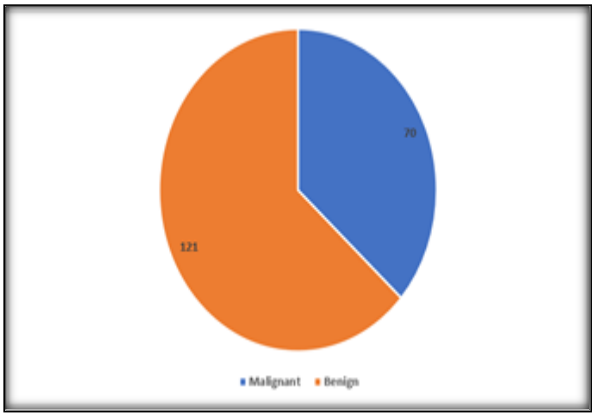

Figure: 5

In spectral doppler, RI values greater than 0.73 were considered malignant and less than 0.73 were considered benign. PI values greater than 1.3 were considered malignant and less than 1.3 was considered benign(Fig 10 and 11) . Among the RI values > 0.73, about 33 cases accounting to 76.77 % were seen in malignant thyroid nodules. The rest 22 cases accounting to 25% belong to the benign thyroid nodules. In the present study, RI values less than 0.73, were seen in 23.23 % of the malignant nodules and 85.14 % of the benign thyroid nodules. In the present study, PI values > 1.3 were seen in 26 malignant cases (42%). The rest 36 cases were seen in benign nodules (58%). In current study, PI values less than 1.3 were seen in 16 malignant cases (12%). The rest 116 cases were seen in benign nodules (88 %).

Table 6: Frequency of benign and malignant nodules detected by RI & PI values.

	Malignant	Benign
RI		
> 0.73	33(76.77%)	22(24.86%)
< 0.73	10(23.23 %)	126(85.14%)
PI		
> 1.3	26(42%)	36(58%)
< 1.3	16(12%)	116(88%)

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Table 8: Accuracy of gray scale, color, spectral doppler and the combined sonography

Modality	Sensitivity	Specificity	PPV	NPV	Accuracy
Gray	83.72%	86.75%	64.28%	94.9%	86.08%
COL	95.34%	80.4%	58.57%	98.34 %	83.76 %
SPE	76.78%	81.7%	55%	92.36%	80.62%
GR+DOP	94.59 %	88.9%	68.62%	98.47%	90.10 %

GR: Gray scale, COL: colour doppler, SPE: spectral doppler, DOP: Doppler.

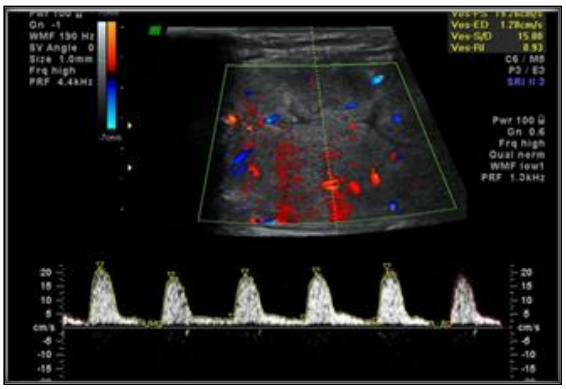

Figure 10: On spectral doppler showing high RI and PI values and report was given as malignant nodule. On FNAC, it was confirmed as follicular carcinoma.

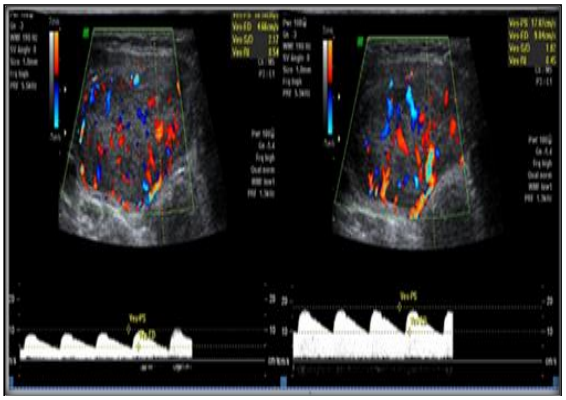

Figure 11: On spectral doppler showing low RI and PI values and report was given as benign thyroid nodule. On FNAC, it was confirmed as adenomatous goitre.

DISCUSSION

A thyroid nodule is a discrete lesion, sonographically distinct from the surrounding thyroid parenchyma. Rather than a single disease, nodules are manifestations of a gamut of thyroid diseases. It is of utmost importance to recognize absolutely reliable criteria for malignancy when using imaging methods.[9] The correct diagnosis is established by means of a histopathological examination. It is suggested in previous guidelines and Ultrasound Consensus Conferences that for nodules less than 10 mm, only those with a high-risk of malignancy or suspicious US features must be biopsied. Present study proposed that age and sex incidence was not an important in differentiating benign and malignant thyroid nodules which is in consensus with other studies.[10]

Our study concluded that nodule number and size is not predictive of malignancy because the likelihood of cancer in a thyroid nodule has been the same regardless of the size of the nodule measured during ultrasonography which substantiates other studies.[4,10] The relationship between solid nodule and malignancy was not statistically significant in our study which is in accordance with the findings of Algin *et al.*,[11] While the presence of cystic components in a thyroid lesion was found to be a significant criterion ($p<0.05$) for benign nodules which was not in agreement with the findings of Iannuccilli *et al.*,[11] .Current study also showed that the risk of malignancy in hypoechoic nodules is about 6 times higher than the iso-hyperechoic nodules.[10,11]

Our present study states that hypoechogenicity, irregular margins, microcalcifications and taller than wide are important features in determining the malignancy risk which is in consensus with other studies.[4,10,11]Current study and other study done by Algin *et al.*,[11] showed the presence of halo alone for detection of malignant thyroid nodules was insignificant ($p>0.05$).A new criteria as thick irregular halo which is seen in 13 malignant nodules (69 %) and 6 benign nodules (31%). This characteristic was not evaluated in other studies. In current study, the p value for thick incomplete halo was significant ($p<0.05$). This can be attributed to irregular growth and infiltration of the fibrous capsule by the malignant thyroid nodule leading this irregular halo.

In present study microcalcifications were seen in 12 nodules of papillary carcinoma. However, none of the benign nodules were seen to have microcalcifications. The positive predictive and negative predictive value of microcalcifications alone for detection of malignant thyroid nodules was 100 % and 82.1%. The p value for microcalcifications was found to be 0.001 was significant ($p<0.05$).[9,10] In present study, comet tail artifacts were seen in seen in 23 nodules of which all are benign (having specificity of 100%). Hence, this is a specific criterion for benign thyroid nodules. Current study states that lymphnode enlargement with loss of fatty hilum and local infiltration are important features in determining the malignancy risk which was a high specificity and positive predictive value of 100%.

The sensitivity of Doppler US investigation is affected by the technical parameters as settings of a wall filter, nodule depth, and pulse repetition frequency (PRF). Individual variations of tissue

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attenuation, patient movement and lack of cooperation, motions as swallowing or breathing and pulsations of adjacent arterial structures may affect Doppler US investigation. Generally, increased central vascularity is accepted in the literature as a supporting feature for diagnosis of malignancy.[11,12] In our study, we found significant relationship between central vascularity and malignancy. Studies done by Moon *et al.*,[13]Argalia*et al.*,[14]and Tamsel*et al.*,[15] did not find any relationship between intratumoral vascularity and malignancy, which is not in consistent with the results of our study.

Assessment of thyroid nodules by RI and PI values measured by spectral Doppler US is not affected from course of artery, angle of insonation, or nodule size. In our study, we found that malignant nodules have significantly higher RI and PI values according to benign nodules. In our study, the RI values of malignant nodules were compatible with the literature and the PI values were a bit higher, but quite similar according to the literature. Other studies by Argalia*et al.*,[14] De Nicola *et al.*[16], Ivanac *et al.*[17], and Yang *et al.*,[18] reported similar results for RI values which were in consensus with our study. It can be postulated that stenosis and/or occlusion of arteries due to excess cellular proliferation in malignant nodules might occur as a result of the high central and peripheral RI-PI values noted in our study.

There are few potential limitations of this study. The main limitation is few overlapping features were seen in both benign and malignant thyroid nodules. In patients with multinodular goitre, only the suspicious and dominant nodules were further evaluated by FNAC. Rest of the nodules were not evaluated. Small nodules less than 10 mm could not be assessed properly on color doppler. Small sample size for individual malignant thyroid lesions.

CONCLUSION

Using morphological pattern recognition features, ultrasound is valuable for identifying malignant or potentially malignant thyroid nodules. The specific malignant features include microcalcifications, hypoechogenicity, taller than wide, irregular thick halo, lymphadenopathy and local extra thyroidal invasion. Intranodular vascularity and high RI indices were the specific signs for malignant thyroid nodules. Since Gray scale and Doppler have their own strengths and weaknesses, they were complementary rather than competitive modalities in diagnosing benign from malignant thyroid nodules.

Conflict of Interest: None to declare

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