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Evaluation of thyroid nodules by ultrasonography with cytological and histopathological correlation

Asish Mandal[1], Sundara Raja Perumal R[2], Debasish Nandi[3]

[1]Associate Professor, [2]Professor, [3]Junior Resident,Department of Radio Diagnosis, Command Hospital (Eastern command), Kolkata, West Bengal, India

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ABSTRACT

Background: Nodular thyroid is a common clinical entity. The optimum diagnostic strategy for the patient with nodular thyroid is still a matter of debate. A thyroid nodule is a well-defined discrete lesion, sonographically distinct from the surrounding thyroid parenchyma. Thyroid nodules occur with relatively high frequency in the general population with prevalence of 4–7% by palpation alone, 13%–67% by sonographic evaluation, and 50% at autopsy. It is estimated that 4–8% of adult women and 1–2% of adult men have thyroid nodules that can be felt on clinical examination. However, in contrast to high prevalence of thyroid nodules, the prevalence of thyroid malignancy is low. <7% of thyroid nodules are malignant. **Aims and Objectives:** The present study was undertaken to evaluate the diagnostic efficacy of ultrasonography (USG) and color Doppler in differentiating benign and malignant thyroid nodules and in comparing the findings with results of fine needle aspiration cytology (FNAC). **Materials and Methods:** A prospective study was carried out on 65 patients from 11–80 years age group of both sexes, presenting with thyroid nodules. All patients were evaluated by gray scale USG and color Doppler and then subjected to FNAC. Histopathology was done whenever required. The results of FNAC were compared with that of USG and color Doppler. **Results:** The majority of the cases presented were females between the age group of 21–50 years. Swelling in the anterior neck was the presenting complaint in all 65 cases (100%). The most of thyroid nodules were benign in nature. The sensitivity and specificity of US in diagnosing malignant lesions were 80% and 86%, respectively. The most common presentation was from the females in the age group of 21–50 years, with swelling in the anterior neck. **Conclusion:** USG with color Doppler is a safe, reliable, and cost-effective diagnostic modality with a high sensitivity and specificity and is the single best radiological investigation for non-invasive evaluation of thyroid nodules. However, a combination of FNAC and USG gives optimum results and can avoid unnecessary surgery.

Key words: Thyroid nodule; Ultrasonography and Doppler study of thyroid nodule; Ultrasonography-guided fine needle aspiration cytology; Benign nodular lesion; Malignant thyroid lesions

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INTRODUCTION

The term "thyroid nodule" refers to focal abnormal growth that forms a nodule in the thyroid gland. The thyroid gland is located below the Adam's apple in the lower part of neck. The gland is butterfly shaped and wraps around the trachea. The two lobes of thyroid on either side of the trachea are joined by isthmus, located anterior to the trachea. Nodular lesion of thyroid can occur in any part of the thyroid gland and few can be palpated easily and few could not be clinically identified due to their deep location and size of nodule. A thyroid nodule is a well-defined discrete lesion, sonographically distinct from the surrounding thyroid parenchyma. Rather than a single disease, nodules are manifestations of a gamut of thyroid diseases. Thyroid nodules occur with relatively high frequency in the general

Address for Correspondence:
Dr. Sundara Raja Perumal R, G 403. TVS Green hills, Perungulathur, Chennai - 600 063, Tamil Nadu, India. **Mobile:** +91-8695019653.
E-mail: rsr_peru@yahoo.co.in

population with prevalence of 4–7% by palpation alone, 13–67% by sonographic evaluation and 50% at autopsy. It is estimated that 4–8% of adult women and 1–2% of adult men have thyroid nodules that can be felt on clinical examination. However, in contrast to high prevalence of thyroid nodules, the prevalence of thyroid malignancy is low. <7% of thyroid nodules are malignant. The vast majority and approximately 88% of these are papillary carcinomas. These are slow growing cancers with excellent prognosis. Other histological types are follicular (5–l0%), medullary (3–5%), anaplastic (l–2%), lymphoma (l–2%), and thyroid metastasizes from other cancers (<l%). The prevalence of thyroid nodules increases with age. The likelihood that a nodule is malignant is affected by a variety of risk factors. Malignancy is more common in nodules found in patients who are younger than 20 or older than 60 years of age than in patients between 20 and 60 years of age. The initial laboratory tests may include measurement of thyroid hormone (thyroxin. or T4) and thyroid stimulating hormone in blood to determine whether the thyroid is functioning normally. However, since it is usually not possible to determine whether a thyroid nodule is cancerous by physical examination and blood tests alone, the evaluation of the thyroid nodules often includes specialized tests such as thyroid ultrasonography (USG), fine needle aspiration cytology (FNAC), and biopsy, if required. The major roles of use of ultrasound include detection and characterization of thyroid nodules and detection of cervical nodal involvement and differentiation of benign from malignant masses on the basis of the sonographic appearance. USG is also useful in following up of malignant nodules after the treatment for early detection of any residual disease or any local or nodal recurrence. USG also provides imaging guidance for FNAC or biopsy. We, therefore, plan this study to evaluate the sonographic and color Doppler findings of thyroid nodules to differentiate benign from malignant lesions. The duplex sonography has been correlated with FNAC which is the gold standard for the diagnosis.

Aims and objectives

The aim of this study is to evaluate the gray scale and color Doppler features of thyroid nodules and to evaluate the diagnostic efficacy of USG and color Doppler in differentiating thyroid nodules into benign and malignant variety and objectives are to compare gray scale and color Doppler findings with FNAC findings.

MATERIALS AND METHODS

A prospective study was conducted in the Radiology Department of Command Hospital Kolkata. Patients presented with palpable nodular thyroid swellings were included in the study. The study was carried out on 65 patients between 11 and 80 year age group, attending various OPD's. A brief clinical history was taken and then gray scale US and color Doppler was performed after taking informed consent. This study was preapproved by Institutional Ethical Committee for final permission. The USG and Doppler findings were recorded and correlated with cytological findings. Patient with following conditions was excluded from the study (a) Patients with diffuse thyroid/neck swellings, (b) Ulcerated and fungating thyroid lesion's, (c) Moribund patients and Unwilling patients to undergo the study, And (d) Post-operative patients. All patients with lesions with nodules in thyroid region were included in this study and all patients were subjected to sonography on LOGIC P-5 (Wiprow GE Healthcare) using 12 MHz linear array transducer. Doppler settings were standardized to compare the vascularity of thyroid pathologies among different patients. The patients were examined in the supine position with the neck slightly hyperextended. The thyroid gland was scanned in transverse and longitudinal planes. Nodular lesions were evaluated by its internal content, echogenicity, shape, presence of halo, margins, internal calcification, and vascularity and evidence of cervical lymphadnopathy US guided FNAC was conducted after interpreting sonological findings after taking due consent. The cytopathologic results (benign/malignant) were compared with sonological findings. Patients with follicular neoplasms in FNAC were subjected to biopsy for histopathological diagnosis for comparison with sonographic findings.

Statistical analysis

Statistical analysis was conducted with the Statistical Package for the Social Science system version (SPSS) 17.0. Continuous variables are presented as mean±SD, and categorical variables are presented as absolute numbers and percentage. Nominal and categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to analyze the diagnostic accuracy of ultrasound and correlating with FNAC as the gold standard. For all statistical tests, $P<0.05$ was taken to indicate a significant difference.

RESULTS

The 65 patients with nodular swelling of thyroid gland were first sonologically evaluated and then they underwent US guided FNAC. The radiological and cytopathological findings were correlated and the data were statistically evaluated.

The age group of patients was ranged from 18–80 years. The youngest was 18 year old male and the oldest was 70 year male. The highest numbers of cases were between 31 and 40 years: 17 out of 65 cases, that is, 26.1%. The least number of cases was seen in < 20 years age group: One out of 65 cases, that is, 1.5%. Out of 65 patients, 44 (67.7%) were female and 21(32.3%) were males.

- Out of 65 cases, 50 are benign and rests of the 15 cases were malignant.
- The spectrum of benign pathology included follicular adenomas and colloid goiters. The most common was colloid goiter which comprised of 24 cases of solitary nodular and 20 cases of MNG.
- The spectrum of malignant pathology included papillary, medullary, follicular, anaplastic carcinomas, and NHL. The most common malignancy was papillary carcinoma (10 out of 15).

Comparison of echogenicity between benign and malignant cases

- Out of 50 benign nodules, maximum were isoechoic (36%) to the normal glandular parenchyma. (Figure 1)
- Out of 15 malignant nodules, 13 (86.7%) were hypoechoic which is significant P<0.001). (Figure 3)
- About 24% (12 out of 50) of benign nodules were hypoechoic as compared to 86.7% (13 out of 15) of malignant nodules which showed hypo echogenecity.
- Out of 50 benign nodules, predominant (64%), that is, 32 out of 50 were having mixed (solid-cystic) composition.
- Out of 15 malignant nodules, 9 (60%) were found to be solid in composition which is significant (P<0.015). None of the malignant nodules were cystic.
- About 26% (13 out of 50) benign nodules were solid as compared to 60% (nine out of 15) of malignant nodules which were solid in composition.

Figure 1: Benign nodule well-defined, rounded, isoechoic, absent calcification, and surrounding halo

Comparison based on margins

- Out of 50 benign nodules, 45 (90%) had well-defined margins. Rest of five nodules had ill-defined margins.
- Out of 15 malignant nodules, 11 (73.3%) had ill-defined margins; rest of 4 nodules (26.7%) had well-defined margins.
- About 10% (5 out of 50) benign nodules had ill-defined margins as compared to 73.3% (11 out of 15) of malignant nodules which is significant (P<0.00).

Distribution of thyroid nodules based on Peripheral Halo (n = 65)

- Out of 50 benign nodules, 14 (28%) showed peripheral halo whereas in 36 (72%) cases peripheral halo was absent.
- The benign nodules which showed peripheral halo were adenomas and colloid goiter.
- Out of 15 malignant nodules, 2 (13.3%) showed peripheral halo whereas in 13 (86.7%) nodules peripheral halo was absent.

Distribution of thyroid nodules based on calcification (n = 65)

- Calcification was present in 10 out of 50 (20%) benign nodules and in one out of 15 (46.7%) malignant nodules.
- Out of 10 benign nodules. Five had micro and five had macrocalcifications.
- Out of seven malignant nodules with calcification, six had microcalcifications (Figure 3) and only one case had macrocalcifications.
- Microcalcifications was present in 40% malignant nodules as compared to 10% of benign nodules which is significant (p<0.001). (Figure 3)

Distribution of thyroid nodules based on cervical lymphadenopathy (n=65)

Cervical lymphadenopathy was seen in seven patients out of 65. All of these cases were malignant. Out of these,

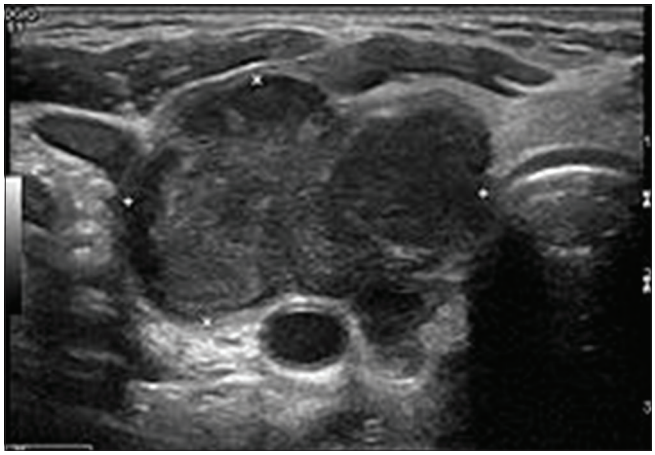

Figure 2: Anaplastic CA

five were papillary and two were medullary carcinomas. (Figure 4) None of the benign nodule showed cervical lymphadenopathy.

Diagnostic accuracy of US as compared to FNAC

True positive: Malignancy on US as well as FNAC (12 cases).

True negative: Malignancy excluded on US as well as FNAC (43 cases).

False positive: Malignancy diagnosed by US but excluded by FNAC (seven cases). False negative: Malignancy not on US but confirmed by FNAC (three cases).

Out of 46 benign cases on US, 43 were benign of FNAC (true negative). However, three cases were malignant on FNAC (false negative). Average age of patient in this study is 34 years (Table 1).

Out of 19 malignant cases on US, 12 were malignant on FNAC (true positive). However, seven cases were benign of FNAC (false positive).

Out of 50 benign cases on FNAC, 53 (86%) were benign on US which is significant (P<0.001) and seven were malignant on US.

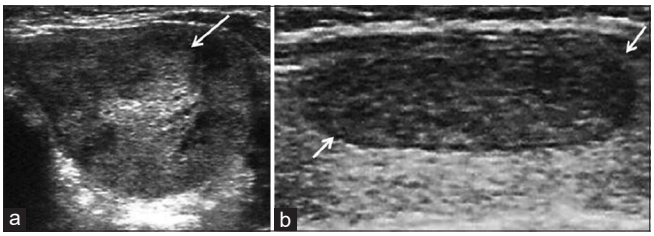

Figure 3: (a and b)Nodule showing malignant features irregular shape, heterogeneous echo, microcalcification, and incomplete halo

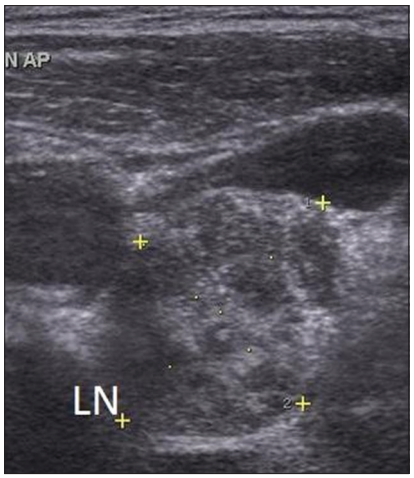

Figure 4: Cervical lymph node in papillary CA

Out of 15 malignant cases on FNAC, 12 (80%) were malignant on US which is significant (P<0.001) and 3 (20%) were benign on US.

DISCUSSION

The goal of conducting this study was to avoid extensive and costly investigations in most patients with benign thyroid disease without missing the minority of patients who have thyroid carcinoma. The aim of this study was to assess various ultrasound criteria including, marked hypoechogenicity, microcalcifications, irregular margins, tall shape, and intranodular pattern of color flow in predicting malignant nature of these lesions. US and color Doppler is a useful imaging modality to distinguish normal from abnormal thyroid gland and to classify these abnormalities as diffuse or focal/nodular and further helping in differentiating thyroid pathologies into benign and malignant varieties. It helps in differentiating the neck swelling between the thyroid origin and other neck pathologies. In our study, the age range of the patients was 11–80 years. The maximum number of patients was seen in the middle age group of 31–50 years (49%). There was only one patient in <20 years age group. Out of 65 patients, 44 were females and 21 were males, showing the female preponderance for thyroid diseases. In our study, 15 cases were malignant, out of which 10 were females and five were males, signifying that malignant thyroid disease is also more common in females. These findings were agreed in other literatures. A similar female preponderance of thyroid nodules was observed by Rojeski and Gharib[1] in there study conducted in 1985. The middle age group prevalence was observed by Abid and Dr Mohammed Nasir[2] in there study on 80 subjects from 2011–2013.

In our study, the benign spectrum of thyroid nodules comprised of colloid goiter, MNG, and follicular adenoma. The most common benign pathology encountered was colloid goiter (44 of total 50 benign case 88%) and follicular adenoma (six out of 50 cases 12%). The malignant spectrum comprised of papillary, follicular, medullary and anaplastic carcinomas, and lymphomas. The most common malignancy was papillary carcinoma[3] which comprised of 10 out of 15 malignant cases (66.7%). These findings were comparable to the findings of the study done by Ali and Nasir in there study on 80 subjects from 2011–2013[2] in which colloid nodule was the most common benign disease (59%). Among the malignant pathologies, papillary carcinomas were most common (68%).[2] In our study, 65 cases of thyroid nodules were taken, which at US were either anechoic (six cases), hypoechoic (25 cases), isoechoic (19 cases), hyperechoic (11 cases), and heterogeneous (four cases). Out of 50 proven benign cases, majority were isoechoic, 18 cases (36%)

followed b\ hypoechoic, 12 cases (24%) and hyperechoic which were II cases (22%). Rest were anechoic (12%) and heterogeneous (6%) to the normal thyroid parenchyma. Out of 15 malignant cases, majority were hypoechoic (13 i.e., 87%). Rest were heterogeneous and isoechoic (6.7% each). We found that there was high sensitivity (87%) and specificity (76%) of hypoechogenicity for malignancy in thyroid nodules. The previous studies also showed similar findings. Moon et al., conducted a study in 2003 which showed a high sensitivity (91%) of ultrasound parameters of hypoechogenicity as a marker of malignancy.[4] Moon et al.,[4] in 2005 reported that incidence of malignancy for hyper echoic nodule is only 4% and thus a hyper echoic nodule is most likely to be benign. In another study conducted by Yen et al., it was concluded that most hypoechoic nodules were benign since benign nodules are overall more common. The incidence of malignancy in an isoechoic nodule was found to be 26% whereas malignancy was seen in 63% of hypo echoic nodules.[5]

In our study, out of 65 nodular lesions, 38 were mixed solid-cystic, 22 were predominantly solid, and five were predominantly cystic in composition. Out of 50 proven benign cases, 32 (64%) were mixed solid-cytic, 13 (26%) were solid, and 5 (10%) were cystic. Out of proven, 15 malignant cases, 9 (60%) were solid and rest of the 6 (40%) cases were solid-cystic. None of the malignant-nodules were cystic. We found that there was high sensitivity (60%) and specificity (74%) and low PPV (41%) of solid composition for malignancy in thyroid nodules.

In 2005, a study by Frates et al., proposed that a predominantly solid component is regarded as being suggestive of a malignant nodule rather than a benign nodule[6,7] with high sensitivity (70–75%) but low PPV (16–27%), In a study by Wienke et al., in 2003 and Lannuccilli et al., in 2004, findings, however, suggest that about 60–83% of benign nodules were predominantly solid.[8,9] In our study, most of the benign nodules, as well as the malignant nodules, were predominantly solid or solid-cystic with predominant solid component. Thus, a predominantly solid component alone cannot be a useful criterion for the differentiation of malignant from benign nodules.

In our study, out of 50 proven benign nodular lesions 5 (10%) showed ill-defined margins and the rest of the 45 (90%) showed well-defined margins. In 15 proven malignant cases, 11 (73.3%) had ill-defined margins and 4(27%) showed well-defined margins. The sensitivity and specificity for poorly defined margins for detection of malignancy was 73% and 90%, respectively.

In studies by Solbiati et al., in 2001 and Papini et al., in 2002, findings suggested that blurred or ill-defined nodular margins favor a diagnosis of malignancy. In our study, the sensitivity and specificity of poorly defined margins for detection of malignancy were 73% and 90%, respectively."[10]

In our study, complete halo surrounding a thyroid nodule was present in 14 out of 50 (28%) benign nodules and was absent in rest of the 36 (72%) nodules. In 15 malignant nodules, halo was present in 2 (13%) nodules and was absent in 13 (87%) nodules. The sensitivity, specificity, and PPV for absent halo in malignant nodules was 13%, 72%, and 12.5%, respectively, thus making it an insignificant marker of malignancy in a thyroid nodule. The studies by Propper et al., in 1980 and by Solbiati et al., in 1985, suggested that the peripheral sonolucent halo that completely or incompletely surrounds a thyroid nodule may be present in 60–80% of benign nodules and 15% of thyroid cancers.[10] Chan et al., in 2003 reported that 10–25% of papillary thyroid carcinomas have either a complete or an incomplete halo.[11]

In our study, the taller than wide shape (A-P'TR >1) on transverse scan was seen in eight out of 50 proven benign (16%) and 12 out of 15 malignant nodules (80%). This shows that it is a good predictor of malignancy in a thyroid nodule. It has high sensitivity (80%), specificity (84%), and accuracy (72%) for predicting malignancy in a thyroid nodule. The previous studies by Kim, et al., in 2002, Alexander et al., in 2004, and Moon et al., in 2008 suggested that taller than wide shape, in which the AP diameter is equal or more than its transverse diameter on a transverse or longitudinal US plane, is specific for

Table 1: Age distribution (n=65)

Age groups	Frequency	%
≤ 20 years	1	1.5
21–30 years	8	12.3
31–40 years	17	26.1
41–50 years	15	23
51–60 years	13	20.2
> 60 years	11	16.9
Total	65	100
Min-Max	18–70 years	
Mean	34.33 years	

Table 2: Correlation of Duplex US with FNAC

USG diagnosis	FNAC				P value
	Benign		Malignant		
	Frequency	%	Frequency	%	
Benign	43	86	3	20	0.001
Malignant	07	14	12	80	
Total	50	100	15	100	

USG: Ultrasonography, FNAC: Fine needle aspiration cytology

Table 3: Diagnostic accuracy of Duplex US features tor malignant nodules (n=65)

DSG features	Sensitivity (%)	Special city (%)	PPV (%)	NPV (%)	Accuracy
Poorly def. margins	73.3	90.0	68.8	91.8	86.2
Solid	60.0	74.0	40.9	86.0	70.8
Hypoechoic	86.7	76.0	52.0	95.0	78.5
Halo absent	13.3	72.0	12.5	73.5	58.5
Micro calcification	40.0	90.0	54.5	83.3	68.0
Internal vascularity	73.3	90.0	84.6	92.3	78.7
Taller than wide	80.0	84.0	60.0	93.3	72.0

PPV: Positive predictive value, NPV: Negative predictive value

differentiating malignant nodules from benign nodules, likely because malignant neoplasms (taller than wide) grow across normal tissue planes, whereas benign nodules grow parallel to normal tissue planes.[12,13]

In our study, calcification within a thyroid nodule was taken as one of the parameters to differentiate benign from malignant thyroid nodules. Out of 50 benign nodules, 5 (10%) showed macrocalcifications and in rest of the 40 benign nodules, calcification was absent. Out of 15 malignant nodules, 1 (7%) had macrocalcifications. Six (40%) had microcalcifications and in the rest of the eight nodules, calcification was absent. We found that microcalcifications was more common in malignant nodules. In our study, the specificity of the microcalcifications for malignant nodules was found to be very high (90%). In results of a previous study[6] conducted by Frates et al., in 2005, the presence of a microcalcifications in a predominantly solid nodule increased cancer risk by threefold, compared with predominantly solid nodules without any calcifications. The PPV for microcalcifications in malignant nodules was 41.8–94.2% but sensitivity was low (26.1–59.1%).[14,16]

Vascular flow within a thyroid nodule can be detected with color Doppler. In our study, the vascularity of thyroid nodule was classified as absent, peripheral, mixed (central and peripheral), and central. Peripheral flow is defined as the presence of vascularity around at least 25% of the nodular circumference without any obvious internal flow. A nodule is said to have central flow when it shows intense intra-nodular vascularity without any obvious peripheral flow.

In our study, flow was absent in 29 (58%) out of 50 benign nodules whereas none of the malignant nodules showed absent flow. Intense central flow was present in 4% of benign nodules as compared to 73% of malignant nodules. Peripheral flow was seen in 22% of benign nodules and 13% of malignant nodules. We found that most of the benign nodules showed either absent or peripheral color flow. Most of the malignant nodules showed central type of color flow (Tables 2 and 3).

The past studies by Fobbe et al., in 1989, Solbiati et al., in 1992, Pappini et al., in 2002, and Chammas et al., in 2005 demonstrated that 80–95% of hyperplastic, goitrous, and adenomatous nodules display peripheral vascularity, whereas 70–90% of thyroid malignancies display internal or central vascularity, with or without a peripheral component.[10,15,16]

In our study, cervical lymph nodes were enlarged in seven out of 15 malignant (47%) malignant nodules. None of the benign nodule showed cervical adenopathy. Five were found in patients with papillary carcinoma and two in patients with medullary carcinoma. At sonography, the enlarged lymph nodes were round and hypoechoic with loss of central fatty echogenic hilum. In one case of papillary carcinoma, bilateral cervical lymph nodes were enlarged. Microcalcifications with internal cystic areas were seen in the enlarged lymph nodes of one patient of papillary carcinoma.

The previous study by Yuen et al.,[5] suggested that the cervical lymph node metastasis occurs most commonly with papillary carcinoma with an associated presentation in 30–40% of patients. Frates et al.,[6] and concluded from their studies that US features of rounded, enlarged, ill-defined, poorly marginated, heterogeneously hypoechoic appearance with loss of fatty hilum, and presence of calcifications and central vascularity in a lymph node suggest possibility of metastatic etiology.

In our study, the diagnostic accuracy of US for malignant nodules as compared to FNAC turned out to be: Sensitivity: 80%, specificity: 86%, PPV: 63.2%, and NPV: 93.4%. The statistical analysis in our study was corroborated with the study conducted by Ali and Nasir[2] from 2011 to 2013 which had a sensitivity of US for malignant nodules of 82%, specificity of 95%, PPV of 86%, and NPV of 93%. Similar findings corroborating out findings were discussed in the study conducted by Kim et al., in 2002[12] where the sensitivity, specificity, PPV, and NPV were 93%, 66%, 57%, and 75%, respectively.

Limitations of the study

USG with color Doppler is a safe, reliable, and cost-effective diagnostic modality with a high sensitivity and

specificity and is the single best radiological investigation for non-invasive evaluation of thyroid nodules. However, a combination of FNAC and USG gives optimum results and can avoid unnecessary surgery.

CONCLUSION

The goal of conducting this study was to evaluate gray scale and color Doppler features to differentiate thyroid nodules into benign and malignant varieties. It was also aimed to assess the diagnostic efficacy of USG and color Doppler in evaluating thyroid nodules after pathological correlation. The high sensitivity and specificity of US in detecting benign and malignant nodules coupled with US assisted FNAC have caused a profound change in the management of thyroid nodules, avoiding unnecessary surgery in patients with benign diseases. USG helps in avoiding extensive and costly evaluations in most patients with benign disease without missing the minority of patients who have thyroid carcinoma.

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Authors Contribution:
DN- Concept and design of the study, prepared first draft of manuscript, interpreted the results, reviewed the literature, and manuscript preparation;
AM and RS- Concept, coordination, statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript.

Work attributed to:
Command hospital, Eastern command, Kolkata, West Bengal, India.

Orcid ID:
Dr. Asish Mandal - https://orcid.org/0000-0002-5300-131X
Dr. Sundara Raja Perumal R - https://orcid.org/0000-0003-0917-8836
Dr. Debasish Nandi - https://orcid.org/0000-0001-6651-8118

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