

Role of Ultrasonography to Differentiate Benign and Malignant Thyroid Nodules in Correlation with Fine-needle Aspiration Cytology

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Abstract

Introduction: The thyroid gland is the largest of all endocrine glands and is the only one which is amenable to direct physical examination because of its superficial location. Superficial location of the thyroid gland allows excellent visualization and evaluation of its normal anatomy and pathologic condition by high resolution real-time gray-scale sonography.

Purpose: The objective was to use sonographic criteria to differentiate benign and malignant thyroid nodules and correlate with fine-needle aspiration cytology (FNAC) findings.

Materials and Methods: From June 2014 to August 2015, 70 cases of thyroid nodules based on inclusion and exclusion criteria were included in this study. The sonographic characteristics of each nodule were determined. The results were then compared with FNAC/histopathological diagnosis.

Results: Of the 70 nodules examined, 6 (8.57%) were found to be malignant on cytopathology. The malignant nodules demonstrated solid or predominantly solid composition (sensitivity 100% and specificity 9.37%); presence of microcalcification (sensitivity 66.6% and specificity 98.4%); irregular or poorly defined margins (sensitivity 83.3% and specificity 92.06%); anteroposterior diameter more than transverse diameter (sensitivity 50% and specificity 93.75%); absent or thick incomplete halo (sensitivity 83.3% and specificity 82.8%); markedly hypoechoic character (sensitivity 66.6% and specificity 90.6%).

Conclusion: Gray-scale ultrasonography (USG) features of thyroid nodules are useful to distinguish benign and malignant thyroid nodules. From our study, it is apparent that the USG findings of poorly defined margins, marked hypoechoic character, microcalcifications, absent or thick irregular peripheral halo, and a taller-than-wider shape have a high diagnostic accuracy for identifying malignant thyroid nodules.

Key words: Fine-needle aspiration cytology, Follicular adenoma, Hyperplastic nodule, Papillary carcinoma, Thyroid nodule, Ultrasound

INTRODUCTION

Nodular thyroid disease is detected in 3-7% of the adult population worldwide. They are common in females with a ratio of 5:1 and prevalence mainly depend on age, sex, iodine intake, diet (goitrogens) therapeutic, and

environmental exposure. The majority of these cases are clinically occult but readily detected by high-resolution ultrasonography (USG).¹⁻⁴

Thyroid cancer is rare and accounts for <1% of all malignant neoplasms. It has a good long-term prognosis after surgical excision. The high prevalence of thyroid nodules in the general population calls for a clear strategy to identify patients in whom surgical excision is genuinely indicated as opposed to those who can be managed conservatively.² Current management guidelines state that diagnostic USG should be performed in all patients with thyroid nodules and fine-needle aspiration cytology (FNAC) in nodules more than 1.5 cm or which are potentially malignant or

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indeterminate on USG.³ Basic use of sonography in nodular thyroid is to determine the location of palpable neck mass, characterize nodule as benign or malignant, know about extent of thyroid malignancy, and guide fine-needle aspiration of the thyroid nodule or cervical lymph node.⁵

The categorization of thyroid nodules into benign and malignant nodules by USG is very important as it helps in the further management of the patients with nodular thyroid disease. Hence, to find out the efficacy of USG in the evaluation of thyroid nodules, the present study is undertaken.

MATERIALS AND METHODS

Based on the inclusion and exclusion criteria, 70 cases of thyroid nodules, diagnosed by ultrasound were included in this study between June 2014 and August 2015. The ultrasound examination was done in the Department of Radiology, MGM Hospital, Warangal, using high-frequency linear array ultrasound transducer. These cases were subjected to FNAC for confirmation of ultrasound findings and establishment of diagnosis. The nodules, which were diagnosed on FNAC as follicular neoplasms, were operated, and biopsy was sent for histopathological examination to differentiating follicular adenoma and follicular carcinoma.

Inclusion Criteria

- All the patients with thyroid nodule detected on ultrasound which is more than 1.5 cm in size were included in the study.
- All patients with thyroid nodules suspicious of malignancy, irrespective of its size.

Exclusion Criteria

- All patients with diffuse thyroid enlargement.

Equipment

In the present study, gray-scale real-time ultrasound examination was done using 7.5 MHz linear array transducer. Ultrasound machines used were Esaote Mylab Classic and Esaote Mylab 40.

Technique of Examination

The patient is examined in the supine position with an extended neck. A pillow is placed under the shoulders to provide better exposure of the neck. Since the gland is situated superficially, 7.5 MHz linear array transducer is used.

The entire thyroid gland from upper to the lower pole and the isthmus is examined in the longitudinal and transverse planes. Bilateral carotid arteries, jugular veins, and supraclavicular fossa are also examined.

FNAC Technique

Before the ultrasound-guided FNAC, the neck is hyperextended, and the skin is cleansed with povidone-iodine (Betadine) solution. The transducer is also cleansed with the same solution. Sterile gel is used as a coupling agent. In the present study, we used 7.5 MHz linear transducer to take FNAC. Then, the needle is held in one hand and the transducer in the other. The needle is inserted through the skin of thyroid region in front of the neck at an oblique angle within the image plane of the transducer.

The needle used for thyroid FNAC is standard 25-gauge, non-cutting beveled edge needle. The needle is attached to 10 ml syringe. After introducing the needle, the needle is moved gently up to the nodule center under the US guidance. Then, gentle suction is done by putting the piston of the syringe. If the specimen contains much blood, a non-aspiration technique is used. In this, 25-gauge needle is inserted under ultrasound guidance into the thyroid gland and no suction is applied, and this needle is moved in back and forth excursions. Due to capillary action, the fluid of cells from the nodule move the needle such fluid specimen is often less bloody. Two drops of the aspirate/fluid in the syringe are ejected over a clean slide and with the help of the other blank slide with 60° angle; the aspirate on the first slide is spread on it to form a film of coating on it. The slide making procedure is repeated once more and after smearing the second slide, these slides are put in a jar containing absolute alcohol for fixation. These two slides in alcohol along with container are sent to the pathology department for cytopathological study.

OBSERVATIONS AND RESULTS

Of the 70 nodules evaluated at USG, 11 were diagnosed to be malignant, using five sonographic features such as shape of the nodule (taller than wide), marked hypoechogenicity, microcalcifications, poorly defined margins, absent or irregular thickened discontinuous peripheral halo (the presence of any two features in a thyroid nodule was considered malignant), and the rest of the nodules (59) were diagnosed as benign. After cytological/histopathological evaluation, 6 (8.57%) of the 70 nodules were found to be malignant and 59 (91.43%) were benign. 5 nodules, which were given as follicular neoplasms on FNAC, were diagnosed as follicular adenomas at histopathology. All the malignant nodules on FNAC were found to be papillary carcinomas.

The sonographic criteria used in the study were based on previously published criteria.⁶⁻⁹ The ultrasound diagnosis was compared with the pathological diagnosis and the sensitivity, specificity, positive predictive value, negative

predictive value, and diagnostic accuracy of ultrasound and five sonographic features (shape of the nodule [taller than wide], marked hypoechogenicity, microcalcifications, poorly defined margins, and absent or irregular thickened discontinuous peripheral halo) in predicting malignancy in a thyroid nodule were calculated using the statistical formulas. The *P* values were calculated for each of the sonographic feature using Chi-square test, and *P* value was found to be statistically significant (*P* < 0.0001).

In this study, the youngest patient was 16 years of age and oldest 70 years. The maximum number of cases are seen in the age group of 31-40 years (41%) and 41-50 years (25.7%) with females (81.42%) predominating over males (18.57%) (Table 1).

The majority of the malignant nodules are ill defined with shape taller than wide. Microcalcifications are seen exclusively in malignant nodules. All the malignant nodules are profoundly hypoechoic with the absence of well-defined peripheral halo. All malignant nodules are predominantly solid. However, the most of the solid nodules are benign.

Most of the benign nodules are well defined with thin peripheral continuous halo. All the nodules with peripheral eggshell calcifications are benign. The most of the benign nodules are predominantly solid; however, all the cystic lesions are benign. Shape of the benign nodule is oval with long axis along the transverse plane. All hyperechoic, isoechoic, and majority of hypoechoic nodules are benign (Table 2).

Microcalcifications have the highest accuracy in diagnosing malignant thyroid nodule followed by taller-than-wide shape, ill-defined margins, marked hypoechogenicity, and absent peripheral halo. The predominant solid character of malignant nodule on USG is not statistically significant and has a poor accuracy in diagnosing malignant thyroid nodules (Table 3).

Ultrasound correctly diagnosed malignancy in 5 out of 6 cases and falsely diagnosed 6 out of 64 benign nodules as malignant. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ultrasound in predicting malignancy were found to be 83.33%, 90.62%, 45.45%, 98.30%, and 90%, respectively (Table 4).

DISCUSSION

A thyroid nodule is defined as a discrete lesion within the thyroid gland that is distinguishable from the adjacent parenchyma at USG. In the present study, a maximum number of cases of thyroid nodules are seen in the age groups of 31-40 years (41%) and 41-50 years (25.7%) with

Table 1: Age and sex wise distribution of thyroid nodules

Age in years	Sex, N (%)		
	Male	Female	Total
11-20	0 (0.0)	3 (4.3)	3 (4.3)
21-30	1 (1.4)	12	13 (18.6)
31-40	4 (5.7)	25 (30.0)	29 (41.4)
41-50	5 (7.1)	13 (18.5)	18 (25.7)
51-60	2 (2.9)	4 (5.7)	6 (8.6)
61-70	1 (1.4)	0 (0.0)	1 (1.4)
Total	13	57	70 (100)

Table 2: Distribution of ultrasound characteristics in benign and malignant thyroid nodules

USG character	Malignant	Benign	Total
Margin			
Well-defined	2	59	61
Poorly defined	4	5	9
Calcification			
Present	4 (microcalcification)	10	14
Absent	2	54	56
Peripheral halo			
Thin and continuous	1	59	60
Absent or thick and regular	5	5	10
Internal contents			
Solid/predominantly solid	6	48	54
Predominantly cystic	0	3	3
Purely cystic	0	3	3
Echogenicity			
Hyperechoic	0	23	23
Isoechoic	0	26	26
Hypoechoic	2	9	11
Markedly hypoechoic	4	0	4
Shape			
Taller than wide	3	4	7
Not taller than wide	3	60	63

females (81.5%) predominating over males (18.5%). The percentage of benign thyroid nodules (91.43%) is higher than the malignant (8.57%) thyroid nodules. These findings correlate with the previous similar studies, but the studies conducted by Popli *et al.* (18.33%)¹⁰ and Lee *et al.* (37.69%)¹¹ showed the relatively increased proportion of malignant thyroid nodules compared to the present study.

The shape of the nodule has been studied as a marker of malignancy. The most of the malignant nodules in the present study showed shape that is taller than wide. In this study, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the shape of the nodule being taller than wide in predicting malignancy is 50%, 93.75%, 42.85%, 95.23%, and 90%, respectively. These findings confirm that shape of the nodule has a poor positive predictive value. However, its high specificity, negative predictive value, and accuracy make it reliable feature in ruling out malignancy in a thyroid nodule on USG. The similar studies conducted

Table 3: USG characteristics in predicting malignancy in thyroid nodules

USG characteristics	Sensitivity	Specificity	PPV	NPV	Accuracy
Poorly defined margins <i>P</i> =0.0000135	83.33	92.06	45.45	98.30	90
Microcalcifications <i>P</i> =0.0000125	66.66	98.46	80	96.92	95.71
Absent or irregular thick peripheral halo <i>P</i> =0.000225	83.33	82.81	31.25	98.14	82.85
Shape-taller than wide <i>P</i> =0.000401	50	93.75	42.85	95.23	90
Markedly hypoechoic <i>P</i> =0.000126	66.66	90.62	40	96.66	88.57
Solid/predominantly solid <i>P</i> =0.432	100	9.37	9.37	100	17.14

USG: Ultrasonography, PPV: Positive predictive value, NPV: Negative predictive value

in the past show that shape of the nodule has statistically heterogeneous significance in predicting malignancy in thyroid nodules, though the study conducted by Lee *et al.* show 100% specificity and positive predictive value, which is significantly different from other studies.¹⁰⁻¹⁴

A nodule is considered markedly hypoechoic when it is relatively decreased in echotexture compared to the adjacent strap muscles of the neck. The previous similar studies have revealed that most malignancies demonstrate a hypoechoic nodule, yet most hypoechoic nodules are benign in view of the high prevalence of benign lesions.¹⁰⁻¹⁴ The most of the nodules in the present study are hyperechoic followed by isoechoic and hypoechoic. Only a few nodules were found to be markedly hypoechoic and are exclusively found in malignant thyroid nodules (4 out of 6; 66.66%). This indicates that presence of marked hypoechoic is a good predictor of malignancy in thyroid nodule on USG. The present study shows sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of marked hypoechoic in predicting malignancy of thyroid nodule is 83.33%, 82.82%, 31.25%, 98.14%, and 82.85%, respectively.

Microcalcifications (Figures 1-3) are seen sonographically as multiple punctate bright echoes that are <2 mm in size, with or without acoustic shadowing.¹⁵ The current study showed that microcalcifications were exclusively seen in malignant nodules though not present in all cases of malignant thyroid nodules (not seen in 2 out of 6 cases). In the present study, microcalcifications were found to have the highest diagnostic accuracy (95.71%), specificity (98.46%), and negative predictive value (96.2%) compared to other sonographic characteristics on USG. Hence, it can be used as a reliable criterion in differentiating benign and malignant thyroid nodules on USG. The most of the previous studies show similar statistical significance, but the studies done by Remonti *et al.*¹⁴ and Lee *et al.*¹¹ show relatively low sensitivity and accuracy.

Table 4: Comparison of ultrasound with fine-needle aspiration/histopathology

USG	FNAC/B _x		
	Malignant	Benign	Total
Malignant	5	6	11
Benign	1	58	59
Total	6	64	70

P value is 0.000002; The result is significant at *P*<0.001. USG: Ultrasonography, FNAC: Fine-needle aspiration cytology

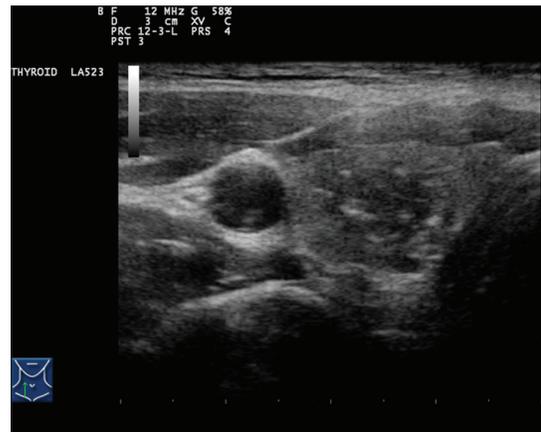


Figure 1: Ultrasonography shows ill-defined heterogeneous isoechoic to hypoechoic lesion noted in right lobe with microcalcification. Shape of the nodule is wider than tall. Right level 2 enlarged cervical lymph nodes with microcalcifications are noted

When more than 50% of the margin of a thyroid nodule is not clearly defined, it is considered as poorly defined.^{16,17} Malignant lesions tend to have poorly defined or irregular spiculated margins. The previously reported sensitivity of poorly defined margins for diagnosing malignant nodules ranges widely from 8.3% to 77.5%.^{16,18} In this study, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of poorly defined margins for diagnosing malignant nodules was found to be 83.33%, 92.06%, 45.45%, 98.30%, and 90% respectively, which was



Figure 2: Ultrasonography shows ill-defined heterogeneous isoechoic to hypoechoic lesion noted in right lobe with microcalcification. Few cystic areas noted. Shape is taller than wide. Right level 2 and 3 enlarged cervical lymph nodes with loss of hilum are noted



Figure 3: Ultrasonography shows ill-defined heterogeneous mildly hypoechoic lesion noted in left lobe with microcalcifications. Left level 2 and 3 enlarged cervical lymph nodes with loss of hilum and similar echotexture as the nodule noted with microcalcifications

similar to the study conducted by Popli *et al.* Although the positive predictive value is relatively low, the diagnostic accuracy and specificity are high making poorly defined margins as a reliable characteristic in predicting malignancy in thyroid nodule on USG.

Peripheral halo is a hypoechoic halo surrounding the thyroid nodule representing blood vessels coursing around the lesion, seen predominantly in benign nodules. The peripheral halo is usually complete and thin. It is irregular, thick, and incomplete or absent in a malignant nodule and is thought to represent compressed normal tissue due to the rapid growth of the tumor.¹ The most of the studies have reported a low sensitivity and specificity for the presence or absence of a halo.^{10,19} The present study showed that absent or irregular halo is mostly seen

in malignant nodules with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 83.33%, 82.82%, 31.25%, 98.14%, and 82.85%, respectively. In a study conducted by Samghabadi *et al.*, the absence of a halo was most predictive of malignancy on conventional USG.²⁰ The sonographic feature of absent or irregular thick discontinuous peripheral halo has a relatively high specificity and negative predictive value making it a reliable feature to rule out malignancy on USG.

In the present study, compared to other sonographic features such as microcalcifications, poorly defined margins and marked hypoechoogenicity, the shape of the nodule has a relatively low accuracy in predicting malignancy. However, the high negative predictive value makes it a good sonographic feature in ruling out malignancy.

The efficacy of USG in picking up malignancy in thyroid nodules was evaluated by comparing with pathological findings of the thyroid nodule. USG features of poorly defined margins, marked hypoechoogenicity, and taller-than-wide shape were found to have high diagnostic accuracy for identifying malignant thyroid nodules.¹⁰

The present study showed that combination of sonographic features suggesting malignancy was more accuracy than a single sonographic feature as the study is based on the assumption that at least two features suggestive of malignancy should be present to diagnose a thyroid nodule as malignant.

The findings in other studies quoted in Table 5 correlate approximately with the present study, specially the study conducted by Popli *et al.*¹⁰ The study conducted by Kim *et al* shows poor specificity, positive predictive value and accuracy of USG compared to other studies;¹² the difference can be explained by the fact that they considered presence of even one sonographic criterion suggestive of malignancy is categorized as malignant nodule. This assumption will cause decrease in specificity and accuracy as relatively more false positives are diagnosed on USG in their study.

Of all the studies mentioned in Table 5, the study conducted by Lee *et al.*¹¹ shows the highest specificity and negative predictive value with accuracy same as the present study. This study is based on the assumption that presence of any two of the above-mentioned features in a thyroid nodule was considered malignant, and the rest of the nodules were categorized as benign nodules which exactly mimics the present study (Table 5).

Table 5: Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of USG in predicting malignancy

Studies	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Present study	83.33	90.62	45.45	98.30	90
Popli <i>et al.</i> ¹⁰	81.81	87.24	59.01	95.53	86.25
Kim <i>et al.</i> ¹²	93.8	66	56.1	95.9	74.8
Lee <i>et al.</i> ¹¹	72	100	100	86	90
Nilakantan <i>et al.</i> ²¹	20	97.67	Not available	Not available	Not available

USG: Ultrasonography, PPV: Positive predictive value, NPV: Negative predictive value

The Efficacy of USG in Predicting Benign Thyroid Nodules

The majority (64 out of 70; 91.42%) of the nodules in the present study were found to be benign, of which adenomatous nodule/colloid nodule/hyperplastic nodule is the most common type followed by follicular adenoma. In the present study, most benign nodules are well defined (92.18%) with regular, well-defined thin peripheral halo (92.14%), and growth is along the tissue planes, i.e. wider than tall in shape (93.75%). Calcifications are generally absent in benign nodules and even if seen, are usually macrocalcifications (peripheral eggshell calcification in 15.62% of benign nodules). The most of the benign nodules are usually solid (75%) with variable echogenicity. However, all cystic or predominantly cystic lesions are exclusively benign. Benign nodules can be hyperechoic (35.93%), isoechoic (40.62%), or hypoechoic (14.06%), but all hyperechoic and isoechoic nodules are benign. In summary, well-defined margins, well-defined thin peripheral halo, and wider than tall shape are commonly seen in benign nodules and are good predictors of benign nature of a nodule. Although calcification is not seen in benign nodules, the presence of macrocalcifications or peripheral eggshell calcifications (Figure 4) favors benign nature. Microcalcifications almost never occur in benign nodules. Although their echogenicity may vary, hyperechogenicity is exclusively noted in benign nodules.

The similar studies done in the past show that the sonographic criteria for predicting benign nature of a thyroid nodule are well-defined margins, well-defined thin peripheral halo, and wider than tall in shape and absence of calcifications (microcalcifications) though macrocalcifications can be seen.^{10,11}

CONCLUSION

Thyroid nodules commonly occur in females with mean age of incidence 39.5 years. Relative incidence of malignancy in thyroid nodules is higher in males compared to females. Overall incidence of malignant nodules is <10% with all the malignant nodules diagnosed as papillary carcinoma. The most of the thyroid nodules are benign (64 out of 70) with the most common type being hyperplastic

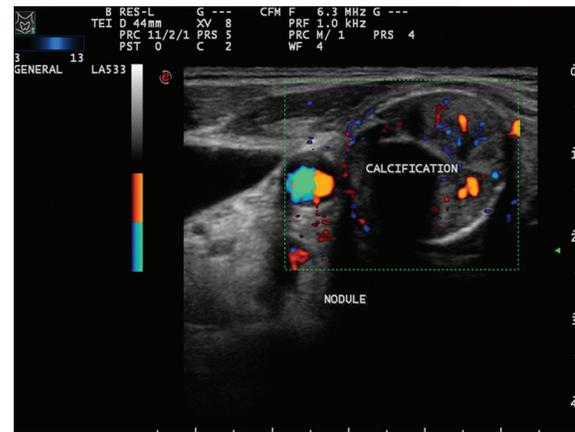


Figure 4: Ultrasonography shows well-defined isoechoic lesion noted in the left lobe of the thyroid with evidence of eggshell like peripheral calcification seen. On color Doppler peripheral vascularity noted. Intralesional macrocalcifications seen

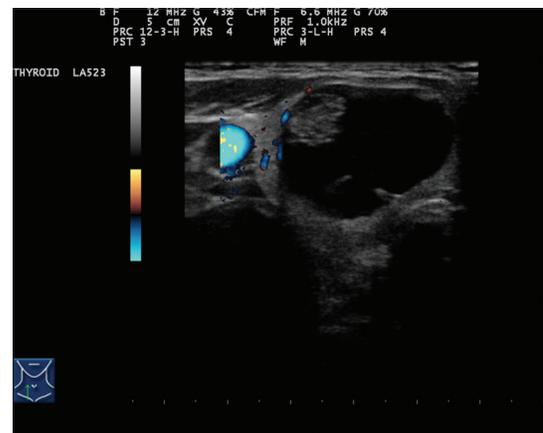


Figure 5: Ultrasonography shows well-defined, predominantly cystic lesion with peripheral vascularity. Shape is wider than tall. No calcifications seen

thyroid nodule (59 out of 64). The US features such as marked hypoechogenicity, poorly defined margins, absent or thick irregular halo, microcalcifications, and a taller-than-wide shape were found to be good predictors of malignancy. Out of all the features mentioned above, microcalcifications are found to have the highest accuracy in predicting malignancy. The most of the malignant nodules are hypoechoic; however, predominant number of hypoechoic nodules are benign. The majority of benign



Figure 6: Ultrasonography showing well-defined multiloculated cystic lesion with well-defined peripheral halo around it. Shape of the nodule is taller than wide

nodules are well defined with thin peripheral halo. The shape is wider than tall, and calcifications are rarely seen. All hyperechoic and cystic/predominantly cystic nodules are benign (Figures 5 and 6).

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