Utility of gray-scale ultrasound to differentiate benign from malignant thyroid nodules

Manju Bala Popli, Ashita Rastogi, PJS Bhalla[1], Yachna Solanki

Departments of Radiological Imaging and [1]Cytopathology, Institute of Nuclear Medicine and Allied Sciences (INMAS), Delhi, India

Correspondence: Dr. Manju Bala Popli, Department of Radiological Imaging, Institute of Nuclear Medicine and Allied Sciences (INMAS), Lucknow Road, Delhi – 110 054, India. E-mail: manju_popli@rediffmail.com

Abstract

Objective: The objective was to assess the utility of gray-scale USG to identify patterns of thyroid nodules and to correlate the characteristics of benign and malignant nodules with pathological diagnosis. **Materials and Methods:** From September 2009 to August 2010, a total of 203 patients (17 males and 186 females), with 240 nodules detected at USG, were included in this study. The characteristics of each nodule were determined. The results were then compared with fine needle aspiration (FNA)/histopathological diagnosis. **Results:** Of the 240 nodules examined, 44 (18.33%) were found to be malignant on cytopathology. The malignant nodules demonstrated solid or predominantly solid composition (sensitivity 88.6%, specificity 53.5%); presence of microcalcification (sensitivity 65.9%, specificity 97.9%); irregular or poorly defined margins (sensitivity 84%, specificity 88.7%); anteroposterior (AP) diameter > transverse diameter (sensitivity 77.2%, specificity 80.1%); absent or thick incomplete halo (sensitivity 70.4%, specificity 65.8%); and markedly hypoechoic character (sensitivity 65.9%, specificity 84.6%). Among males, malignant nodules were found in 36.8%, whereas in females the occurrence was 16.7%. **Conclusion:** Gray-scale USG features of thyroid nodules are useful to distinguish patients with clinically significant thyroid nodules from those with innocuous nodules despite the overlap of findings. From our study, it is apparent that the USG findings of poorly defined margins, marked hypoechogenicity, microcalcifications, and a taller-than-wider shape have a high diagnostic accuracy for identifying malignant thyroid nodules.

Key words: Thyroid; nodule; ultrasonography

Introduction

Nodular thyroid disease is detected in 3–7% of the adult population worldwide. 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 (American Thyroid Association) state that diagnostic USG should be performed in all patients with thyroid nodules and fine needle aspiration (FNA) in potentially malignant nodules.[3] Various features seen on USG, such as irregular margins, hypoechogenicity, absence of a surrounding halo, calcifications, and solid internal composition, have been investigated as predictors of malignancy.

The purpose of this study was to assess the utility of gray-scale USG in evaluating thyroid nodules and to correlate the characteristics of benign and malignant nodules with the pathological diagnosis.

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Materials and Methods

Patients

From September 2009 to August 2010, a total of 203

patients with clinically palpable nodules referred from the thyroid outpatient department (OPD) of our institute were included in this study. Of these, 17 were males and 186 were females. In all, 240 nodules were detected and evaluated sonographically in these patients, and all patients then proceeded for an FNA exam. The patients were in the age range of 15–62 years. A thorough clinical history was obtained. Investigations to be performed were explained to each patient and written informed consent was taken. The study was approved by the ethics committee of the institute.

USG examination

All USG examinations were performed with an ATL Philips HDI 5000® unit using 5--12 MHz transducer or a GE Logiq 200® USG scanner equipped with a 7.5 MHz transducer.

USG features of each thyroid nodule were assessed in consensus by a radiologist and a radiology resident (experience of 20 years and 1 year, respectively) prior to FNA examination; both were blinded to the pathology result.

The 240 nodules in 203 patients were evaluated for their margins, shape, echogenicity, presence of calcification, presence of circumferential halo, and internal composition.

The margins were assessed as smooth or irregular (further subclassified as lobulated or poorly defined) and whether surrounded by a peripheral halo or not [Figures 1 and 2]. The echogenecity was assessed as hypoechoic, hyperechoic, isoechoic or anechoic in comparison to normal thyroid parenchyma [Figure 3]. The hypoechoic nodules were further subclassified as markedly hypoechoic if less echogenic than strap muscles. The nodules were also categorized as solid, predominantly solid (<50% cystic change), predominantly cystic (>50% cystic change) or cystic based on their composition [Figures 4 and 5]. The presence of calcification as well as type of calcification whether micro- or macro-calcification was noted [Figures 6 and 7]. The shape was determined by measuring the antero-posterior diameter to transverse diameter ratio on transverse USG images [Figure 8].

If a patient had several thyroid nodules, each thyroid nodule was classified separately. A diffusely enlarged thyroid gland with multiple nodules and no intervening normal parenchyma was classified as multinodular goiter 73 patients with these findings were excluded from the study. Nodules less than 1 cm in size were also excluded

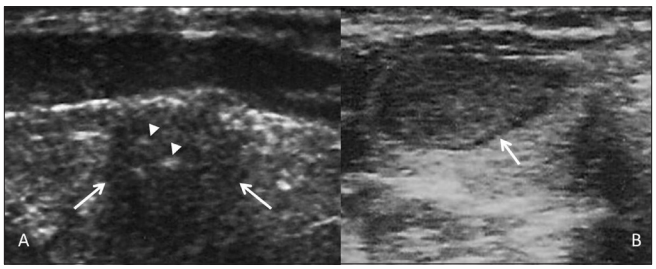

Figure 1 (A, B): Margins. Longitudinal USG image (A) of the right lobe of the thyroid gland shows a hypoechoic nodule (arrows) with poorly defined margins and microcalcifications (arrowheads). The FNA diagnosis was papillary carcinoma. Transverse USG scan (B) shows a hypoechoic nodule (arrow) with well-defined margins, in the right lobe of the thyroid gland

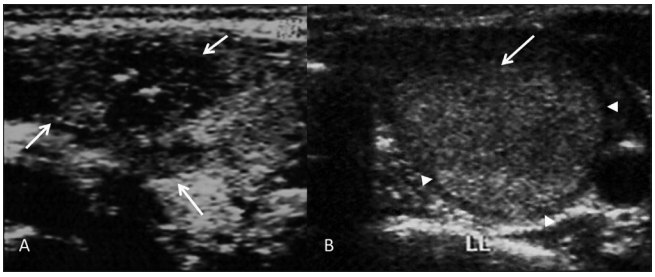

Figure 2 (A, B): Peripheral halo. Transverse USG image (A) of the left lobe of the thyroid gland shows a hypoechoic nodule (arrows) with poorly defined margins and absence of a surrounding halo. Transverse USG scan (B) of the left lobe of the thyroid gland in another patient shows a well-defined isoechoic nodule (arrow) with a surrounding, thin, regular, complete, hypoechoic halo (arrowheads) in the left lobe of the thyroid gland

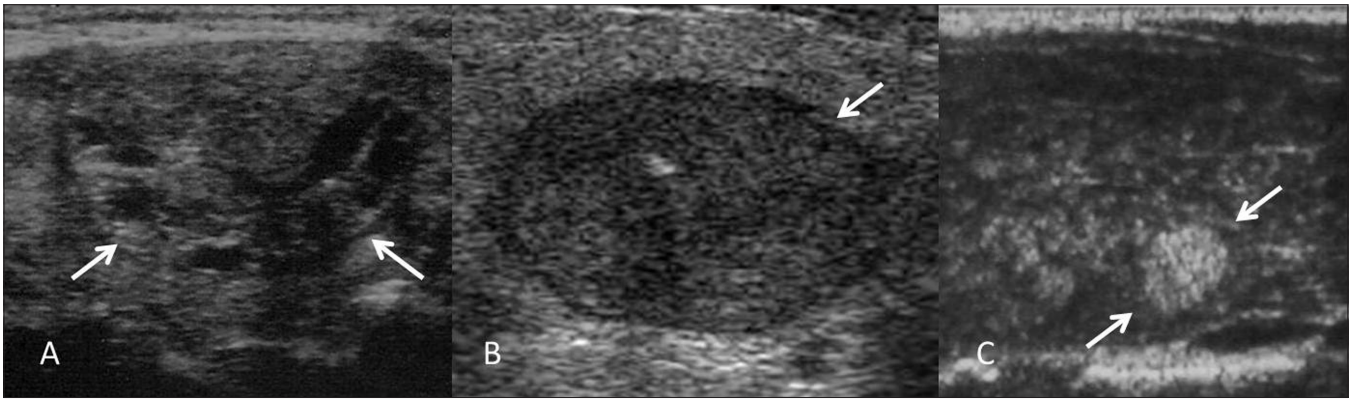

Figure 3 (A-C): Echogenecity. Longitudinal USG scan (A) of the right lobe of the thyroid gland shows a well-defined isoechoic nodule (arrows). Longitudinal USG image (B) shows a hypoechoic nodule (arrow) in the right lobe of the thyroid gland. Longitudinal USG scan (C) of the left lobe of the thyroid gland shows a small hyperechoic nodule in the lower pole (arrows)

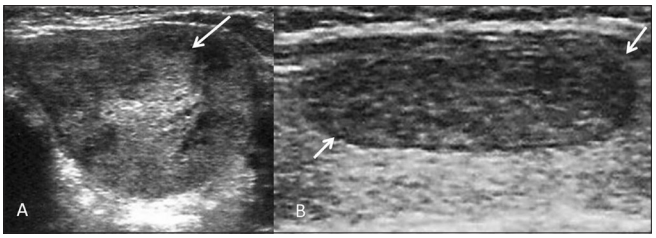

Figure 4 (A, B): Internal composition. Transverse USG image (A) of the left lobe of the thyroid gland shows a solid hypoechoic nodule (arrow) with well-defined margins. The FNA diagnosis was papillary carcinoma. Longitudinal USG scan (B) shows a hypoechoic solid nodule (arrows) in the right lobe of the thyroid gland. The cytopathology result was medullary carcinoma

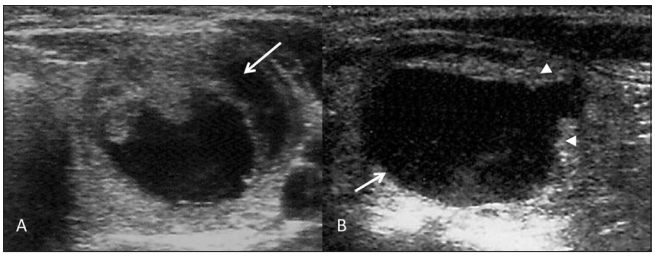

Figure 5 (A, B): Internal composition. Transverse USG scan (A) of the left lobe of the thyroid gland shows a predominantly cystic nodule (arrow). Longitudinal USG scan (B) shows a cystic nodule (arrow) with minimal solid components (arrowheads) in the right lobe of the thyroid gland

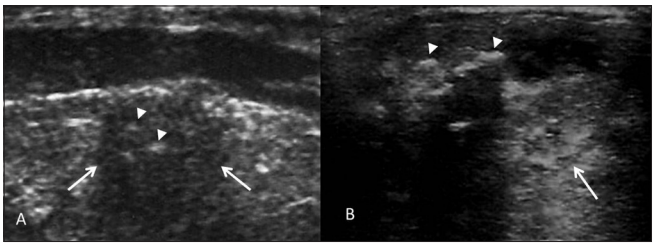

Figure 6 (A, B): Calcifications. Longitudinal USG image (A) of the left lobe of the thyroid gland shows microcalcifications, i.e., multiple punctate bright echoes (arrowheads) without shadowing in a hypoechoic ill-defined nodule (arrow). The FNA diagnosis was papillary carcinoma. Transverse USG scan (B) of the right lobe of the thyroid gland shows multiple foci of calcification (arrowheads) within a nodule (arrow) classified as the "not-otherwise-specified" variety of macrocalcification. The pathologic diagnosis was hyperplastic nodule

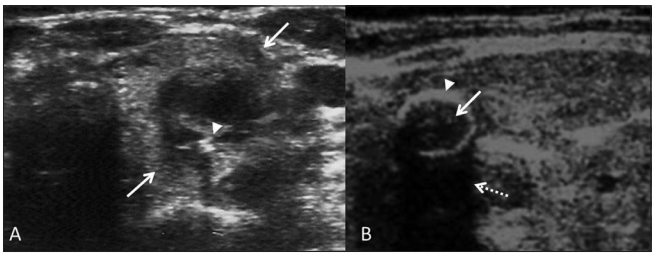

Figure 7 (A, B): Calcifications. Transverse USG image (A) shows a solitary macrocalcification (arrowhead) with distal shadowing in a heterogeneous nodule (arrows) in the left lobe of the thyroid gland. The FNA diagnosis was papillary carcinoma. Transverse USG image (B) shows smooth egg-shell type of macrocalcification (arrowhead) with shadowing (dotted arrow) along the periphery of an isoechoic nodule (arrow) in the left lobe. The FNA result was hyperplastic nodule

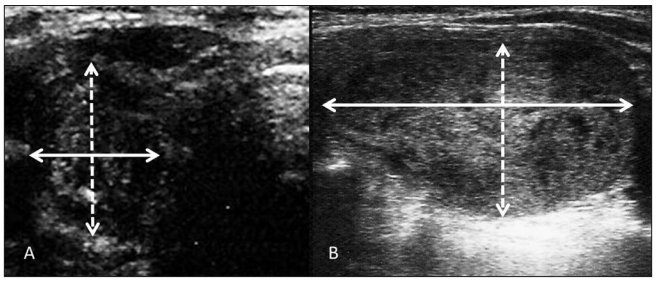

Figure 8 (A, B): Shape [solid arrow – transverse diameter (Tr); dashed arrow – antero-posterior diameter (AP)]. Transverse USG image (A) of the right lobe of the thyroid gland shows a poorly defined hypoechoic nodule, which is taller than wide. [AP>Tr] Transverse USG scan (B) shows a heterogeneous nodule, which is not taller-than-wide [AP<Tr] in the left lobe of the thyroid gland

from this study, since the recommended minimum size for ultrasound guided FNA is 1.5 cm.[5] Purely cystic nodules were not subjected to FNA.

Pathologic evaluation

All FNAs were performed under USG guidance. The cytopathology result was considered as the final diagnosis. Tissue diagnosis was available for 54 of the surgically resected nodules. Fourteen of these nodules for which FNA was inadequate and those that could not have a tissue diagnosis were not included in the study.

Results

Of the 240 nodules evaluated at USG, 35 were diagnosed to be malignant, 186 benign, and 19 were labeled suspicious for malignancy. After histopathological evaluation, 44 (18.33%) of the 240 nodules were found to be malignant and 196 (81.67%) were benign. Fifteen of the suspicious nodules were follicular neoplasms, while nine were subsequently diagnosed as follicular carcinomas at histopathology after surgical resection and six as adenomas. The remaining malignant nodules were diagnosed as papillary carcinomas in 32 patients and medullary carcinomas in 3 patients. In males, 36.8% (7/19) of the nodules were found to be malignant, whereas in females malignancy was seen in 16.7% (37/221) nodules.

The majority of the malignant lesions (37/44) had irregular, lobulated, or poorly defined margins. None of the nodules with cystic/predominantly cystic composition were found to be malignant. Most malignant nodules (34/44) demonstrated a taller-than-wide shape in comparison to benign nodules. Although the majority of the hypoechoic nodules were found to be benign, none of the hyperechoic nodules were malignant. Calcification occurred with greater frequency in malignant nodules, i.e., in 86.3% (38/44) malignant nodules vs. 23.9% (47/196) benign nodules. Thyroid

nodules with calcification were classified into those with microcalcifications and those with macrocalcifications. In our series, nodules with microcalcifications were found to be malignant in 87.8% cases, while those with macrocalcifications were found to be malignant in 17.3% cases [Table 1].

The sensitivities and specificities for each USG characteristic of thyroid nodules were determined. Poorly defined margins, marked hypoechogenicity, and a taller-than-wide shape were found to have a high diagnostic accuracy for distinguishing malignant from benign thyroid nodules [Table 2].

Table 1: Various USG features of benign and malignant thyroid nodules

Fine needle aspiration		Malignant	Benign	Total
Gender	Females	37	184	221
	Males	7	12	19
Margin	Smooth	4	135	139
	Lobulated	3	39	42
	Poorly defined	37	22	59
Calcification	Present	38	47	85
	Absent	6	149	155
Internal Contents	Solid	33	48	81
	Predominantly solid	6	43	49
	Predominantly cystic	5	101	106
	Cystic	0	4	4
Peripheral Halo	Present, thin and regular	13	129	142
	Absent or thick and irregular	31	67	98
Echogenecity	Hyperechoic	0	7	7
	Hypoechoic (excluding markedly hypoechoic nodules)	10	113	123
	Markedly hypoechoic	29	25	54
	Isoechoic	5	47	52
	Anechoic	0	4	4
Shape	Taller than wide	34	39	73
	Not taller than wide	10	157	167

The overall sensitivity, specificity, positive and negative predictive values for the ultrasound diagnosis of benign and malignant thyroid nodules were 81.8%, 87.2%, 59.0%, and 95.5% respectively [Table 3].

Discussion

Thyroid nodular disease is characterized by the presence of one or more palpable or nonpalpable nodules within the substance of the thyroid gland. A thyroid nodule is defined as a discrete lesion within the thyroid gland that is distinguishable from the adjacent parenchyma at USG.[4]

We found an overall higher percentage of malignant nodules in our series (18.33%) than has been previously reported in other studies.[1,5] However, we cannot exclude the possibility of a bias toward inclusion of nodules with higher risk of malignancy since our institute is a tertiary-care referral center for patients with thyroid disorders. As thyroid problems are much more common in women than men, this is probably the reason for the increased incidence found in women, in our series.

When more than 50% of the margin of a thyroid nodule is not clearly defined it is considered as poorly defined.[5,6] Malignant lesions tend to have poorly defined or irregular margins, whereas benign thyroid nodules tend to have sharp well-defined margins. The previously reported sensitivity of ill-defined or irregular margins for diagnosing malignant nodules ranges widely from 8.3% to 77.5%.[5,7] We found that poorly defined or irregular margins had a negative predictive value of 96.1% and the highest diagnostic accuracy (87.9%) amongst all the USG characteristics for diagnosing malignant nodules.

Table 3: Comparison of ultrasound with Fine needle aspiration/ histopathology

		Fine needle aspiration/ histopathology		Total
		Malignant	Benign	
USG	Malignant	36	25	61
	Benign	8	171	179
	Total	44	196	

Table 2: Diagnostic accuracy of USG features of malignant nodules

USG characteristic	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Poorly defined margins	37/44 (84.0)	174/196 (88.7)	37/59 (62.7)	174/181 (96.1)	211/240 (87.9)
Calcification	38/44 (86.3)	149/196 (76.0)	38/85 (44.7)	149/155 (96.1)	187/240 (77.9)
Microcalcification	29/44 (65.9)	192/196 (97.9)	29/33 (87.8)	192/207 (92.7)	221/240 (92.0)
Macrocalcification	9/44 (20.4)	153/196 (78.6)	9/52 (17.3)	153/188 (81.3)	162/240 (67.5)
Solid or predominantly solid composition	39/44 (88.6)	105/196 (53.5)	39/130 (30.0)	105/110 (95.4)	144/240 (60.0)
Absent or thick irregular halo	31/44 (70.4)	129/196 (65.8)	31/98 (31.6)	129/142 (90.8)	160/240 (66.6)
Markedly hypoechoic	29/44 (65.9)	171/196 (87.2)	29/54 (53.7)	171/186 (91.9)	200/240 (83.3)
Shape taller than wide	34/44 (77.2)	157/196 (80.1)	34/73 (46.5)	157/167 (94.0)	191/240 (79.5)

Values were found to be statistically significant (P value <0.05) using the chi-square test except for macrocalcification

Our experience shows that calcification occurs more commonly in malignant nodules (38/44) than in benign nodules (47/196). Also, the occurrence of malignancy was more common in nodules with calcification than in those without. We assessed nodules for presence of micro- as well as macrocalcification. Microcalcifications are seen sonographically as multiple punctate bright echoes that are less than 2 mm in size, with or without acoustic shadowing. As categorized by Kim *et al*.,[8] among the macrocalcifications were solitary calcifications (hyperechoic foci, >2 mm linear or round structures within the nodule or encircling less than 1/3rd of the nodule's margin), eggshell calcification (curvilinear hyperechoic shadow that extends along the margin of the nodule for more than 1/3rd of its circumference), and the not-otherwise-specified (NOS) variety (comprising the rest). Microcalcifications were found to be a highly specific USG feature of malignant thyroid nodules, with a high positive predictive value of 87.8%.

Moon *et al*. categorized the internal composition of a nodule according to the ratio of the cystic portion to the solid portion in the nodule; thus, the nodule could be predominantly solid (<50% cystic) or predominantly cystic (≥50% cystic).[9] Using the same criteria, our analyses showed that most thyroid nodules were solid or predominantly solid rather than cystic or predominantly cystic. The sensitivity of solid/predominantly solid composition was found to be the high (88.6%) but the positive predictive value was only 30%, indicating that most malignant nodules are solid or predominantly solid; however, most solid or predominantly solid nodules are benign.

A peripheral sonolucent halo surrounding the thyroid nodule represents blood vessels coursing around the lesion in a benign nodule. This halo is usually complete and thin. The irregular, thick, and incomplete halo seen around a malignant nodule is thought to represent compressed normal tissue due to rapid growth of the tumor.[1] Though in a recent series[10] the absence of a halo was the sign that was most predictive of malignancy on conventional USG, most studies have reported a low sensitivity and specificity for the presence or absence of a halo.[5,7] Our study demonstrated the sensitivity and specificity of an absent or thick, irregular halo to be 70.4% and 65.8%, respectively, making it an insignificant marker of malignancy.

Current 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.[11] In our series also, most of the malignant nodules (33/44) were hypoechoic in appearance, though the majority of the hypoechoic nodules were benign (165/198). In contrast, none of the malignant nodules were found to be purely hyperechoic or anechoic. Kim *et al*.[12] defined a markedly hypoechoic nodule as one that is hypoechoic to the strap muscles anterior to the thyroid gland. We found a low sensitivity (65.9%) but an appreciable specificity (87.2%) of marked hypoechogenecity for malignant thyroid nodules. The USG feature of marked hypoechogenecity has a high negative predictive value of 91.9% indicating that nodules that are not markedly hypoechoic are likely to be malignant in only about 8% of cases.

The shape of the nodule has also been studied as a marker of malignancy. The width of the nodule on a transverse scan corresponds to the natural growth planes. Malignant tumors have a tendency for centrifugal growth and show expansion perpendicular to the natural growth plane.[13–15] The appearance at USG is of a nodule that is taller than wide (i.e., anteroposterior diameter > transverse diameter on transverse scan). In 2006, Cappelli *et al.* in their series concluded that a taller-than-wide shape was a useful criterion for identifying a malignant lesion.[15] Popowicz *et al.* indicated hypoechogenicity, the presence of microcalcifications, and the shape (with height-to-width ratio >1) to be independent features suggestive of malignant lesions, irrespective of their size.[14] In the present study, we measured the anteroposterior (AP) and transverse (T) diameters and found AP≥T to have a moderately high specificity and diagnostic accuracy of 80.1% and 79.5%, respectively.

In conclusion, gray-scale USG features of thyroid nodules are useful to identify patients with clinically significant thyroid nodules from those with innocuous nodules. In our study, the USG features of poorly defined margins, marked hypoechogenicity, and taller-than-wide shape were found to have high diagnostic accuracy for identifying malignant thyroid nodules.

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