ORIGINAL ARTICLE

ULTRASOUND ASSISTANCE IN DIFFERENTIATING MALIGNANT THYROID NODULES FROM BENIGN ONES

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Background: The search is ongoing for simple, effective ways to identify and differentiate thyroid nodules in order to avoid invasive procedures. This study aims to perform an ultrasound assessment of clinically suspected patients with malignant nodules, to perform a fine needle biopsy on them, and to compare the results obtained. **Methods:** In total, 135 patients with thyroid nodules suspected to be malignant in the ultrasound underwent ultrasound-guided fine needle biopsies. The patients' gender, age, ultrasound views (echogenicity, shape, and calcification type), nodule size, number of nodules, and needle biopsy results were retrospectively evaluated. **Results**: Of the 135 patients, 117 (86.7%) were female and 18 (13.3%) were male. In terms of age, 67 (49.16%) were younger than 40 and the rest were older. According to the Chi-square test, a significant relationship was found between the type of nodule and calcification found in the ultrasound views (p=0.001). The nodule type was not significantly related to gender (p=0.563) or to the number of nodules (p=0.128); however, there was a significant relationship between nodule size and type (p=0.001). Ultrasound specificity, sensitivity, positive and negative predictive values, and accuracy for differentiating benign from malignant nodules were 93.2%, 93.8%, 81.1%, 98%, and 93.3%, respectively. **Conclusions**: Ultrasound views (comet tail artefact and linear echogenic foci) were better predictors of benign nodules than of malignant ones, while round, echogenic foci, brighter and larger than typical micro-calcifications without any visible echoes and multiple punctuate round echogenic foci were better predicted malignancy.

Keywords: Aspiration; Fine-Needle; Nodules; Thyroid; Ultrasound Imaging

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INTRODUCTION

Thyroid nodule is a common clinical finding with a prevalence of 3–7% in the general public based on a sensory examination and 20–76% based on an ultrasound examination (similar to autopsy results).[1] Because only 5% of thyroid nodules are malignant, the surgical removal of every thyroid nodule is neither acceptable nor practical. Fine needle aspiration (FNA) has been widely accepted as the preferred detection technique for the assessment of non-toxic thyroid nodules and aims primarily to triage patients in order to identify those requiring surgery and then to decide on appropriate surgical procedures.[2] Depending upon the type of lesion, thyroid FNA can be considered a diagnostic screening tool.[3] However, thyroid FNA is a limited technique, owing mainly to uncertain cytological features in differentiating benign from malignant follicular neoplasms, Hurthle cells, hyperplastic nodules, and follicular variants of papillary cancer.[3,4] At best, thyroid FNA results are non-diagnostic, suspicious, or unclear in 20–30% of the cases and the risk of cancer varies from 5–75.5% in the above-mentioned group.[3] The majority of thyroid nodules (more than 67%) are smaller than 15 mm in diameter. In the past, small nodules were considered benign and not to require further examination; however, recent studies have revealed these nodules may also be malignant.[5] There is a general consensus that ultrasound imaging and FNA are the preferred modalities for differentiating benign from malignant thyroid nodules.[6,7] The diagnostic value of FNA has not been extensively examined in small nodules[5], although if FNA is performed as and when required, it can prevent unnecessary surgeries[8]. Although ultrasound imaging can lead to findings that may help detect malignancies, it does not provide a definitive diagnosis of malignancy, because these findings may be common to both malignant and benign varieties.[5–9] Many studies have been conducted on the diagnostic value of ultrasound imaging for malignant thyroid nodules; however, their results are difficult to interpret. Echogenicity, nodule margin, calcification and its type, and the presence or absence of a halo may be helpful, but are not definitive diagnostic markers; FNA needs to be performed in conjunction with these findings.[5,10,11] One third of thyroid nodules are diagnosed as cysts, which can be detected using sensitive techniques such as ultrasound imaging.[7] Nodules are palpable only when they are larger than one centimetre and their palpability depends upon their location inside the gland (superficial or deep), the patient's neck anatomy, and the examiner's skills. A more sensitive diagnostic technique, such as ultrasound imaging, might therefore increase diagnostic accuracy. Moreover, despite its high sensitivity and specificity,

FNA has some limitations and should be performed by an experienced physician and cytopathologist to provide proper results. In addition, 20–30% of cases are reported in non-diagnostic form for different reasons, including fibrotic reactions that reduce the availability of cells for aspiration, cystic lesions with cell components that collect around the edge of the cyst, or excessively tiny nodules that render accurate aspiration impossible.[12] In addition, an ultrasound biopsy is more accurate and the location of the nodule can be better detected with this technique. The present study was therefore conducted to assess the ultrasound characteristics of thyroid nodules and then to assess their needle aspiration results, so as to identify a specific view for identifying benign and malignant nodules and to use this view to differentiate between nodule types. This would reduce FNA of nodules with benign ultrasound appearances and thus reduce the financial burden imposed on the health system and the psychological burden on patients.

MATERIAL AND METHODS

The present diagnostic test evaluation study was conducted on patients admitted to an endocrine clinic (from July 2015 to January 2016), by using census method, who underwent ultrasound (US) imaging for a suspected tumour or thyroid nodule following the endocrinologist's clinical examination. The research deputy of the medical school of our University of Medical Sciences approved this study. The ultrasound criteria assessed included the ultrasound view of echogenicity, calcification type (micro-calcification, coarse calcification, and peripheral rim calcification), the presence or absence of a halo surrounding the nodule and the shape of the nodule. All calcifications less than 2 millimetres were considered micro-calcifications. Based on the classification system proposed by Beland *et al*[13], the ultrasound results were divided into four groups:

1. Showing a classic comet tail artefact where an inverted echogenic triangle was clearly documented posterior to the focus (on US, small particles have effect on posterior aspect of them as comet tail artefact which define as bright triangular) (Figure-1A)
2. Containing linear echogenic foci larger than micro-calcifications (If posterior echoes present, not clearly triangular in shape) (bright foci on US which define as linear instead of dot like or triangular tail appearance hence are demonstrated bigger) (Figure-1B)
3. Containing round echogenic foci, brighter and larger than typical micro-calcifications without any visible echoes (round foci which are bigger and more bright in comparison with micro-calcification are seen therefore display non-echoic dot like appearance without tails) (Figure-1C)
4. Containing multiple punctuate round echogenic foci suggestive of micro-calcifications (innumerable white spots or echogenic foci are seen that originally belong to calcification) (Figure-1D)

Cases that belonged to one of the four groups or had no specific outcomes in terms of their ultrasound views, but which had a high clinical suspicion of malignancy according to the endocrinologist, were referred to the hospital's radiology department for FNA after consenting and then underwent an ultrasound-guided needle biopsy. Patients with calcified nodules and posterior shadowing in their ultrasound view, and who had nodules with a diameter less than 0.5 centimetres, were excluded from the study. Two pathologists separately examined the cytological specimens obtained from nodule aspiration. In order to reduce the error rate, the pathologists were kept blinded to the clinical and ultrasound results until diagnosis. Along with ultrasound views, baseline characteristics of the nodules, such as size and number of nodules, were evaluated. The nodules were divided into groups of larger and smaller than 1.5-centimetre diameters, based on the criteria outlined by the American Thyroid Association.[1] They were divided into groups of one nodule and more than one nodule. The cytological diagnosis was reported as a strong suspicion of benignity or malignancy, including also the type of nodule in some cases. Surgical resection was performed in cases of suspected or definitive diagnosis of malignancy; in all other cases, 3- or 6-month follow-ups were conducted through clinical examinations and ultrasound imaging. Finally, patients who met the inclusion criteria (n=135) and their FNAC results were consistent with the histopathological results of surgical resection. Data were gathered using a questionnaire including variables such as age, sex, ultrasound findings, cytopathology, and histopathology results, number of nodules, and nodule size. All patients' data were approved for use by the institutional review board of University of Medical Sciences and Services. All statistical analyses were performed using SPSS-17 for windows (IBM Inc., NY, US). Fisher's exact and Chi-square tests were used to compare the properties of the patients and ultrasound and pathological findings. Categorical data were expressed as frequency counts. The coefficient of agreement between the ultrasound and pathological diagnosis was determined using the Kappa test, in order to compare ultrasound characteristics and cytopathological findings. The level of statistical significance was set at $p<0.05$.

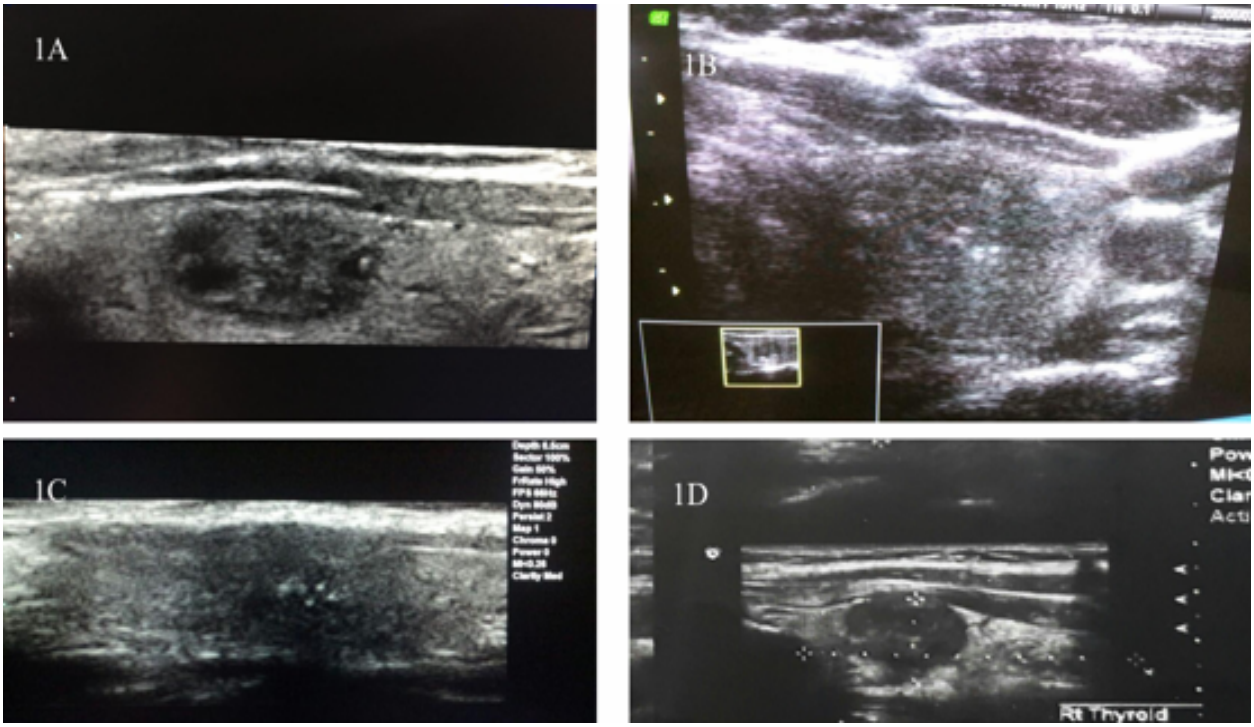
RESULTS

Of 135 patients, 117 (86.7%) were female and 18 (13.3%) male. In terms of the frequency distribution of age, 67 patients (49.6%) were younger than 40 and the remaining 68 (50.4%) were older. One hundred & eleven (82.2%) nodules were smaller than 1.5

centimetres in diameter and the remaining 24 (17.8%) were larger than 1.5 centimetres. In terms of the type of the nodule, 103 (76.3%) were benign and 32 (23.7%) were malignant. One hundred & nine (80.7%) of patients presented with one nodule and the remaining 26 (19.3%) with more than one nodule (Table-1).

In terms of the ultrasound view, 60 patients (44.4%) presented with view 1, 38 (28.1%) with view 2, 20 (14.8%) with view 3 and 17 (12.6%) with view 4. In terms of the relationship between the ultrasound characteristics and the type of nodule, in ultrasound view 1, 59 (98.3%) were benign and one (1.7%) was malignant. In ultrasound view 2, 37 (97.4%) were benign and 1 (2.6%) malignant. In ultrasound view 3, 7 (35%) were benign and 13 (65%) malignant. In ultrasound view 4, 17 (100%) were malignant. Given that ultrasound views 1 and 2 were almost identical in terms of their cases of malignancy and benignity, they were placed in one group (1A) for the statistical analyses and a total of three groups (1A, 2A, and 3A) were ultimately analyzed. In ultrasound group 1A (Beland *et al* view 1, 2), 98% of the cases were benign and 2% were malignant. In group 2A (Beland *et al*.; view 3), 35% of the cases were benign and 65% were malignant. In group 3A (Beland *et al*.; view 4), 100% of the cases were malignant. There was a significant relationship between the type of nodule and the ultrasound view (Chi-square test, p=0.001) (Table-2).

There was no significant relationship between gender and tumour type, in terms of its malignancy or benignity (Fisher's exact test, p=0.563). Only four benign nodules (16.7%) were larger than 1.5 cm in diameter, while the same was true for 20 malignant nodules (83.3%; Fischer exact test, p=0.001). Moreover, in terms of number of nodules, 23 (88.5%) benign nodules were more than one in their cluster, while the same was true for only three (11.5%) malignant nodules. However, the relationship between the two variables was not statistically significant (Fisher's exact test, p=0.128; (Table-1). According to the Kappa test, there was an acceptable correlation between an ultrasound view showing micro-calcification (view 4) and type of nodule (p=0.001). In terms of age and its relationship with type of nodule, 24 (35.3%) malignant nodules were in patients older than 40 while only eight (11.95%) of the nodules were malignant in patients younger than 40, indicating a significant relationship between age and nodule type; that is, the chance of the malignancy of nodules increases with age (Fisher's exact test, p=0.002). Ultrasound specificity, sensitivity, positive and negative predictive values and accuracy for the type of calcification observed were 93.2%, 93.8%, 81.1%, 98%, and 93.3% for differentiating benign from malignant nodules (Table-3).



Figures-1A: Ultrasound reveals classic comet tail artefact, 1B: linear echogenic foci larger than micro-calcifications, 1C: round echogenic foci, brighter and larger than typical micro-calcifications without any visible echoes, ID: multiple punctuate round echogenic foci suggestive of micro-calcifications

Table-1: Baseline characteristics of patients with thyroid nodules based on sex, age, nodule size and number of nodules

Patients		Malignant (n=32, 23.7%)	Benign (n=103, 76.3%)	*p-value
Gender, n (%)	Female	29 (24.8)	88 (75.2)	0.563
	Male	3 (16.7)	15 (83.3)	
Age (year)	<40	8 (11.9)	59 (88.10	0.002
	>40	24 (35.3)	44 (64.7)	
Size of nodule(s)	<1.5 cm	12 (10.8)	99 (89.2)	0.001
	>1.5 cm	20 (83.3)	4 (16.7)	
Number of nodule(s)	Single	29 (26.6)	80 (73.4)	0.128
	More than one	3 (11.5)	23 (88.5)	

*p-value: Fisher's exact test

Table-2: Frequency distribution of thyroid nodules based on ultrasound classification and findings

Ultrasound	Nodule type		Total n (%)	* P value
	Benign n (%)	Malignant n (%)		
1A	96 (98)	2 (2)	98 (100)	0.001
2A	7 (35)	13 (65)	20 (100)	
3A	0 (0)	17 (100)	17 (100)	
Total	103 (76.3)	32 (23.7)	135 (100)	

*p-value: Chi-square test

Table-3: Correlation between ultrasound views and FNAC results in diagnosis of thyroid tumours

		Nodule type		Total
		Benign (% of total)	Malignant (% of total)	
Sonography result	Benign	96 (71.1)	2 (1.5)	98
	% within Sono- result	98.0%	2.0%	100%
	%within Nodule type	93.2%	6.3%	72.6%
	Malignant	7 (5.2)	30 (22.2)	37
	% within Sono- result	18.9%	81.1%	100%
	%within Nodule type	6.8%	93.8%	27.4%
	Total	103	32	135
	% within Sono- result	76.3%	23.7%	100%
	%within Nodule type	100%	100%	

Accuracy: 93.3%, Sensitivity: 93.8%, Specificity: 93.2%, PPV: 81.1%, NPV: 98%, Fischer's Exact test, p-value=0.001

DISCUSSION

Thyroid nodule is a common endocrine clinical finding.[1] FNAC is widely accepted as the preferred diagnostic technique used to assess non-toxic thyroid nodules and aims primarily to triage patients so as to identify those requiring surgery and to decide upon an appropriate surgical procedure.[2] However, despite its high sensitivity and specificity; FNA has a number of limitations. Another modality that may increase the accuracy of FNA is ultrasound imaging (for example, for finding the exact location of the nodule). The present study was conducted to assess the ultrasound characteristics of thyroid nodules compared to cytological findings obtained from ultrasound-guided FNA, in order to differentiate benign from malignant nodules. Although no radiographic modalities can accurately identify the type of a nodule, a set of criteria can help make the right diagnosis, including the presence or absence of calcification, the type of calcification, the nodule dimensions (for instance, the length-to-width ratio), nodule margins (organized or disorganized), nodule echogenicity, and a view of the intra-nodular vessels.[14,15] The nodule can be better identified with two or more of these diagnostic criteria. The pattern of calcification is also interesting in that fine, macro and micro calcifications are highly consequential, as micro-calcification triples the rate of nodule cancers while macrocalcification approximately doubles the risk.[16–18] In the present study, the lowest number of malignant cases was found in the comet-tail view, in which particles were seen with a luminous tail, consistent with the study by Beland *et al.*[13] However, in our study, 1.7% of nodules belonging to US view 1 were malignant, in contrast with Beland *et al*, in which all cases with this view were benign. In the present study, all nodules with micro-calcification (ultrasound view 4) were malignant in the needle biopsy, while in ultrasound view 3, in which calcification had occurred in the form of macro-particles, only 65% of the nodules were malignant. By contrast, Beland *et al* found that only 4% and 29% of nodules with the characteristics of views 3 and 4, respectively, were malignant.[13] The discrepancy between our results those of Beland *et al* could be due to their study limitations: in their study, some of the nodules containing echogenic foci lacked FNA data; in ours, the FNA results of all patients were included. In studies conducted on the ultrasound characteristics of thyroid nodules by Chammas *et al*[19] and Shi C *et al*[20], fine micro-calcifications were associated with higher malignancy. The positioning of the particles and the calcification pattern (the particles being fine or coarse) are considered one of the most helpful ultrasound findings. Another criterion is nodule shape. According to previous studies, although the

majority of benign and malignant nodules are either round or oval, the halo around them is critical. The nodule is more likely to be benign if the halo surrounding it is full and uniform. According to published reports, malignant tumours are approximately 2.5 times more common in women compared than in men; in the present study, no significant differences were observed between the two groups in terms of gender.[21–23] Nevertheless, consistent with other studies, malignancy increased in thyroid nodules with age.[23–29] According to previous studies, the size of the nodule cannot predict nodule type. The American Thyroid Association and the Society of Radiologists recommend further investigations for malignancy in thyroid tumours larger than 10 millimetres, as they run a greater risk of malignancy[18]. However, in nodules smaller than 10 millimetres, further investigations are only necessary when the ultrasound or examination results and the patient'' history imply risk[23]. Nam Goong *et al* found a 64% concordance between ultrasound results and FNAB at the 5-millimetre cut-off point in nodules smaller than 5 millimeters[22]. In a study by Betul Unal, this concordance was 52.4% in nodules smaller than 10 millmeters.[23] The present study found a significant relationship between tumour size and type. Other studies have shown no significant differences in the risk of malignancy between nodules smaller and larger than 10 millimetres; however, Kovacevic suggests FNA for 5 millimetre nodules.[21] The disparity of findings between the present study and other studies appears to be due to the difference in the cut-off points. In the present study, 80% of patients had nodules smaller than 1.5 centimetres. Future studies are recommended to base their cut-off points on smaller tumours, so as to enable a reliable comparison between results. In a study conducted by Yoon *et al* comparing FNA and ultrasound results in nodules larger than 3 centimetres, the ultrasound sensitivity was reported as 96.7%, specificity as 85.9%, positive predictive value as 76.6%, negative predictive value as 98.2% and accuracy as 89.4%. Based on these results, FNA was recommended for nodules larger than 3 centimeters[17], consistent with the results of the present study. Ultrasound characteristics, rather than nodule size, should be used to differentiate between nodules. In the majority of cancer cases, the nodule is single in its cluster rather than multiple. In a study by Kunreuther *et al*, the majority of malignant nodules were single, and the risk of cancer decreased with each additional nodule.[21] In the present study, no significant relationships were found between number of the nodules and malignancy. Studies conducted by Ugurlu *et al*[19] and Rahimi *et al*[17] showed an increased risk of malignancy with single nodules or with a maximum of two nodules; however, Taneri *et al* showed that multiple nodules increase this risk[29]. Higher numbers of nodules do not increase the risk of malignancy, but there is no consensus among researchers about this relationship. Further studies with larger sample might clarify the relationship. The majority of malignant nodules were also shown to be hypo-echoic compared to benign nodules[27,28], whereas most benign nodules are either iso-echoic or hyper-echoic. Similar to our study, Kim *et al* compared ultrasound and FNA results of thyroid nodules to ultrasound criteria for the diagnosis of malignancy, including micro-calcification, disorganized margins, and hypo-echogenicity.[14] In the present study, the US calcification patterns (views 1–4) had a 93.8% sensitivity, 93.2%, specificity, 93.3% accuracy, 81.1% PPV, and 98% NPV for differentiating between malignant and benign nodules, which shows a higher specificity, diagnostic accuracy, and PPV compared to other studies.[14] Tae *et al* assessed the ultrasound value in differentiating malignant from benign thyroid nodules in Korea and reported an ultrasound sensitivity of 87%, specificity of 86.5%, positive predictive value of 48.4%, negative predictive value of 97.8%, and accuracy of 86.5%. Given the negative predictive value of the ultrasound, they concluded that a more invasive technique such as FNA should be performed in cases where there is even one sign of malignancy, but that the ultrasound results are reliable when there is no sign of malignancy.[15]

Rahimi *et al* evaluated ultrasound and FNA results in their ability to differentiate malignant from benign nodules and found the signs associated with malignancy in the ultrasound results to include disorganized margins, calcification, single nodules and solid and hypo-echoic nodule, and found no relationships between nodule size and malignancy.[17] They suggested that thyroid nodules of any size should be further examined for malignancy, consistent with the results of the present study, as ultrasound results have greater predictive power than tumour size in differentiating malignant from benign nodules.

CONCLUSIONS

According to the results, type of calcification in the ultrasound view assists in the differentiation of malignant from benign nodules. Both US views (comet tail artefact and linear echogenic foci) were better predictors of benign nodules than of malignant ones, while round, echogenic foci, brighter and larger than typical micro-calcifications without any visible echoes (view 3) and multiple punctuate round echogenic foci (view 4) were better predicted malignancy. In addition, the risk of malignancy increased with the nodule size and age. Therefore, it is suggested that patients older than 40 years with nodules larger than 1.5 centimetres with a hypo-echogenic ultrasound view and a calcification view of 3 or 4 are considered high-risk and undergo needle biopsy.

AUTHORS' CONTRIBUTION

SHT: Conceived the study design, supervised the study, write up and proof reading, MV, AG, NS, FH: Data collection, Statistical analysis and Literature review.

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