Original Article

Utility of ultrasound elastography in evaluation of thyroid nodules and correlation with cytology

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Abstract

Background: Ultrasound elastography (USE) has emerged as a potentially useful tool in the evaluation of thyroid nodules. The aim of this study was to assess the efficacy of elastography in differentiating benign from malignant thyroid nodules with fine-needle aspiration cytology (FNAC) analysis as reference standard.

Materials and Methods: This was a cross-sectional prospective study carried out at a tertiary care center in South India between May 2014 and March 2015. Consecutive patients with solid nodule in the thyroid gland on conventional ultrasound (US) underwent USE, followed by US-guided FNAC of the thyroid nodule. The findings of B-mode images and USE were correlated with cytology. Statistical analysis was performed using SPSS version 24. Descriptive statistics were presented as mean ± standard deviation. The diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of USE were calculated.

Results: A total of sixty patients with sixty solid thyroid nodules were enrolled in the study. The mean age of the patients was 48.27 ± 16.10 years. About 83.3% were females. The frequency of benign nodules on cytopathologic analysis was 60% (n = 36). Seventy-five percent of the malignant lesions had irregular or poorly defined borders with lobulated margins on US. The sensitivity, specificity, positive predictive value, and negative predictive value of USE were 91.7%, 77.77%, 73.33%, and 93.3%, respectively, with FNAC as reference standard. Higher elastography scores were found to be significantly associated with malignant cytology (P = 0.0001).

Conclusion: Elastography, with its fairly high diagnostic accuracy and correlation with malignant cytology, can be an effective noninvasive adjunctive tool in distinguishing benign from malignant thyroid nodules.

Keywords: Elastography, thyroid nodules, ultrasound

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INTRODUCTION

The prevalence of thyroid nodules which are clinically palpable is about 2%–6% in the general population.[1] Although majority of these nodules are benign, up to 7% can be malignant.[2,3]

On palpation, a hard or firm nature is associated with an increased risk of malignancy. However, palpation is a highly subjective method and its value is limited in patients with multinodular goiter or deep-seated nodules. Ultrasonography (USG) is the most commonly used imaging modality to diagnose thyroid nodules. The utility of

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USG in differentiating benign from malignant lesions has been established by several studies.[4-6] However, no USG feature has been shown to have both high sensitivity and high specificity in detecting malignancy in thyroid nodules.[7] Elastography is a newly developed noninvasive dynamic imaging technique analogous to manual palpation. This technique uses ultrasound (US) to estimate tissue stiffness by measuring the degree of distortion under application of an external force.[8] Several studies have used US elastography (USE) for evaluation of thyroid disorders.[9-11]

Fine-needle aspiration cytology (FNAC) is an efficient tool in distinguishing benign nodules that can be managed conservatively from those with suspicious or malignant features that warrant further intervention. Limited data exist on the utility of elastography in differentiating benign from malignant lesions of the thyroid and its correlation with FNAC, especially from India. The aim of this study was to assess the efficacy of elastography in differentiating benign from malignant thyroid nodules with FNAC analysis as reference standard.

MATERIALS AND METHODS

This prospective study was carried out at a tertiary care center in South India between May 2014 and March 2015. Consecutive patients of either gender who were found to have thyroid swelling/goiter on clinical examination and referred for USG were considered. Only those with solid thyroid nodules at least 8 mm in size on conventional US were included in the study. Cystic lesions with no solid component, multinodular goiters with coalescent nodules, and nodules with eggshell calcification were excluded from the study. A large nodule involving more than 75% of thyroid lobe volume was also excluded because of inadequate normal thyroid tissue to be used as reference. The institutional review board approved the study protocol, and the protocol complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

With a patient in supine position and neck fully extended, B-mode US of the thyroid gland was performed with SIEMENS ACUSON S2000 machine using high-frequency probes 9 L4 and 14 L5. US features studied included echogenicity, regularity of borders, presence of halo, vascular pattern, and calcification. Thyroid imaging reporting and data system (TIRADS) scoring was used to categorize the lesions[12] [Table 1].

USE was performed with SIEMENS ACUSON S2000 at the same time as the B-mode examination. The probe was placed over the region such that the lesion is in the center of the image, holding the scan plane perpendicular to the skin surface. At least 5 mm of normal adjacent tissue was included to assess the lesion stiffness in relation to the average elasticity of surrounding tissue. Patients were asked to hold their breath and avoid swallowing during examination in order to minimize the motion of the thyroid gland. The elasticity images were obtained by appropriate compression, followed by decompression of the transducer. The images were displayed on split-screen mode with US grayscale images on the left and USE images on the right. Multiple frames were acquired, and the best-fit B mode-USE image pairs were selected for examination [Figures 1 and 2]. The targeted lesion was scored as 1–4, using strain elastographic scores proposed by Asteria *et al*.[9] [Table 2].

US-guided FNAC of the thyroid nodule was done using a 22G needle, and the lesion was aspirated at least twice with the freehand technique. The aspirated contents were expelled onto glass slides and immediately fixed with 95% ethyl alcohol. The slides were stained with modified Papanicolaou staining and examined under light microscopy. The cytological results were classified

Table 1: Thyroid image reporting and data system scoring of thyroid nodules

Category	Description
TIRADS 1	Normal thyroid gland
TIRADS 2	Benign conditions
TIRADS 3	Probably benign nodules (<5% malignant)
TIRADS 4	Suspicious nodules (5%-80% malignancy rate)
TIRADS 5	Probably malignant nodules (malignancy rate >80%)
TIRADS 6	Biopsy-proven malignant nodules

TIRADS – Thyroid image reporting and data system

Table 2: Asteria's criteria of scoring of thyroid nodules on elastography

Elasticity Score	Description
Score of 1	Elasticity in the entire examined area
Score of 2	Elasticity in a large part of the examined area
Score of 3	Stiffness in a large part of the examined area
Score of 4	Nodule without elasticity

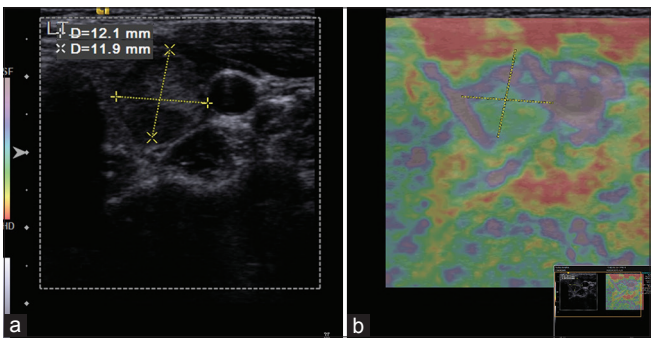

Figure 1: Thyroid nodule images obtained on conventional ultrasound (a) and ultrasound elastography with elasticity score 2 (b)

as benign, indeterminate/suspicious (follicular lesions), and malignant according to standard pathological criteria.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, SPSS Inc., Chicago. IL, USA) version 24. Descriptive statistics were presented as mean ± standard deviation. Qualitative variables were presented in the form of frequency and percentages and compared using the Chi-square test. The diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Statistical significance was set at $P < 0.05$.

For statistical purposes, USE score of 2 was strongly predictive of a benign lesion and therefore considered sample negative for malignancy. Scores of 3 and 4 describing stiffness in a large part of the examined area and nodule without elasticity, respectively, were considered as positive for malignancy in our study. With regard to cytology, two groups were considered for evaluation: benign and malignant. Patients with fine-needle aspiration (FNA) reports of indeterminate/suspicious (follicular lesions) were also included in the malignant group for statistical purposes.

RESULTS

A total of sixty patients with sixty solid thyroid nodules were enrolled in the study. The age of the patients ranged from 19 to 85 years (mean: 48.27 ± 16.10 years). About 83.3% (n = 50) were female and 16.7% (n = 10) were male. The frequency of benign nodules on cytopathologic analysis was 60% (n = 36), whereas 40% (n = 24) were nonbenign (follicular lesions and malignant tumors). Of the 24 nonbenign thyroid nodules, 20 had been reported as papillary carcinoma, 2 as medullary carcinoma, and 2 as follicular neoplasm. Table 3 shows the presenting clinical features and cytologic diagnoses of patients with thyroid nodules.

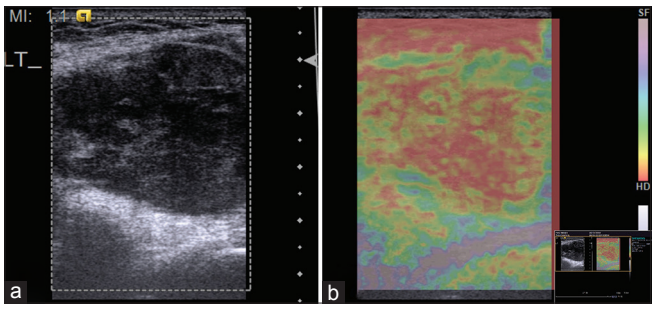

Figure 2: Heterogeneous nodule on conventional ultrasound (a) and ultrasound elastography with elasticity score 4 (b)

Seventy-five percent of the malignant lesions had irregular or poorly defined borders with lobulated margins on US and 68% had microcalcification. Seventy-seven percent of the benign nodules were hyperechoic. On TIRADS scoring, score of 2 was found in 24 cases, all benign lesions; score 3 in 14 cases, 8 benign and 6 malignant; score 4 in 12 cases, 4 benign and 8 malignant; and score 5 in 10 cases, all malignant lesions. Table 4 shows the correlation of USE scores and FNAC diagnoses of patients.

The sensitivity, specificity, positive predictive value, and negative predictive value of US elastography were 91.7%, 77.77%, 73.33%, and 93.3%, respectively, with FNAC as a reference standard [Table 5]. Higher elastography scores were found to be significantly associated with malignant cytology ($P = 0.0001$).

DISCUSSION

Thyroid nodules are common in the general population, and the reported prevalence varies depending on the identification method. Apart from serum markers and FNAC, USG plays an important role in the detection and evaluation of thyroid nodules. Being noninvasive conventional US provides information regarding the nodule dimensions, structure as well as parenchymal changes and is widely used to determine which nodules should be biopsied. Microcalcifications, hypoechogenicity,

Table 3: Clinical presentation of thyroid nodules

Clinical feature	Benign	Malignant	Total number of patients, *n* (%)
Neck swelling	26	2	28 (46.7)
Weight loss	2	8	10 (16.7)
Dysphagia	2	6	8 (13.3)
Pain	6	2	8 (13.3)
Hoarseness of voice	0	6	6 (10)

Table 4: Correlation of elastography scores and cytologic diagnoses of patients with thyroid nodules

Elastography score	Benign	Malignant	Total
2	28	2	30
3	8	2	10
4	-	20	20
Total	36	24	60

Table 5: 2×2 table for calculation of sensitivity, specificity, positive predictive value, and negative predictive value of ultrasound elastography taking cytology as a reference standard

USE	Malignancy (positive on FNA)	Malignancy (negative on FNA)	Total
Positive	22 (true positive)	8 (false positive)	30
Negative	2 (false negative)	28 (true negative)	30
Total	24	36	60

FNA – Fine-needle aspiration; USE – Ultrasound elastography

irregular or microlobulated margins, taller than wide shape, and increased intranodular vascularity have been reported as independent risk factors for malignancy.[13,14] Although these features are characterized by high specificity, their positive predictive value is lowered by their relatively low sensitivity.[15]

USE is based on the principle that the softer parts of tissues deform easier than the harder parts, under compression, thereby allowing an objective determination of tissue consistency. Malignancy is often associated with changes in the mechanical properties of a tissue, and USE has been used to differentiate benign from malignant lesions in the breast, liver, and prostate.[16-18] The two general criteria for evaluating the efficacy of USE are elasticity scores and strain ratio. Although elastography has been suggested to be of great use as an adjunctive tool in the diagnosis of thyroid cancer, studies have reported conflicting evidence on its additional value in predicting thyroid malignancy.[19-21]

This study was planned to assess the efficacy of elastography in differentiating benign from malignant thyroid nodules with FNAC analysis as a reference standard. The mean age of presentation for benign nodules was 44.31 ± 14.28 years, whereas that for malignant lesions was 54.21 ± 17.13 years ($P = 0.018$) A majority of our cases diagnosed with thyroid nodules were females (83.3%). Thyroid nodules are reported to be four times more common in women than men, and their frequency increases with age and low iodine intake.[22] The female preponderance has been explained by the hormonal influences of estrogen and progesterone, as increasing nodule size and new nodule development have been demonstrated to be related to pregnancy and multiparity.[23]

Of the sixty nodules studied, 60% were benign ($n = 36$) and 40% ($n = 24$) were nonbenign. Of the 36 benign nodules, 26 were colloid nodules and 10 were adenomatoid nodules. The 24 nonbenign lesions included 20 papillary carcinomas, 2 medullary carcinomas, and 2 follicular neoplasms. The most common clinical presentation was painless mass in the neck which was encountered in almost 47% of the patients. Majority of the patients who presented with significant weight loss, dysphagia, and hoarseness of voice were found to have malignant lesions. Dysphagia, dysphonia, reports of rapid growth, male gender, prior head-and-neck irradiation, and presentation at extremes of age have been reported as significant elements in the patient's history, which increase the likelihood of malignancy.[24]

Our study found that 75% of malignant lesions had irregular or poorly defined borders with lobulated margins, whereas 68% of malignant lesions had microcalcification. Seventy-seven percent of the benign nodules were hyperechoic, whereas 23% were hypoechoic. None of the hyperechoic nodules was malignant. Although none of these US features is sufficient to differentiate benign lesions from malignant ones, studies have shown that a combination of at least two of the features is better helpful in pointing out a subset of lesions at high risk for malignancy.[25,26]

With regard to TIRADS score, all the nodules with TIRADS score of 2 ($n = 24$) had benign FNA characteristics, whereas all the patients with TIRADS score of 5 ($n = 10$) were found to have malignant lesions on FNA. Among TIRADS 3 lesions ($n = 14$), 57% were benign, and among TIRADS 4 lesions ($n = 12$), 33% were found to be benign on FNA.

On US elastography, score of 2 was found in 30 nodules, 28 benign and 2 malignant; score 3 in 10 cases, 8 benign and 2 malignant; and score 4 in 20 cases, all malignant. The sensitivity, specificity, positive predictive value, and negative predictive value of US elastography were 91.7%, 77.77%, 73.33%, and 93.3%, respectively, with FNAC as a reference standard.

The elastography scores of 3–4 were achieved in 22 of the 24 malignant nodules in our study. Among the 20 nodules with cytologic diagnosis of papillary carcinoma, 18 were correctly scored as malignant by USE, thus achieving 90% diagnostic accuracy in terms of confirming the malignant etiology. Only two nodules were incorrectly given a USE score of 2. Both of the two nodules with medullary carcinoma thyroid had been scored as malignant on USE (score 4). We had eight false-positive nodules (score 3) which can be attributed to the fibrotic changes and calcification that lead to hardness of the nodule under study.

Our observations are in line with that of Mehrotra *et al.* who have reported the sensitivity and specificity of USE for thyroid malignancy to be 90% and 79.6%, respectively.[27] Of the 147 nodules examined by USE and US-guided FNAC, 122 were nonneoplastic, 5 were benign neoplasm, 10 had indeterminate cytologies, and 10 had malignant neoplasms. The observed positive and negative predictive values were 24.3% and 99.1%, respectively. In contrast, we found the positive predictive value of elastography to be 73.3% in our study. This can be explained by the high prevalence of malignant lesions among our study population.

The sensitivity and specificity of elastography based on elastography scores have been reported to vary from

86% to 97% and 66%–100% from various studies.[8,9,28] The observed wide differences are due to the fact that these studies involve different groups of populations, referral bias (patients referred for FNAC/surgery), varied inclusion and exclusion criteria, different machines as well as criteria for USE scoring. A recent comprehensive meta-analysis to investigate the diagnostic value of qualitative elastography in distinguishing benign from malignant thyroid nodules included 20 studies involving 3973 thyroid nodules.[29] Pooled results of elastography have shown a summary sensitivity of 85% (95% confidence interval [CI], 79%–90%) and specificity of 80% (95% CI, 73%–86%). The respective pooled negative predictive and positive predictive values were 97% (95% CI, 94%–98%) and 40% (95% CI, 34%–48%), respectively.

Despite the potential limitations of USE such as intra/interobserver variability and nodule characteristics such as calcification and follicular carcinoma (which appears soft), USE is considered to be reliable in the diagnosis of benign nodules in view of the high negative predictive values observed in most of the studies including ours.

FNAC is an essential diagnostic modality in the evaluation of thyroid nodules and features in all the guidelines in patient management.[30] Although the use of FNAC in the evaluation of thyroid nodules provides reliable results, it is invasive and the potential for complications such as postprocedural hematoma, increased patient morbidity, cost, and possibility of nondiagnostic specimen does exist. Unnecessary/repeat FNACs and FNA-induced changes can result in false-positive results on thyroid cytology and false-negative results or understaging of the tumor on thyroid pathology.[31,32]

Higher elastography scores were found to be significantly associated with malignant cytology ($P = 0.0001$) in our study. Merino *et al*. have also noted a statistically significant association between elasticity scores and cytological results, suggesting that malignant nodules could be excluded by elastography.[33]

Limitations of our study include small sample size and the fact that observations are from a single center.

CONCLUSION

With scanty literature comparing elastography with FNAC available from this part of the world, our study highlights that elastography has a fairly high diagnostic accuracy and correlation with malignant cytology. It can be an effective noninvasive adjunctive tool in distinguishing benign from malignant thyroid nodules and reduce the burden of unnecessary invasive procedures.

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Conflicts of interest
There are no conflicts of interest.

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