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ORIGINAL ARTICLE

Role of combined grey scale US and US tissue elastography in differentiating solid thyroid nodules

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Abstract *Background:* Ultrasonographic (US) examination is an accurate method for detecting thyroid nodules, but its use in differentiating between benign and malignant thyroid nodules is relatively low. US elastography has been applied to study the hardness/elasticity of nodules to differentiate malignant from benign lesions thus deviating a significant group of patients from unnecessary FNAB.
Objectives: The aim of the study is to evaluate the validity of combined grey scale US and tissue elastography in differentiating benign form malignant solid thyroid nodules.
Methods: The study included 46 selected patients with solid thyroid nodules according to our inclusion and exclusion criteria. The patients underwent surgery for compressive symptoms or suspicion of malignancy on FNA cytology. US features and tissue elastography were scored according to the Rago criteria (1).
Results: On US elastography: all the 31 cases with a final diagnosis of benign nodule had a score of 1–3, while 14 of 15 (94.1%) with a final diagnosis of carcinoma had a score of 4–5, with a sensitivity of 93.3%, a specificity of 100% and an accuracy of 97.8%. Combined US and elastography reveals that hypoechogenicity/score 4–5 was most predictive of malignancy with sensitivity 80% and specificity 100%; and accuracy 93.4%.
Conclusions: US elastography seems to have great potential as a new tool for differentiating solid thyroid nodules and for recommending FNAC. Combined grey scale US features and US elastography added no significant value when compared with US elastography alone. Further prospective studies are needed.

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1. Introduction

The prevalence of thyroid nodules is about 3–8% in the general population (2–5) and is greater than 50% after age of 65 years (2). Most thyroid nodules are benign, with 5–15% being malignant (7). The challenge of managing thyroid

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nodules is to reassure patients with benign disease and to diagnose patients with malignant disease (6). A firm and hard thyroid nodule on palpation is associated with an increased risk of malignancy. Palpation is subjective and highly dependent on the examiner and on the size and location of the nodules (8).

Ultrasonographic (US) examination is an accurate method for detecting thyroid nodules, but its use in differentiating between benign and malignant thyroid nodules is relatively low (2). Fine-needle aspiration (FNA) is the standard procedure to determine whether a thyroid nodule is cancerous. However, FNA is an invasive procedure, and about 10–20% of FNAs yield inadequate results and lead to repeat biopsy (4). Palpation has been used in clinical examination to assess the degree of firmness of a thyroid nodule. However, palpation is a subjective method, and the assessment varies depending on the size and location of the nodule and on the examiner (5).

Indeed, as compared with FNA, thyroid US has the advantage of being a noninvasive procedure giving immediate information. Among several US patterns, hypoechogenicity of the nodule, spot microcalcifications, and the absence of halo sign have been useful for predicting thyroid malignancy (9,10). However no ultrasound feature has both high sensitivity and high specificity in detecting malignancy of thyroid nodules (6).

Ultrasonographic (US) elastography (sonoelastography) is a noninvasive imaging technique that can be used to depict relative tissue stiffness or displacement (strain) in response to an imparted force. Stiff tissues deform less and exhibit less strain than compliant tissues in response to the same applied force. Thus, the basis of elastography is analogous to manual palpation (1,11). The application of US elastography for imaging tissues is relatively novel, first described in 1987 by Krouskop et al. (12).

Elastography is a newly developed dynamic technique that uses US to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. US is applied to study the hardness/elasticity of nodules to differentiate malignant from benign lesions. A recent report on thyroid nodules concluded that US elastography may predict malignancy in a score of 4–6 with a sensitivity of 89.3%, a specificity of 88.2% and an accuracy of 88.9% (6)

2. Patients and methods

The study included 70 patients with solid thyroid nodule on grey scale US, and 24 patients were excluded according to our exclusion criteria, so the total number of selected patients were 46 patients (31 females, mean age of 43 years, and 15 males, mean age of 39 years), seen from January 2011 till January 2013.

****Inclusion criteria by grey scale US***: any solid thyroid nodule included in a total of 70 patients

*Exclusion criteria by grey scale US:

1. Cystic thyroid nodules (6 patients).
2. Calcified shell thyroid nodules (10 patients).
3. Coalescent nodules in multinodular Goitre (8 patients).

The selected 46 patients underwent surgery for compressive symptoms or suspicion of malignancy on FNA cytology. Approval of the medical ethics committee was obtained and all patients gave their informed consent prior to the study. Serum calcitonin was undetectable in the 46 patients. All patients were euthyroid. FNA was performed under US guidance by a skilled radiologist using a 23-gauge needle attached to a 10 ml syringe. The material was sent for histological examination by an experienced cytologist.

**The indications for surgery were:

1. Large size nodule with benign cytology (12 patients) for cosmetic reason because of disfigurement.
2. An indeterminate FNAC (16 patients).
3. Non diagnostic cytology (6 patients).
4. A cytological diagnosis suggestive (in 7 patients) or suspicious (in 4 patients) of papillary carcinoma.
5. Suspected medullary carcinoma in one case.

2.1. Thyroid conventional US and US elastography

Thyroid US and US elastography were performed using a real-time ultrasound (GE LOGIQ P6, using linear high frequency probe with frequency of 10 MHz, GE Medical Systems, USA). A careful evaluation of the following US parameters was performed on all thyroid nodules: **echogenicity** (hyperechoic, isoechoic, or hypoechoic with respect to normal thyroid parenchyma), presence or absence of the **halo sign**; **spot microcalcifications** (presence of hyperechoic spots less than 2 mm, without acoustic shadowing); and colour flow **Doppler pattern** that was defined as the absence of blood flow (type I), perinodular and absent or slight intranodular blood flow (type II), and marked intranodular and absent or slight perinodular blood flow (type III) (9). US elastography was performed during the US examination, using the same machine and the same probe. The probe was placed on the neck with light pressure, and a box was highlighted by the operator that included the nodule to be evaluated. In the case of multiple nodules, each nodule is evaluated separately. The principle of US elastography is to acquire two ultrasonic images (before and after tissue compression by the probe) and track tissue displacement by assessing the propagation of the imaging beam. A scale is available on the machine to measure if adequate compression was used (Fig. 1). The US elastogram was displayed over the B-mode image in a colour scale that ranges from red, for components with greatest elastic strain (i.e. softest components), to blue for those with no strain (i.e. hardest components) (Fig. 2). The elastograms thus obtained were classified according to the scores by Rago et al. (1). Elasticity according to Rago et al. (1) (thereafter, Rago criteria) originated from the elastography scale by Ueno et al. (13) and was applied to thyroid nodules and elastography scores were classified on a scale of 1 to 5 (Fig. 2). Nodules with Rago scores of 4 and 5 were classified as suspicious for malignancy (Table 1 and Fig. 2). It is important that the level of pressure is maintained constant throughout the examination (see Figs. 3–5).

All examinations were performed by the same operator, who was not aware of the results of cytology. Static and moving images were also recorded to be reviewed subsequently by a second skilled US examiner. The agreement on the scoring of US parameter was more than 92% between the two observers. In particular, scoring by the two examiners was coincident in 42 of 46 patients. In four cases the final score was agreed after conjoint re-examination of the recorded movies.

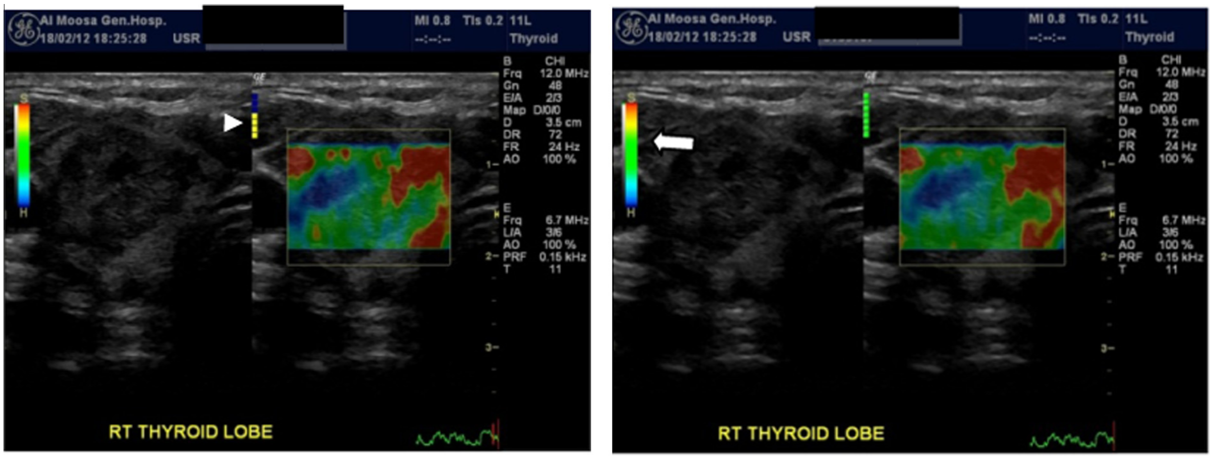

Fig. 1 Showing the automated calibrated compression scale (white head) (a) the scale is not totally full so inadequate, (b) the scale is full so the images can be interpreted. Colour scale (white arrow) that ranges from red (i.e. softest components), to blue (i.e. hardest components).

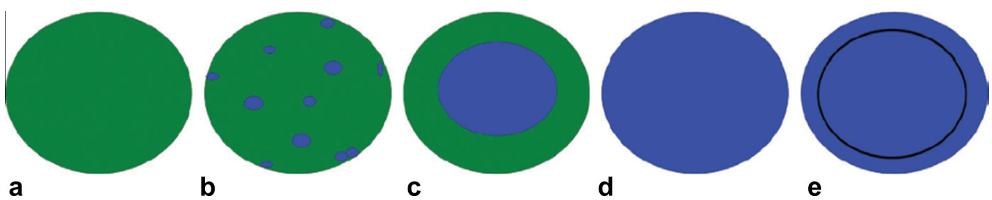

Fig. 2 Elastogrphy scores according to Rago criteria (quoted from **8**).

Table 1 Elasticity score (1,15).

Score	
1	Elasticity in the whole nodule
2	Elasticity in a large part of the nodule
3	Elasticity only at the peripheral part of the nodule
4	No elasticity in the nodule
5	No elasticity in the nodule and in the posterior shadowing

3. Results

3.1. Histology

Of 46 cases, 15 (32.6%) had a final diagnosis of malignancy on histology: **13** papillary thyroid carcinomas, including 8 classic variants, four follicular variants, and one tall cell variant; **one** minimally invasive follicular carcinoma; and **one** medullary carcinoma. Of 46 nodules, **31** (67.4%) were benign at histology: **24** follicular adenomas, **6** hyperplastic nodules, and **one** oxyphilic adenoma.

3.2. Grey scale US

Nodule hypoechogenicity (sensitivity 80% and specificity 61.2%; accuracy 67.4), absent halo sign (sensitivity 40% and specificity 19.3%; accuracy 26.1%), spot microcalcifications (sensitivity 66.7% and specificity 70.9%; 69.5%) were the US patterns most predictive of malignancy. The pattern of intranodular blood flow, taken alone, was not predictive of malignancy (sensitivity 6.7% and specificity 96.7%; accuracy 67.4) (Table 2). The absence of halo sign combined with the presence of spot microcalcifications as well as absent halo sign/hypoechogenicity was most predictive of malignancy (sensitivity 60% and specificity 93.5%; and accuracy 78.3% and 82.6% respectively) (Table 3).

3.3. US elastography

On US elastography: **score 1** was found in 21 cases, all benign lesions; **score 2** in 4 cases, all benign; **score 3** in 7 cases, 6 benign and one carcinoma; **score 4** in 2 cases, all carcinomas and **score 5** in 12 cases; all carcinomas (Table 4).

Thus, all 31 cases with a final diagnosis of benign nodule had a score of **1–3**, while 14 of 15 (94.1%) with a final diagnosis of carcinoma had a score of **4–5**, with a sensitivity of 93.3%, a specificity of 100% and an accuracy of 97.8% (Table 4). One of the 15 nodules with the histological diagnosis of papillary cancer had a score of 3.

Among benign lesions, the score was 1 in 4 and 2 in 2 of the 6 **hyperplastic nodules**; it was 1 in17, 2 in 2, and 3 in 6 of the 25 **adenomatous nodules**. Although the number of hyperplastic nodules is too small to allow a reliable statistical evaluation, these data suggest that adenomatous nodules have a higher stiffness with respect to the hyperplastic nodules.

Combined US findings and US elastography reveals that hypoechogenicity/score 4–5 was most predictive of malignancy with sensitivity 80% and specificity 100%; and accuracy 93.4% in addition to the presence of spot microcalcifications/score

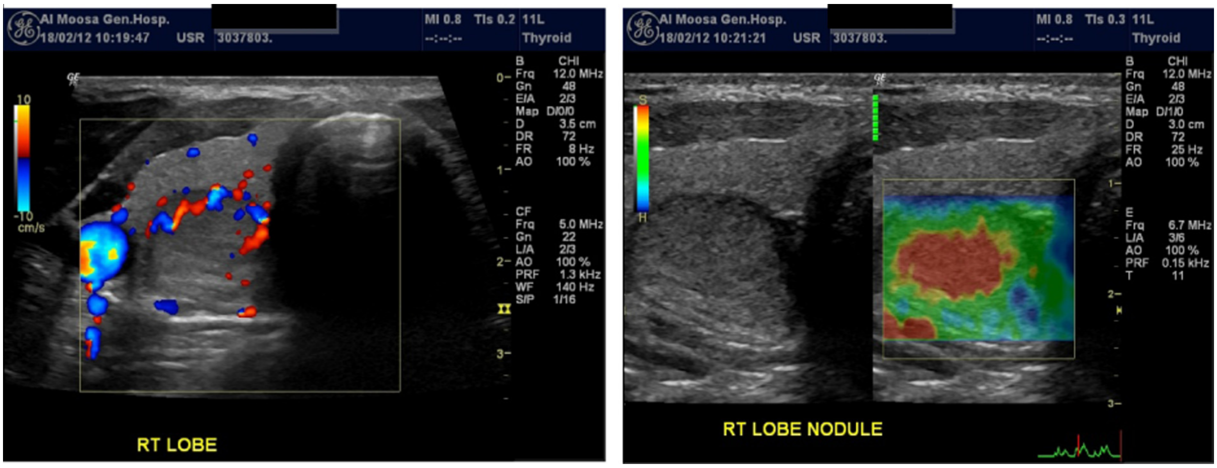

Fig. 3 Forty one year-old female patient with solitary right thyroid nodule proved to be papillary adenoma by histopathology: (A) Colour Doppler study revealed type II vascularization. (B) Grey scale US showing hypoechoic nodule with halo sign (C) US elastography reveals elasticity score 2.

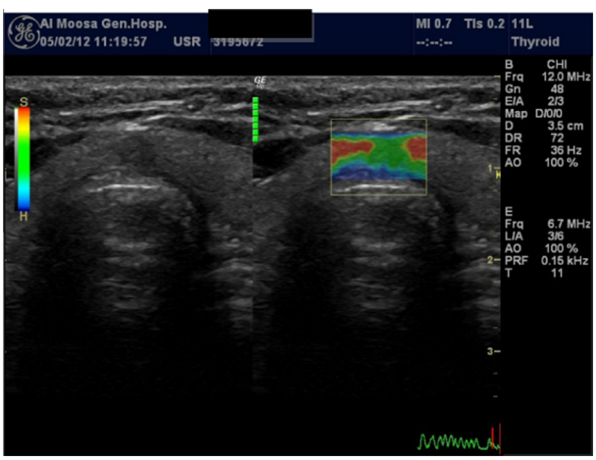

Fig. 4 Forty seven year-old female patient with solitary isthmic thyroid nodule proved to be papillary adenoma by histopathology: (A) grey scale US showing hypoechoic nodule with absent halo sign, (B) US elastography reveals elasticity score 1.

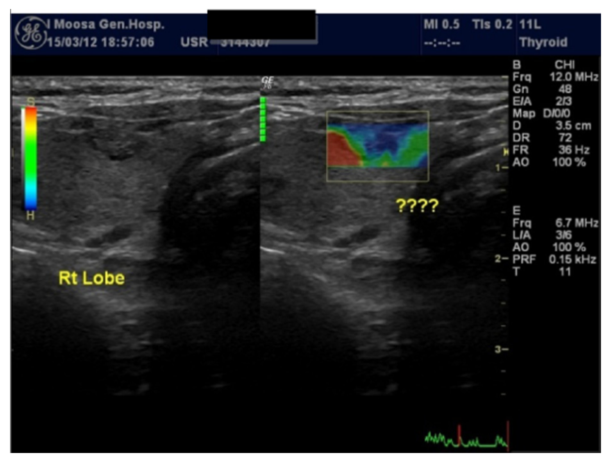

Fig. 5 Thirty seven year-old female patient with solitary isthmic thyroid nodule proved to be Follicular carcinoma: (A) US showing hypoechoic nodule with halo sign, (B) US elastography reveals elasticity score 5.

4–5 with sensitivity 66.7% and specificity 100%; and accuracy 89.1% in addition to absent halo sign/score 4–5 with sensitivity 60% and specificity 96.7%; and accuracy 84.7% (Table 5).

Of the 16 patients with a FNA result of indeterminate (follicular) lesion, 12 had a benign follicular adenoma on histology and 4 a carcinoma: one papillary, classic variant; two papillary follicular variants; and one minimally invasive follicular carcinoma. The conventional US, as previously shown in a larger series of patients (14), was not predictive in these patients.

At variance, an US elastography score of 4–5 was observed in 3 of 4 (75%) patients with carcinoma and a score of 1–3 in all 13 patients, 12 of them with benign lesions and one was malignant (Table 6).

4. Discussion

There is a general agreement that ultrasound features indicating a high risk for malignancy should be an indication for an FNAB and even further treatment such as surgery. Ultrasound features predictive of malignant nodules include the presence of irregular margins, marked hypoechogenicity, microcalcifications, taller-than-wide shape, and intranodular vascularity (6,7,15).

Sensitivity, specificity, PPV and NPV for these criteria are extremely variable from one study to the other (16). Our study revealed that nodule hypoechogenicity (sensitivity 80% and specificity 61.2%; *P* 0.008), absent halo sign (sensitivity 40% and specificity 19.3%; *P* 0.008), spot microcalcifications (sensitivity 66.7% and specificity 70.9%; *P* 0.01) were the US patterns most predictive of malignancy in agreement with Rago. Another recent study (6) revealed that ill-defined margins, spot microcalcifications and AP/T diameter more than 1 cm were the most predictive ultrasound patterns of malignancy.

In the present study, absence of halo sign combined with the presence of spot microcalcifications as well as absent halo sign/hypoechogenicity were most predictive of malignancy

Table 2 Sensitivity, specificity and accuracy US patterns in histopathologically proved thyroid nodules.

	BN (n = 31)	CA (N = 15)	P value	Sensitivity (%)	Specificity (%)	Accuracy
Hypoechogenicity			0.008**	80.0	61.2	67.4
Present	12	12				
Absent	19	3				
Halo sign			0.008**	40.0	19.3	26.1
Present	25	6				
Absent	6	9				
Spot microcalcifications			0.01**	66.7	70.9	69.5
Present	9	10				
Absent	22	5				
Type III vascularization			1.0	6.7	96.7	67.4
Present	1	1				
Absent	30	14				

** $P < 0.01$ highly significant.

Table 3 Sensitivity, specificity and accuracy of combination of US patterns in histopathologically proved thyroid nodules.

	BN (n = 31)	CA (N = 15)	P value	Sensitivity (%)	Specificity (%)	Accuracy (%)
Absent halo sign/Hypoechogencity			0.0001**	60.0	93.5	78.3
Both Present	2	9				
One Absent	29	6				
Absent halo sign/spot microcalcifications			0.0001**	60.0	93.5	82.6
Both Present	2	9				
One Absent	29	6				
Hypoechogenicity/spot microcalcifications			0.002**	53.3	90.3	78.2
Both Present	3	8				
One Absent	28	7				
Absent halo sign/hypoechogenicity/type III vascularization			0.32	6.7	100.0	69.4
Both Present	0	1				
One Absent	31	14				
Hypoechogenicity/spot microcalcifications/type III vascularization			0.32	6.7	100.0	69.4
Both Present	0	1				
One Absent	31	14				
Absent halo sign/spot microcalcifications/type III vascularization			0.32	6.7	100.0	69.4
Both Present	0	1				
One Absent	31	14				

** $P > 0.05$ not significant, $P < 0.05$ significant, $P < 0.01$ highly significant.

(sensitivity 60% and specificity 93.5%; P 0.0001); in agreement with (1) who stated that combined US features and colour Doppler become highly predictive of malignancy only when multiple patterns are simultaneously present in a thyroid nodule.

Table 4 Distribution of elasticity scores in the study group patients.

Elasticity score	BN (n = 31)	CA (N = 15)	Sensitivity (%)	Specificity (%)	Accuracy
Score 1	21	–			
Score 2	4	–			
Score 3	6	1			
Score 4	–	2			
Score 5	–	12			
Score 1–3	31	1	93.3	100.0	97.8
Score 4–5	–	14			

Conventional US does not provide information regarding hardness of the nodule and this is the role of USE (6). US elastography was developed to determine tissue stiffness and strain information noninvasively (17–19). Strain represents the amount of deformation; thus, stiff tissue shows less strain than softer tissue. A thyroid lesion may have different levels of stiffness within it, depending on the cellularity and the composition of the nodule. Information from these elastograms helps to assess the relative stiffness of the lesion compared with its surrounding tissues and within itself (2).

Several previous studies have used ultrasound elastography for evaluation of thyroid nodules (6). Many of them reported variable sensitivity and specificity of USE for predicting

Table 5 Sensitivity, specificity and accuracy of combined US and US elastography in histopathologically proved thyroid nodules.

	BN ($n = 31$)	CA ($N = 15$)	P value	Sensitivity (%)	Specificity (%)	Accuracy (%)
Absent halo sign/score 4-5			0.000	60.0	96.7	84.7
Both Present	1	9				
One Absent	30	6				
Present halo sign/score 1–3			0.008	40.0	19.3	26.1
Both Present	25	6				
One Absent	6	9				
Hypoechogenicity/score 4–5			0.000	80.0	100.0	93.4
Both Present	0	12				
One Absent	31	3				
Absent hypoechogenicity/score 1–3			0.000	6.7	38.7	28.3
Both Present	19	1				
One Absent	12	14				
Spot microcalcifications/score 4–5			0.000	66.7	100.0	89.1
Both Present	0	10				
One Absent	31	5				
Absent Spot microcalcifications/score 1–3			0.000	6.7	29.0	21.7
Both Present	22	1				
One Absent	9	14				
Type III vascularization/score 4–5			0.32	6.7	100.0	69.5
Both Present	0	1				
One Absent	31	14				

$P < 0.01$ (H.S) $P > 0.05$ (NS).

Table 6 Sensitivity, specificity and accuracy of combined US and US elastography in 16 patients with indeterminate thyroid nodules on FNA.

	BN ($n = 12$)	CA ($N = 4$)	P value	Sensitivity (%)	Specificity (%)	Accuracy (%)
Hypoechogenicity			1.0	75.0	41.6	50.0
Present	7	3				
Absent	5	1				
Halo sign			1.0	100.0	8.3	31.2
Present	11	4				
Absent	1	0				
Spot microcalcifications			1.0	25.0	75	62.5
Present	3	1				
Absent	9	3				
Type III vascularization			1.0	0.0	91.6	68.7
Present	1	0				
Absent	11	4				
Score 1–3 on US elastography	12	1	0.007	75.0	100.0	93.7
Score 4–5 on US elastography	0	3				

malignancy. Lyshchik et al. (20) reported 82% sensitivity and 96% specificity, Rago et al. (1) reported sensitivity of 97% and specificity of 100%,, Hong et al. (21) reported sensitivity of 88% and specificity of 90%, Rania and Khaled (6), reported sensitivity of 89.3% and specificity of 82.2%.

The study included 46 selected patients with thyroid nodules. In our study group, the highest elasticity scores, indicative of a greater nodular consistency, were invariably associated with malignancy (specificity 100%, sensitivity 93.3%, accuracy 97.8%) in agreement with (1,6). However, it is important to note that the study group included selected patients with solid nodules in which thyroid surgery had been already planned because of cytological suspicion or large nodular size which could represent a bias that amplifies the predictive value of US elastography.

In the present study the most US features suggestive of malignancy were, absence of halo sign combined with the presence of spot microcalcifications as well as combined absent halo sign/hypoechogenicity (sensitivity 60% and specificity 93.5%; with accuracy 82.6% and 78.3% respectively) and all were confirmed by US elastography that revealed a score of 1–3 in all benign cases with only one case scored as score 3 and had these US suspicious features, revealed after that being a follicular carcinoma.

Combined US findings and US elastography reveals that hypoechogenicity/score 4–5 was most predictive of malignancy with sensitivity 80% and specificity 100%; and accuracy 93.4% followed by the presence of spot microcalcifications/score 4–5 with sensitivity 66.7% and specificity 100%; and accuracy 89.1%.

These results revealed that combined techniques were superior to US alone and added no significant value when compared with US elastography alone in agreement with (8) study that revealed that the combination of elastography and grey-scale US, showed inferior performance in differentiating malignant and benign thyroid nodules. But we disagree with (8) who mentioned that US elastography alone shows inferior performance when compared with grey-scale US features. We think this controversy may be explained by many limitations in (8) study, one of them was that about half of the nodules in the mentioned study were not surgically correlated.

Although presently, FNA remains the most important procedure for the diagnostic management of thyroid nodules, yet a substantial proportion (up to 20%) of cytological specimens yields indeterminate results (22) and the distinction between benign and malignant lesions can only be made on histological criteria.

In follicular lesions, conventional echographic patterns were found to be of minor relevance for predicting carcinoma in agreement with (14). These results have been confirmed in the present series of 16 patients with indeterminate nodules on cytology, 7 of whom resulted to have a papillary or follicular thyroid carcinoma on histology. The predictivity of US elastography in this subgroup of patients was rewarding, scores 4–6 being found in 3 of 4 patients having a final diagnosis of malignancy and a score of 1–3 in all 12 patients with a histological diagnosis of benign lesion.

On the other hand, conventional US maintains a pivotal importance to define which nodules are suitable for the US elastographic characterization in agreement with (22).

Nodules in which US reveals the presence of calcified shell were excluded from the US elastographic evaluation because the US beam does not cross the calcification, and the probe compression does not result in tissue strain deformation. Similarly, in cystic nodules, US elastography cannot give useful information, the main determinant of nodule stiffness being the fluid content, and not the solid wall. For this reason, we selected 46 patients who had solid nodules for the analysis in agreement with (10).

We also excluded cases with multinodular goitres with coalescent nodules in agreement with (10) because the nodule to be examined must be clearly distinguishable from other nodules present in the thyroid, to select it for the US elastography measurement.

5. Conclusion

US elastography seems to have great potential as a new tool for differentiating solid thyroid nodules and for recommending FNAC. Combined grey scale US features and US elastography added no significant value when compared with US elastography alone. Further prospective studies are needed.

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