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Conventional sonography and strain sonoelastography in the evaluation of solid thyroid nodules

Zainab Ali Abd_Alrahman, Noor Abass Hummadi, Huda Ali Hussaini, Sajid H-al-Helfy, Wasan Ismail Al-Saadi

Abstract

Thyroid nodule represents diagnostic challenge. Conventional ultrasound provides information regarding the nodule`s shape but does not provide clue regarding its hardness. Strain Elastography is a promising technique that assess tissue elasticity. The objectives of this study is assessed the validity of conventional US features and elastographic parameters regarding characterization of solid thyroid nodules. The prospective study design of this study included 30 patients with thyroid nodule assessed initially by US then elastography to define elasto score and strain ratio. 23 nodules were benign 7 were malignant as confirmed at histopathology. The most sensitive US features to predict malignancy were nodule orientation and microcalcification, with overall US TIRADs sensitivity of 50% and specificity of 100%. On the other hand, comparable sensitivity of elasto score and strain ratio of 85.7% with higher specificity for the latter (93.2% vs.73.9%). Combination of conventional US and elastography features raised the sensitivity & specificity to 95% and 100 % respectively. A cutoff strain ratio of 2.88 was optimum to differentiate benign from malignant nodules. In conclusion; combination of US\USE improves differentiation benign from malignant nodules and recommended in daily practice to characterize thyroid nodules.

Keywords: Thyroid nodules; TIRADS; Ultrasound elastography; Elasticity score; Strain ratio

*Corresponding author email: hudamhm@yahoo.com
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Introduction

Thyroid nodule is a commonly encountered issue , discovered by palpation in 4%-8% of adult population, 41% at sonographic examination, the greater part of these nodules are benign with < 5% of them are found to be malignant [1] .Ultrasound (US) is accurate in the detection of thyroid nodules, but it has a relatively low diagnostic performance for the differentiation between benign and malignant nodules [2–4] .Various sensitivity and specificity of US for characterizing thyroid nodules have been proposed by several studies ranging between 52 and 97% and 26.6 and 83%, respectively [5, 6]. The ultrasound-based thyroid imaging reporting and data systems (TIRADS) classifications have been developed to stratify the risk for malignancy [7] using 12 conventional ultrasound features. According to the American Thyroid Association guidelines, no definite US feature (s) alone or in combination has outstanding sensitivity or specificity to identify all malignant nodules [8]. Consequently, fine needle aspiration biopsy (FNAB) is required for the nodules greater than 10mm or those with questionable ultrasound signs [8-11]. Nevertheless, FNAB has considerable limitations, with specificity of 60–98% and a sensitivity ranging from 54% to 90% in various studies [12-14]. Therefore, many patients underwent unnecessary thyroid surgery. The previously mentioned limitation of US and FNAB have raised the need for improvement and refinement of non-invasive methods to depict malignancy in a thyroid nodule.

Sonoelastography is a relatively new dynamic ultrasound technique that provides an assessment of the tissue elasticity by evaluating the degree of distortion of that part when applying an external force. In soft structures, the applied pressure causes the tissue to compress more whereas hard tissues compress less. This compressibility property, defined as "strain" is displayed either as an image with different color score (elastogram) or as a measurement using a specially designed software [15,16]. US elastography has been applied to study the hardness/elasticity of masses in different organs as the breast,

Research Article doi:10.18081/2333-5106/017-10/538-557

thyroid, prostate , liver and lymph nodes [17-20]. Strain Elastography allows both a qualitative and a semi-quantitative evaluation of nodule elasticity [21] in the form of elastoscore with its 4 patterns (qualitative assessment) and semi-quantitative assessment (the strain ratio) [22]. We aimed at this study to assess the validity of conventional US features and elastographic parameters in the characterization of solid thyroid nodule.

Patients and Methods

This prospective study was approved by the institutional review board and an informed written consent was obtained from each patient. A total of 30 patients with solitary thyroid nodule were enrolled in this study that was conducted from September 2015 to September 2016. Conventional and elastography ultrasound examination was performed and only those patients for whom final diagnosis of the nodule obtained through histopatholoy, were included. The exclusion criteria were complex nodules with > 30 % cystic component, Large nodule occupying more than 75% of the thyroid lobe with little or no discernible normal thyroid tissue (because insufficient surrounding normal thyroid tissue to be used as reference), nodules with egg shell or completely calcified nodule, patients with abnormal ultrasound texture of the thyroid tissue and patients with previous thyroid surgery or previous radiation to the head and neck region. All patients underwent surgery, and the histopathology diagnosis was considered as the gold standard reference.

Imaging techniques

Ultrasound examination was performed using high frequency linear array transducer mounted on Voluson E6 ultrasound system (GE Healthcare). The patient was placed at supine position after full exposure of the neck region. Scanning of the thyroid gland was performed at different planes (axial, sagittal and oblique) and the patient was instructed to keep quite respiration & avoid repeated swallowing at the time of scanning. Initially, the examination was performed using 2D mode to assess the nodule for size, outlines, shape, texture, orientation, the AP diameter, the width, presence of fine calcifications and vascularity, as well as the assessment of the cervical lymphadenopathy. After completion of gray scale assessment, the nodule was assigned at one of the TI-RAD categories according to its criteria.

Sonoelastographic examination

The sampling box was placed in a way that the whole nodule and part of the

Research Article doi:10.18081/2333-5106/017-10/538-557

surrounding normal thyroid tissue be included within the box. Slight rhythmic pressure is then made by the probe upon the nodules until an optimal pressure is reached as indicated by the appearance of the green color at the indicator shaft at the upper left corner of the screen. The gray-scale images and elastogram were real -time displayed and monitored at the same time on splitted screen. The color criteria of each nodule were recorded, and the elasticity score was determined. After that the objective elastographic assessment was made by placing two rounded regions of interest (ROIs) over the normal tissue adjacent (reference region) and the target region (nodule), respectively. Then, a strain ratio is automatically calculated.

Histopathology were used as the gold standard to assess the diagnostic performance of the TI-RADS gray-scale score and the elastography alone and in combination.

Statistical analysis

Microsoft excel 2013 and Graphpad prism 6 software were uses for statistical analysis. Data were presented as frequency and percentage and Chi square test and exact Fisher test was used to show the significance difference between malignant and benign cases. Only age and Strain ratio were presented as mean ± standard deviation, and unpaired student T test was done to show the significance difference between malignant and benign cases. A p value less than 0.05 was considered significant.

Results

A total of 30 patients with solitary solid thyroid nodule were evaluated in this prospective study: 24 Females (80 %), mean age =34.5+10.01 years with an age range from 18-50 years) and 6 Males (20%), mean age= 46.5+10.7 years with an age range of 36-63 years. Seven out of 30 nodules were found to be malignant (4 as papillary thyroid carcinomas, 1 as follicular carcinoma, 1 as anaplastic carcinoma and 1 as Non-Hodgkin lymphoma). The remaining 23 nodules were benign (18 as Colloid nodular hyperplasia, 4 as Follicular adenomas and 1 as Hashimoto`s thyroiditis). The criteria of the nodules according to conventional US (table 1) and their diagnostic performance (table 2). Twenty-five nodules (83.3%) were solid and 5 nodules (16.7%) nodules were predominantly solid.

Echogeneity

The majority of the nodules (14 nodule) were isoechoic of which only one nodule was malignant. Most malignant nodules were hypo echoic (6 out of 10)

Nodule orientation

Twenty-four nodules were wider than taller of which only two nodules were malignant, and 6 nodules were taller than wide of which only one nodule was benign.

Calcification

Seven nodules showed coarse calcification, all of which were benign, and 4 nodules showed fine calcification and all of them were malignant and 19 nodules did not show any calcification and 16 of them were benign.

Nodule Edge

Eight nodules show micro-lobulation, of which 6 were malignant and 22 had regular edge of which only one nodule was malignant.

Hypoechoic circumferential halo

Ten nodules were not surrounded by circumferential edge and all of them were benign,14 nodules were surrounded by continuous edge, of which 12 were benign and 6 nodules show interruption of the circumferential hypoechoic edge, 5 of which were malignant.

Doppler color flow

Nineteen benign nodules were predominantly peripherally vascular, one benign nodule was predominantly centrally vascular and three benign did not nodules show any vascularity. Four malignant nodules were predominantly centrally vascular, three malignant nodules were predominantly peripherally vascular. Among the 23 benign nodules in our study,16 nodules showed TIRAD score of 2 and 6 nodules show TIRAD score of 3 and 1 nodule show TIRAD score of 4b. Among the 7 malignant nodules, 3 nodules show TIRAD score of (4b) and 4 nodules show TIRAD score of (4C).

Research Article doi:10.18081/2333-5106/017-10/538-557

Table 1.

The conventional US features of benign and malignant nodules

ultrasound feature	Benign Total=23	Malignant Total= 7
1.Echogeneity		
Hyper echoic	6	0
Iso echoic	13	1
hypo echoic	4	6
2.Orientation		
Wider than tall	22	2
Taller than wide	1	5
3.Calcification		
No calcification	16	3
Coarse calcification	7	0
Fine calcification	0	4
4.Edge		
Regular edge macrolbulation	21	1
Irregular edge microlobulation	2	6
5.Halo		
No halo	10	0
Continuous halo	12	2
Uncontinous halo	1	5
6.Doppler color flow		
No vascularity	3	0
Central vascularity	1	4
Peripheral vascularity	19	3

Table 2.

The diagnostic performance of conventional ultrasound feature

Parameters	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Echogeniety	85.7`1%	82.6%	60%	95%	83.3%
Orientation	71%	100%	100%	92%	93%
Calcification	84.4%	73.6%	73.2%	96.2%	88.1%
Edge	85.7%	91.3%	75%	95.5%	90%
Halo	100%	93%	53.8%	100%	80%
Color flow	50%	95%	75%	86.4%	84.6%

The criteria of the nodules according to elastography

Ultrasound elastography color score

On ultrasound elastography color score:

- 4 nodules show elastoscore of 1, all were benign.
- 16 nodules show elastoscore of 2, 15 nodules of them were benign and only one nodule was malignant.
- 7 nodules show elastoscore of 3, 4 were benign and 3 were malignant.
- 3 nodules show elastoscore of 4 all of them were malignant.

The elastography color scores of benign and malignant nodules and of each specific pathology are shows in table 3 and table 4 respectively.

Table 3.

The nodules distribution according to the elastography color score

Elastoscore	Benign N=23	Malignant N=7	total
1	4	0	4
2	15	1	16
3	4	3	7
4	0	3	3
Total	23	7	30

American Journal of BioMedicine
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Research Article doi:10.18081/2333-5106/017-10/538-557

Table 4.

The elastography color score of each nodule according to the specific histopathology

Histopathology	1	2	3	4	total
colloid nodules	3	11	4	-	18
Follicular adenoma	-	4	-	-	4
Hashimoto thyroidits	1	-	-	-	1
Papillary carcinoma	-	-	2	2	4
Follicular carcinoma	-	1	-	-	1
lymphoma	-	-	1	-	1
Anaplastic carcinoma	-	-	-	1	1

Elastography strain ratio (SR) measurement

For benign lesions the mean strain ratio was found to be 1.33 ± 0.57 (range 0.43 - 2.36) while for malignant nodules the mean SR found to be 3.35 ± 2.36 (range 1.35 - 4.1). ROC curve was applied to assess the optimum cutoff value to differentiation between benign and malignant thyroid nodules which was found to be 2.88. Using this cutoff value, 22 out of 30 nodules showed an SR less than 2.88, 21 of these were diagnosed histopathologically as benign lesions (figure).

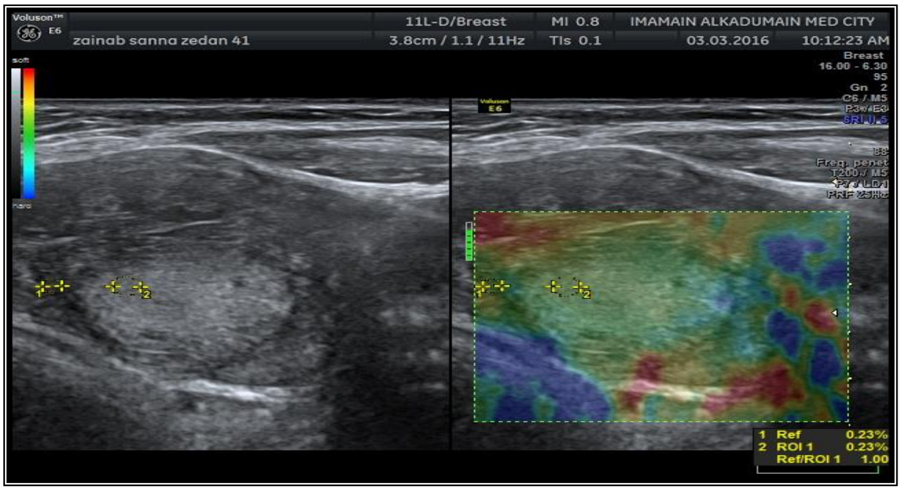

Figure 1.

41 years old female with colloid nodular hyperplasia. Lt: thyroid.grayscale image, show well defined hyperechoic nodule. Rt: Elastography image show elastoscore of 1 and SR ratio of 1.00.

American Journal of BioMedicine
AJBM 2017;5(10): 538-557
Research Article doi:10.18081/2333-5106/017-10/538-557

Only one nodule among the malignant nodules was found to have an SR < 2.88 and this nodule was follicular carcinoma (figure 2).

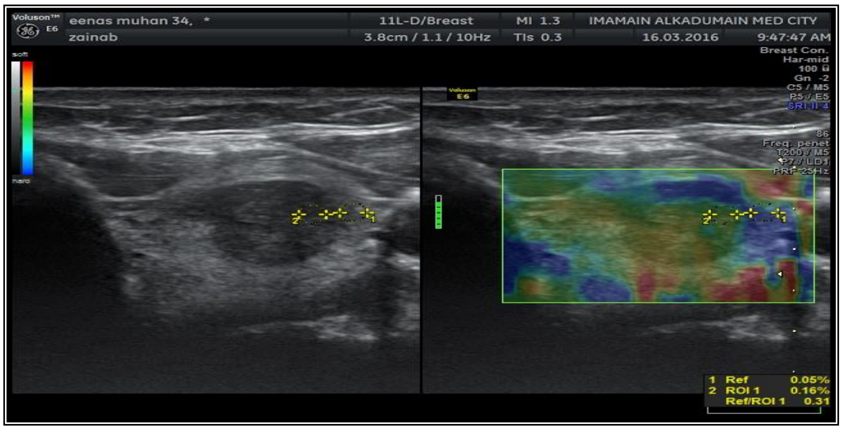

Figure 2.

34 years old female follicular carcinoma. Lt: gray scale image show well defined hypo echoic nodule with focal area of microlobulation Rt: Elastography image show elastoscore of 2 and strain ratio of 0.31.

On the other hand, 8 nodules had an SR equal or more than 2.88. Six of these were diagnosed histopathologicaly as malignant as shown in figure (3).

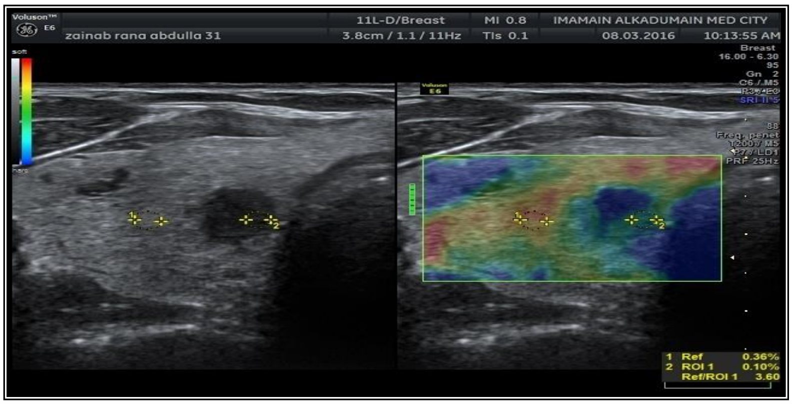

Figure 3.

31 years old female papillary carcinoma. A: gray scale, show microlobulated well defined taller than wide hypoechoic nodule with few tiny foci of calcifications B: Elastography image show elastoscore of 4 and strain ratio of 3.60.

The two benign nodules which had an SR ≥2.88 were hyper plastic nodules which contained peripheral discontinuous rim of coarse calcifications as shown in figure (4).

AJBM 2017;**5**(10): 538-557
Research Article doi:10.18081/2333-5106/017-10/538-557

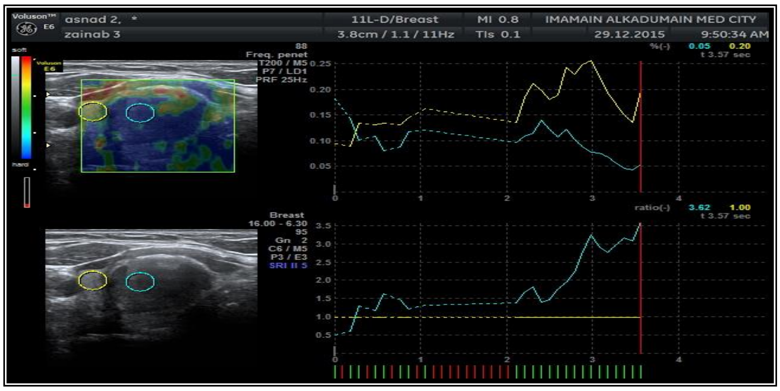

Figure 4.

31 years old female with colloid nodular hyperplasia. Well defined isoechoic nodule with peripheral discontinuous rim of coarse calcification elastography scan of the nodule show elastoscore of 3 and strain ratio of 3.6.

SR showed comparable sensitivity than elastography however with higher overall diagnostic performance (table 5).

Table 5.

The diagnostic performance of the elastography parameters

Scoring type	Parameter	Value
Elastoscore	Sensitivity	85.7%
	Specificity	73.9%
	Positive predictive value	50.0%
	Negative predictive value	94.4%
	Accuracy	76.7%
Strain ratio	Sensitivity	85.7%
	Specificity	93.2%
	Positive predictive value	72%%
	Negative predictive value	95.8%
	Accuracy	93.3%

Research Article doi:10.18081/2333-5106/017-10/538-557

Distribution of the nodules according to elstrography score against TIRAD category (table 6)

On elastographic examination, 18 benign nodules showed an elastography score of 1 and 2, while elastography score of 3 was assigned for 4 hyperplastic nodules some these with coarse calcification. Of these benign nodules 22 nodules had a TIRAD score of 2 or 3 and only one nodule was classified as TIRAD score of 4b. The elastographic examination of the 4 papillary carcinoma nodules showed an elasto score of 3 and 4. All of these were categorized as TIRAD 4 category. The single nodule of lymphoma and anaplastic carcinoma exhibited an elasto score of 3 and 4 respectively. Both were categorized as TIRAD 4b. The only malignant nodule that showed a soft configuration at elastography was follicular carcinoma (ES = 2) however TIRAD category of 4b was given to the lesion. When we take SR cut off value of 2.88 and assigned SR against TIRAD score we found the following: twenty-one of the benign nodules had SR less than 2.88 and only two hyperplastic nodules with prominent coarse calcification of TIRAD 2 had a SR greater than 2.88. _six malignant nodules had a SR greater than 2.88 and only the follicular carcinoma (TIRAD 4 b) had SR less than 2.88.

Table 6

Distribution of TIRAD score categories according to the strain ratio of the nodules.

Strain ratio of the benign nodules	**TIRAD 2**	**TIRAD 3**	**TIRAD 4**			**TIRAD 5**
			a	**b**	**c**	
SR<2.88	2 follicular adenomas 12 colloid nodules	2 follicular adenomas		1 hashimoto thyroiditis nodule 1 follicular carcinoma		

Research Article doi:10.18081/2333-5106/017-10/538-557

The diagnostic performance of each modality alone and in combination is shown in (table 7)

The only malignant nodule that showed a soft configuration at elastography was follicular carcinoma (ES = 2) however TIRAD category of 4b was given to the lesion. One nodule was classified as TIRAD score of 4b which was diagnosed histopathologicaly as Hashimoto thyroiditis and its elastographic examination show elastoscore of 1 and SR of 0.57 as shown in (figure 5).

Table 7.

Diagnostic performances of gray scale ultrasound,strainelastography and the combination of them (TIRAD)

parameters	**Conventional ultrasound feature**	**Elastography strain ratio**	**Combined US\USE strain ratio**
Sensitivity	50%	85.7%	100%
Specificity	100%	93.2%	95.7%
PPV	100%	72%	87.5%
NPP	82.1%	95.8%	100%
Accuracy	83.1%	93.3%	96.7%

Figure 5.

46 years old malehashimoto thyroiditis. Lt: gray scale image, show ill-defined taller than wide hypoechoic nodule. Rt: Elastography image show elastoscore of 2 and strain ratio of 0.57.

American Journal of BioMedicine
AJBM 2017;5(10): 538-557
Research Article doi:10.18081/2333-5106/017-10/538-557

Discussion

The goal for this study was to evaluate the performance of real-time elastography alone and in conjunction with known sonographic characteristics of malignancy. In this study it has been found that thyroid nodules are 4 times more common in females than in males however; the incidence of thyroid malignancy was higher in males than in females (3 out of 6 nodules in males were malignant vs. 4 out of 24 nodules in females). This finding contradicts the data from Cancer Research UK who reported a higher annual incidence of 3.5 per 100 000 women as compared to 1.3 per 100000 men [23], This can be explained by the limited number of males in the study sample and the overall sample size which confidently affect the result of the study in this respect. The commonest echo pattern encountered in this study was the isoechoic nodules, the majority of these were benign nodules (13 out of 14 isoechoic nodule) and only one isoechoic nodule was anaplastic carcinoma, on the other hand 6 out of 7 malignant nodules were hypoechoic. The significance of the echogeniety of the nodule was 85.7 % sensitivity, 82.6%specificity, PPV of 60%, NPP of 95% with 83.3% accuracy. These findings agree with the study of Solbiativolterani *et al.*, who concluded that hyperechoic malignant nodules are extremely rare [24]. For Nachiappan *et al.*, [25], marked hypoechogeneity is one of suspicious US features. The orientation of the nodules can be a very useful sign as 5 out of 7 malignant nodules were taller than wide, while only one benign nodule shows this feature which histopathologicaly proven to be Hashimoto thyroiditis. This agree with study done by moon et al who has found that a taller-than-wide shape in either the transverse or longitudinal plane was a useful sonographic feature for predicting thyroid malignancy [4, 26]. Another sonographic sign was the boundary of the nodules. In the current study it has been found that (85.7%) of the malignant nodules had an irregular edge. The edge pattern criteria of the nodule show sensitivity of 85.7%. Koiek *et al* (27) reported rather higher sensitivity for the ill-defined irregular margins approaching 89%. On the other hand, Moifo *et al.*, [28] reported rather low sensitivity for the irregular and ill-

Research Article doi:10.18081/2333-5106/017-10/538-557

defined margin (34%). Regarding the hypoechoic circumferential edge, this sign was seen in all the malignant nodules, of which 5(71%) nodules show interrupted halo while 2(29%) show continuous halo. While 10 (43.5%) of the benign nodules were not surrounded by halo, 12(52%) nodules show continuous halo and only1(0.5%) benign nodule shows non-continuous halo. Our study show that the continuous halo was significantly seen in benign nodules and interrupted halo is significantly seen in malignant nodules with specificity of 93%. Several studies have investigated this sign and some agreed that the presence of complete uniform halo is highly specific of benignity 95% [29]. However, it can be absent in half of the benign nodules [30]. Moreover; 10-24% of papillary CA have been reported to have complete or interrupted halo [30, 31]. Regarding the presence of calcification, 7 benign nodules (30%) nodule showed coarse calcification, 16(70%) nodules show no calcification. Our study shows that 4 out of 7 malignant nodules showed micro-calcifications and they were histopathologicaly diagnosed as papillary carcinoma, while (lymphoma, anaplastic carcinoma and follicular carcinoma not show any pattern of calcification. pathologically Micro-calcifications correspond to psammoma bodies that are typical of papillary carcinoma [32]. We have found that microcalcification shows sensitivity of 84.4% for malignancy which agree with the study of Salmaslioglu *et al.*, who found that the presence of microcalcifications had a sensitivity of 89.3% for malignancy [32]. Finally, regarding the Doppler color flow, 80% of the nodules that had predominantly central vascularity been malignant. This finding agrees with that of Chan *et al.*, [33] who found that all the malignant nodules in their study showed some intranodular vascularity. However, this finding is not specific for thyroid malignancy as Frates *et al.*, study [34] showed that > 50% of vascular solid thyroid nodules turned out to be benign. While 86%nodules of the nodules that had predominantly peripheral vascularity were benign indicating that the peripheral flow is rather more characteristic of benign thyroid lesions but not confined to them as 22% of the malignant nodules exhibited the same pattern [34]. Also, the three avascular nodules were benign, so complete vascularity is a more specific sign as completely avascular nodule is almost benign. And all the malignant nodule must have some intrinsic or peripheral blood flow [34]. The assumption of a totally non-vascular nodule being very unlikely to be malignant is challenged by certain large studies done by Hoang *et al.,* [35] and Papinin *et al*., [36]. For color scoring systems. Most of the benign nodules assessed in this study showed a score of 1 and 2, 4 hyperplastic nodules showed elastoscore of 3. On conventional ultrasonography these nodules show dense coarse calcification which increase the stiffness of the nodules. On the other hand, 6 out of the 7 malignant nodules showed a score of 3 and 4. the remaining single malignant nodule showed a score of 2 and was proved to be follicular carcinoma. In fact, this tumor is considered as one of the soft tumor that is characterized by the formation of many follicles with abundance of amyloid with little if any fibers [37]. Our study revealed significant statistical significances when using the elastography score to differentiate benign from malignant thyroid nodules with sensitivity of 85.7%, specificity of 73.9%, positive predictive value of 50%, negative predictive value of 94.4% and accuracy of 76.7%. Similar conclusion regarding the value of the elastographyscore in the evaluation of the nature of the thyroid nodules was reached Rago *et al*., [38]. The study showed that ultrasound elastography had Sensitivity of 94.1% and specificity 81%. The positive predictive value was 55.2% and negative predictive values was 98.2%. And The accuracy of the technique was 83.7%. A national study conducted at 2015 involving 92 thyroid nodules done by Abbas w *et al.*, has found that the scores of 1 and 2 were significantly seen in benign nodules, whereas, scores of 3 and 4 were significantly seen in malignant nodules ($p < 0.001$). [39]. In the current study, SR cutoff value of 2.88 was found with sensitivity of 85.7%, specificity of 93.2%, ppv of 72%, npp of 95.8% and accuracy of 93.3%. Several researches support our results . Abbas W et al (39) showed that the best cutoff value of SR was 3.58 with the diagnostic performance of as follow (sensitivity of 85.7%, specificity of 93.2%, ppv of 72%, npv of 95.8% and accuracy of 93.3% (39). Two studies by Wange *et al.,* Have found that the mean SR for malignant lesions is significantly higher than that of benign nodules [40, 41]. Upon reviewing most of the studies that

Research Article doi:10.18081/2333-5106/017-10/538-557

have dealt with the best SR cutoff values, no definite match or approximation in the cutoff value has been found and wide range of the proposed cutoff values was found ranging from 2.2 in a study by Refaat *et al.*, [42] to 4.4 in a study by Ning *et al.*, [43]. All this variability in the cutoff values could be attributed to variations in the technique of examination. Our study showed that the SR had a higher sensitivity and accuracy than conventional ultrasound features. Our result matches those of Lyshchik *et al.*, [44] and Kagoya *et al.*, [45]. his study assessed the joint performance of USE with TI-RAD score framework and we accomplish fabulous sensitivity (100%), negative predictive value of 100% and accuracy of 96.7% superpassing conventional ultrasound or strain elastography alone. Our outcome coordinate with the results of other 4 studies Unluturk *et al.*, [46], Moon *et al* [26], Sebg *et al.*, [47], Russ *et al.*, [7] and several authors recommended that conventionalUS/US can accomplish both superb sensitivity and negative predictive values (NPV) for malignancy (92–100 %), surpassing traditional US [7, 26–48].

In conclusions; the combination of elastography with gray-scale need to be used in the daily practice to improve sensitivity and specificity particularly in equivocal or borderline cases to reduce the need for more invasive procedures are FNAB or surgery

Competing interests

Authors declare that we have no competing interests.

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