Real Time Ultrasound Elastography in the Differential Diagnosis of Benign and Malignant Thyroid Nodules

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Abstract:

Background: Elastosonography is a promising non-invasive technique that developed in recent years for evaluating thyroid nodules. It assesses nodule stiffness or displacement depending on the applied force to differentiate malignant from benign thyroid nodules.

Objectives: The aim of this study was to evaluate the diagnostic utility of real time US elastography in the differentiation the benign from malignant thyroid nodule.

Patients and methods: A cross-sectional was carried out on 40 patients attending ultrasound unit/radiology in Al-Imamein Al-Kadhimein Medical city in Baghdad/Iraq from September 2018 to August 2019. All patients were examinedby B-mode ultrasound, color Doppler, and real-time elastography by Voluson-E6 Ultrasound machine. Final diagnoses obtained from histological and/or cytological evaluation.

Results: The mean age of 40 patients was 43.7±11.7 years with the range of 25-70 years. 28 (70%) of them were female and 12 (30%) were male. Of the 40 lesions 34 (85%) were benign and 6 (15%) were malignant lesions. Malignant thyroid nodules were significantly hypoechoic, with irregular margin, taller than wider, showed microcalcification and exhibited a significant increase in vascularitywith varying rate of sensitivity and specificity. Orientation (taller than wider) was the most ultrasound predictive pattern of malignancy with sensitivity, specificity, and accuracy of 66.7%, 100%, and 92.5% respectively. The mean strain ratio of all nodules was 2.7±2.1 ranged 0.4- 13.5 with significant result. The optimal strain ratio cutoff value was >2.5 and showed to have a sensitivity of 100%, specificity 88.2%, positive predictive value 67%, negative predictive value 100%, and accuracy rate 90%.

Conclusion: Elastosonography can assist in the differential diagnosis of malignant and benign thyroid nodules, as strain elastosonography improve the diagnostic performance in differentiating the benign and malignant thyroid nodule. strain ratio is higher in malignant than benign nodules

Keywords: Elastosonography, malignant thyroid nodules, benign thyroid nodules,

Introduction

The thyroid gland is a symmetrical, butterfly-shaped gland draped over the trachea with the isthmus positioned over tracheal rings. The echogenicity of the normal thyroid is a silver gray that is brighter than the surrounding strap muscles and similar to the echogenicity of the submandibular glands [1]. The normal thyroid gland is homogeneous in echotexture. It appears hyperechoic as compared to the overlying strap muscles. Each lobe sits snuggly between the trachea medially and the carotid artery laterally. The two lobes normally appear as mirror images of each other and usually are quite similar in size [2].

Thyroid nodules are a common finding in the general population and the number has increased in recent years. [3]. According to the data from Framingham Heart Study published in 1968, in persons over 60 years of age palpable nodules occurred in 6.4% of women and 1.5% of men [2]. According to the most recent 2015 American Thyroid Association (ATA) Guidelines, current prevalence of palpable thyroid nodules is approximately 5% in women and 1% in men living in iodine sufficient parts of the world [3].

High-resolution ultrasound can detect thyroid nodules in 19–68% of randomly selected individuals, with higher frequencies in women and the elderly [3]. Many thyroid nodules in clinical diagnosis are detected incidentally with imaging studies, usually for other reasons. Most thyroid nodules diagnosed are asymptomatic and benign, whereas only about 5% are malignant nodules [1]. Diagnosing the benign or malignant thyroidnodules is the foundation for its subsequent treatment. As guidelines generally recommend fine needle aspirate biopsy (FNAB) as the best method to differentiate between benign and malignant thyroid nodules. FNAB has some limitations, such as being invasive and time-intensive [4]. During the last decade, elastography, a novel imaging technique that is noninvasive and easily available, was added to the diagnostic list for the evaluation of thyroid nodules [5]. Elastography is a promising technology based on measuring thetissue strain, and because of its easy assessment and efficient compressing against underlying anatomic structures, the thyroid gland would be well-positioned [6].

US is a practical and reliable imaging modality for assessment of the thyroid. Differentiating the malignant from more frequently occurring benign thyroid disease has proved challenging, as there may be significant overlap in their clinical presentation and sonographic appearance. Ultrasound has high sensitivity but less specificity to distinguish benign from malignant lesions, and diffuse infiltration, in the thyroid. Improvement in US specificity of thyroid disease has been attempted bythe employment of contrast agents (1998), harmonic imaging (2001), and elastography (2005) [(2)].

The echogenicity of a thyroid nodule refers to its brightness relative to the normal thyroid parenchyma. Normal parenchyma appears homogeneously hyperechoic or relatively bright on sonography as a consequence of the high number of acoustic interfaces within the normal follicles of the thyroid gland [(1)].

Nodule Margin can be defined because of either a difference in echogenicity between the nodule and the thyroid parenchyma or a border that demarcates a nodule when it is similar in echogenicity to the background thyroid. Halo Sign is a hypoechoic rim surrounding a nodule (caused by fibrous connective tissue, compressed thyroid tissue, and chronic inflammatory changes) [(3)].

Calcifications may be present in up to 30% of nodules and can bedivided into different categories [(3)].

The vascularity of a thyroid nodule is evident with color flow Doppler (CFD) imaging. Based upon the Doppler frequency shift detected in the reflected ultrasound beam caused by moving blood, CFD imaging can show which regions have vascular flow, as well as measure the velocity of the blood flow. Perinodular flow is mainly a characteristic finding for benign nodules (however, it is observed in 22% of malignant nodules) [(1)].

Currently, there are several systems of sonographic patterns for thyroid nodule risk stratification developed for the most part by single institutions. They share the fact that pattern recognition is more reproducible among different operators [(7,8)] and is less influenced by physician experience [(9)].

One of the shortcomings of the pattern approach of nodule classification is the inability to classify all nodules [(10)]. For this reason, the American College of Radiology (ACR) began the development of the ACR. TIRADS using a point system for the evaluation of nodular features, with the ultimate aim of applying it to risk stratification and triage of nodules for FNA or observation [(1)].

Elastography is a promising new technology for noninvasively distinguishing benign thyroid nodules from thyroid cancer through tissue stiffness measurement. Elastography was developed in 1991 by Ophir and colleagues at the University of Texas Medical School, Houston. B-mode ultrasound imaging provides excellent visualization of thyroid nodules. However, it has a low sensitivity for predicting thyroid cancer and provides only limited information about the mechanical properties of benign and malignant thyroid nodules [(11)]. Elastography is a novel ultrasound-based technique that has been shown to have considerable success in identifying malignant thyroid nodules [(12)].

Real-time strain elastography (RTE) of thyroid NodulesTechnical considerations, It is of importance to choose the shortest path for the exploratory US beam to the nodule. This will allow the placement of the elastographic region of interest (ROI) as close to the transducer as possible, thus avoiding strain decay with distance [(13)].

The aim of this study is to evaluate the diagnostic utility of real time USelastography in the differentiation the benign from malignant thyroid nodule.

Patients and Methods

This study is a prospective cross-sectional study carried out in US unit of Radiology Department in Al-Imamein Al-Kadhimein Medical city in Baghdad during the period from 1st of September, 2018 to 30th of August, 2019.

A total of 40 selected patients with thyroid nodules (solitary and multiple nodules) who had been referred to sonographic department of Al-Imamein Al-Kadhimein Medical city during the study period were the study population.

Inclusion criteria established to include all adults (age>18 years), with thyroid nodule size of > 5 mm, and euthyroid or hypothyroid on thyroid function test. Exclusion criteria was set to exclude pure or predominant cystic nodules, nodules with coarse calcifications or eggshell calcifications, large nodules occupying > 75% of the volume of the thyroid lobe, coexistence of thyroiditis (heterogeneous texture), histopathology not given, loss of follow up, and hyperthyroidism on thyroid function test.

All of the referred selected patients were examined sonographically with B-mode then by elastographic US, then send for fine needle aspirate cytology (FNAC) under ultrasound guide by pathologist regardless of the elastographic result. Patients with multiple thyroid nodules, only nodule with FNAC result was included.

The data were collected by researcher from the patients directly and filled in a prepared questionnaire. The questionnaire was designed by the researcher and supervisor. The questionnaire included the followings.

1. Demographic characteristics of patients.
2. History of patients with thyroid cancer
3. Sonographic findings of the selected thyroid nodules.
4. Elastographic findings of the selected thyroid nodules.
5. Histopathological findings of the selected thyroid nodules.

The ethical approval was taken from Institutional Al-Nahrain College of Medicine with oral informed consent was taken from patients.

The thyroid ultrasonic examination was carried out using Voluson-E6 Ultrasound machine (GE Healthcare, USA) with 5 to 12 MHz linear array transducer. Thyroid nodules criteria were taken with the patient lying in supine position with exposed neck and with slightly neck extension. Thyroid glands scanning performed at axial, sagittal and oblique planes. The size, margin, composition, echogenicity, orientation, and the presence of calcification were all recorded. Doppler characteristics of the nodules were also recorded whether central or peripheral vascularity. Each selected thyroid nodule was classified at one of the TIRAD categories based on B- mode ultrasonic features.

Then elastography patterns of the nodules were performed in the same nodule that detected at B-mode US and underwent FNAC. The operator placed the probe perpendicular to the skin on the neck, then a box washighlighted which included the selected nodule and adequate surroundingnormal thyroid tissue, the common carotid artery was avoided to prevent its pulsatile compressive effect.

During the examination, the patient was asked to hold their breath and avoid swallowing to minimaize the motion artifact of the thyroid gland. Slight external compression was applied by the probe till an optimum pressure is achieved by the appearance of a green colour on the indicator bar at the left upper corner of the screen. Images were showed in a split screen, with the B- mode images on the left and the color scale elastography images corresponding to the gray-scale US image were on the right. For each selectednodule, the color criteria were recorded, and elastographic scale determined. The elastographic scale ranged from red (shows areas of greatest strain), i.e. softest component, to blue (shows no strain), i.e. hardest component. The ROI of the lesion was manually selected and as strain varies as a function of depth the homogenous adjacent thyroid tissue at the same depth as the lesion is used as a reference to calculate strain ratio (SR) automatically using dedicated software in the ultrasound machine. The mean value for each selected nodule was calculated (at least two measurements were recorded) and the average was taken as the final result.

FNAC was used as a diagnostic gold standard and performed under ultrasound guide by using a 23-gauge needle and a 2 ml plastic syringe done by pathologist. All subjects who had FNAC results that were read as malignant or indeterminate underwent thyroid surgery. For these patients, the histopathology reading was used as the reference standard. In patients who didnot have thyroid surgery, the FNAC reading was used as the reference standard.

Data were statistically computerized using Statistical Package for Social Sciences (SPSS) version 27 for windows. Descriptive statistics presented as (Mean±standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed Chi- square and Fisher's exact tests were used for categorical variables when appropriate. ANOVA test was used for continuous variable. Sensitivity, specificity, accuracy and cutoff value were calculated. In all statistical analysis, level of significance P value set at <0.05.

Results:

The histopathological diagnosis of 40 lesion revealed that 34 (85%) of themwere benign and 6 (15%) were malignant, of these 6 (15%) malignant nodules; 4 were papillary carcinoma and 2 werefollicular carcinoma. The age of our patients was ranging from 25-70 years. The most common age group affected significantly in benign lesions was 40-49 years, mean 43.7±11.7 years , whereas, in malignant lesions, the age ranged from 43 to 65 years, mean 56.8±7.7 years (P<0.05). 28 patients (70%) were female and 12 (30%) were male. Gender distribution in relation to histopathological results among the patients (Table 1).

Table 1: The age distribution for malignant and benign lesions among the patients.

	Benign (n=34)		Malignant (n=6)		P-value
	No.	%	No.	%	
Age: <30 years	4	14.7	0	0	0.047*
30-39	5	11.8	0	0	
40-49	17	50.0	1	16.7	
50-59	5	14.7	2	33.3	
≥ 60 years	3	8.8	3	50.0	
Mean±SD (range)	43.7±11.7 (25-70)		56.8±7.7 (43-65)		
Gender: Female	23	67.6	5	83.3	0.44
Male	11	32.4	1	16.7	

*The result was significant at P<0.05.

Conventional ultrasonographic criteria; the ultrasonographic criteria of the thyroid nodules are demonstrated in table 2. Of total 40 nodules, 16 of them (40%) were hyperechoic, all of which were benign represent 16 (47.1%) of the benign nodules, and 11 (27.5%) nodules were hypoechoic, four of them were malignant. The isoechoic nodule were 13 (32.5%) of them 11 (32.4%) of the isoechoic nodules were benign and 2 (33.3%) of the isoechoic nodules were malignant. The result was significant regarding hypoechoic nodules at P-value <0.05. The majority of thyroid nodules were wider than taller 36 (90%), most of them were benign 34 (100%), and all of nodules that are taller than wider 4 (66.6%) were malignant with significant result. Half of the nodules show no calcification 20 (50%), of which the majority were benign 19 (55.9%), while most of the malignant nodules had microcalcification 4 (66.7%) out of 6 with significant result regarding microcalcification (P=0.018). The majority of the benign nodules had smooth margin 28 (70%), all of which were benign. All of the nodules with irregular margin were malignant 4 (66.7%) with significant result regarding irregular margin, P-value <0.05. Composition; Most of the nodules were solid 29 (72.5%), of which 24 (70.6%) were benign and 5 (83.3) were malignant, and all spongiform nodules were benign 3 (8.8%); however, the result was not significant regarding solid nodules. Halo sign; More than half of the nodules 25 (62.5%) were not surrounded by thehypoechoic rim (halo sign). The result was significant at P<0.05. Vascularity on Doppler US. 17 of the nodules (42.5%) were avascular on Doppler US, all of which were benign, the majority of nodules which show predominantly peripheral vascularity were benign 15 (44.1%), while most of the nodules that shows predominantly central vascularity were malignant 5 (83.3%) out of 7 with significant result regarding central vascularity, P<0.001.

Table 2: The ultrasonographic criteria of the thyroid nodules in relationto histopathological results among the patients.

Ultrasonographic criteria		Benign (n=34)		Malignant (n=6)		P-value
		No.	%	No.	%	
Echogenicity	Hyperechoic	16	47.1	0	0	0.030*
	Isoechoic	11	32.4	2	33.3	
	Hypoechoic	7	20.6	4	66.7	
Orientation	Wider than taller	34	100	2	33.3	<0.001*
	Taller than wider	0	0	4	66.7	
Calcification	No calcification	19	55.9	1	16.7	0.018*
	Microcalcification	5	14.7	4	66.7	
	Macrocalcification	10	29.4	1	16.7	
Margin	Smooth	28	82.4	0	0	<0.001*
	Irregular	0	0	4	66.7	
	Illdefined	6	17.6	2	33.3	
Composition	Solid	24	70.6	5	83.3	0.700
	Mixed	7	20.6	1	16.7	
	Spongiform	3	8.8	0	0	
Halo Sign	No Halo	23	67.6	2	33.3	0.029*
	Continuous Halo	11	32.4	3	50	
	Non continuous	0	0	1	16.7	
Vascularity	Avascular	17	50	0	0	<0.001*
	Peripheral vascularity	15	44.1	1	16.7	
	Central vascularity	2	5.9	5	83.3	

* The result was significant at P<0.05.

* diagnostic performance (sensitivity,specificity, ositive predictive value (PPV), negative predictive value (NPV), and accuracy) of the conventional ultrasonographic criteria of the thyroid nodules were shown in table 3

Table 3: The diagnostic performance of the conventional ultrasonographic criteria of the thyroid nodules among the patients.

Parameters	Sensitivity	Specificity	PPV	NPV	Accuracy
Echogenicity	77.8	83.9	58.3	92.9	82.5
Microcalcification	88.9	68	68.1	94.7	72.5
Orientation	66.7	100	100	91.2	92.5
Irregular Margin	88.9	80.7	67.1	96.2	82.5
Composition	88.9	51.6	34.8	84.1	60
Halo Sign	90	83.3	64.3	96.2	85
Vascularity	70	90.7	87.5	90	83.4

IRAD (TR); Most of the thyroid nodules 17 (42.5%) were TR2, and 13 (32.5%) of the nodules show TR3, while only 9 (22.5%) nodules show TR4, as shown in table 4. Regarding the TIRAD distribution in relation to histopathological results; most of the thyroid nodules were benign as all TR2 and TR3 30 out of 40 (75%) were benign, while more than half of TR4 were malignant 5 out of 9 with significant result, P<0.05 (Table 4).

Table 4: TIRAD distribution of thyroid nodules in relation to histopathological result among the patients.

Parameters	With thyroid nodule (n=40)		Benign (n=34)		Malignant (n=6)		P-value
	No	%	No.	%	No.	%	
Benign (TR 2)	17	42.5	17	50.0	0	0	<0.001*
Mild suspicious (TR 3)	13	32.5	13	38.2	0	0	
Moderate suspicious (TR 4)	9	22.5	4	11.8	5	83.3	
High Suspicious (TR 5)	1	2.5	0	0	1	16.7	

* The result was significant at P<0.05.

The diagnostic performance of the TIRAD were as followed; Sensitivity 90%, Specificity 80%, PPV 64.2%, NPV 96% & Accuracy 83.5%. Strain Ratio; the mean of the SR of all nodules was 2.7±2.1 ranged 0.4-13.5, with significant difference between benign (1.87±0.82; range 0.4-3.6) and malignant (5.71±3.8, range 2.1-13.5) (P=0.001). The SR was represented at the ROC curve (Figure 1) and the best SR Cut-off value derived from analysis was >2.5 (a higher values were more indicative of malignancy, whereas values below this cut-off value suggest benignity) as demonstrated in table 5.

Table 5: SR Cut-off value to differentiate between benign andmalignant thyroid nodules among the patients.

Area Under the Curve (AUC)	Std. Error	P-value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.972	0.0227	<0.0001*	0.863	1.000
Positive if Greater Than			Sensitivity	Specificity
>2.4			100.0	76.67
>2.5			**100.0**	**88.2**
>2.6			90.0	96.67
>3.8			80.0	100.0
>4.2			70.0	100.0

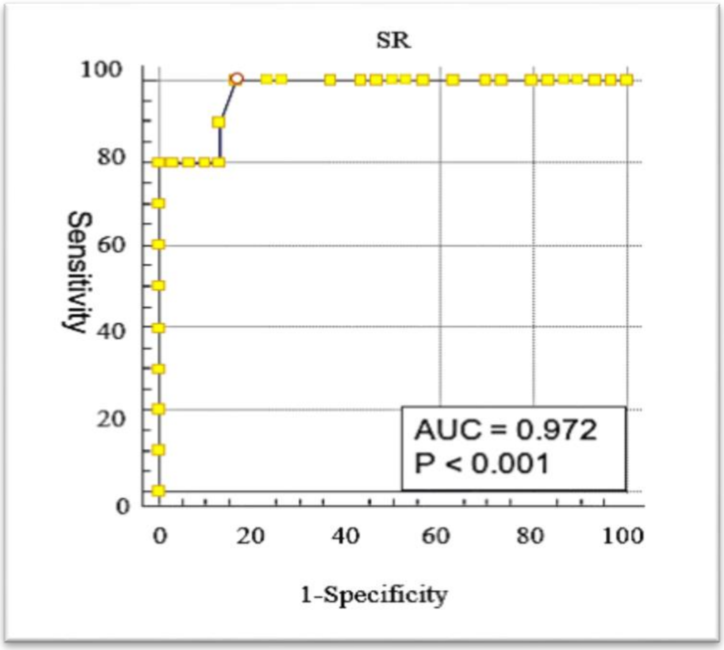

Figure 1: The Strain ratio at ROC curve.

Regarding the distribution of the TIRAD score according to SR of the thyroid nodules; all thyroid nodules of TR2 have SR lesser than 2.5, while thyroid nodules of TR3 and TR4 had both lesser and greater than the cut off value with significant result as shown in table 6 & 7.

Table 6: TIRAD score distribution in relation to SR among the patients.

SR	TR2		TR 3		TR 4		TR5		P-value
	No.	%	No.	%	No.	%	No.	%	
>2.5	0	0	3	23.1	6	66.7	1	100	<0.001*
≤2.5	17	100	10	76.9	3	33.3	0	0	
Total	17	100	13	100	9	100	1	100	

*The result was significant at P<0.05.

Table 7: SR distribution in relation to histopathological result amongthe patients

SR	Malignant		Benign		P-value
	No.	%	No.	%	
>2.5	6	100	4	11.8	<0.001*
≤2.5	0	0	30	88.2	
Total	6	100	34	100	

*The result was significant at P<0.05.

The diagnostic performance of both the conventional US criteria and strainelastography were demonstrated in table 8.

Table 8: The diagnostic performance of the conventional US criteriaand strain elastography of the thyroid nodules among the patients.

Parameters	Conventional US criteria	Elastography SR
Sensitivity	90.0	100
Specificity	80.0	88.2
Positive Predictive Value	64.2	67.0
Negative Predictive Value	96.0	100
Accuracy rate	83.5	90.0
P value	<0.001*	<0.001*

*The result was significant at P<0.05.

Discussion

Conventional gray-scale and Doppler US had high malignant predictability only when several patterns are present simultaneously in a single nodule. In the literature, their predictive value rise only at expense of sensitivity [14]. USEdescribed as a promising technique that developed in recent years. It assesses nodule stiffness to identify malignant from benign thyroid nodules, thus providing a new approach for differentiating malignant from benign thyroidnodules. USE can be used as a complementary tool for conventional gray-scale and Doppler US [15,16].

In the present study, all malignant nodules were hypoechoic with significant result, this agrees with Moon et al [17],Asteria et al [18], and Colakoglu et al [19] studies. Moreover, all nodules that shaped taller than wider were malignant with significant result and high specificity. This result agrees with Moon et al [17] study. Additionally, there were statistically significant differences between malignant and benign thyroid nodules concerning microcalcification and irregularmargin, non-continuous halo sign, Doppler patterns (central vascularity). This agrees with Asteria et al [18] and Colakoglu et al [19] studies.

In agreement with the literature, malignant thyroid nodules were significantly hypoechoic, with irregular margin, taller than wider, showed microcalcification and exhibited a significant increase in vascularity. However, these features are not accurate as a predictor of malignancy if they exist alone [18,20]. In this study, orientation (taller than wider) was the most US predictive pattern of malignancy. This disagrees with Asteria et al [18] study in which irregular margin and microcalcification were the most US predictive patterns of malignancy as their study lack orientation US criteria.

Regarding TIRAD classification, this study shows significant difference of TIRAD in differentiation of benign and malignant thyroid nodules. This agrees with Fahad et al study. Regarding the diagnostic performance, the present study had lower diagnostic performance (sensitivity, specificity and accuracy) (90%, 80%, 83.5% respectively) in this study in compared with (100%, 94.8%, 95.7% respectively), this may be due to lower patients population in this study (40 patients) in comparison to Fahad et al study (116 patients) [21].

Regarding the elastography, the optimal SR cutoff value was >2.5 and showedto have a sensitivity of 100%, a specificity of 88.2%, PPV of 67%, NPV of 100%, and an accuracy rate of 90%. The current result is supported by several studies; Rago et al [22] study had reached an excellent result with the USE sensitivity, specificity, PPV, NPV and accuracy of (97%, 100%, 100% and 98%, 98.9% respectively), and Fahad et al study which carried out in Iraq, showsthe cut-off value of 2.45 with sensitivity 100%, specificity 94.8%, PPV 80%, NPV 100%, and accuracy rate of 95.7% [21].

In Ciledag et al study [23], SR (>2.31) predicted thyroid malignancy with a sensitivity and specificity of (86% 82%) respectively, whereas another study showed SR cutoff value of (>2) had a sensitivity and specificity of (97%, 92%) respectively [24]. Xing et al. [25] reported that SR cutoff of (>3.79) had a sensitivity and specificity of (98%, 86%) respectively in predicting thyroid malignancy. Moreover, Ning et al. showed that SR cutoff value of (>4.2) had a sensitivity of 81% and a specificity 83% [26].

However, by reviewing previous studies, the SR cut-off values were reported as widely results of sensitivity (ranging from 15.7% to 98%) and specificity (ranging from 58.2% to 100%) [17,19,21-29] as shown in table 9 . This may be due to variation in the examination techniques, and different sample size in these studies. In all form of strain elastosonography, their methods depend on the examiner. In real-time elastography, variable tissue deformation induced, depending on the compression force applied by the radiologist. Non-uniform compressions yield variability in inter- and intra-observer results [30]. Training and experience are important for a good examination result.

Table 9: Strain elastography cut-off value, sensitivity & specificity of thethyroid nodule

Strain elastography Studies	Strain ratiocut-off value	Sensitivity	Specificity	Accuracy
Rago et al 2007 [22]	-	97	100	98.9
Xing et al 2011 [23]	>3.79	98	86	-
Ciledag et al 2012 [24]	>2.31	86	82	82.4
Cantisani et al 2012 [25]	>2	97	92	94
Ning et al 2012 [26]	>4.2	81	83	-
Şahin et al 2014 [27]	>2.45	73.9	73	-
Abd-Alrahman et al 2016 [28]	> 2.88	85.7	93.2	93.3
Rago et al 2016 [29]	>1.1	86	90	-
Colakoglu et al 2016 [19]	-	100	80.2	85
Fahad et al 2018 [21]	>2.45	100	94.8	95.7
Mean	-	90.46	87.42	91.55
Current study 2019	>2.5	100	88.2	90

In conclusion, SR is higher in malignant thyroid nodules than the benign nodules. Ultrasound elastography can assist in the differential diagnosis of malignant and benign thyroid nodules, as Strain sonoelastography improve the diagnostic performance in differentiating the benign and malignant thyroid nodules.It is recommended to use US elastography as a routine examination in combination with Grey scale ultrasound for assessment of thyroid nodules with encouraging the Iraqi radiologists to use and gain more experience in addition to conducting further studies to make the technique easy and more applicable clinically.

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