Original Article

Evaluation of the diagnostic value of Ultrasound Elastography in TIRADS 4 categories of Thyroid nodules

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ABSTRACT

Introduction: This paper evaluated the diagnostic performance of shear wave elastography (SWE) alone and in combination with the Thyroid Imaging Reporting and Data System (TI-RADS) with the end of improving the distinction between benign or malignant thyroid nodules.

Methodology: 55 nodules were estimated in 50 patients (36 females and 19 males, with a mean age of 51.98±9.98) by conventional ultrasound and SWE. Size, echogenicity, margin, calcification, composition, shape, and color Doppler were reviewed separately in each nodule. Elasticity was assessed qualitatively by examining color maps and was quantitatively measured by appraising velocity in Region of Interest (ROI) in the stiffest areas and eventually the maximum and mean velocity were achieved. The ROC curve was analyzed in order to specify the best cut-off point of SWV (Shear Wave Velocity).

Results: Among the B-mode and color Doppler features, shape features ($p<0.001$), Halo ($p=0.001$), Doppler grade ($p<0.001$), and among the SWE features, grade II color map ($p=0.001$), grade IV color map ($p<0.001$), grade V color map ($p=0.024$), maximum velocity ($p<0.001$) and mean velocity ($p<0.001$) were significantly and statistically associated with malignancy. According to Nagelkerke R2, it was demonstrated in statistical analysis that the maximum velocity was designated as the strongest predictor of malignancy. The area under the Curve (AUC) for maximum SWE was considered to be 0.854 (0.969-0.749 confidence interval, ($p<0.001$)). The best cut-off point for maximum and mean velocity for differentiating between benign and malignant nodules was 3.61 m/s (sensitivity was 87.5% and specificity was 79.49%) and 3.44 m/s, respectively.

Conclusion: SWE was an encouraging test for estimating preoperative malignancy risk in suspected patients with TIRADS 4 category of thyroid nodules. The maximum velocity had the strongest prediction of malignancy among conventional and elastographic ultrasound variables.

Keywords: Thyroid nodules, Shear Wave Elastography, Ultrasonography, Thyroid cancer

Introduction

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The prevalence of thyroid nodules was widely observed even in the population living in iodine-sufficient countries. The malignancy risk in each thyroid nodule was between 7% and 15% and might differ concerning age, sex, radiation history, family history, and other factors [1]. The goal of assessing thyroid nodules was to stamp those nodules that were most exposed to the risk of malignancy to evaluate them more precisely.

Thyroid ultrasonography, as the main imaging technique, was highly used for thyroid nodules evaluation, since there were special features in malignant-related ultrasonography such as microcalcification, irregular margins, and taller-than-wide shape. Several ultrasonographic-based risk classification systems were considered to provide instructions for evaluating thyroid nodules based on nodule size and ultrasonographic features [2-4]. Observing these guidelines, it was supposed to aspirate a subset of nodules with fine-needle aspiration (FNA). The results were achieved based on the Bethesda classification system [5]. FNA cytology (FNAC) was transduced as the gold standard for detecting thyroid nodules due to its accuracy and efficiency [6, 7]. Based on the Bethesda System for reporting thyroid cytology [5], the thyroid nodules were classified into six diagnostic categories with high sensitivity and high negative predictive value (NPV), thus presenting a strong tool for the management of patients with thyroid nodules [8]. Although FNAC was known as a method with low levels of invasive, its results relied on the expertise of the operator and the pathologist. Another limitation of FNAC was that approximately 25% of nodules were placed in an uncertain group, in which the distinction between malignant and benign was not possible.

In the area of molecular biology and imaging, diagnostic tools were directed towards correcting the diagnosis of thyroid nodules by unknown cytology. Elastography was numbered among ultrasonographic techniques assessing the elasticity of tissue to distinguish between malignant or benign nodules, as malignant nodules were harder than benign nodules. Most of the studies were hitherto carried out in the field of elastography for thyroid nodules using Strain Elastography (SE) method, measuring the degree of tissue stiffness only qualitatively compared to the surrounding tissue. However, SWE was a quantitative method applied for the prediction of the malignancy or benignity of nodules. SWE was known as a real-time imaging technique using a linear ultrasound transducer, and its performance was not accompanied by applying additional pressure. Tissue elasticity was calculated immediately by measuring the wave propagation velocity. The data were provided in real-time color images and were quantified regarding the shear wave velocity (m/s) or as Young's modulus (kPa) [9]. In 2010, one conducted study on SWE demonstrated that this technique could predict malignancy with 85% sensitivity and 94% specificity with 65 kPa cut-off point [10].

Presently, some promising reports were obtained on usefulness of SWE, but the performed studies and the number of examined patients were still limited [11-13]. Regarding the studies in the past few years on the role of elastography in determining the malignancy of thyroid nodules, as well as the limited studies on a newer field of elastography (shear-wave), this paper was attempted at fleshing out more comprehensive information to available sources and illustrating the role of this new method of elastography as a complementary method for the diagnosis of malignancy of thyroid. This study was categorically aimed at assessing the SWE diagnostic performance in TIRADS 4 categories of thyroid nodules, which gave birth to a significant part of the diagnostic challenge.

Methodology

Patients, who were referred by a clinician for a thyroid ultrasound and had at least one TIRADS 4 nodule, referred to Imam Reza and Shariati Hospitals in Tehran from 2018 to 2020 and were included in the study after obtaining informed consent. (Conventional and shear-wave elastography) ultrasound was performed by a radiologist with more than 10 years of history in performing thyroid ultrasound. After completing ultrasound through the B-mode method and based on inclusion criteria, these patients' data were gathered. The patients older than 18 years with one or more nodules larger than 1 cm and at least one nodule with TIRADS 4 were included in the study.

Gold standard test was the pathology of thyroid tissue after FNAB or thyroidectomy, which was performed in response to both benignity and malignancy. The mentioned test was one ultrasound performed by SWE method, the result of which was shown as SWV in m/s.

The collected data from patients involved the demographic characteristics such as age and sex of patients, and number of nodules, nodule features such as size, site, margin, calcification (micro or macro), and echogenicity. Other data contained Maximum SWV, Mean SWV, and pathology result obtained from surgery.

Evaluation of nodule properties was completed by means of Siemens device and 18L6 High Definition (HD) probe. In ultrasound evaluation, the following criteria were determined in patients and correspondingly, the TIRADS score was specified in them: Composition, Echogenicity, Shape, Margin, Echogenic Foci, and Micro-calcification. Patients posed in TIRADS 4 category were included in the study.

The same device took SWE place with 9L4 Multi-D probe using VTIQ software.

Elastography was performed after B-mode and before surgery or FNA. During the elastography performance, the patient was told to stop swallowing and breathing for a few seconds in order to present the SWV map by the device. To increase accuracy, SWV map was prepared in two times.

Tissue velocity was measured after preparing the map. To this end, an ROI box with a diameter of 1.5 mm was placed on the nodule's stiffest area, and the SWV was measured two times. Then, SWV was recorded in the thyroid tissue around the nodule at one time. The highest velocity in the nodule was recorded as maximum SWV, and the mean of the two measured velocities was viewed as mean SWV.

After checking the findings extracted from the surgery, the features of the diagnosed sample (site, size, and needle tract) were corresponded with the B-mode result to prevent the incidental cancers from the incorrect entrance into the study results.

After following up on the pathology outcomes of the surgery along with the previously obtained data, the SWV cut-off point was computed concerning the ROC curve as well as sensitivity, specificity, positive predictive value (PPV), and NPV of SWV cut-off point.

The gathered data was inserted in SPSS version 22. The ROC curve method was used to gain the SWV cut-off point and distinguish between benign and malignant thyroid nodules.

Results

In the current study, 55 nodules were estimated in 50 patients (36 females and 19 males, with a mean age of 51.98±9.98). The FNA process was completed for the whole nodules. Among all cases, 39 nodules (70.9%) were benign, and 16 nodules (29.1%) were malignant or suspected of being malignant and were referred for surgery. Among the malignant lesions, 6 (37.5%) cases were detected with follicular thyroid carcinoma (FTC), 2 (12.5%) cases with medullary thyroid carcinoma (MTC), and 8 (50/0%) cases with papillary thyroid carcinoma (PTC). The results of histology and pathology were presented briefly in Table 1.

Table 1. Histology, Surgery Type and Pathology Result

Histology Result	Surgery Type	Pathology Result
FTC (n = 6)	Lobectomy (n = 6)	Benign (n = 0)
PTC (n = 8)	Thyroidectomy (n = 10)	Malignant (n = 16)
MTC (n = 2)		

Imaging Results

Each nodule was surveyed in terms of echogenicity, calcification, shape, composition, and color Doppler. Moreover, qualitative (color map) and quantitative (velocity) features of each nodule were acquired during real-time SWE. There was no statistically significant relationship between age and sex with malignancy (p = 0.927 and p = 0.119, respectively). Among the B-mode, color Doppler and SWE features, the following features were statistically and significantly related with malignancy: shape (p <0.001), Halo (p = 0.001), Doppler degree (p <0.001), grade II color map (p=0.001), grade IV color map (p<0.001), grade V color map (p=0.024), maximum velocity (p<0.001) and mean velocity (p<0.001). The maximum and mean SWE for malignant nodules were equal to 4.24±0.68 m/s and 4.08±0.78 m/s, respectively, which was significantly higher than the maximum and mean SWE in benign nodules (3.16±0.78 m/s and 2.97±0.81 m/s, respectively and p <0.001). Based on the maximum velocity in the SWE, the nodules were categorized as presented in Table 2. A statistically significant relationship was observed between groups 3 and 4 and malignancy (p = 0.01 and p = 0.032, respectively).

Table 2. Nodules Frequency based on Maximum Velocity

	Frequency	Percent
Reference Group (0-2.5 m/s)	5	9.1
Group 1 (> 2.5 – 3.2 m/s)	15	27.3
Group 2 (> 3.2 - 3.8 m/s)	17	30.9
Group 3 (> 3.8 – 4.5 m/s)	12	21.8
Group 4 (> 4.5 m/s)	6	10.9

Table 3 summarized the sensitivity, specificity, PPV, and NPV of each conventional ultrasonographic feature and SWE findings. It also specified the variance amount of the pathology results as elucidated by the univariate regression model (Nagelkerke R2). The findings with the most considerable amount of Nagelkerke R2 were maximum velocity, mean velocity, grade 3 color map, and grade IV color Doppler.

Table 3. B-Mode, Color Doppler and SWE Findings

Finding	Frequency	Percent	Benign	Malignant	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Nagelkerke R2 (%)
Echogenicity									
Isoechoic	11	20	9	2	12.5	76.92	18.18	68.18	2.2
Hyperechoic	2	3.63	2	0	-	-	-	-	-
Hypoechoic	41	75.54	28	13	81.25	28.20	31.7	78.58	1.4
Marked Hypoecho	1	1.81	0	1	-	-	-	-	-
Calcification Pattern									
None	42	76.36	29	13	81.25	25.64	30.95	76.92	0.8
Macrocalcificaton Central	10	18.18	7	3	18.75	82.05	30	71.11	0
Macrocalcificaton peripheral	1	1.81	1	0	-	-	-	-	-
Microcalcification	2	3.63	2	0	-	-	-	-	-
Margin									
Smooth	47	85.45	34	13	81.25	12.82	27.65	62.5	0.8
Irregular	8	14.54	5	3	18.75	87.17	37.5	72.34	0.8
Shape									
Taller than Wide	4	7.27	1	3	18.75	97.43	75	74.5	9.8
Oval	27	49.09	15	12	75	61.53	44.44	85.71	15.4
Round	24	43.63	23	1	-	-	-	-	-
Composition									
Solid	38	69.09	28	10	62.5	28.20	26.31	64.70	1.2
Predominantly Solid	16	29.09	10	6	37.5	74.35	37.5	74.35	1.9
Predominantly Cystic	1	1.81	1	0	-	-	-	-	-
Color Doppler Grade									
Grade I	5	9.09	5	0	-	-	-	-	-
Grade II	31	56.36	26	5	31.25	33.33	16.12	54.16	14.4
Grade III	14	25.45	7	7	43.75	82.05	50	78.4	9.4

Grade IV	5	9.09	1	4	25	97.43	50	76	15.1
Color Map Grade									
Grade I	5	9.09	5	0	-	-	-	-	-
Grade II	17		17	0	-	-	-	-	-
Grade III	19	34.54	14	5	31.25	64.1	26.31	69.44	0.3
Grade IV	12	21.81	3	9	56.25	92.3	75	83.72	33.3
Grade V	2	3.63	0	2	12.5	100	100	73.58	12.7
SWE									
Maximum Velocity >3.61 m/s	21	38.18	7	14	87.5	79.49	66.66	94.11	51.1
Mean Velocity >3.44 m/s	24	43.63	10	14	87.5	73.35	58.33	93.54	41.5

ROC Analysis

The area under the curve (AUC) for the maximum and mean SWE was considered to be 0.854 (confidence interval 0.960-0.749, p <0.001) and 0.837 (confidence interval 0.946-0.728, p < 0.001), respectively. The best cut-off point for maximum and mean velocity for differentiating between benign and malignant nodules was 3.61 m/s (sensitivity was 87.5% and specificity was 79.49%) and 3.44 m/s, respectively (Figure 1). The cut-off degree was demonstrated in Table 4 concerning the pathology results.

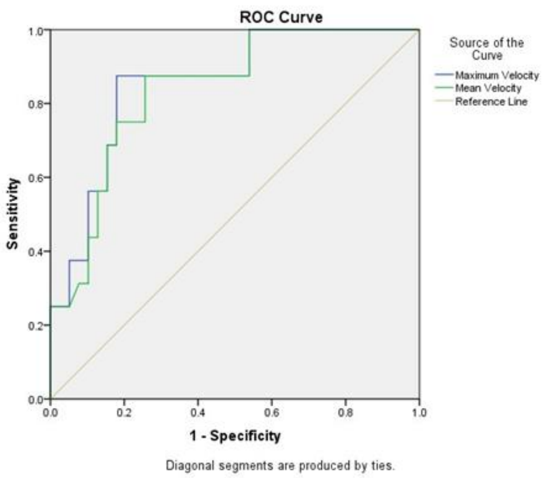

Figure 1. ROC curve analysis of maximum and mean SWV

Table 4. SWE Cut-off and Histology Details

SWE	PTC	FTC	MTC
Mean Velocity < 3.44 m/s	2	0	0
Mean Velocity >3.44 m/s	6	6	2
Maximum Velocity < 3.63 m/s	2	0	0
Maximum Velocity > 3.63 m/s	6	6	2

Logistic Regression Analysis

Univariate logistic regression took place for each conventional ultrasonographic feature and SWE findings to attain sensitivity, specificity, PPV, and NPV of tests. The results of these models were exhibited in Table 3. Based on Nagelkerke R2, it was substantiated that the maximum velocity of 3.61 m/s < and the mean velocity of 3.44 m/s < in SWE were predicted to be 51.1% and 41.5% variance in the pathology results of the nodule, respectively. These values were higher than Nagelkerke R2 values for every single feature in conventional ultrasonography. So, the maximum velocity was regarded as the strongest predictor of malignancy.

Discussion

The high prevalence of nodular thyroid disease caused the distinction between benign and malignant lesions as a main problem in the endocrinological area. Ultrasound manifestations were greatly contributed to the detection and management of malignant and benign nodules [14-16]. Making use of elastography was first approached by Lyshchik et al. for the improvement of the diagnostic accuracy of ultrasound examinations in thyroid nodules [17]. SWE was a novel technique with high sensitivity and specificity in the evaluation of nodular thyroid disease, potentially minimizing unnecessary FNAB [18]. In this regard, this cross-sectional study was carried out to evaluate the SWE diagnostic performance in predicting the risk of benign and malignant in TIRADS 4 categories of thyroid nodules.

In the current study, the maximum SWV in malignant thyroid nodules was higher than in benign thyroid nodules. Based on ROC curve, the maximum SWV cut-off point was equal to 3.61 m/s for the prediction of thyroid cancer, which its sensitivity, specificity, PPV, and NPV were equal to 87.5%, 74.49%, 66.66%, and 94.11%, respectively.

Liu et al. [19] exhibited that SWE might be instrumental in forecasting malignant thyroid nodules with comparable results. In line with recent studies, Liu's study also indicated that elasticity indices in SWE were significantly different in the distinction between benign and malignant thyroid nodules (P<0.001) [20]. The study by Cantisani et al., which was conducted in this field, stated the sensitivity of 78.7% and the specificity of 80.5% concerning the diagnostic performance of SWE [21].

Totally, although Veyrieres et al. [13], Bhatia et al. [22], Sebag et al. [10] and Kim et al. [23] respectively reported that elasticity indices in malignant nodules were significantly greater than in benign nodules, the most accurate SWE cut-off point did not reach a single value. The explanation of this issue that the cut-off point value was different from one study to another might be as a result of the selection of different standards: for example, the Youden's index was used in the study by Liu et al., while other studies used the best NPV [13] or PPV (at least over 80%) [10]. In a retrospective study performed by Xu et al. [24], in which 441 thyroid nodules were evaluated in 375 patients (with a malignancy rate of 26.3%), the value of 2.87 m/s was obtained as the best cut-off point for distinguishing between benign and malignant thyroid nodules. This value was less than the value achieved in the current study (3.61 m/s) and the study by Azizi et al. (3.54 m/s) [25]. In the study of Aghaghazvini et al. [26] based on the ROC curve, the maximum SWV cut-off point was equal to 3.61 m/s, and its sensitivity, specificity, PPV, and NPV were equal to 90%, 77.67%, 44%, and 98%, respectively. The cut-off point value derived in the study by Aghaghazvini et al. largely corresponded to the calculated value in this study. The disparity in the cut-off point in the studies was more probably related to the area of the thyroid nodule chosen for the SWV measurement since the stiffness of the thyroid nodule was heterogeneous. Furthermore, in different imaging systems, the intended ROI differed in size, which might be considered as the factor leading to differences in the measured value for the tissue stiffness amount.

Meanwhile, it was safe to state that the findings of the present study were highly in line with the study conducted by Aghaghazvini et al. [26] with 3.63 m/s cut-off point and the study by Azizi et al. [25] with 54.5 m/s cut-off point. Moreover, it was figured out that the maximum SWV was the strongest single predictor of thyroid nodule malignancy than B-mode and Doppler findings. In this finding, which the maximum SWV exceeded other B-mode and demographic predictors in thyroid nodule malignancies, were consistent with the results of the study conducted by Azizi et al. [25].

To prevent unnecessary surgical removal or biopsy in thyroid nodules, high sensitivity, and great NPV were required in ultrasound screening to ponder surgery [27]. In the current study, among the B-mode and color Doppler features, features such as shape, Halo, Doppler degree, grade II, IV, and V color maps had a statistically significant relation malignancy. In the study by Aghaghazvini et al. [26], among the B-mode and color Doppler features, irregular margin, hypoechogenicity, microcalcification, grade III and IV color Doppler, and grade IV and V color map were significantly related to malignancy. In the study conducted by Liu et al., the strongest predictive feature in microcalcifications conventional ultrasound was attributed to the highest sensitivity and specificity [20]. However, in conventional ultrasound, no single feature had enough accuracy in distinguishing between benign and malignant lesions. Still, the combination of several features ended with an increase in sensitivity and specificity [16]. Non-diagnostic thyroid nodules without suspected features on conventional ultrasound or those with only one suspected feature were followed up with ultrasound, but non-diagnostic nodules containing two or more suspected features were supposed to be under ultrasound-guided FNA [28]. Horvath et al. [29] developed TIRADS for the classification of thyroid cancer risk for clinical measures (88% sensitivity and 88% NPV). Russ et al. [30] manifested that TIRADS had a sensitivity of 95.7% and a high NPV of 99.7% in the diagnosis of thyroid carcinoma. Lately, Kwak et al. created a classification in the TIRADS system [31] that was applied in the study by Liu et al., and more data were provided for the ultrasound to the classification of benign and malignant nodules. On this basis, in their study, the sensitivity and NPV for TIRADS were equal to 89.69% and 84.00%, respectively [20].

Respecting the results obtained from the study by Liu et al. [20], it was demonstrated that the combination of TIRADS and SWE partly increased diagnostic performance in differentiating benign and malignant thyroid nodules. In the case of using TIRADS and SWE "in parallel", they found higher sensitivity (94.85%) and NPV (90.00%) compared to the two methods separately. According to the findings, it was appeared that SWE and TIRADS could establish a complementary relationship concerning the advantages. TIRADS could make up SWE limitations caused by macrocalcifications and carotid arteries. Furthermore, SWE had a complementary role besides TIRADS, which could be influenced by the operator's influence and dominance. It was principally suggested that SWE be a complementary tool for TIRADS 3-4a nodules, rather than as a separate diagnosis.

Some limitations were involved in the present paper, the most of which was the small sample size that prevented the performance of multivariate analysis and evaluation of possible confounding factors including calcification, tumor depth, and elasticity of surrounding tissues. In this study, the histological type of thyroid cancer did not interfere with SWV results, showing that SWV was appropriate for different types of thyroid cancers. Another limitation of this study was the lack of lymphoma and metastatic lesions. Recently, it was stressed in one study that the shape and arrangement of extracellular matrix fibers were positively associated with the mean and maximum velocity of breast lesions in SWE, which was able to exert an effect on the SWV [32]. Hence, this study recommended performing a study scheme by centralizing a specific histological type of thyroid cancer.

Cibas and Ali (2009) declared that lower than 3% of thyroid nodules with benign FNA results would eventually turn as malignant nodules [33]. Therefore, false negative FNA could partially influence the results and estimations of the study.

Conclusion

Concerning these results, it was clear that SWV could predict the probability of malignancy of one thyroid nodule and might be efficient in selecting nodules for FNA. Further data were necessary to propagate one or more SWV cut-off values for the malignancy risk assessment. Among the features of conventional ultrasonography, microcalcification, hypoechogenicity, and irregular margins were known as the other malignancy predictors but were less significant than SWV. The features of conventional ultrasound were still remarkable traces in differentiating between benign and malignant nodules and should not be left unnoticed within the context of the novel and emerging ultrasonographic techniques, but increased NPV and PPV and reduced surgery for benign thyroid nodules were compromising through the addition of new imaging techniques, including SWE.

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