Original Article

Journal of Iranian Medical Council, Volume 6, Issue no. 4
http://dx.doi.org/10.18502/jimc.v6i4.13446

Diagnostic Value of Shear Wave Elastography in Differentiation between Benign from Malignant Cervical Lymph Nodes

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Received: 29 Sept 2022
Accepted: 29 Apr 2023

Citation to this article
Chavoshi Mr, Taghavi M, Hashemi H, Davoodi M, Rouzrokh P, Aghaghazvini L. Diagnostic Value of Shear Wave Elastography in Differentiation between Benign from Malignant Cervical Lymph Nodes. *J Iran Med Counc.* 2023;6(4):664-73.

Abstract

Background: This study aims to evaluate the role of Shear Wave Elastography (SWE) in the differentiation of malignant from benign cervical lymph nodes and compare its accuracy with conventional ultrasound.

Methods: Seventy-one lymph nodes (malignant=52, benign=19) were investigated by both conventional sonography and SWE. Shear Wave Velocity (SWV) and color map were obtained for each lymph node before tissue sampling. R statistical software (x64, v3.6.1) was used for statistical analysis.

Results: Among all the conventional and elastography features, color map grading and shear wave velocity (SWV) had the most correlation with malignancy, even in normal-sized nodes. SWV was significantly correlated with the pathology (rpb=0.62, p<0.00). The best cutoff-value for SWV was 2.71 *m/s* (sensitivity: 82.7%, specificity:84.2%, AUC=0.92). The best predicting model by multivariate analysis was obtained by a combination of SWV and color map grading (sensitivity=92.3%, specificity=94.7%).

Conclusion: SWE is a valuable method for the differentiation of malignant from benign lymph nodes. It would help to find the proper lymph node for biopsy.

Keywords: Cervical, Lymph node, Malignant, Shear wave elastography, Ultrasound

Introduction

Ultrasonography (US) is the first-line imaging modality in the cervical lymph nodes assessment. For many years, conventional ultrasonography has been used to differentiate the malignant from benign lymph nodes. Since the introduction of ultrasound elastography in the 1990s, many studies have evaluated its value in the differentiation of malignant and benign lesions (1). Thyroid, liver, breast, prostate and lymph nodes are some of the target organs for US elastography.

Elasticity is defined as the resistance of the tissue to be changed by an external force. Shear Wave Elastography (SWE) is a new method that in contrast to its old counterpart, strain elastography, is less operator-dependent and more quantitative (2). In shear wave imaging technique, a dynamic stress is used to generate shear waves which are perpendicular to the primary force. The shear wave speed in the tissue is measured and a quantitative and qualitative result is given by the applied software. The latest method of SWE is 2D-SWE that uses dynamic stress to produce shear waves in multiple focal zones, monitors shear waves real-time in 2D, and measures the velocity of the tissue (3). It is believed that malignant tissues have more stiffness and less elasticity than benign ones, resulting in higher shear wave velocity. The implication of 2D-SWE in the diagnosis of the malignant lesions has been studied in the liver (4,5), breast (6,7), thyroid (8-10), and lymph nodes (11).

It has been proposed that metastatic lymph nodes are stiffer than benign or reactive ones (2,12), magnifying the value of elastography in lymph nodes' assessment. Excisional biopsy, as a gold standard method alongside Fine Needle Aspiration (FNA) or Core Needle Biopsy (CNB) in known malignant lesions, are the modalities of choice in the evaluation of lymph nodes. However, considering their complications and difficulties in some conditions (post-radiation, surgical scar, and fibrosis), deep position or vicinity of lymph nodes to vessels and contraindications to surgery, there is still a need to consider other preoperative diagnostic modalities. Elastography can provide more pre-operative information, including the selection of the proper place for the biopsy. Although in recent years, more studies have focused on validation of SWE for lymph node evaluation, to our knowledge, there are limited studies that have used the 2D-SWE method to evaluate the lymph nodes. Therefore, we designed a comprehensive study to investigate the role of this new technique in differentiating malignant from benign lymph nodes and compared it with conventional US features.

Materials and Methods

This study was approved by the ethics committee of the Tehran University of Medical Sciences. Written informed consent was obtained from all the participating patients, and their data remained confidential throughout the study.

Study population

This is a prospective cross-sectional study from December 2018 to December 2019. Patients were considered eligible to be included in the study if: there was a large or suspicious lymph node that required further evaluation in patients between 18-70 years old. Exclusion criteria included a history of previous invasive neck procedures, recent CNB or FNA, neck surgery and dissection with large scar or neck radiotherapy, coarse calcified containing lymph nodes, complete cystic nature, or non-diagnostic FNA/ biopsy result, or patients who refused to follow up or sign the informed consent forms. Following the sampling of 75 eligible patients, 10 were excluded, and 65 patients with 71 cervical lymph nodes entered the study.

Data gathering and imaging interpretation

Age and gender of all the patients were recorded. An expert radiologist with more than five years of experience in cervical sonography investigated all the lymph nodes using conventional sonography (grayscale and color Doppler) and SWE. In our patients, all the suspicious lymph nodes were detected in the second, third or fourth neck zones. Investigations were performed between 10 to 15 minutes, while patients were lying supine, and their necks were mildly extended and placed in the standard position for the neck sonography.

A Siemens device Acuson S2000, linear probe, frequency: 5-13 megahertz (Siemens Medical Solution, Mountain View, CA, USA) was used for the sonography. The following features were

reported in the grayscale (Conventional): Short axis diameter ([based on *Millimeter (mm)*]), short to long axis diameter ratio, presence of micro-calcification (defined as an echogenic focus of fewer than1 millimeters without posterior shadow), normal or abnormal echogenicity (considered abnormal in case of increase in cortical echogenicity) and the loss or squeezing of a hyper-echogenic hilum for the lymph node. The vascularity of the lymph node was then evaluated using color Doppler sonography (or power Doppler in the absence of flow observation), and categorized as either of the following: no vascularity, hilar vascularity, and peripheral vascularity. The elasticity of each LN was assessed both qualitatively and quantitatively and SWE was done using the same device and the VTIQ software. During SWE, the probe was pressed gently for 5 seconds over a fixed area on lymph node away from the great vessels if possible and patients were asked not to swallow or breathe for a few seconds while the shear wave image was created. For each lymph node, SWE was conducted twice and in several locations. Color maps were obtained for each location and ranged from red (the stiffest parts) to blue (the softest parts). The map with the stiffest areas was chosen as the final map and reported based on a scoring scale, proposed by a previous study (13). Table 1 shows the lymph nodes' elastography scoring scale system based on the color map pattern.

To obtain Shear Wave Velocity (SWV), several Regions of Interest (ROI) with a diameter of 0.5 *mm* were put on different areas of the lymph node, preferably away from the cystic and coarse calcified areas and in a way to cover the softest to stiffest areas of the final color map. The average of waves' velocity in different ROIs was then reported by the device (in *m/s*). For each lymph node, SWV was calculated and the mean velocity of the 3 highest levels was recorded. The measurement result of "X.XX *m/s*" was encountered infrequently, which indicated that the target tissue was either extremely soft or extremely hard, after excluding other factors considering color mapping.

All biopsies were obtained after the velocity measurements. Figure 1 shows an example of VTIQ mode, including conventional US, color Doppler US, color map grading and SWV measurement. Finally, the benign or malignant pathology of all lymph nodes was reported using excisional biopsy or FNA.

Statistical analysis

R statistical software (x64, v3.6.1) was used for statistical analysis. Frequencies and descriptive statistics were calculated for all the variables. To determine the relationship between input and output variables, Pearson's chi-square test and the Spearman rank-order correlation test were utilized where appropriate. To predict the pathology by input variables, sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated and univariate or multivariate logistic regression models (using both step-wise and non-stepwise approaches) were developed. Receiver Operating Characteristic (ROC) curves were then plotted for models, and cut-offs with the best trade-off for sensitivity and specificity were proposed. p-values less than .05 were considered significant.

Results

65 patients, (including 35 females (age=46.74±10.56) and 30 males (age=51.02±7.99) participated in the study. In total, 71 lymph nodes (malignant=52(73.2%); benign=19(26.8%)) were investigated. The pathology showed 31 metastatic papillary thyroid carcinoma and 21 metastatic SCC.

Table 2 shows the descriptive statistics for the conventional ultrasonography measurements including echogenicity (normal or abnormal), hilum presence

Table 1. Elastographic grading system based on the color map pattern

Grade	1	2	3	4	5
Patterns on elastographic findings	No stiff area or very small area	Stiff area <45%	Stiff area >45%	Peripheral stiff and central soft areas due to necrosis	Peripheral and central stiff areas with or without a soft rim

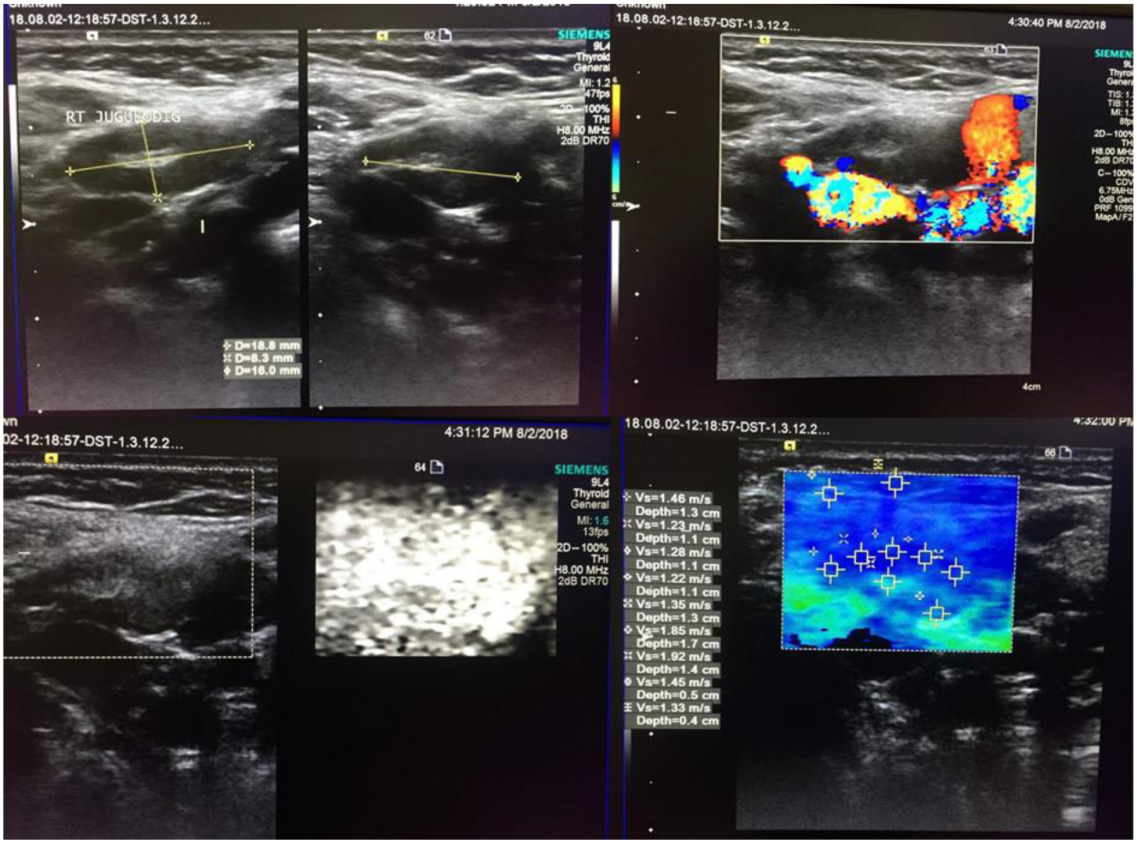

Figure 1. A prominent reactive lymph node in zone 4 of the right jugular chain with a history of recurrent tongue SCC. No evident vascularity is observed, and the elastography color mapping shows grade 1 and homogeneous appearance. Note multifocal low-velocity areas. Pathology proved a reactive lymph node.

Table 2. Conventional ultrasonography variables' frequencies

Variables	Status (count)	Benign lymph node	Malignant lymph node	p-value
Echogenicity	Normal (30)	18 (60%)	12 (40%)	<0.00
	Abnormal (41)	1 (2.4%)	40 (97.6%)	
Hilum presence	Present (22)	15 (68.2%)	7 (31.8%)	<0.00
	Absent (49)	4 (8.2%)	45 (91.8%)	
Microcalcification (MC) presence	MC+ (13)	0 (0%)	13 (100%)	0.02
	MC- (58)	19 (32.8%)	39 (67.2%)	
Short axis diameter	<8 *mm* (43)	15 (34.9%)	28 (65.1%)	0.06
	≥8 *mm* (28)	4 (14.3%)	24 (85.7%)	
Short axis to long axis ratio	<0.5 (29)	16 (55.2%)	13 (44.8%)	<0.00
	≥0.5 (42)	3 (7.1%)	39 (92.9%)	
Vascularity pattern	Absent/hilar (39)	18 (46.2%)	21 (53.8%)	<0.00
	Peripheral (32)	1 (3.1%)	31 (96.9%)	

(present or absent), Micro-Calcification (MC) presence (MC+ or MC-), short axis diameter (<8 *mm* or ≥8 *mm*), short axis to long axis ratio (<0.5 or ≥0.5), and vascularity pattern (absent/hilar or peripheral) in each lymph node. There was a significant association between the lymph nodes' pathology and their echogenicity [X2 (1)=29.29, p<0.001], hilum presence [X2 (1) = 27.91, p<0.001], micro-calcification presence [X2 (1)= 5.81, p<0.05], size ratio [X2 (1)=20.19, p<0.001], and vascularity status [X2 (1)=16.60, p<0.001]. There was also a marginally significant association between lymph nodes' size and the pathology [X2 (1)=3.67, p=0.055). Based on the odds ratios, malignant pathology was 60 times more probable if the lymph nodes had abnormal echogenicity, 24.11 times if the hilum was absent and 3.21 times if the size was ≥8 *mm*.

Considering SWE, lymph nodes' elasticity had a significant association with their pathology. Table 3 summarizes the frequencies of elasticity grades and the test statistics. As both correlation and chi-square analyses depicted the relationship between first and second grades with benign lymph nodes and the remainders with malignant ones, we split our data into two categories: Low Grade (LG) for grades 1 and 2, and High Grade (HG) for grades 3-5. Elasticity grading (categorized as HG and LG) and pathology had a significant association [X2 (1)=43.05, p<0.001, OR=138]. The association was also significant when only considering nodes smaller than 8 *mm* [X2 (1)=26.49, p<0.001] and larger than 8 *mm* [X2 (1)=14.05, p<0.001].

Regarding velocity, the average SWV of lymph nodes was 2.44±0.3 *m/s* for benign and 3.56±0.7 *m/s* for malignant lymph nodes (Figure 2). SWV was also significantly correlated with the pathology (rpb=0.62, p<0.001). Figure 3 shows the ROC curves for lymph nodes' pathology prediction based on the

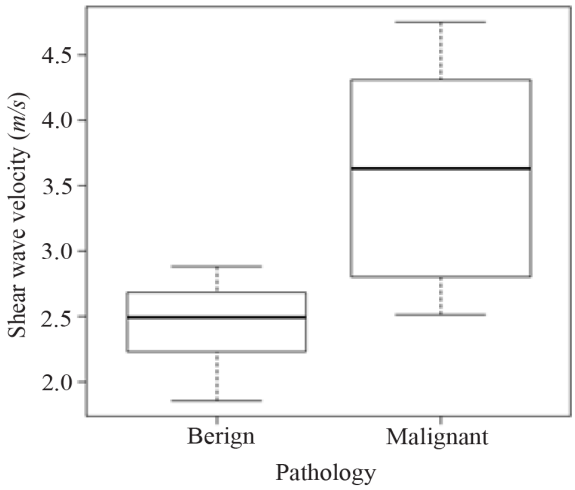

Figure 2. Boxplot of Shear Wave Velocity (SWV) analysis of benign and metastatic lymph nodes. Mean SWV was 3.56± 0.7 *m/s* and 2.44±0.3 *m/s* in malignant and benign nodes, respectively. Each box represents the values of the lower to upper quartiles; the central line represents the median, and the whiskers extend from minimal to maximal values.

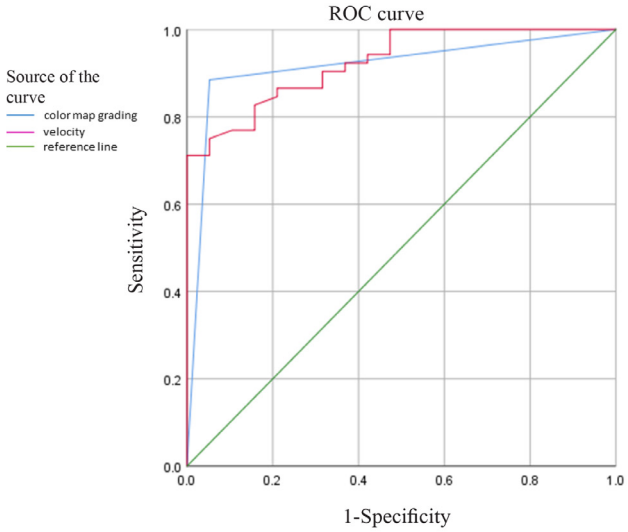

Figure 3. ROC curve for a regression model to predict the pathology based on the elasticity grading (AUC=0.92, p<0.001) and shear wave velocity (AUC=0.92, p<0.001) as predictors.

Table 3. Different elasticity grades' frequencies, relationship (X^2) with pathology, and correlation (r_s) with malignancy

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Frequency (malignant %)	16.9% (16.7%)	16.9% (33.3%)	26.76% (94.7%)	21.13% (100%)	18.31% (100%)
Chi-square (1)	23.58 (p<0.001)	11.73 (p<0.001)	6.12 (p<0.05)	6.95 (p<0.01)	5.81 (p<0.05)

elasticity grading with the AUC of 0.916 (CI=0.838 -0.994; p<0.001) and SWV with the AUC of 0.925 (CI=0.866-0.984; p<0.001). For elasticity grading, a cutoff of 2.5 (as a border of LG and HG) was determined to have the best trade-off for sensitivity (88.5%) and the specificity (94.7%). Looking at the SWV, the cutoff of 2.71 *m/s* had the best trade-off, showing the sensitivity and the specificity of 82.7 and 84.2%, respectively. Table 4 summarizes the sensitivity, specificity, PPV, and NPV for all the predictors mentioned above.

All in all, based on the stepwise and non-stepwise multivariable regression models, the combination of SWV and elasticity grading was the fittest model in prediction of the pathology outcome [X2(2)=55.431, p<0.001, Nagelkerke R2=0.78, Hosmer-Lemeshow R2=0.67]. The ROC curve of this model (Figure 4) has an AUC of 0.965 (CI=0.924-1; p<0.001) and the predicted probability cutoff of 0.63 [SWV cutoff=2.8, elasticity grading cutoff=2.5] at the accuracy level

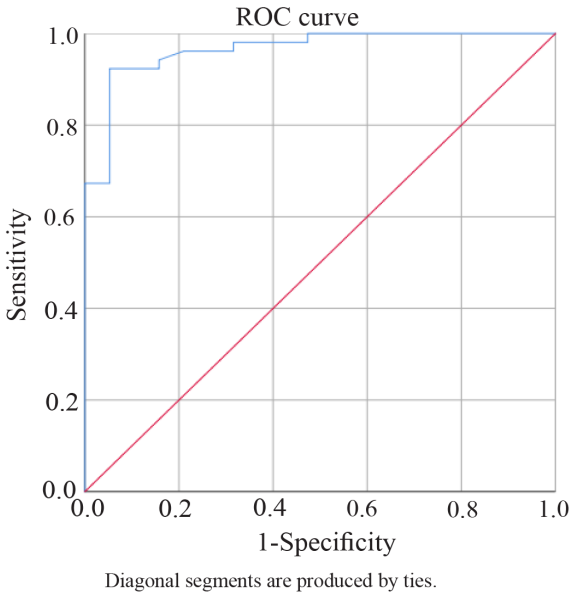

Figure 4. ROC curve for regression model based on the pathology as outcome and combination of the velocity (cutoff=2.8) and elasticity grading (cutoff=2.5) as a predictor. AUC=0.96, p<0.001.

Table 4. Sensitivity, specificity, positive and negative predictive values for conventional and shear wave elastographic features

Variables	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Shear wave velocity (cutoff: 2.71)	82.7	84.2	93.5	64
Echogenicity	76.9	94.7	97.6	60
Elastography grade I	3.8	47.4	16.7	15.3
Elastography grade II	7.7	57.9	33.3	18.6
Elastography grade III	34.6	94.7	94.7	34.6
Elastography grade IV	28.8	100	100	33.9
Elastography grade V	25	100	100	32.8
Elastography grading based on the high-grade and low-grade model	88.5	94.7	97.9	75
Hilum presence	86.5	78.9	91.8	68.2
Microcalcification presence	25	100	100	32.8
Size	46.2	78.9	85.7	34.9
Size ratio	75	84.2	92.9	55.2
Vascularity pattern	59.6	94.7	96.9	46.2

of 93% as the best trade-off (Sensitivity=92.3%, Specificity=94.7%, PPV=98%, NPV=81.8%).

Discussion

2D-SWE is the latest technique of shear wave elastography imaging that has surpassed the previous methods, including both strain elastography and point SWE. It gives a quantitative result and color image with high intra-observer reliability, which makes it more popular than previous methods (14). Although a meta-analysis found that the pool sensitivity and specificity of 2D-SWE (with studying 426 lymph nodes) to differentiate malignant and benign lymph nodes are 84% and 76%, respectively (11), it only included three articles which is not adequate for the comprehensive evaluation of a new technique. In this study, it was shown that 2D-SWE could be used in cervical lymph nodes assessment in order to distinguish the malignant nodes from the benign ones, and compared it with the conventional US features.

Like previous studies (15,16), we found that conventional ultrasound features including shape, size, short axis to long axis ratio, microcalcification, echogenicity, hilum morphology, color, and power doppler features are all useful in determining the malignant lymph nodes. However, we found that the correlation of both SWV and elastography color-map grading with malignancy was higher than all conventional US criteria.

Different sensitivities and specificities have been reported for 2D-SWE in previous studies. The sensitivity ranged from 77.1 to 92.59%, and the specificity ranged from 74.4 to 85.7% (14,17,18). This is incompatible with our study. In the current study, the sensitivity and specificity for color map grading was 88.5 and 94.7%, respectively. SWV had a sensitivity of 82.7% and specificity of 84.2% in our study.

Consistent with the previous studies (14,17,18), we found that the mean SWV in malignant nodes (3.56 *m/s*) was higher than the benign nodes (2.44 *m/s*) (Figures 5 and 6). In the present study, the best cut-off value for SWV was found at 2.71 *m/s*, with AUC of 92.5%. This is a little lower than the previous studies offered values (11). More studies are needed to reach a consensus about the best cut-off value.

In one study that performed multivariate analysis, the malignant predictive factors were calcification, axis ratio >0.5, cystic appearance, peripheral and central power Doppler flow, SWV >2.6 *m/s*, and the absence of fatty hilum (18). In our study, the multivariate regression analysis indicated that the best model to predict the probability of lymph nodes malignancy is when both color-map scaling and velocity are considered. The AUC, sensitivity, and specificity of this model were 0.96, 92.3, and 94.7%, respectively, which are all higher than the univariate models. This represents that designing a model which encompasses both color map grading and SWV would be more valuable in clinical practice to find the pathologic

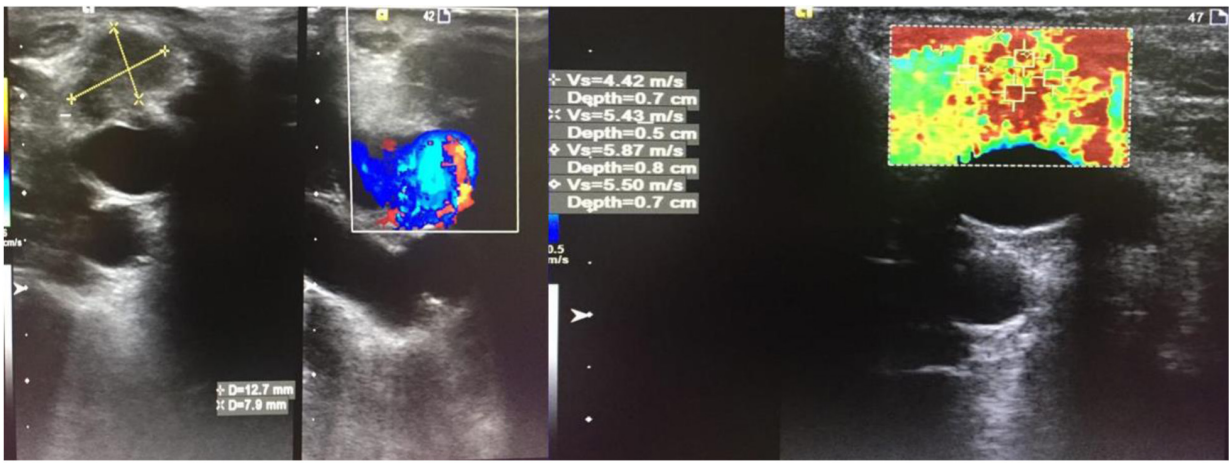

Figure 5. A borderline suspicious lymph node in right zone 3 without vascularity and high velocity (mean velocity=3.75 *m/s*) and red dominancy in color elastography mapping consistent with metastatic lymph node. Pathology proved PTC metastasis.

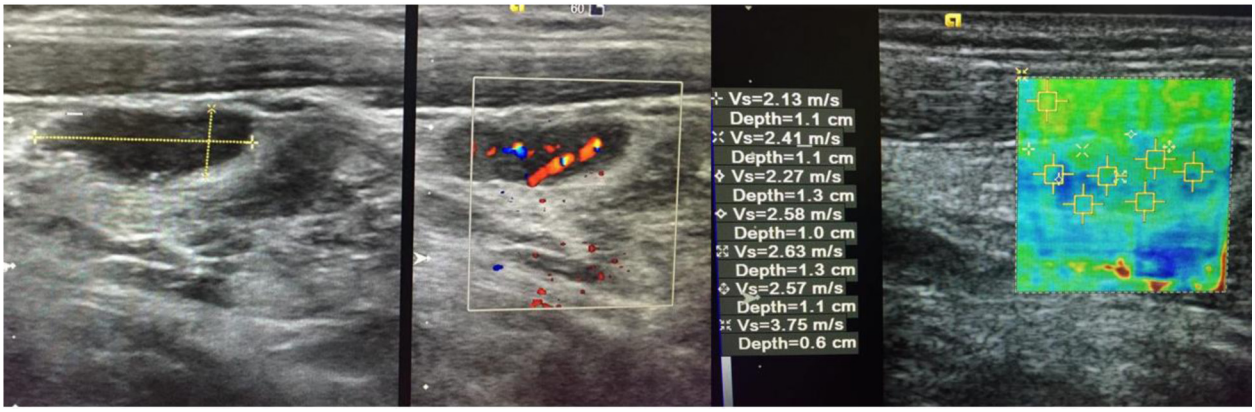

Figure 6. A suspicious hypoechoic lymph node with abnormal vascularity and blue green color elastography and mean velocity of 2.68 *m/s*. Pathology proved reactive lymph node.

lymph nodes. However, none of these models are still optimal for this purpose. Therefore, a study with more cases including clinical laboratory and imaging data would be more accurate for this matter.

Although size is an important criterion to evaluate a lymph node, it is shown that 30% of metastatic lymph nodes could have a normal size (19). This would be of remarkable clinical importance since in most cases, normal-sized lymph nodes are considered as benign nodes and less frequently are a candidate for biopsy. It is specially most challenging in patients with a known history of malignancy. On the other hand, it has been reported that focal cortical changes in ultrasound of lymph nodes could be early signs of malignant changes (20). However, these changes could also be observed in benign pathologies and making the differentiation more difficult which leads to more false-positive results in FNA samplings (20). An alternative approach to find out whether these lymph nodes are malignant or not is contrast-enhanced ultrasonography (21). This is a new method with high expenses and less available due to special contrast agents. Considering this dilemma, we found that even in lymph nodes with less than 8 mm short-axis diameter, SWE could predict the malignancy with sensitivity and specificity of 82 and 100%, respectively. This is consistent with another study that found SWE as a useful modality to diagnose metastatic small cervical lymph nodes (22). It is useful in determining the proper lymph node for biopsy in suspicious cases, even with normal lymph node sizes. Also, using the color map could demonstrate the most suspicious place for fine-needle aspiration in cases with only focal changes.

Regarding our study's limitations, the data sample was not sufficient to include more variables in the multivariate analysis, including other grayscale, color Doppler, and elastography features. Studies with more cases including different pathologic lymph nodes (both benign and malignant pathologies) are necessary to reach the more accurate estimation of SWV value and find the best cut-off for velocity. The limitation of elastography in the evaluation of cystic lymph nodes made us eliminate these cases. In addition, due to the small sample size, our malignant lymph nodes were not divided based on their origin of metastasis. However, we believe that this study provides essential information about the application of SWE in cervical lymph node assessment.

Conclusion

We found that 2D-SWE is a valuable method to differentiate malignant and benign lymph nodes with higher sensitivity and specificity compared with conventional US features. This modality is useful in normal-sized lymph nodes, too. It is more valuable in identifying the proper lymph node for tissue sampling. Utilizing only SWE, the cutoff value of 2.71 *m/s* is suggested to find malignant lymph nodes. However, the best model for predicting malignant lymph nodes was a combination of color map grading and SWV. Using this combination, the SWV cut off point of 2.8 alongside the cutoff of 2.5 for color map grading is the best predictor at the accuracy level of 93%.

Ethical issue

The ethical code of this study was IR.TUMS.REC. 1396.3065.

Acknowledgements

Special thanks to Ultrasound ward of Department of Radiology, Shariati Hospital for arranging cases and gathering data.

Conflict of Interest

There is no conflict of interest to declare.

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