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ORIGINAL ARTICLE

Can ultrasound elastography distinguish metastatic from reactive lymph nodes in patients with primary head and neck cancers?

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KEYWORDS

Cervical lymph node;
Elastography;
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Abstract *Objectives:* The purpose of this study was to evaluate the diagnostic utility of real-time elastography (RTE) in differentiating between reactive and metastatic cervical lymph nodes (LN) in patients with primary head and neck cancer in comparison with the conventional B mode and power Doppler parameters.

Methods: A total of 127 lymph nodes in 78 patients with primary head and neck cancer were examined by B-mode sonography, power Doppler ultrasound and elastography. Elastographic patterns were determined on the distribution and percentage of the lymph node area with low elasticity (hard), with pattern 1 being an absent or very small hard area to pattern 5, a hard area occupying the entire lymph node. Patterns 3–5 were considered metastatic. Ultrasound guided aspiration cytology was done for 57 lymph nodes. Excision biopsy was done for 52 lymph nodes. Eighteen lymph nodes responded to conservative treatment, and were considered reactive.

Results: The majority (85.3%) of the metastatic lymph nodes had elastography pattern 3–5. This finding was observed in only 5% of the benign lymph nodes ($P < 0.001$). The elastography pattern had sensitivity of 85.3%, specificity of 95.5%, PPV of 97.2%, NPV of 78.1% and overall accuracy of 88.9% in differentiation between benign and malignant lymph nodes. On the other hand, for the B mode criteria, the best accuracy was given to abnormal hilum (83%). The accuracy of power Doppler ultrasound pattern was 70.8%.

Conclusions: The accuracy of sonoelastography is higher than usual B mode and power Doppler ultrasound parameters in differentiation between benign and malignant nodes. The integration of

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lymph node sonoelastography in the follow up of patients with known head and neck cancer may reduce the number of biopsies.

1. Introduction

Metastatic cervical lymph nodes are common in patients with head and neck and non-head and neck cancers (1,2). In patients with squamous cell carcinoma of the head and neck, the presence of a metastatic node reduces the 5-year survival rate to 50%, and the presence of another metastatic node on the contralateral side further reduces the 5-year survival rate to 25% (3). Therefore, evaluation of cervical lymph nodes is important in patients with cancers because it aids in the assessment of patient prognosis and helps in planning treatment (1).

High-frequency sonography has become the examination method of choice for the diagnosis of superficial lymph nodes in clinical practice. The commonly used high frequency sonography includes B-mode sonography, color Doppler sonography and power Doppler sonography, which can display the size, location, shape and blood flow distribution of the lesion and play important roles in the differential diagnosis of lymph nodes. However, the indices, given by these methods and reflecting the benign or malignant lesions, always overlap in large measure (4–7), therefore causing difficulties in the judgment.

Elastography is based on a principle similar to manual palpation, in which the examiner detects tumors because they feel neoplatic tissues harder than surrounding tissues (8). In elastography, a mechanical force (compression or vibration) is applied to the soft tissues, and a conventional imaging technique such as US or MR imaging is used to create a map of soft-tissue deformation (8). The results are displayed on an image called an elastogram, on which hard areas appear dark and soft areas appear bright. Elastography has been shown to be useful in the diagnosis of breast, thyroid, and prostate cancers (9–11).

The purpose of this study was to evaluate the diagnostic utility of real-time elastography (RTE) in differentiating between reactive and metastatic cervical lymph nodes (LN) in patients with primary head and neck cancer in comparison with the conventional B mode and power Doppler parameters.

2. Patients and methods

2.1. Patients

From April 2011 to March 2013 a total of 78 patients with primary head and neck cancers were included in the study. Before enrollment, each patient gave written informed consent. The largest lymph nodes (maximum 2 lymph nodes for each patient) were included in the study, depending on size, loss of hilum, or presence of degeneration.

The exclusion criteria included patients who received specific treatment (chemotherapy–radiotherapy) prior to the examination and patients who refused to give written consent.

2.2. Ultrasound examination

Both conventional ultrasound imaging and real-time ultrasound elastography were done by using compatible linear probe of 10–12 MHz frequency (Voluson E8; GE Healthcare Technologies, Milwaukee, WI, USA).

For all patients, the US examination started with gray-scale imaging. The positioning of the patients for imaging was identical to that used for standard clinical neck US: The patient was positioned on his or her back with the neck slightly extended over a pillow. At gray-scale US, the following US characteristics of the examined lymph nodes were evaluated: short-axis diameter and short-to-long-axis diameter ratio in the longitudinal plane. Lymph nodes were assessed for echogenicity with respect to the surrounding muscles and classified as hypoechoic, isoechoic, or hyperechoic. The lymph node hilum, which normally appears as a hyperechoic region was classified either as normal (central), or abnormal (absent of eccentric).

2.3. Power Doppler ultrasound

At power Doppler US, the type and intensity of nodal blood flow were evaluated for all examined lymph nodes. Two types of lymph node vascularity were identified: In type 1, flow signals were absent or the blood flow was limited to the lymph node hilum. In type 2, there was increased peripheral (parenchymal) blood flow (12).

2.4. Real time elastography (RTE)

After changing the system into the elastography mode, real-time freehand elastography was performed using the same probe for an additional 1–2 min. For elastography, compression with light pressure followed by decompression was repeated until a stable image was obtained. Grade of compression appeared on a 0 scale on the monitor. Real-time elastographic and B-mode images simultaneously appeared as a two-panel image. Figs. 1–5 show a typical image displayed on the monitor during elastography, in which the elastogram appears in a region-of interest (ROI) box. We avoided tissues (bone, blood vessel) that might disturb the appropriate analysis of the relative hardness of the target lymph node. The patient was asked to avoid swallowing and hold their breath during the examination to minimize motion of lymph node.

The elastography images were obtained with the elasticity color map, superimposed on the B-mode images, and displayed on the left side of a dual-display image while the corresponding B-mode image was on the right in order to maintain continuous real-time visualization. The region of interest (ROI) was set within a box highlighted manually. Each ROI included the lymph node and sufficient surrounding adjacent tissue. To maintain a constant level of pressure throughout the examination, a standardized external compression was applied to the ROI by using real-time measurements displayed on an indicator-bar with a numerical scale (graded from 1 to 5) which gives a feedback on the compression quality. To provide an accurate measurement of tissue distortion, a dedicated software [combined autocorrelation method (CAM); GE Health Care Technologies] was used.

Elastogram evaluation—One of the five patterns for the elastograms was given to each node (Table 1 and Fig. 1) depending on the distribution of the blue (i.e., hard) area in the lymph node. Elastographic patterns were determined on the distribution and percentage of the lymph node area with high elasticity (hard): pattern 1, an absent or a very small hard (i.e., blue) area (Fig. 2); pattern 2, hard area $<45\%$ of the lymph node (Fig. 3); pattern 3, hard area $\geqslant 45\%$ (Fig. 4); pattern 4, peripheral hard and central soft areas (Fig. 5); pattern 5, hard area occupying entire lymph node with or without a soft rim (Fig. 6) (13).

2.5. Final diagnosis

The final diagnosis of the examined lymph nodes was determined on the basis of histopathologic findings in most patients. Ultrasound guided aspiration cytology was done for 57 lymph nodes. Excision biopsy was done for 52 lymph nodes. Eighteen lymph nodes responded to conservative treatment on ultrasound follow up and were considered reactive.

2.6. Statistical analysis

The unit of analysis was each LN rather than each patient, and all data were registered separately and processed blindly. Differences in continuous measurements were checked using the SPSS for Windows version 18.0 software package (SPSS Inc., Chicago, IL). Data were expressed as mean ± SD. The paired *t*-test was used to compare two techniques for each of the benign and malignant cases. The Mann–Whitney test was used for comparing non-parametric data in both benign and malignant cases. The ultrasonographic results obtained were compared using the chi-square test. The diagnostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and accuracy were calculated, with the final histopathological diagnosis as the reference standard. *P*-value <0.05 was considered statistically significant.

3. Results

3.1. Patients

The study included 78 patients (48 men, 30 women; mean age, 58 ± 13.4 years; range, 32–85 years), the primary malignancy site was distributed as follows: 34 patients with thyroid cancer (24 patients with papillary carcinoma and 9 patients with follicular carcinoma), 17 patients with hypopharyngeal carcinoma, 11 patients with nasopharyngeal carcinoma, 10 patients with oral (tongue or tonsillar malignancy), 6 patients with salivary gland malignancy.

3.2. Lymph nodes

A total of 127 neck lymph nodes (82 [64.5%] metastatic and 45 [35.5%] benign/reactive) were examined.

3.3. B-Mode US

The characteristics of the examined lymph nodes are listed in Table 2, and the diagnostic accuracy of each of the features tested is detailed in Table 3. There was a significant difference in short-axis diameter between the metastatic (mean 10.2 mm ± 6.2mm; range: 7.5–11.4 mm) and benign (mean 6.4 mm ± 3.4 mm; range: 5.8–7.4 mm) lymph nodes ($P \leqslant 0.01$). Forty two percent of the benign lymph nodes were larger than 8 mm, whereas 80% of the metastatic nodes were larger than 8 mm ($P < 0.01$).

With use of the short-to-long-axis diameter ratio criteria: 79.2% of the metastatic lymph nodes versus 51.1% of the benign nodes showed a diameter ratio greater than 0.5 ($P < 0.01$). The hilum was abnormal in 84% of the metastatic and 17.8% of the benign lymph nodes ($P < 0.001$). With respect to echogenicity, 62.1% of the metastatic lymph nodes showed heterogenous echogenicity versus 20% of the benign nodes ($P < 0.01$) (Tables 2 and 3).

3.4. Power Doppler US

Peripheral parenchymal flow was observed in only four (1%) of the benign lymph nodes. This feature was observed in 65% of the metastatic lymph nodes ($P < 0.01$) (Tables 2 and 3).

3.5. Real time elastography (RTE)

The majority (85.3%) of the metastatic lymph nodes had elastography pattern 3–5 This finding was observed in only 5% of the benign lymph nodes ($P < 0.001$) (Table 2).

The elastography pattern had sensitivity of 85.3%, specificity of 95.5%, PPV of 97.2%, NPV of 78.1% and overall accuracy of 88.9% in differentiation between benign and malignant lymph nodes.

4. Discussion

Lymph node status is one of the most important predictors of poor prognosis in head and neck cancers (14). Literature

Table 1 Patterns and scoring system on elastographic findings (Quoted from Alam et al. (13)).

Pattern	Description	Elastographic diagnosis
1	Absent or very small blue area(s)	Reactive
2	Small scattered blue areas, total blue area $<45\%$	Reactive
3	Large blue area(s), total blue area $\geqslant 45\%$	Metastatic
4	Peripheral blue area and central green area, suggesting central necrosis	Metastatic
5	Blue area with or without a green rim	Metastatic

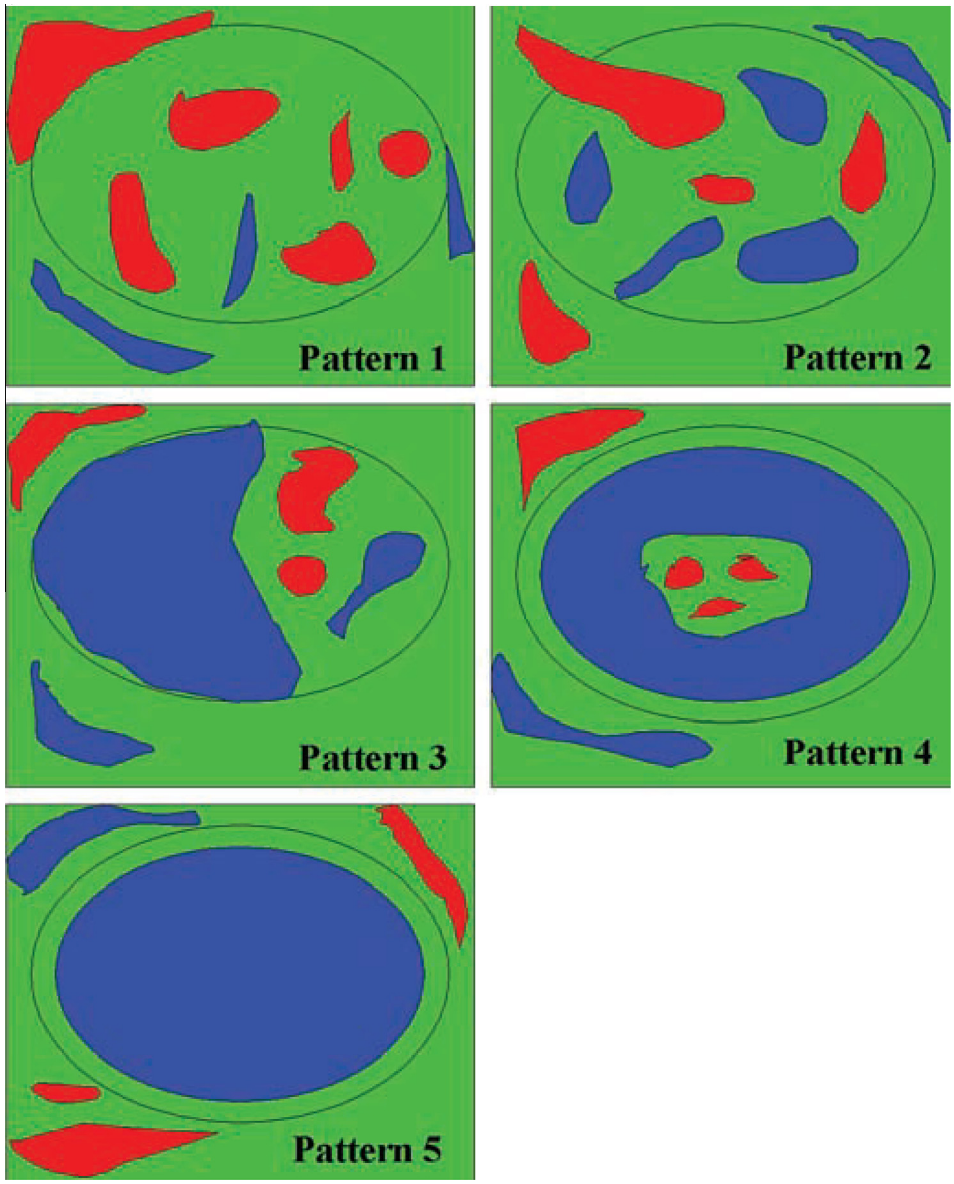

Fig. 1 Drawings show typical diagrammatic appearance of five patterns of lymph nodes. Elastographic patterns were determined on distribution and percentage of lymph node area having high elasticity (hard): pattern 1, absent or small hard area; pattern 2, hard area <45% of lymph node; pattern 3, hard area ⩾45%; pattern 4, peripheral hard and central soft areas; pattern 5, hard area occupying entire lymph node. Increasing tissue hardness appears in ascending order as red, yellow, green, and blue (Quoted from Alam et al. (13)).

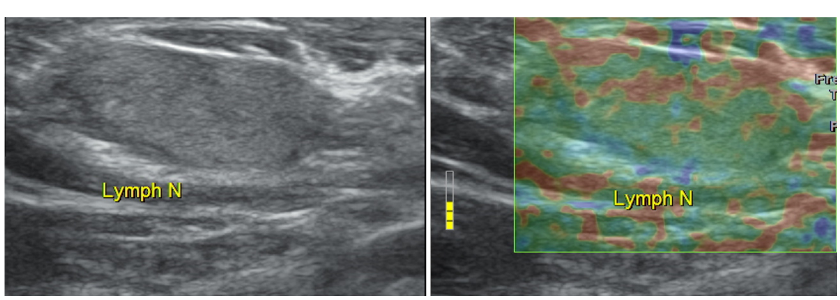

Fig. 2 Split-screen B-mode ultrasound image (left) and US elastogram (right) show that the entire lymph node is evenly shaded in green (pattern of 1). The elastogram (right) shows the node and normal surrounding tissue of good elasticity. Histopathological examination: Reactive lymph node.

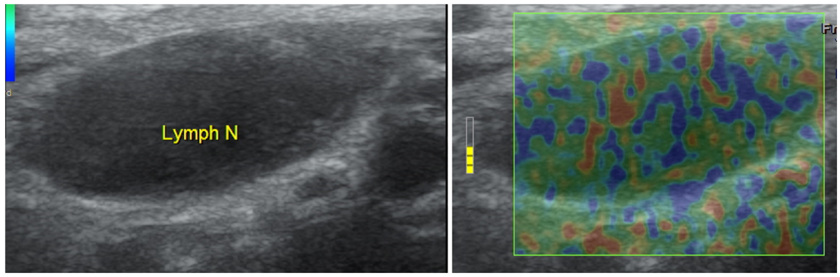

Fig. 3 Split-screen B-mode ultrasound image (left) and US elastogram (right) show scattered area of blue throughout the gland, blue areas represent <45% of the lymph node. Histopathological examination revealed reactive lymph node.

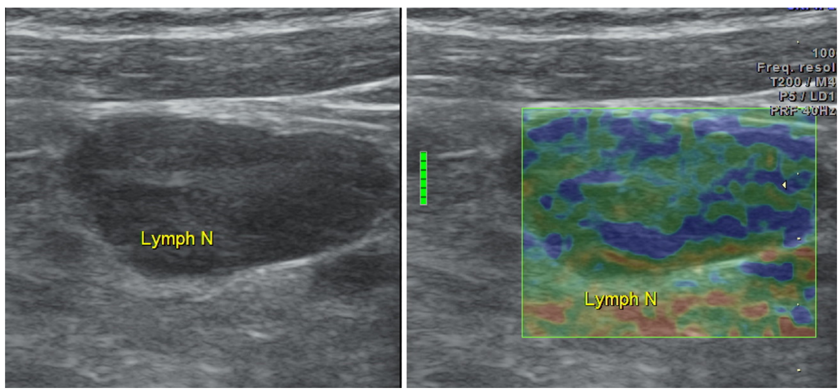

Fig. 4 Split-screen B-mode ultrasound image (left) and US elastogram (right) show scattered area of blue throughout the gland, blue areas represent >45% of the lymph node. Histopathological examination revealed metastatic lymph node.

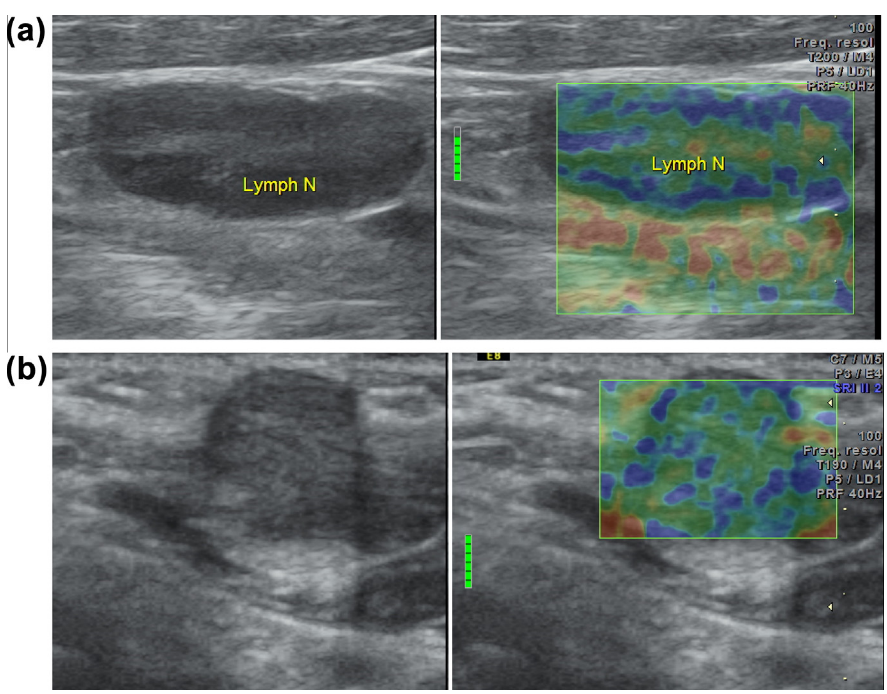

Fig. 5 (a and b) Split-screen B-mode ultrasound image (left) and US elastogram (right) show ring like blue areas in the periphery of lymph nodes (pattern IV). Histopathological examination revealed metastatic lymph node.

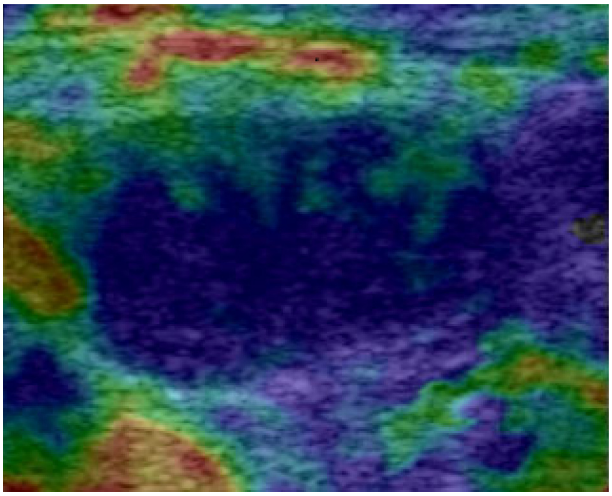

Fig. 6 US elastogram shows blue areas almost entirely filling the lymph node (pattern V). Histopathological examination revealed metastatic lymph node.

Table 2 Results according to criteria for reactive and metastatic lymph nodes.

	Benign lymph nodes, $N = 45$	Malignant lymph nodes, $N = 82$
Sonographic findings		
Short-axis diameter		
$\leqslant 8$	26	14
>8	19	68
S/L axis ratio		
$\leqslant 0.6$	23	17
>0.6	22	65
Border		
Regular	36	35
Irregular	11	47
Hilum		
Normal	37	13
Abnormal	8	69
Echogenicity		
Homogeneous	40	31
Inhomogeneous	5	51
Power Doppler findings		
Hilar flow	41	28
Parenchymal flow	4	54
Elastographic findings		
Pattern		
1	23	4
2	20	8
3	1	29
4	1	23
5	0	18

contains several studies published on the diagnosis of metastatic cervical lymph node by B-mode sonography (15–21). A variety of diagnostic criteria have been reported to be useful for the distinction between benign and metastatic lymph nodes. However, specific criteria for distinguishing reactive from metastatic cervical lymph nodes are not yet clear. B-mode criteria for evaluating superficial LNs are size, shape, the presence or the absence of the hilum, ratio of the cortex to hilum, borders, echogenicity, and homogeneity of internal structures. However no single ultrasonography criterion for malignant LNs had high sensitivity and specificity (22,23). In the current study, the best sensitivity and specificity of the B-mode criteria were given to abnormal hilum, with overall accuracy of 83%. The presence or absence of a hilum has been reported to be an important criterion for lymph node diagnosis (17,24). In Alam et al. study, this criterion showed the best accuracy (86%) (13). It has been reported that 84–92% of benign nodes but less than 5% of metastatic nodes have a hyperechoic hilum (25). On the other hand, some authors have reported that a hyperechoic hilum can be visualized in up to 51.5% of metastatic nodes (26).

In this study, we used real-time elastography (RTE) as it is less time consuming (27) and allows dynamic visualization of the lymph nodes during compression (28). Also, we performed RTE using external compression by slight raising and lowering movement with the transducer and the elastogram is generated in real-time. We did not use internal compression like carotid artery pulsation because not all lymph nodes are near carotid artery and also because it is time consuming and technically more difficult (29). In the current study, we excluded patients with previous radiotherapy or chemotherapy because comparison of metastatic lymph nodes before and after chemotherapy is out of the scope of the current study, and needs separate study.

In the current study, a total of 127 neck lymph nodes were included, 82 [64.5%] were found to be metastatic and 45 [35.5%] to be benign/reactive. The percentage of metastatic lymph nodes is relatively high in the study because we simply selected the lymph nodes of high probability and most lymph nodes were included in the study after failure of medical treatment. Alam et al. (13) found 53 metastatic lymph nodes in his study which included 85 lymph nodes (62.3%).

In the current study, we used the qualitative criteria suggested by Alam et al. (13), dividing the sonoelastographic patterns into five types (Table 1).

In the endoscopic sonographic elastography of lymph nodes, Saftoiu et al. (30) reported 91.7% sensitivity and 94.4% specificity using a pattern analysis. Alam et al. (13) obtained a similar level of results with 100% specificity, 83% sensitivity, and 89% accuracy. In the current study, the elastography pattern had 95.5% specificity and 85% sensitivity, and overall accuracy of 89.9%. High specificity is the greatest advantage of elastography, which has been found not only in our study but also in other studies (24,25). Because of this, elastography may reduce unnecessary biopsy for the diagnosis of cervical lymph node metastasis.

On the other hand, Lo et al. (31) in a study included 131 patients, found that the elasticity pattern system had sensitivity of 66.7%, specificity of 57.1%, the positive predictive value was 52.2% and the negative predictive value was 71.0%. They concluded that elastography offers no additional value over conventional ultrasound in predicting malignancy in cervical LNs.

Alam et al. found the elastography pattern to have the highest accuracy in differentiation between benign and malignant lymph nodes (89%), and height than all B mode criteria. Our results are in agreement with his results. We found the overall accuracy of RTE to be 88.9%, which is higher than all B mode criteria and higher than power Doppler ultrasound. Also, our results are in agreement with Bhatia et al. (32), who

Table 3 Diagnostic performance of B-mode sonography, power Doppler sonography and elastography.

	Sensitivity	Specificity	PPV	NPV	Accuracy
Sonographic findings					
Short-axis diameter	82.9	57.7	78.0	65.0	74.0
S/L axis ratio	79.2	51.1	73.8	57.5	69.2
Border	57.3	77.7	81.0	50.7	65.3
Hilum	84.1	82.2	89.6	74.0	83.4
Echogenicity	62.1	80.0	91.0	56.3	71.6
Power Doppler	65.8	91.1	91.5	59.4	70.8
Elastographic pattern	85.3	95.5	97.2	78.1	88.9

stated that elastography has high accuracy for malignancy in cervical lymph nodes, which have surpassed conventional sonographic criteria.

Also, in the current study, accuracy of elastography surpassed the accuracy of power Doppler ultrasound vascular pattern (88.9% versus 70.8%). Teng et al. (33) in a recent study reported sensitivity of 88.4% for elastography pattern versus 67.3% for power Doppler in differentiation between benign and malignant lymph nodes.

In general, elastography can improve the performance of sonography in the diagnosis of enlarged metastatic cervical lymph nodes and elastography has a bright future in detecting cervical lymphadenopathy, thereby improving the diagnosis and prognosis of head and neck cancer (34).

Some of the limitations of our study should be addressed. No inter- and intraobserver variability was studied, the final diagnosis of some reactive lymph nodes was done based on follow-up findings instead of histopathologic findings. Also, elastographic findings of normal-sized lymph nodes were not included in the study and in patients with multiple lymph nodes, only one or two lymph nodes were included in the study.

5. Conclusion

The accuracy of sonoelastography is higher than usual B mode and power Doppler ultrasound parameters in differentiation between benign and malignant nodes. The integration of lymph node sonoelastography in the follow up of patients with known head and neck cancer may reduce the number of biopsies.

Conflict of interest

None.

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