

Original Article

Diagnostic efficacy of color Doppler ultrasound in evaluation of cervical lymphadenopathy

Deepankar Misra¹, Sapna Panjwani¹, Shalu Rai¹, Akansha Misra², Mukul Prabhat¹, Prashant Gupta³, Subrata K. Talukder³

Departments of ¹Oral Medicine and Radiology and ²Oral Pathology, Institute of Dental Studies and Technologies, Modinagar, Kadrabad, ³Department of Oral Medicine and Radiology, Institute of Dental Sciences, Bareilly, Uttar Pradesh, India

ABSTRACT

Background: To evaluate the efficacy of color Doppler ultrasound (CDUS) in differentiating benign and malignant cervical lymph nodes by detecting differences in blood flow patterns.

Materials and Methods: In this cross-sectional prospective study, 25 untreated patients with clinical evidence of cervical lymphadenopathy were evaluated. CDUS was performed for 80 cervical lymph nodes. The gray scale parameters of the lymph node and intranodal perfusion sites were the key CDUS features used to differentiate between reactive and metastatic lymph nodes. Histopathological confirmations were obtained and compared with the results of CDUS.

Results: Initially, 53 cervical lymph nodes were evaluated by clinical examination. Twenty-seven additional lymph nodes (53 + 27 = 80) were discovered by CDUS evaluation. Gray scale parameters for lymph nodes such as size of lymph node, shape of lymph node, and presence or absence of hilum revealed highly significant results ($P < 0.0001$). Color Doppler flow signals revealed that central/hilar flow was characteristic for benign nodes whereas peripheral/mixed flow was characteristic for malignant nodes, the findings were highly significant ($P < 0.0001$). Gray scale and color Doppler features are used to differentiate benign and malignant nodes.

Conclusion: Within the limitations of this study, CDUS evaluation was found to be highly significant with a high sensitivity and specificity over clinical evaluation CDUS examination provides a prospect to reduce the need for biopsy/fine needle aspiration cytology in reactive nodes.

Key Words: Doppler color ultrasonography, histopathology, lymph node, lymphadenitis

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Address for correspondence:

Dr. Deepankar Misra,
Department of Oral
Medicine and Radiology,
Institute of Dental
Studies and Technologies,
Modinagar, Kadrabad,
Uttar Pradesh, India.
E-mail: deepankarmisra@rediffmail.com

INTRODUCTION

Cervical lymphadenopathy is the most common finding in the head and neck disorders. It is likely that over half of the patients examined each day may have enlarged lymph nodes in the head and neck region.^[1] Cervical lymphadenopathy may be the only clinical finding or one of the several nonspecific findings, and the discovery of enlarged cervical lymph nodes will often raise the spectrum of serious illness.^[2] The common

causes of lymphadenitis are malignancies, bacterial, viral, protozoal, fungal infections; autoimmune disorders; drugs such as phenytoin and certain vaccines.^[3]

A majority of patients have benign lymphoid hyperplasia or reactive lymphadenitis. However, in few cases, it may be a serious disease. It is therefore important to differentiate the patients with serious illness from many with benign lymphadenopathy.^[4]

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The advent of ultrasonography (US) has revolutionized the field of oral and maxillofacial radiology. US is the name given to high-frequency sound waves over 20,000 Hz, inaudible to humans. It is a noninvasive, nonionizing imaging technique which enables to see the anatomical structures with the use of ultrasound waves and provides valuable diagnostic information with a high degree of diagnostic accuracy.^[3,5] The conventional ultrasound uses a gray scale to detect the various anatomical structures of the body and study their morphological characteristics and is capable of detecting vessels as small as those found in lymph nodes.^[5]

Continuous advancement in the field of imaging leads to increase sensitivity of these imaging modalities. An advancement of this gray scale US is color Doppler ultrasound (CDUS). CDUS is based on the principle of Doppler effect which is responsible for the variation in the pitch of sound waves. CDUS is used to evaluate and determine the presence of vascularity, direction, and velocity of blood flow within the ultrasound image of the tissue.^[6] It may also be used for a variety of conditions such as evaluation of swellings of the neck including lymph node, thyroid and salivary glands, detection of vascular structures and vascularity of masses, and assessment of space infections.^[6]

The distribution and direction of flowing blood are shown as a two-dimensional image in which velocities are distinguished with different colors. CDUS instrument uses transducer probes consisting of two piezoelectric elements, one to transmit ultrasound by converting the electric signal into ultrasound energy and other to receive returning echoes backscattered from the moving blood cells. Thus, it acts as both transmitter and receiver.^[6]

CDUS can define both morphological and vascular characteristics of lymphadenopathies. Vascularity of lymph nodes is directly related to the actual pathology present within the lymph node. Both angioarchitecture and hemodynamics differ among various diseases affecting these cervical lymph nodes. Blood vessel morphology in malignant or metastatic nodes is usually deranged as internal nodal architecture is destroyed by neoplastic infiltration. Inflammatory or benign nodes have dilated intranodal vascular alteration due to local humoral agents.^[7] The pattern of vascular flow in the lymph nodes aids in differentiating benign from malignant lymphadenopathy.^[4]

Considering this, one is determined to accept the various advantages of CDUS examination and its importance over conventional methods of clinical examination and fine needle aspiration. Dangore *et al.*^[3] conducted a study to evaluate the efficacy of CDUS in the diagnosis of cervical lymphadenopathy. However, there have been very few studies to determine the efficacy of CDUS in the diagnosis of cervical lymphadenopathy.^[3,7-9] Hence, this study was carried out to differentiate benign and malignant cervical lymph nodes using CDUS examination.

The aims of this study was to differentiate benign/inflammatory/reactive lymph nodes from malignant/metastatic nodes and examine the status of clinically nonsignificant (deep) lymph nodes by means of CDUS, and also to correlate between CDUS findings and cytological or histopathological findings of cervical lymph nodes and determine the value of CDUS to minimize the need of fine needle aspiration cytology (FNAC).

MATERIALS AND METHODS

The study was carried out at the Department of Oral Medicine and Radiology, Institute of Dental Sciences, Bareilly, Keshlata Hospital, Bareilly, India, and Sai Hospital, Bareilly, India. Patients with clinically suspected cervical lymphadenopathy were selected in the study after obtaining an informed consent. Twenty-five patients were selected from the outpatient department and were divided into two main groups: Group I: Thirteen patients were clinically suspected to be having malignant cervical lymphadenopathy. Group II: Twelve patients who were clinically suspected to be having benign cervical lymphadenopathy.

The clinical examination of the lymph nodes was done for their location, number, size, shape, consistency, and fixity to decide whether the palpable node is benign or malignant. In cases of oral cancer, all the palpable lymph nodes were assumed to be metastatic. If the lymph node was larger than 1 cm, it was considered abnormal. Stony hard/indurated lymph nodes were considered malignant, whereas soft or firm nodes were considered benign. Fixity to underlying structures is a classic sign of malignancy. If the node was fixed it was considered malignant, implying that the tumor cells have broken through the capsules of the lymph node or that necrosis and inflammation have produced peri-nodular scarring

and adhesions, but this feature will usually be absent except with the most aggressive or advanced tumors. Mobile lymph nodes were considered benign. Lymph node tenderness was considered an indication of inflammatory process.^[10]

Diagnosis of cervical lymphadenopathy was made on the basis of history and clinical examination. All the patients were subjected for CDUS and histopathological examination (by means of FNAC). For CDUS evaluation, sonosite, diagnostic ultrasound system, Model Micromax, Bothell (USA), a high-frequency linear transducer of 6–13 MHz was used.

The patient was positioned supine with the neck hyper-extended. Settings for CDUS were standardized and the wall filters, pulse repetition frequency, color gain, and focusing depth were set upon automatic mode. The technique used was continuous transverse and saggital sweep covering entire neck on both sides.^[11] The examination was started with a transverse scan of the submental area, followed with a sequence from the submandibular area to parotid area to upper, middle, and lower cervical area to supraclavicular fossa to the posterior triangle. Initially, adequate observation of the lymph node with gray scale sonography was done. The minimal and maximal axial diameters of the nodes were measured and their ratios were calculated. The presence or absence of wide echogenic hilum, calcification, and necrosis of the node was also assessed on gray scale ultrasound. Then, the color Doppler examination was performed and sonographic features studied were distribution, number, size and shape of nodes, echogenic hilum, internal architecture, ancillary features such as matting of nodes and color Doppler flow pattern. The distribution of lymph nodes was classified into eight anatomic areas similar to the ones described by Hajek *et al.*, 1986.^[12] All sonographically detectable lymph nodes were first scanned in the longitudinal plane (L) and the transverse plane (T) to measure the size of each lymph node L/T ratio is considered. The presence or absence of hilar structure was also recorded. The vascular pattern and displacement of vascularity of the lymph nodes were assessed by CDUS. After the color Doppler, flow in the lymph node was stabilized or freezed and the color flow pattern was determined. The vascular pattern of the enlarged lymph nodes with long-axis diameters >10 mm was classified into the following four groups according to CDUS findings:^[3]

- Central - Flow signals branching radially from the center and the signals are not the periphery of the nodes
- Peripheral - Flow signals along the periphery of the lymph nodes, with branches perforating the periphery of the node and not arising from the hilar vessels
- Mixed- Presence of central and peripheral flow signals
- No flow or apparently avascular - Absence of vascular signals within the lymph nodes.

The cytological and/or histological diagnosis was obtained from the largest node. FNAC or biopsy and its histopathological appearance were considered for its correlation with CDUS features of all lymph nodes of the same group. Only cases confirmed with clinically malignant/metastatic nodes were biopsied whereas clinically confirmed/suspected benign/reactive lymph nodes were confirmed cytologically with fine needle aspiration. Following this, comparative study was done between clinical features, CDUS features, and cytological/histological features of enlarged cervical lymph nodes.

Data were collected and results were statistically analyzed using Student's *t*-test test and Chi-square test.

RESULTS

Twenty-five patients with clinically suspected cervical lymphadenopathy were examined, 15 patients were male and 10 patients were female with age range 10–60 years. Of 25 patients, 13 patients were clinically suspected to have malignant cervical lymphadenopathy whereas remaining 12 patients were suspected to have benign cervical lymphadenopathy (3 patients: Primary extraoral malignancy, 10 patients: Unknown primary malignancy, and 12 patients: Lymphadenitis due to chronic specific or nonspecific infection).

Initially, 53 cervical lymph nodes were detected in 25 patients using the clinical criteria, of which 38 were suspected to be clinically benign lymph nodes and 15 were suspected clinically malignant. Following this, the same patients were evaluated with CDUS and compared with cytological/histological features of enlarged cervical lymph nodes. When the clinical findings of 38 benign lymph nodes were compared with CDUS, the result was 33 benign and 5 malignant

lymph nodes. Of clinically diagnosed 15 malignant lymph nodes, 13 confirmed malignant and 2 were benign. This suggests that the findings of CDUS are close to histopathologic findings with 2 false positive results in CDUS.

While performing CDUS of palpable 53 lymph nodes, additional 27 lymph nodes were discovered as they were located in clinically inaccessible region. Following CDUS evaluation of these lymph nodes, total number of lymph nodes included in the study were 80 (53 + 27), all were evaluated by FNAC/histopathological examination.

Spectrum of distribution of cervical lymphadenopathy for total 80 lymph nodes was done and it was found that left and right submandibular nodes were most commonly affected (61 of 80). Submental lymph nodes involvement was observed in 3 reactive and 1 malignant lymph nodes and supraclavicular group was involved only in benign lymphadenopathy.

Dimensions

The smallest lymph node detected by CDUS examination measured 7 mm × 3 mm, proved benign and the largest lymph node was 46 mm × 42 mm, proved malignant. The mean short axis diameters of malignant and benign nodes in centimeters were 1.89 ± 1.06 and 0.83 ± 0.54 , respectively, and mean long axis diameters of malignant nodes and benign nodes were 1.63 ± 0.91 and 1.23 ± 0.50 , respectively. It was found that the malignant nodes were significantly greater in short axis diameter than other group nodes whereas reactive nodes had the smallest short axis diameter. There was a statistically significant difference between the mean values of the short axis ($P < 0.001$) and statistically significant difference between the long axis ($P < 0.01$) among the benign and malignant cervical lymph nodes [Table 1].

Shape

Twenty-six nodes were round in shape and 54 lymph nodes were oval/elliptical in shape. Of 54 oval/elliptical nodes, 52 were benign/reactive whereas only 2 elliptical nodes were malignant. Among 26 round nodes, 19 were malignant and 7 were found to be benign. The difference in shape was statistically significant with $P < 0.001$ [Figures 1, 2 and Table 1].

Hilum

Hilum was present in 55 of 80 nodes whereas it was absent in 25 lymph nodes. Of these 55 nodes with

Table 1: Comparison of mean values of size, shape, hilum, and color Doppler flow in benign and malignant groups of lymph nodes (80 nodes)

Size	Number of LN		<i>t</i>	<i>P</i>
	Benign (n=59)	Malignant (n=21)		
Short axis (mm)	0.83±0.54	1.89±1.06	5.926	<0.001***
Long axis (mm)	1.23±0.50	1.63±0.91	2.635	0.0102*
			Total	χ²
Shape				
Oval	52	0	52	53.577 2 <0.001***
Elliptical	0	2	2	
Round	7	19	26	
Grand total	59	21	80	
Hilum				
Present	54	1	55	62.644 1 <0.001***
Absent	5	20	25	
Grand total	59	21	80	
Vascularity				
Mixed	0	4	4	75.138 4 <0.001***
Peripheral	2	16	17	
No flow	8	1	9	
Hilar	29	0	29	
Central	20	0	20	
Grand total	59	21	80	

* $P < 0.05$: Significant; *** $P < 0.001$: Highly significant. χ^2 : Chi-square; df: Degree of freedom; LN: Lymph node

hilum presence, 54 nodes were histopathologically proven as benign nodes and 1 node as malignant. It had been observed that the presence of echogenic hilum within an enlarged lymph node can be considered a sign of its benign nature. Of 25 nodes with absent hilum, 20 were histopathologically proven as malignant whereas 5 as benign nodes. The criterion was statistically significant with $P < 0.0001$ [Table 1].

Color Doppler flow

CDUS detected color flow signals in 71 of 80 lymph nodes. Of these 71 nodes, 20 lymph nodes showed central color flow signal and 29 nodes showed hilar signal which are suggestive of benign nature, and all 49 nodes (20 + 29) were confirmed as benign on histopathologic findings. Eighteen lymph nodes showed peripheral flow, of which 16 nodes were malignant and 2 were benign lymph nodes by histopathology. Four lymph nodes showed mixed vascularity and all were malignant. Nine lymph nodes showed no flow, of these 8 were (reactive) benign and 1 node was malignant by histopathology. In this study, central flow for benign nodes and peripheral flow for malignant nodes were highly significant parameters ($P < 0.0001$) [Figures 3 and 4, Table 1].

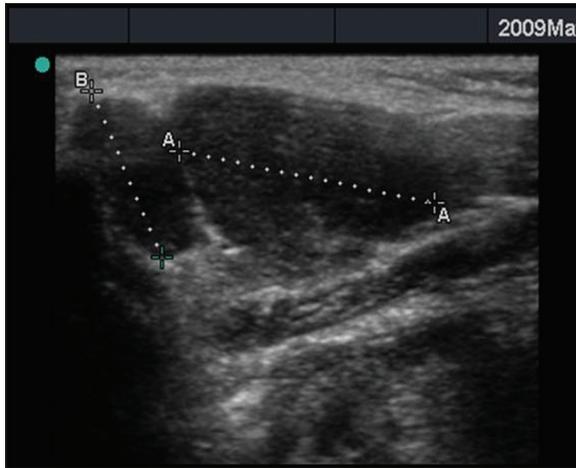


Figure 1: Gray scale color Doppler ultrasound image of oval-shaped reactive/benign lymph node.

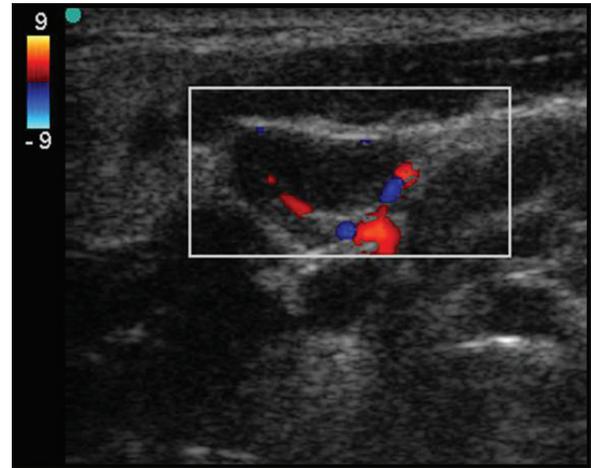


Figure 3: Color Doppler ultrasound image of benign lymph node showing hilar/central vascularity.

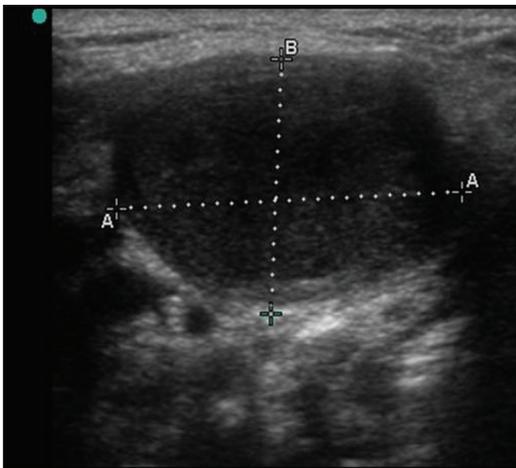


Figure 2: Gray scale color Doppler ultrasound image of round-shaped mitotic malignant lymph node.

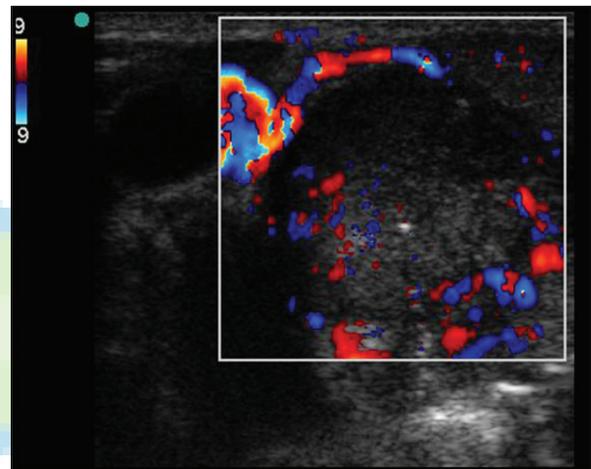


Figure 4: Color Doppler ultrasound image of malignant lymph node showing mixed/peripheral vascularity.

Comparison of the results between clinical examination, color Doppler ultrasound, and fine needle aspiration cytology/histopathology to find out efficacy of color Doppler ultrasound

In this study, a total of 53 lymph nodes were examined by clinical examination. Clinically suspected benign lymph nodes = 38; in CDUS examination total benign lymph nodes = 33 + 24 + 2 = 59 (33: Of 38 clinically suspected benign lymph nodes; 24: Of additional 27 nodes; 2: Clinically malignant were found to be benign). Histopathological confirmation of 59 CDUS confirmed benign nodes revealed 56 lymph nodes to be histopathologically benign and 3 as malignant (false positive + 3). Benign lymph nodes were characterized by the presence of neutrophils and immature lymphocytes within the sinuses and medullary cords whereas malignant nodes showing increased nucleocytoplasmic ratio, hyperchromatism,

cellular pleomorphism, and dyskeratosis, thus suggestive of squamous cell carcinoma histologically [Figures 5 and 6].

Clinically suspected malignant lymph nodes = 15; in CDUS examination total malignant nodes = 13 + 3 + 5 = 21 (13: Of 15 clinically suspected malignant lymph nodes; 3: Of additional 27 nodes; 5: Clinically benign were found to be malignant). Histopathological confirmation of 21 CDUS suspected malignant nodes revealed 21 lymph nodes to be malignant and 1 as benign.

Comparison of the reliability of clinical examination and color Doppler ultrasound examination

On clinical examination, the sensitivity and specificity for benign nodes were 94.29% and 72.22%, respectively. For malignant nodes, the sensitivity and specificity were

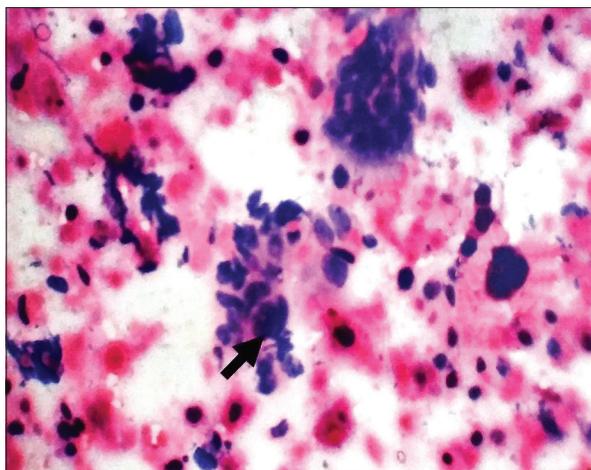


Figure 5: Histopathologic picture showing malignant/metastatic node with mitotic bodies ($\times 40$).

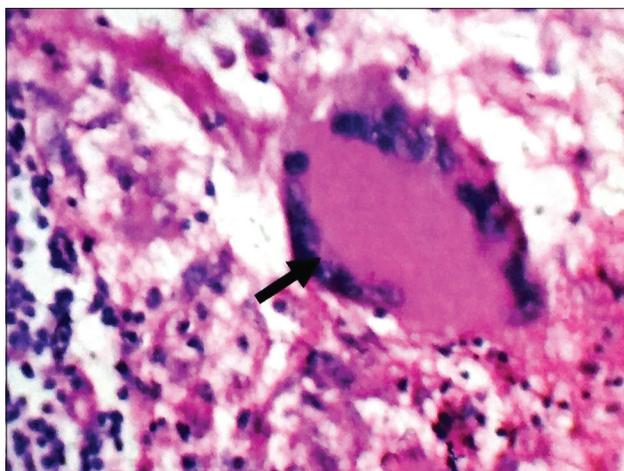


Figure 6: Histopathologic picture showing reactive/tubercular node with multinucleated giant cell ($\times 40$).

94.29% and 72.22%, respectively. The accuracy of clinical examination was found to be 86.79%.

On CDUS examination, the sensitivity and specificity were 98.25% and 86.96%, respectively, for benign nodes. For malignant nodes, the sensitivity and specificity were 72.22% and 94.29%, respectively. The accuracy of CDUS examination was found to be 95.00%.

The comparison between histopathologically proven benign and malignant lymph nodes with clinically suspected and CDUS evaluated lymph nodes revealed that CDUS evaluation is highly significant ($P < 0.001$ by Z-test).

DISCUSSION

In this study, of total 80 lymph nodes which were evaluated, only 53 lymph nodes could be detected by

clinical examination. Additional 27 lymph nodes were detected using CDUS. The results of our study are consistent with Bruneton *et al.*,^[13] who demonstrated the unquestionable value of ultrasound in detection of subclinical nodes.

In this study, the clinical examination yielded false negative results of 5, and similar results were found by Hain^[14] where clinical palpation was found inaccurate with the false negative rates of 5–44%.

Our study showed statistically significant difference between mean values of short axis diameter and long axis diameter of the malignant and benign nodes. Malignant nodes showed greater short axis diameter and long axis diameter than the benign nodes and similar observations were made by Yusa *et al.*^[8]

Overall reliability of shape to differentiate between benign and malignant lymph nodes was statistically significant in our study. Hence, the shape appears to be significant in distinguishing between the various abnormal nodes. Similar observations were reported by Vassallo *et al.*^[15]

In this study, the diagnostic accuracy of the presence of hilum (which shows the benign nature of the node) was highly significant. Fifty-five nodes of 80 displayed the presence of hilum whereas 25 nodes displayed its absence. Of these, 54 were benign nodes and 1 was malignant. Sato *et al.*^[9] stated that rarely metastatic nodes have an intranodally hyperechogenic appearance similar to that of the echogenic/line or hilus as seen in 1 malignant node in our study. The cause of this hyperechogenic appearance in the metastatic nodes is considered ischemic degeneration or extensive keratinization, which occurs within metastatic nodes. The hilum was absent in 25 nodes, of which 20 were histopathologically proven as malignant whereas 5 as benign. This could be due to diffuse adipose infiltration in the node and also seen in the nodes of elderly or immune-compromised patients.^[16] The overall reliability of hilum criteria showed sensitivity and specificity of 93.22% and 100.00%, respectively, which is comparable to the study by Michael Ying *et al.*^[17]

CDUS detected color flow signals in 71 lymph nodes whereas 9 nodes did not show any signals. A total 49 of lymph nodes displayed central/hilar color flow signal, which is suggestive of benign/reactive nature due to increase in vessel diameter and blood flow. Eighteen lymph nodes displayed peripheral flow of blood, of which 16 were malignant and 2 were reactive

nodes. Destruction of hilar vascularity by tumor cells in malignant nodes may be due to induction of vascular supply from the peripheral preexisting vessels or from vessels in the perinodal soft tissue.^[9] Four lymph nodes displayed mixed vascularity, which were confirmed histopathologically as malignant nodes. Similar results were reported by Na *et al.*^[18] Mixed flow of the metastatic node may be due to the fact that as the tumor replaces the node, the preexisting nodal vessels may be proliferated and transformed into feeding vessels by tumor angiogenesis, resulting in central aberrant nodal vessels. Nine lymph nodes did not show any flow, 8 nodes were histopathologically proven to be benign, and 1 as malignant. Absent flow signals may be due to the relatively low number of backscattering erythrocytes in the peripheral vessels decreasing the signal intensity.

In our study, comparative findings between clinical, CDUS, and histopathologic evaluation show that the overall reliability of CDUS examination for lymphadenopathy of 80 cervical lymph nodes is highly significant with the sensitivity and specificity of 98.25% and 86.96%, respectively, for benign nodes. For malignant nodes, the sensitivity and specificity were 98.25% and 86.96%, respectively. The overall accuracy of CDUS examination was 95%. The results of our study are consistent with that of Dangore *et al.* and Dangore-Khasbage *et al.*^[3,19]

CDUS is a reliable and reproducible method which helps in differentiation between reactive and malignant changes of superficial lymph nodes using findings of intranodal angio-architecture. Dangore-Khasbage *et al.*^[19] recommended the use of CDUS in every patient of primary oral cancer before surgical treatment so that reactive and mitotic nodes can be differentiated.

In this study, an additional 27 lymph nodes were detected by CDUS examination apart from clinically palpable 53 nodes. Thus, it can be concluded that CDUS evaluation is superior over clinical examination for detection of cervical lymphadenopathy before proceeding for surgeries of primary and secondaries in the neck.

CONCLUSION

Within the limitations of this study, it can be concluded that CDUS examination is a valuable and a highly specific diagnostic tool in differentiating cervical lymphadenopathy over clinical and histopathological examination.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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