Efficacy of Colour Doppler Ultrasound in Diagnosis of Cervical Lymphadenopathy

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Abstract

Objectives The purpose of the study was to evaluate the efficacy of colour doppler ultrasound (CDUS) in diagnosis of cervical lymphadenopathy.

Materials and Methods The study group consisted of 30 patients with clinical evidence of cervical lymphadenopathy (19 patients with clinically suspected reactive/benign cervical lymphadenopathy and 11 patients with clinically suspected malignant/metastatic cervical lymphadenopathy). CDUS examinations were carried out for one lymph node (LN) in each patient and fine needle aspiration cytology of the same LN was obtained. To evaluate the efficacy of CDUS, comparison between clinical features, CDUS features and cytological features of enlarged cervical LNs were then done.

Results Clinical examination evaluated 54 cervical LNs. CDUS evaluation discovered an additional 55 LNs ($54 + 55 = 109$). Accuracy of the CDUS examination was higher than clinical evaluation. Patterns of colour doppler flow signals when correlated with cytological diagnosis showed central flow for benign nodes and peripheral flow for malignant nodes. The mean pulsatility index (PI) was 1.977 ± 0.669 in LNs involved with metastases and

0.839 ± 0.135 in LNs affected by benign processes. LNs involved with metastases showed a characteristic high resistive index (RI) and a high pulsatility index than the lymph nodes affected by benign processes. The RI and PI were significantly different between LNs affected by benign versus malignant disease.

Conclusion Nodal vascularity of the LNs can be used to differentiate benign from malignant lymphadenopathy. CDUS can be trusted upon as a reliable marker for the diagnosis of cervical lymphadenopathy.

Keywords Colour doppler ultrasound · Cervical lymphadenopathy · FNAC

Introduction

Lymphadenopathy is defined as an abnormality in the size or character of LNs, caused by the invasion or propagation of either inflammatory cells or neoplastic cells into the node. It results from a vast array of disease processes, whose broad categories are easily recalled using the mnemonic acronym “MIAMI,” representing Malignancies, Infections, Autoimmune disorders, Miscellaneous and unusual conditions, and Iatrogenic causes. Among the serious illnesses that can present with lymphadenopathy, perhaps the most concerning to the patient and physician is the possibility of underlying malignancy [1].

Early detection of metastases is of great clinical importance because it enables more successful surgery and radiation therapy treatments. [2] The diagnosis of malignant lymphadenopathy is crucial for therapeutic planning in patients with suspected malignant neoplasms and for pretreatment staging in patients with primary malignant tumours of the head and neck [3].

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Substantial efforts have been directed toward differentiating benign from malignant causes of lymphadenopathy on the basis of imaging findings. Colour doppler sonography provides information about blood flow and morphology. The use of higher frequency transducers improves the ability to detect low velocity signals from superficial structures. Vessels in inflamed LNs are dilated; vessels in LNs involved with metastasis may be compressed by tumour cells [4].

There are many studies which demonstrate the usefulness of colour doppler imaging in differentiating cervical lymphadenopathy. The present study shows the importance of CDUS in the discovery of clinically non palpable cervical LNs, and also evaluates the value of CDUS in minimizing the need for invasive methods like biopsy or FNAC.

Materials and methods

The study group consisted of 30 patients with cervical lymphadenopathy. Patients were selected among the out patients attending the department of oral medicine and radiology. The institutional ethical committee-approved prospective study comprised 30 patients, in which 19 patients were clinically suspected of having benign cervical lymphadenopathy and other 11 patients were clinically suspected of having malignant cervical lymphadenopathy. All patients with clinical evidence of cervical lymphadenopathy due to disorders like infections, reactive and

malignancies diagnosed on the basis of thorough history and clinical examination were included in the study, irrespective of their age, sex, religion, socioeconomic status and the clinical diagnosis of the chief complaint of the patients. Patients with cervical LN enlargement due to acute infection without any clinical evidence of oral and extraoral malignancy were excluded. Initially LNs were assessed by clinical examination; clinical criteria used for differentiating malignant LNs were,

1. In cases of oral cancer, all of the palpable lymph nodes were assumed to be metastatic.
2. Regarding location, in cases of enlargement of supraclavicular LNs, malignant disease was suspected either by metastatic infiltration or lymphoma.
3. LN size larger than 1 cm in diameter.
4. A hard, stony hard or indurated consistency.
5. Fixation to underlying structures, implying that the tumour cells had broken through the capsule of the lymph node.
6. Rubbery consistency for lymphomatous nodes.

In tuberculosis, matted LNs and in inflammation soft/firm LNs were considered. Other features also were taken into consideration such as age of the patient, his detailed medical history and other signs/symptoms.

After obtaining informed written consent from the patients, they were subjected to CDUS to evaluate cervical lymphadenopathy. Colour doppler sonographic procedures were done with 11L linear probe (GE Logiq P6 premium ultrasound system) with the frequency of 4.5–12 MHz, by

Fig. 1 CDUS picture showing benign lymphadenitis

Fig. 2 CDUS picture showing malignant lymphadenitis

the radiologist who was unaware of the pathologic findings (Figs. 1 and 2). Colour doppler studies were done with optimized colour doppler parameters. Colour gain was adjusted dynamically to maximize visualization of blood vessels while avoiding colour noise resulting from the pulsation of the carotid artery. CDUS evaluation of the cervical LNs for RI and PI were carried out by a senior radiologist. Any clinical data or pathological diagnosis, in any of the cases and finding recorded in a tabular format were not given to the radiologist.

FNAC of the same LNs were done to confirm the etiology of the LN enlargement which was performed within a week of CDUS examination. For cytological examination of LNs, the slides were fixed in 90 % alcohol and stained by Giemsa or PAP (Papanicolaou) stains. Each LN was evaluated pathologically with an emphasis on the dysplastic cells in cytology. An experienced pathologist performed the cytological evaluation of the LNs.

Statistical analysis was carried out by the Mann–Whitney U test which, is a non-parametric statistical hypothesis test for assessing whether two independent samples of observations have equally large values.

Results

On clinical examination 54 LNs were detected in 30 patients with cervical lymphadenopathy in a variety of disorders. Out of those 54 LNs, 21 were suspected to be benign and 33 were suspected to be malignant on clinical evaluation. During CDUS examination of these 54 cervical lymph nodes in the same patients, an additional 55 lymph nodes were discovered, as shown in Table 1. CDUS evaluation was done for one superficial LN (30 LNs) in each patient. This showed 21 LNs as benign and nine LNs as malignant. On cytological confirmation of those 30 lymph

Table 1 Number of lymph nodes detected clinically and on CDUS in different Spectrum of diseases

Lymph nodes	No. of clinically palpable lymph nodes	No. of lymph nodes in colour doppler	Mann–Whitney U test	<i>p</i> value	Significance
Benign	21	33	100.5	0.004	S
Malignant	33	76	9.00	0.001	S
Overall	54	109	280.5	0.008	S

$p < 0.05$, S Significant

Table 2 Comparison of clinical findings with cytological & CDUS of 30 LN

	Number clinically palpable LN	Cytological findings		CDUS	
		Benign	Malignant	Benign	Malignant
Benign	19	21	0	21	0
Malignant	11	0	9	0	9

Table 3 CDUS blood flow correlated with cytological findings

Cytological findings			CDUS blood flow		
Benign	21	0	21	0	0
Malignant	0	9	0	8	1

nodes, the result was 21 benign and nine malignant cervical lymphadenopathy, shown in Table 2.

CDUS detected colour flow signals in all the lymph nodes. Out of 30 lymph nodes, 21 lymph nodes showed central colour flow signal, eight lymph nodes showed peripheral flow, one lymph node showed mixed vascularity as shown in Table 3. The study showed that central flow for benign nodes, peripheral and mixed flow for malignant nodes, which were highly significant parameters.

In this study, the resistive indices from the vessels of benign lymph nodes ranged from 0.50 to 0.76, with a mean value of 0.66 ± 0.586 (mean $\pm$ SD). The resistive indices, from the vessels of malignant lymph nodes ranged from 0.57 to 0.96, with a mean value of 0.96 ± 0.787 (mean $\pm$ SD), as shown in Table 4. Malignant LNs showed higher RI index, when compared with benign LNs. The pulsatility indices from the vessels of benign lymph nodes ranged from 0.70 to 1.6, with a mean value of 0.839 ± 0.135 (mean $\pm$ SD). The pulsatility indices, from the vessels of malignant lymph nodes ranged from 1.18 to 2.9 with a mean value of 1.97 ± 0.669 (mean $\pm$ SD), shown in Table 5. Malignant LNs showed higher PI index, when compared with benign LNs. The RI & PI values were significantly different between benign and malignant LNs ($p < 0.05$).

Table 6, shows, when echo pattern was taken into the consideration, 21 LNs showed homogenous echo pattern and hypoechoic pattern was seen in nine LNs. All 21 lymph

Table 4 Mean values of resistive index in benign and malignant cervical lymph nodes

	Mean RI value	Standard deviation	<i>t</i> value	<i>p</i> value	Significance
Benign	0.66	0.586	5.789	0.000	S
Malignant	0.96	0.787			

$p < 0.05$, S Significant

Table 5 Mean values of pulsatility index in benign and malignant cervical lymph nodes

	Mean PI value	Standard deviation	<i>t</i> value	<i>p</i> value	Significance
Benign	0.839	0.135	7.246	0.000	S
Malignant	1.977	0.669			

$p < 0.05$, S Significant

nodes which showed homogenous echo pattern were confirmed cytologically as benign and nine LNs which showed hypoechoic pattern were confirmed as malignant by cytological study. When echo pattern in colour doppler ultrasound correlated with blood flow, showed homogenous echo pattern in 21 LNs with central flow, hypoechoic pattern in eight LNs with peripheral flow and one LN with mixed flow. These LNs with central flow were confirmed as benign and LNs with peripheral and mixed flow were confirmed as malignant by cytological study.

A comparison of clinical findings with cytological findings in 30 clinically palpable cervical lymph nodes showed that 19 LNs to be benign and 11 were confirmed to be malignant LNs. The CDUS showed that 21 LNs to be benign and nine to be malignant LNs giving a 100 % accuracy compared to cytological findings.

Discussion

The sensitivity of doppler US equipment has greatly improved in the past two decades, and blood flow has become detectable nearly in all superficial LNs. Since 1991 several studies have aimed to prove the value of doppler spectral analysis in predicting the cause of lymph node enlargement [4].

Different approaches have been used to differentiate benign from malignant lymphadenopathy by means of CDUS [4, 5]. The presence of extrahilar vessels is thought to be one of the signs of malignancy in the sonographic diagnosis of lymph nodes. Even when the nodes were normal in size, the presence of extrahilar vessels and high PI and RI values were almost always diagnostic for malignancy [6].

In our study, CDUS identified 109 LNs in the neck of 30 patients. On CDUS examinations of those clinically palpable lymph nodes (54), an additional 55 LNs were discovered, which were either located in clinically inaccessible region, were deep situated, or because of the obesity, some of the LNs were obscured by the neck tissue.

The role of doppler ultrasound in the evaluation of metastatic nodes is based on the fact that tumours larger than a few millimeters in diameter stimulate the growth of new vessels [7, 8]. This tumour neovascularity has certain characteristics that enable a presumptive diagnosis of

Table 6 Echo pattern in colour doppler ultrasound correlated with cytological findings and blood flow

Echo pattern	Number of LN	Cytological findings		CDUS blood flow		
		Benign	Malignant	Central	Peripheral	Mixed
Homogenous	21	21	0	21	0	0
Hypo echoic	9	0	9	0	8	1

malignancy to be made. In evaluating nodal vascularity, doppler ultrasound assesses two main features:

1. Distribution of vessels within the node, and
2. Vascular parameters detecting intravascular resistance (RI, PI) [9].

In 1973, Mountford and Atkinson reported that pathologically enlarged lymph nodes gave rise to significant doppler- shift signals by means of doppler flow meter. The signals have been spectrum analyzed and the large diastolic flow components suggest that there is considerable arterio-venous shunting within lymph glands involved in leukemia, lymphoma and carcinoma [10].

In this study, 21 lymph nodes showed central colour flow signal, suggestive of a benign nature, all 21 nodes proved to be benign, as per the cytological reports. Reactive nodes tend to have prominent hilar/central vascularity due to the increase in vessel diameter and blood flow as seen in these reactive nodes [11]. Considered together with the previous reports, the present findings suggest that the presence of central flow is an indicator of reactive nodes [11, 12]. According to Ahuja et al. [13], both tuberculous and reactive nodes frequently demonstrate central vascularity. In their study, 50 % of tuberculous nodes showed hilar vascularity while in our study, all tuberculous nodes showed central vascularity.

In metastatic lymphadenopathy, destruction of hilar vascularity by tumour cells may result in the induction of vascular supply from the peripheral pre-existing vessels or from vessels in the perinodal soft tissue. Thus, they have peripheral flow. The findings of our study are comparable with a previous study which suggested that the peripheral flow in malignant nodes is in aberrant arterioles or veins within the capsule, subcapsular area or surrounding connective tissue. Eight lymph nodes showing displaced or peripheral flow represent an earlier stage of metastasis than metastasis with no colour flow signals, which indicates that there has not yet been a complete replacement of the lymph node by tumour tissue and that a certain residual amount of lymphatic tissue with sinusoidal vessels still persists and is displaced peripherally [13].

According to Giovagnorio et al. [14], in cases of lymphoma the centre of the node is initially infiltrated and the periphery may remain untouched for a long time, and depending on the aggressiveness, the subcapsular area

infiltrates. So, according to them, lymphomatous lymph nodes can frequently be distinguished from metastatic lymph nodes by colour doppler sonography. In contrast to this, our study showed peripheral perfusion in lymphoma node. One malignant lymph node showed mixed vascularity. Mixed flow of the metastatic node might be explained by two pathogeneses. First, as the tumour nests replace the node, the pre-existing nodal vessels may be proliferated and transformed into feeding vessels by tumour angiogenesis, resulting in central aberrant nodal vessels. Second, advanced tumour infiltration of a node will destroy the hilar blood supply, resulting in induction of the vascular supply from the peripheral pre-existing vessel or vessels in perinodal connective tissue, which may be accelerated by extracapsular invasion. Overall results of colour doppler flow criteria were highly statistically significant in this study.

As tumour cells spread into the lymph node, they grow and replace a large portion of the lymph node. Finally, the lymph node is totally replaced by tumour cells. At this stage, tumour cells compress vessels in the lymph node because of the limited space therein. This vascular compression by tumour cells increases vascular resistance, causing an increase in the RI [11, 14].

The role of intravascular resistance parameters (RI, PI) in differentiating benign from malignant nodes has been a subject of controversy. It has been reported that the RI and PI of reactive nodes is lower than that of metastatic lymph nodes because of dilatation of blood vessels. However, other studies suggested that the vessels in a malignant node had lower resistance (as reflected by a low RI) due to the absence of a muscle layer in tumour vessels and the presence of arteriovenous shunting [15].

Chang et al. reported that lymph nodes affected by the malignant process showed a low resistive index (RI less than 0.6) in their study. While in keeping with the high values of RI and PI observed in malignant nodes in other studies, high mean values of RI and PI in malignant nodes were found in our study on CDUS evaluation. According to Ahuja et al. [11, 15], the reason for the contrasting results of the values of RI and PI between the study by Chang et al. and other studies is the differences in methodology and vessel sampling used for evaluating the RI and PI, such as (1) which node should be evaluated, and (2) how the RI and PI are calculated. In our study, the mean of randomly

obtained RI and PI within the node was used. In our study, 1 lymphoma node showed low RI and PI (RI, 0.78, PI, 1.39). These findings support a previous study by Brnic et al. [15] and SB Dangore. The explanation for lower values of RI and PI in lymphoma is that, just like in chronic lymphadenitis, the normal intranodal structure in lymphoma is not damaged by the growth of neoplastic tissue [15].

Our study showed that there was a statistically significant difference between the mean values of RI and PI for benign and malignant nodes, which was comparable with previous studies by Steinkamp et al. and Shirakawa et al. while the findings of the other studies showed that benign and malignant lymphadenopathy cannot be distinguished solely on the basis of these doppler indices. However, there is controversy regarding its reliability. Giovagnorio et al. [14, 15] reported that CDUS is promising because it is easily applicable and does not require calculations. Another study stated that tissue characterization is not possible by ultrasound and it cannot detect early stage malignant lymphadenopathy.

However, the use of high frequency transducers has improved the ability to detect and interrogate the vascular signals. Wu et al. suggested that power doppler ultrasound combined with a computed image processing system is an objective tool for assessing tumour vascularity quantitatively, which is also applicable for lymph node lesions.

In our study, color doppler sonography showed blood flow in all affected lymph nodes. The ability to detect a color flow pattern within a small lymph node depends on the transducer and equipment used. Newly developed sonographic units equipped with a high frequency transducer have greatly improved the ability to detect superficial low-velocity signals. Failure to find a pulsed doppler signal may be the result of faulty machine settings, such as the wall filter, velocity scale, and doppler gain. The level of the filter is another important parameter, because a high filter level obliterates low-velocity flow [14, 15].

In our study, all of the findings suggested superiority of the CDUS investigation. One of the goals of this study was to differentiate between benign and malignant cervical lymph nodes using the CDUS investigative procedure, and the present study appreciates the important role of CDUS in the diagnostic approach to cervical lymphadenopathy.

Comparison of clinical with histopathological findings in the diagnosis of benign and malignant lymph nodes in clinical practice was over diagnosing the malignant nature of lymph nodes, especially in those cases where there is the presence of primary malignant tumour in the oral cavity. These findings suggest a re-evaluation of the clinical criteria for suspicion of cervical lymph nodes in patients with primary oral cancer.

The comparison between clinical and CDUS evaluation of cervical lymph nodes with cytological findings

suggested that the sensitivity and specificity of both cytological and CDUS were equal. And also, the accuracy of the CDUS examination was definitely higher than the clinical examination. Eleven malignant lymph nodes were detected by clinical examination, but cytological study confirmed only nine lymph nodes as malignant lymph nodes correlated CDUS with findings. This study suggests that all clinically palpable cervical lymph nodes in oral cancer patients cannot be ascribed to malignant metastasis.

It has been stated in a previous study that doppler ultrasound would not eliminate the need for biopsy. Our study suggests that proper judicious CDUS examination gives an opportunity to eliminate the need for biopsy/FNAC in cases of reactive lymph nodes. In cases when CDUS indicates the presence of malignant nodes, biopsy is required to confirm the findings in an attempt to arrive at a final diagnosis. Even though ultrasound-guided fine needle aspiration biopsy (FNAB) has a higher diagnostic accuracy [11, 13, 15], puncturing the metastatic node with a needle carries the risk of micro dissemination of cancer cells, rupturing the capsule of the metastatic node and infection following the FNAB procedure. Although CDUS evaluation cannot replace histopathological procedure in knowing the status of cervical lymphadenopathy, it plays a definite role as an adjunct to the clinical evaluation of cervical lymphadenopathy and proves its value as an important investigation for differentiating between benign and malignant lymphadenopathy.

Conclusion

Color doppler ultrasound can show flow in all lymph nodes, regardless of whether they are affected by a benign or a malignant process. The analysis of patterns of nodal vascularity can be used to differentiate benign from malignant lymphadenopathy with high sensitivity. Doppler indices are also useful in the diagnosis of malignant lymphadenopathy with high specificity.

Conflict of Interest None declared.

References

1. Bazemore AW, Smucker DR (2002) Lymphadenopathy and malignancy. *Am Fam Physician* 66:2103–2110
2. Kuna SK, Bracic I, Tesic V, Kuna K, Herceg GH, Dodig D (2006) Ultrasonographic differentiation of benign from malignant neck lymphadenopathy in thyroid cancer. *J Ultrasound Med* 25:1531–1537
3. Na DG, Lim HK, Byun HS, Kim HD, Ko YH, Baek JH (1997) Differential diagnosis of cervical lymphadenopathy: usefulness of color doppler sonography. *Am J Roentgenol* 168:1311–1316

4. Choi MY, Lee JW, Jang KJ (1995) Distinction between benign and malignant causes of cervical, axillary, and inguinal lymphadenopathy: value of doppler spectral waveform analysis. *Am J Roentgenol* 165:981–984
5. Steinkamp H-J, Mueffelman M, Bock JC, Thiel T, Kenzel P, Felix R (1998) Differential diagnosis of lymph node lesions: a semiquantitative approach with colour doppler ultrasound. *Br J Radiol* 71:828–833
6. Chang D-B et al (1994) Differentiation of benign and malignant cervical lymph nodes with color doppler sonography. *Am J Roentgenol* 162:965–968
7. Wu C-H, Hsu M-M, Chang Y-L, Hsieh F-J (1998) Vascular pathology of malignant cervical lymphadenopathy. *Cancer* 83(6):1189–1196
8. Shirakawa T, Miyamoto Y, Yamagishi J, Fukuda K, Tada S (2001) Color/power doppler sonographic differential diagnosis of superficial lymphadenopathy. *J Ultrasound Med* 20:525–532
9. Dangore SB, Degwekar SS, Bhowate RR (2008) Evaluation of the efficacy of colour doppler ultrasound in diagnosis of cervical lymphadenopathy. *Dentomaxillofac Radiol* 37:205–212
10. Mountford RA, Atkinson P (1979) Doppler ultrasound examination of pathologically enlarged lymph nodes. *Br J Radiol* 52:464–467
11. Ahuja AT, Ying M, Hoa SSY, Metrewelia C (2001) Distribution of intranodal vessels in differentiating benign from metastatic neck nodes. *Clin Radiol* 56(3):197–201
12. Sato N, Kawabe R, Fujita K, Omura S (1998) Differential diagnosis of cervical lymphadenopathy with intranodal color doppler flow signals in patients with oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86(4):482–488
13. Ahuja A, Ying M, Yuen YH, Metreweli C (2001) Power doppler sonography to differentiate tuberculouscervical lymphadenopathy from nasopharyngeal carcinoma. *Am J Neuroradiol* 22:735–740
14. Giovagnorio F, Galluzzo M, Andreoli C, De Cicco ML, David V (2002) Color doppler sonography in the evaluation of superficial lymphomatous lymph nodes. *J Ultrasound Med* 21:403–408
15. Brnic Z, Hebrang A (2003) Usefulness of doppler waveform analysis in differential diagnosis of cervical lymphadenopathy. *Eur Radiology* 13:175–180