Role of color Doppler ultrasound in differentiation between benign and malignant lymphadenopathy

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Received 10 May 2023
Revised 01 July 2023
Accepted 12 July 2023
Published 23 December 2023

Journal of Current Medical Research and Practice
2023, 8:165–170

Objective
To evaluate the accuracy of color Doppler ultrasound in differentiation between benign and malignant enlarged lymph nodes compared with histopathological correlation.

Patients and methods
In all, 100 patients with lymphadenopathy in various age groups participated in this prospective study. Grayscale and color Doppler ultrasound (CDUS) was done for all of them, and then a comparison with histopathological data was done.

Results
Grayscale ultrasound had 88.9% sensitivity and 100% specificity with an area under the curve of 0.94 in the prediction of malignant LNs, while CDUS had 100% sensitivity and 87.8% specificity with an area under the curve of 0.93, The pulsatile index at a cutoff point >1.39 had 77.8% sensitivity and 100% specificity in the prediction of malignant LNs with an area under the curve of 0.87, while the resistive index at a cutoff point >0.69 had 78% sensitivity and 100% specificity with an area under the curve of 0.89.

Conclusion
Differentiation between benign and malignant lymph nodes using CDUS is a reliable and noninvasive technique.

Keywords:
color Doppler, lymphadenopathy, ultrasound

J Curr Med Res Pract 8:165–170

2357-0121

Introduction

Lymphadenopathy (LAP) is the medical term for aberrant lymph nodes that might range in size, consistency, or number [1]. Although most lymph nodes have a diameter of less than 1 cm, there are certain exceptions in different locations and at different ages [2]. Larger lymph nodes, whose size is greater than 2 cm in children (aged 2 to 10), can be deemed healthy and may be a sign of a tumor (including lymphoma) or granulomatous disease like cat scratch disease or TB [3].

Although studies have revealed that less than 1% of people with undiagnosed LAP in general practice develop malignancies, it continues to be the main concern of both patients and clinicians despite the reduced incidence of malignancies among those with LAP [4].

The identification of LAP should take into account many factors. Most of the time, the initial assessment clarifies the cause (such as infection), thus further investigation is not required. In cases of unexplained illnesses, laboratory tests, radiographic imaging, and tissue biopsies are recommended [5]. Due to the overlooking of small metastatic lesions or even moderately sized nodes in people with thick necks and misclassifying larger inflammatory or specific lesions, palpation is considered a poor diagnostic technique [6].

Since more than 20 years ago, ultrasound (US) has been used as a very trustworthy and affordable screening tool for evaluating superficial lymph nodes. Initial research from the 1980s showed that the US was capable of making diagnoses [7]. By the turn of the millennium, it appeared that the US had become significant in the grading of lymphadenopathy [8]. Ultrasound can also be utilized to describe the size, forms, borders, internal structures, vasculature, and perinodal connective tissues of an aberrant lymph node [9]. The lack of ionizing radiation and the ability to distinguish between cystic and solid lymph nodes are considered other benefits of ultrasonography [5].

Color Doppler markers have been described for the diagnosis of malignant lymph glands. These markers include peripheral and mixed vascularity, resistive indices (RI) larger than 0.7, and pulsatile indices (PI) greater than 1.4. Furthermore, color

Doppler ultrasound improves diagnostic accuracy and serves as an essential supplemental treatment to grayscale ultrasonography in differentiating between benign and malignant lymph glands. In addition, ambiguous grayscale ultrasonography findings that boost diagnostic confidence in predicting malignant development in enlarged lymph nodes are useful [5].

So the study aims to evaluate the accuracy of color Doppler ultrasound in differentiation between benign and malignant enlarged lymph nodes compared with histopathological correlation.

Patients and methods

The study was approved and monitored by the Medical Ethics Committee, Assiut Faculty of Medicine (IRB # 17100641).

In all, 100 patients with palpable lymphadenopathies at different age groups were randomly selected, after the exclusion of those having: (a) previous chemotherapy or radiotherapy, (b) undergone excisional biopsies or fine-needle aspiration screening, (c) suffered from a severe and permanent bleeding disease, or (d) having their biopsy data destroyed while the study was still running.

Prothrombin time, concentration, and platelet count were evaluated to rule out bleeding disorders.

Routine US examinations of the neck, axilla, and abdomen.

All patients were subjected to full history taking and clinical examination by a referral physician, then examined by the grayscale and CDUS to identify the nature of the enlarged lymph nodes whether it is benign or malignant.

Technique

A Logic P7 GE healthcare Ultrasound Scanner was used with a linear probe 7.5 MHz frequency. Parameters of grey scale US , Color Doppler and Power Doppler are summarized in (Table 1).

Data on Grayscale and CDUS were gathered and Doppler indices were measured, to distinguish between benign and malignant lymph nodes, taking into account the various criteria that are summarized in (Table 2).

All data were analyzed prospectively, and comparisons with histopathological data (either excisional (58 patients), true-cut (9 patients), or fine-needle aspiration cytology (33 patients)) were made.

Table 1 parameters of grey scale US, Color Doppler and Power Doppler

	Grey scale	Color Doppler	Power Doppler
Frequency (Frq)	11.0	5.0	5.0
Gain (Gn)	57	25.5	38
Pulse Repetition Frequency (PRF)	_	1.8	5.4
Wall filter (WF)	_	258	96
Stroke Volume (SV)	_	_	1.0
Singular Value Decomposition (SVD)	_	_	1.3

Table 2 Difference between benign and malignant lymph nodes

	Malignant	Benign
B Scan criteria		
Margins	Irregular, blurred, angular, invasive	Sharp
Echogenicity	Marked hypoechoic	Moderate or low
Hilum	Absent	Present
Shape	Rounded	Oval
Size	Large	Small
Doppler criteria		
Impedance values	High	Low
Vascular pattern	Chaotic	Regular
Vascular pedicles	Multiple	Single
Vessel location	Peripheral	Central
Flow	Present	Absent
PI	>1.4	<1.4
RI	>0.7	<0.7

Data was collected and analyzed by using SPSS (Statistical Package for the Social Sciences, version 20, IBM, and Armonk, New York). Quantitative data were expressed as mean ± standard deviation, while nominal data were given as number (n) and percentage (%).

The diagnostic accuracy of different parameters for the prediction nature of LNs was determined by the ROC curve. The level of confidence was kept at 95% and hence the *P* value was considered significant if <0.05.

Results

In all, 100 patients (53% females and 47% males) were included in the study; their mean age was 35.05 ± 17.29 years with a range between 5 and 78 years. Sixty-six patients (55 benign and 11 malignant) were below the age of 40 years, while 34 patients (15 benign and 19 malignant) were above the age of 40 years, with the most common age of malignancy being above the age of 40 years.

The most frequent diagnosis was cervical lymphadenopathy (64%), followed by axillary lymphadenopathy (17%), then generalized and inguinal lymphadenopathy (11% and 8%, respectively); 58% had an excisional biopsy, 33% had FNAC and 9% had a tru-cut needle biopsy, with 27% having malignant lymphadenopathy, while the other 73% had benign lymphadenopathy.

Reactive lymphoid hyperplasia was the most common pathology by 60%, followed by Hodgkin lymphoma (13%), TB (11%), metastasis (9%), non-Hodgkin lymphoma (5%), and finally nonspecific lymphadenitis in three cases (3%).

Of the patients, 24% and 36% had malignant lymphadenopathy, while 76% and 64% had benign lymphadenopathy by grayscale ultrasound and CDUS, respectively.

So, the grayscale had 88.9% sensitivity and 100% specificity in the prediction of malignant LNs with the area under the curve being 0.94, while color Doppler had 100% sensitivity and 87.8% specificity with the area under the curve being 0.93 (Table 3).

The mean PI at its standard cutoff point was 1.08 ± 0.42, while the mean RI was 0.60 ± 0.13 with 21 patients having malignant lymphadenopathy and 79 patients having benign lymphadenopathy, so each PI and RI had 77.8% sensitivity and 100% specificity in the prediction of malignant LNs with the area under the curve beings 0.78 (Tables 4 and 5).

While PI at a new cutoff point >1.39 had 77.8% sensitivity and 100% specificity in the prediction of malignant LNs with an area under the curve of 0.87 and RI at a new cutoff point >0.69 had 78% sensitivity and 100% specificity with an area under the curve of 0.89 (Table 6). And based on this new cutoff point in the current study, 21% and 79% of the patients had malignant and benign LNs, respectively (Table 7).

Finally, we found that the combination of the various four ultrasound measures had 91% overall accuracy, an area under the curve of 0.87, 100% sensitivity, and 87.7% specificity in the prediction of malignant LNs (Table 8).

Discussion

Although magnetic resonance imaging (MRI) and CT scanning are excellent for identifying lymphadenopathy, US has traditionally been thought of as a potent tool for determining lymphadenopathy growth, especially when high-frequency probes are used (7.5–15 MHz) [10–12]. Also, blood flow and nodal anatomy can be revealed by CDUS [13].

Table 3 Accuracy of Grayscale and color Doppler Ultrasound in the diagnosis nature of LNs

	Grayscale	Color Doppler
Sensitivity	88.9%	100%
Specificity	100%	87.8%
Positive predictive value	100%	75%
Negative predictive value	96%	100%
Accuracy	97%	91%
Area under the curve	0.94	0.93
P	<0.001	<0.001

P<0.05. LNs, lymphadenopathy.

Table 4 Pulsatile index and resistive index among the studied patients

	n=100
Pulsatile index	1.08±0.42
Diagnosis based on PI	
Malignant lymphadenopathy	21 (21%)
Benign lymphadenopathy	79 (79%)
Resistive index	0.60±0.13
Diagnosis based on RI	
Malignant lymphadenopathy	21 (21%)
Benign lymphadenopathy	79 (79%)

Data expressed as frequency (percentage) and mean (SD).
PI, pulsatile index; RI, resistive index.

Table 5 Accuracy of Pulsatile index and Resistive index in the diagnosis nature of LNs

Indices	Value
Negative predictive value	92%
Positive predictive value	100%
Sensitivity	77.8%
Specificity	100%
Accuracy	94%
P	<0.001
Area under the curve	0.78

P<0.05. LNs, lymphadenopathy.

Table 6 Accuracy of Pulsatile index and Resistive index in the diagnosis nature of LNs based on the new cutoff point

	Resistive index	Pulsatile index
Negative predictive value	92.4%	92.4%
Positive predictive value	100%	100%
Accuracy	94%	94%
Specificity	100%	100%
Sensitivity	78%	77.8%
Cutoff point	>0.69	>1.39
P	<0.001	<0.001
Area under the curve	0.89	0.87

P<0.05. LNs, lymphadenopathy.

Table 7 Diagnosis among the studied patients based on the new cutoff point

	n=100
Diagnosis based on PI (>1.39)	
Malignant lymphadenopathy	21 (21%)
Benign lymphadenopathy	79 (79%)
Diagnosis based on RI (>0.69)	
Malignant lymphadenopathy	21 (21%)
Benign lymphadenopathy	79 (79%)

Data expressed as frequency (percentage) and mean (SD).
PI, pulsatile index and RI, resistive index.

So, the study aimed to evaluate the accuracy of CDUS in differentiation between benign and malignant enlarged lymph nodes.

George and Appukuttan *et al.* [14] reported, in agreement with our research, that 49% compared with 34% in our study were in the age group of over 40 years, and it was the common age group of the majority of patients presenting with malignant lesions.

Abdelgawad *et al.* [15] demonstrated contrary to our study that 69% of the lymph glands were cancerous. This higher percentage can be attributed to the selection of the most suspicious lymph nodes. However, in some other studies as performed by Lyshchik *et al.* [16], only 43% of the total 114 examined lymph nodes were found to be malignant which is in agreement with our study, which informed that only 27% of the patients were found to be malignant.

According to grayscale US, there are multiple criteria denoting the benign nature of the lymph node which are of small size, oval-shaped, preserved hilum, and of sharp margin Fig. 1, while, on the contrary, the malignant criteria are large-sized, round-shaped, absent hilum, and blurred or invasive margin) Fig. 2.

The Elzawawy *et al.* [17] study results agree with the current research that the shape of the lymph node was an important parameter, as reported 81% of inflamed lymph nodes were oval, while 80% of cancerous nodes were rounded, compared with our study, which showed that all benign lymph nodes are oval-shaped and 88.9% of the cancerous lymph glands were rounded, while only 11.1% were oval.

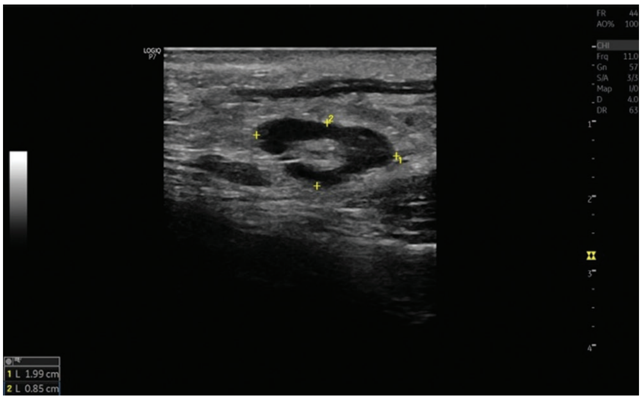
Elzawawy *et al.* [17] also reported that in 93% of the noncancerous tissues and 6.5% of the lymphomatous nodes, echogenic hila were preserved, while 81% of malignant had lost their echogenic hila, in agreement with our study which informed that among 73 benign lymph nodes, 93.1% of them showed preserved echogenic hilum, while among 27 malignant lymph nodes, there were 88.9% that showed loss of echogenic hilum, and only 11.1% showed a preserved hilum. As a result, our research suggests that the existence of a central echogenic hilum may serve as a predictive biomarker and an indicator of benignity.

Table 8 Accuracy of the combination of different parameters in the diagnosis nature of LNs

	Combination of the 4 parameters
Sensitivity	100%
Specificity	87.7%
Positive predictive value	75%
Negative predictive value	100%
Accuracy	91%
Area under curve	0.87
P	<0.001

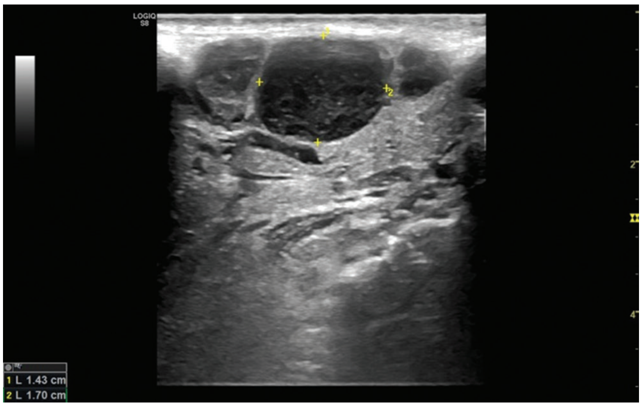
P<0.05. LNs, lymphadenopathy.

Figure 1



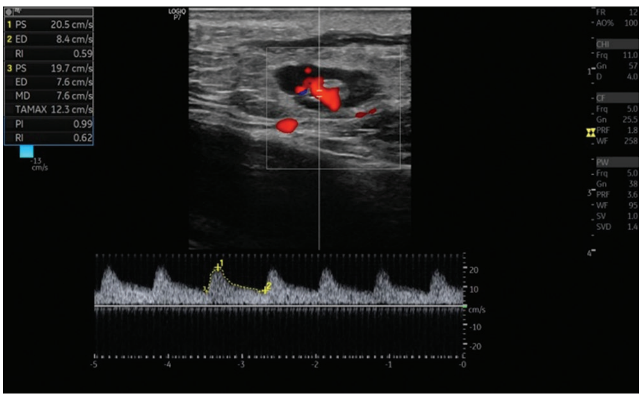
Grayscale US shows an enlarged cervical lymph node, oval, with preserved central fatty hilum, and measures about 2 × 0.85 cm suggesting a benign nature.

Figure 2



Grayscale US shows an enlarged cervical lymph node, round in shape with loss of echogenic hilum, and measures about 1.7 × 1.4 cm, suggesting a malignant nature.

Figure 3



CDUS shows central vascularity with RI and PI are 0.62 and 0.99, respectively, suggesting a benign nature.

According to CDUS, there are multiple criteria denoting the benign nature of the lymph node, which are centralized vessel location, single vascular pedicle, and regular vascular pattern Fig. 3, while, on the contrary, the malignant criteria are peripheral vascular location, multiple vascular pedicles, and chaotic vascular pattern Fig. 4.

Regarding the Misra *et al.* study [18] which was performed on 63 patients and used CDUS to assess cervical adenopathy, 178 nodes in total showed vascularity, with substantial hilar vascularity seen in approximately 92% of reactive LNs, which is in keeping with our research results that 87.6% out of the 73 lymph nodes that histopathology determined to be benign showed hilar vascularity.

The relationship between malignancies and peripheral vascular patterns is highly particular and varies in sensitivity, so central hilar vascular patterning is more common in reactive lymphatics [19].

A useful sign of carcinoma is the existence of periphery vessels in lymph glands, as stated in the Leboulleux *et al.* [20] and Ying *et al.* [21] studies, which show agreement with our study that demonstrated that among 36 lymph nodes that showed peripheral or mixed vascularity, 75% were malignant and only 25% were benign.

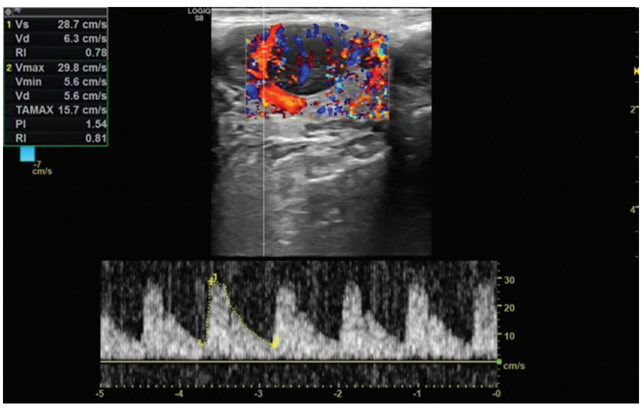
Vascular resistance (RI and PI) in LNs have been offered as a way to distinguish cancerous LNs from reactive or normal ones [22,23]. According to the hypothesis, tumors enter malignant nodes, compressing the LN's internal structure and vasculature, raising vascular resistance; in addition, desmoplasia is produced, creating additional structural alterations to the LN that further raise RI and PI [24,25].

In this study, we found that the pulsatile index at a cutoff point >1.39 had 77.8% sensitivity and 100% specificity in the prediction of malignant LNs with the area under the curve being 0.87, and the resistive index at a cutoff point >0.69 had 78% sensitivity and 100% specificity with the area under the curve being 0.89 Figs. 3 and 4. This is consistent with Brnic and Hebrang's study [25] which showed that RI and PI between reactive and metastatic LNs were statistically different.

It has been reported that the RI of metastatic lymph nodes is higher compared with reactive nodes [9]. However, other studies have suggested that metastatic nodes may have lower or similar vascular resistance compared with benign lymph nodes [26]. As in previous studies by Steinkamp *et al.* [27] and Chang *et al.* [28], various RI cutoff thresholds (0.6, 0.7, and 0.8) with various sensitivities (47-81%) and specificities (81-100%) for identifying reactive and cancerous lymph nodes were reported, which is similar to our study which showed that resistive index at a cutoff point >0.69 had 78% sensitivity and 100% specificity in predicting malignant LNs with the area under the curve being 0.89.

Lastly, we can conclude that CDUS assessment can play an important role as an adjunct to the clinical assessment of lymphadenopathy and confirms its significance as an essential investigation for the differentiation between benign and malignant lymph nodes, even though it cannot completely replace the histopathological process in determining the status of lymphadenopathy.

Figure 4



CDUS shows peripheral vascularity with RI and PI are 0.81 and 1.54, respectively, suggesting a malignant nature.

Conclusion

Differentiation between benign and malignant lymph nodes using color Doppler ultrasound is a reliable and noninvasive technique.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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