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Original Article

Radiology Section

Role of Sonoelastography for Differentiating Benign and Malignant Cervical Lymph Nodes: A Cross-sectional Study

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ABSTRACT

Introduction: Cervical nodes form one of the major groups of Lymph Nodes (LN) that are frequently involved in inflammatory and neoplastic diseases. Metastasis causes the most apparent change in consistency of the node among the various nodal pathologies. Ultrasound elastography provides an estimate of tissue consistency by measuring the degree of distortion under the application of an external force.

Aim: To estimate the diagnostic accuracy of sonoelastography in the differentiation of malignant and benign cervical LN with Fine Needle Aspiration Cytology (FNAC)/biopsy considered as a gold standard.

Materials and Methods: A cross-sectional study was carried out from March 2020 to January 2021 in a tertiary care hospital in south India, a total of 50 patients with cervical lymphadenopathy underwent ultrasonography followed by elastography of superficial neck LN using high frequency linear transducer by freehand technique. The ultrasound characteristics of selected LN were determined and colour elastogram pattern was assessed using colour mapping elastography. The Chi-square test was performed. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were obtained. The results were then compared to the fine needle aspiration cytology.

Results: A total of 50 subjects (median age of 40.5±18.71 years; 19 (38%) males and 31 (62%) females). The grayscale and colour Doppler features of cervical LN which helped predict malignancy were short axis ≥8 mm, Short:Long axis diameter ratio (S:L) ≥0.5, absence of normal central fatty hilum, abnormal echogenicity, lobulated border, presence of calcification and peripheral/mixed vascularity. With reference to the above variables of cervical LN characterisation on grayscale, colour doppler ultrasound and sonoelastography findings, elastography pattern was the most promising variable to differentiate malignant from benign cervical LN with 95.2% sensitivity, 75.0% specificity, 95.2% PPV, 75.0% NPV and 92.0% accuracy.

Conclusion: Sonoelastography is useful in the assessment of elastic properties of cervical LN with short examination time required, real-time display, immediate interpretation and limited cost. Sonoelastography had higher diagnostic accuracy than gray scale and doppler ultrasound in differentiating benign from malignant cervical LN. Sonoelastography is an effective supplement to conventional gray scale and colour doppler ultrasound and that the combination is clinically recommended for a more accurate diagnosis of metastatic LN.

Keywords: Colour elastogram pattern, Colour doppler, Elastography

INTRODUCTION

Lymphadenopathy is one of the common daily clinical encounters, and it holds high clinical significance as it could be a manifestation of a number of pathological entities [1]. Head and neck cancers account for nearly one-third of the cancer burden in India, and it is a well-known fact that status of cervical LN is the single most important prognostic factor in squamous cell carcinoma of the head and neck [2]. The differentiation of malignant from benign LN is essential because it predicts the patient prognosis and helps in decision-making and planning of management [3].

Although grayscale sonography in combination with doppler has been suggested to be useful in differentiating metastatic LN from reactive ones based on various criteria, there is no single ultrasound criterion for diagnosing malignant LN with satisfactory sensitivity and specificity [4,5]. The Fine-Needle Aspiration Cytology (FNAC) is considered as the most efficient method for differentiating benign and malignant LN. However, it is considered as an invasive method which is prone to sampling errors and analytic uncertainty [6]. Its false negative rate has been reported to be between 12.5% and 25% [7,8]. Sonoelastography has been recently introduced as a non invasive imaging technique for the evaluation of cervical LN [9]. It assesses tissue elasticity by the comparison of local tissue displacements from ultrasound signals before and after the application of a compressive force [10]. Because malignant tissues are generally harder than normal surrounding tissues, measurement of tissue elasticity might be useful for the differential diagnosis of different pathologic changes [9,10]. So, in this study we aim to estimate the diagnostic accuracy of sonoelastography in comparison with FNAC/Biopsy as reference standard, in differentiation of malignant and benign superficial cervical LN.

MATERIALS AND METHODS

A cross-sectional study was conducted in Krishna Rajendra tertiary care hospital attached to Mysore Medical College and Research Institute, Mysore, Karnataka, India from 50 patients who were referred to the Radiology Department from March 2020 to January 2021. The Institutional Ethics Committee (IEC) approval was obtained (ref number EC REG: ECR/134/Inst/KA/2013/RR-19).

Inclusion criteria: All the patients referred for Ultrasonogram of enlarged cervical LN felt clinically or referred for thyroid sonography where cervical LN were examined as a part of neck examination or for ultrasound guided FNAC/Biopsy of LN were included in study.

Exclusion criteria: Patients with enlarged level VII cervical nodes or in whom the cervical nodes are cystic or completely necrotic as performance of strain elastography will be difficult in these patients were excluded. Patients with history of chemotherapy or radiotherapy or patients with contraindications for FNAC/Biopsy; and those who cannot comply with study protocol were excluded from the study.

Study Procedure

The LN included in the study were subjected to B-mode ultrasound followed by Doppler evaluation, then Ultrasound elastographic evaluation, using 5-18 MHz high frequency linear transducer in PHILIPS Affiniti 70 ultrasound machine and compared with the histological results of fine needle aspiration cytology or biopsy results which ever was feasible.

A two dimensional (2D) Ultrasonography and colour doppler: On B mode, the LN was evaluated for short-axis diameter, short to long axis diameter ratio (S/L ratio) in the longitudinal plane, borders (regular or lobulated), echogenicity (homogenously hyperechoic/ homogenously hypoechoic/ homogenously isoechoic), hilum (present or absent) and calcification (present or absent). The doppler evaluation showed intra-nodal vascular pattern (central/ peripheral/mixed).

Sonoelastography: The freehand technique of data acquisition for an elastogram was used. A linear ultrasound probe was held perpendicular to the plane parallel to the skin overlying a cervical LN. A constant precompression was applied to fix the node against the underlying structures and a controlled compression was applied in the direction of propagation of the ultrasound waves followed by decompression. A cine loop of elastograms was recorded during a few such cycles of compression-release.

On the colour elastogram, red represents the softest and blue represents the hardest areas, while intermediate stiffness is indicated by green. Elastographic images were given 1-8 elasticity scores based on a study by Lenghel LM et al., as given in [Table/Fig-1] [11].

Pattern	Presentation
Pattern-1	No or minimum blue area (suggestive of soft consistency similar to the surrounding tissues).
Pattern-2	Less than 50% blue area, no individualised hypoechoic nodules.
Pattern-3	Less than 50% blue area, individualised soft hypoechoic nodules present.
Pattern-4	Less than 50% blue area individualised hard hypoechoic nodules present.
Pattern-5	50-100% blue area, no individualised hypoechoic nodules.
Pattern-6	50-100% blue area individualised hard hypoechoic nodules present.
Pattern-7	Blue area covers the whole nodules and extends into the soft tissues.
Pattern-8	Blue (hard) nodule containing fluid areas (suggestive of liquefactive necrosis)

[Table/Fig-1]: Elasticity scores based on a study by Lenghel LM et al., [11].

Qualitative analysis was done using an elastography pattern where pattern I, II and III indicated benign and pattern IV and above indicated malignant cervical lymphnodes.

Histopathologic diagnosis: This was followed by fine needle aspiration cytology of these LN. In cases where FNAC results were inconclusive, (FNAC) biopsy was done which served as the reference standard. The results of FNAC/Biopsy were compared with grey scale, doppler and elastography patterns.

STATISTICAL ANALYSIS

The Microsoft Excel and Statistical Package for Social Sciences (SPSS) (SPSS Inc, Chicago v 18.5) software packages were used for data entry and analysis respectively. The results were averaged (mean±standard deviation) for each parameter for continuous data and numbers and percentage for categorical data. Univariate analyses of the dichotomous variables encoded were performed by means of the Chi-square test with Yates correction if required. In all the above tests, a p-value of less than 0.05 was accepted as indicating statistical significance.

RESULTS

Out of total 50 study participants included, 19 (38%) were males and 31 (62%) were females. Hence, a total of 50 enlarged cervical LN were evaluated. The age range for both benign and malignant LN patients was 3-64 years, with median age of 40.5±18.71 years with maximum prevalence 16 (32%) was in the age group of 31-45 years.

Histological results: The prevalence of benign LN was 8/50 (16%), Metastatic LN was 42/50 (84%) (metastasis from squamous cell carcinoma was 21/42, metastasis from adenocarcinoma was 9/42 and metastasis from papillary carcinoma was 9/42, 3/42 were non hodgkin's lymphoma).

Gray scale ultrasound parameters: On Brightness (B) mode, USG LN were evaluated for the short axis diameter, Short:long axis ratio, shape; echogenicity, hilum and calcification [Table/Fig-2]. For the short axis to long axis ratio, benign nodes were less than 0.5, while malignant lymphnodes tend to be rounded with short:long axis ratio of more than 0.5. The p-value <0.001; 7.3% of benign nodes had round shape, while 92.7%of malignant nodes had round shape. The p-value <0.001; 48 (96%) cervical lymphnodes did not show central fatty hilum of which 12.5% were benign, while 87.5% were malignant. (p-value=0.001); Of 32 lymphnodes with lobulated borders, 93.8% proved to be malignant, while 6.2% benign (p-value=0.012);

Short:long axis ratio of 0.5; round shape of LN; absence of central fatty hilum; abnormal echogenicity; lobulated border was proved to be a significant gray scale ultrasound characteristic to differentiate malignant and benign nodes. While short axis diameter cut-off 8 mm (p-value = 0.574); presence of punctuate calcification was not statistically significant to differentiate malignant from benign nodes (p-value=0.254) [Table/Fig-2].

Parameters		Histopathology Malignant n=42 (%)	Histopathology Benign n=8 (%)	Total n (%)	p-value
Short axis diameter	≥8 mm	35 (85.4)	6 (14.6)	41 (82)	0.574
	<8 mm	7 (77.8)	2 (22.2)	9 (18)	
S:L axis	≥0.5	38 (92.7)	3 (7.3)	41 (82)	**<0.001****
	<0.5	4 (44.4)	5 (55.6)	9 (18)	
Shape	Round	38 (92.7)	3 (7.3)	41 (82)	**<0.001****
	Oval	4 (44.4)	5 (55.6)	9 (18)	
Central fatty hilum	Absent	42 (87.5)	6 (12.5)	48 (96)	**0.001****
	Present	0 (0.0)	2 (100)	2 (4.0)	
Border	Lobulated	30 (93.8)	2 (6.2)	32 (64)	**0.012****
	Regular	12 (66.7)	6 (33.3)	18 (36)	
Echogenicity	Hyperechoic	9 (81.8)	2 (18.2)	11 (22.0)	**0.007****
	Hypoechoic	26 (86.7)	4 (13.3)	30 (60)	
	Isoechoic	7 (100.0)	0 (0.0)	7 (14.0)	
	Hypoechoic with central hyper echogenicity	0 (0.0)	2 (100.0)	2 (4.0%)	
Calcification	Present	6 (100.0)	0 (0.0)	6 (12)	0.254
	Absent	36 (81.8)	8 (18.2)	44 (88)	
Vascularity	Peripheral	33 (94.3)	2 (5.7)	35 (70.0)	**<0.001****
	Mixed	9 (69.2)	4 (30.8)	13 (26)	
	Central	0 (0.0)	2 (100.0)	2 (4.0)	

[Table/Fig-2]: Association of gray scale and doppler ultrasound parameters and histopathology.
**Strongly Significant (p value:p≤0.001)

Colour doppler parameters: [Table/Fig-3]: Among 35 cervical lymphnodes with peripheral vascularity, 94.3% were malignant and 5.7% benign; 13 nodes with both central and peripheral vascularity, 69.2% were malignant and 30.8% benign; two nodes with central vascularity were benign (100%). Thus, abnormal vascularity (peripheral and mixed) proved to be statistically significant (p-value <0.001) to differentiate malignant from benign nodes.

Sonoelastography pattern	HPE		Total n (%)	p-value
	Benign n (%)	Malignant n (%)		
1	0 (0)	0 (0)	0 (0)	<0.001** #Chi-square test
2	2 (100.0)	0 (0.0)	2 (100.0)	
3	4 (66.7)	2 (33.3)	6 (100.0)	
4	2 (100.0)	0 (0.0)	2 (100.0)	
5	0 (0.0)	7 (100.0)	7 (100.0)	
6	0 (0.0)	16 (100.0)	16 (100.0)	
7	0 (0.0)	17 (100.0)	17 (100.0)	
8	0 (0)	0 (0)	0 (0)	
Total	8	42	50	

[Table/Fig-3]: Association of Sonoelastography pattern and histopathology.
Significant figures; **Strongly significant (p-value: p≤0.001)

Colour Doppler Ultrasonography evaluation of nodal vascular pattern had sensitivity (66.2%), specificity (75%), and accuracy (78%) for differentiating metastatic and benign nodes [Table/Fig-4].

Calcification in metastatic LN is usually rare [14]. However, Ahuja AT et al., have reported that 68.7% of metastatic nodes from papillary cancer of the thyroid had calcification [15]. Hence, short axis diameter and punctate calcifications cannot be an accurate method to differentiate benign from malignant LN. Among the gray scale ultrasound criteria, absent central fatty hilum showed high diagnostic accuracy of 88%, high sensitivity of 100% but low specificity of 25% [Table/Fig-4].

Ying M et al., in their study have reported that the presence of a central hyperechoic hilum is considered strong diagnostic criteria for benign LN [16]. Similarly, Rubaltelli L et al., have reported that central hyperechoic hilum is seen in <5% of metastatic and 84%-92% of benign nodes [17]. However, Vassallo P et al., have reported that a hyperechoic hilum can be visualised in up to 51.5% of metastatic nodes [18].

The shape of LN (S/L ratio) showed high accuracy of 86% similar to the studies done by Lyshchik A et al., and Mahrokh IM et al., [19,20]. On colour Doppler Ultrasound, internal nodal vascularity was evaluated, benign LN tends to show hilar vascularity or appear avascular. In contrast, metastatic nodes tend to have peripheral or mixed (both peripheral and hilar) vascularity.

Test variable	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)	Accuracy %	Kappa value
Short axis	83.3 (72.0-94.6)	25.0 (0.0-55.0)	85.4 (74.6-96.2)	22.2 (0.0-49.4)	74.0 (61.8-86.2)	0.079
S:L axis ratio	90.5 (81.6-99.4)	62.5 (29.0-96.0)	92.7 (84.7-100.0)	55.6 (23.1-88.1)	86.0 (76.4-95.6)	0.504
Shape	90.5 (81.6-99.4)	62.5 (29.0-96.0)	92.7 (84.7-100.0)	55.6 (23.1-88.1)	86.0 (76.4-95.6)	0.504
Central fatty hilum	100.0	25.0 (0.0-55.0)	87.5 (78.1-96.9)	100.0	88.0 (79.0-97.0)	0.359
Echogenicity	61.9 (47.2-76.6)	50.0 (15.4-84.6)	86.7 (74.5-98.9)	20.0 (2.5-37.5)	60.0 (46.4-73.6)	0.704
Border	71.4 (57.7-85.1)	75.0% (45.0-100.0)	93.8 (85.4-100.0)	33.3% (11.5-55.1)	72.0 (59.6-84.4)	0.308
Calcification	14.7 (4.95-31.06)	100.0 (54.07-100)	100.0 (89.7-100)	17.14 (15.3-19.2)	27.5 (14.6-43.8)	0.051
Vascularity	78.6 (66.2-91.0)	75.0 (45.0-100.0)	94.3 (86.6-100.0)	40.0 (15.2-64.8)	78.0 (66.5-89.5)	0.396
Elastography pattern	95.2 (88.7-100.0)	75.0 (45.0-100.0)	95.2 (88.7-100.0)	75.0 (45.0-100.0)	92.0 (84.4-99.5)	0.702

[Table/Fig-4]: Diagnostic value of the following variables to differentiate malignant from benign cervical LNs.
K-value (kappa value) Poor agreement: <0.20; Fair agreement: 0.20-0.40; Moderate agreement: 0.40-0.60; Good agreement: 0.60-0.80; Very good agreement: 0.80-1.00; S:L: Short:Long; PPV: Positive predictive value; NPV: Negative predictive value

Sonoelastography: Lymphnodes of pattern 1, 2, and 3 were considered benign with total number 10, whereas lymphnodes of pattern 4, 5, 6, 7 and 8 were considered malignant with total number 40. Among the 50 cervical LN, elastography pattern was proved to be statistically significant to differentiate malignant and benign nodes (p-value <0.001) [Table/Fig-3].

Comparison between the diagnostic value of gray scale, doppler sonography, and sonoelastography score of LN is given in [Table/Fig-4]. Elastography pattern showed good agreement (K-value: 0.70) and the most promising variable to differentiate malignant from benign cervical lymphnodes among gray scale US, colour doppler and elastography findings.

DISCUSSION

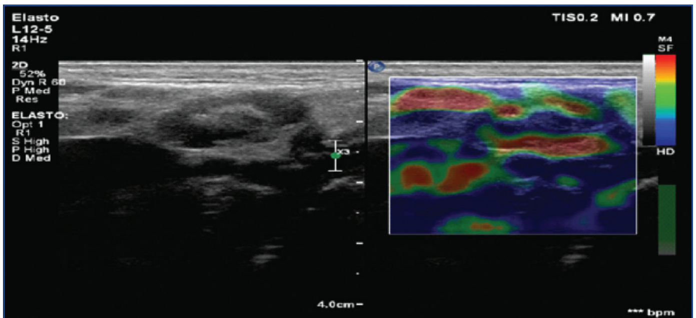
Sonoelastography is a non invasive, safe, easily available, less expensive and less time-consuming imaging technique that provides information on cervical LN elasticity and describes its displacement (i.e., strain) or stiffness in response to a given force [12,13].

The size of LN, shape, short axis diameter, short:long axis ratio, absence of fatty hilum, calcification, echogenicity and vascularity are used as ultrasound and doppler criteria for differentiation between benign and malignant LN.

In the present study, we found that the short axis diameter, presence of punctate calcification in LN was not an accurate method for differentiating benign from malignant LN (p-value=0.254) [Table/Fig-2]. This can be accounted as generally malignant LN are larger; and also, inflammatory conditions can increase in size of LN.

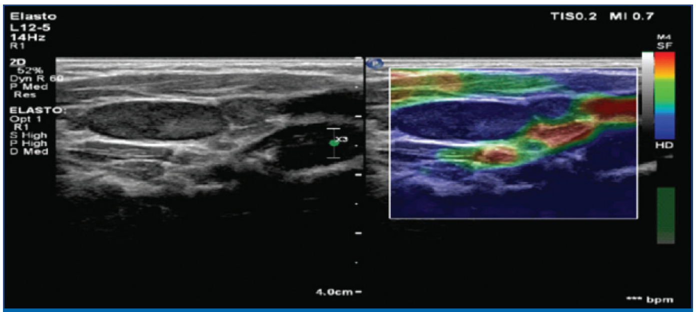
For colour doppler, there was 78.6% sensitivity and 75.0% specificity with 78% accuracy in the present study. These findings corresponded to previously published reports by Giovagnorio F et al, Ying M et al., and Ahuja A and Ying M [21-23].

Giovagnorio F et al., evaluated power doppler sonography to detect peripheral vascularity in 105 benign and malignant cervical LN and found 55% sensitivity and 91% specificity in detecting neoplasm [21]. We found the overall accuracy of real-time elastography to be 92%, which is higher than all B-mode criteria of 72%-86.6% and higher than colour doppler ultrasound of 78% [Table/Fig-4,5].



[Table/Fig-5]: Ultrasound elastography images of Level II oval hypoechoic cervical LN with central fatty hilum having pattern III that is less than 50% blue area, individualised soft hypoechoic nodules present. This was confirmed as reactive lymphadenitis on FNAC.

In the present study, we used qualitative criteria proposed by Lenghel LM et al., which used a seven-pattern colour scoring system which was based on the percentage and distribution of area with high elasticity in the cervical lymphnodes [Table/Fig-3,6] [11].



[Table/Fig-6]: Ultrasound elastography images of Level II oval cervical LN with pattern VII that is blue area covers the whole nodules and extends into the soft tissues. This was confirmed as squamous cell carcinoma on FNAC.

Bhatia KSS et al., in 2010 proposed another classification, which had Elastography Score (ES) from 1 (entirely soft) to 4 (completely stiff), with ES >2 as a cut-off for malignancy [24]. Alam F et al., used a 5-point elastography scale and Ishibashi N et al., in 2012 further modified the 5-point scale of Alam F et al., where metastatic cervical lymphnodes with central necrosis was considered as ES 5 instead of ES 4. This classification system is similar to the one used in the present study and concluded that the combination of highly specific Ultrasound Elastography (USE) with highly sensitive conventional B-mode USG was better than individual evaluation [12,25].

Our results agree with results reported by Ishibashi N et al., and with the results of Bhatia KSS et al., and Alam F et al., [Table/Fig-7] [12,24,25].

Authors	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy
Alam F et al., [12]	83%	100%	-	-	89%
Ishibashi N et al., [25]	83.8%	82.5%	78.8%	86.8%	83.1%
Bhatia KSS et al., [24]	62.2%	83.8%	-	-	73%
Present study	95.2%	75.0%	95.2%	75.0 %	92%

[Table/Fig-7]: Diagnostic accuracy values for ultrasound elastography in various studies and present studies [12,24,25].

Sonoelastography would thus be an important tool in precluding the unnecessary FNAC and accurately differentiating malignant/metastatic from benign cervical lymphnodes which would be useful in future to radiologist for everyday use. High specificity is the greatest advantage of elastography, as reported in study by Lyshchik A et al., [19]. So, the elastography can reduce the number of unnecessary biopsy in the diagnosis of metastatic cervical LN.

Limitation(s)

Sonoelastography using free hand compression is dependent on the compression technique, and excessive compression can alter tissue stiffness. The sample size was small, and only enlarged lymphnodes were included. Sonoelastography is not useful for calcified lymphnodes and those with cystic degeneration A single expert radiologist performed all the elastograms and no intraobserver variability was studied.

CONCLUSION(S)

Sonoelastography is an effective supplement with conventional grayscale and doppler ultrasound and the combination is promising non invasive imaging technique that can aid in the differentiation of benign and metastatic cervical lymphnodes compared to invasive methods.

In the present study, the diagnostic accuracy of sonoelastography was higher than gray scale ultrasound and colour doppler to differentiate benign from malignant cervical LN sensitivity and specificity of elastography can be increased especially if combined with gray scale and doppler ultrasound which can reduce unnecessary biopsy in the diagnosis of cervical LN. With short examination time, real-time display, immediate interpretation and limited cost sonoelastography can be highly useful technique.

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