Role of Acoustic Radiation Impulse Ultrasound Elastography in the Assessment of Cervical Lymphadenopathy

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Abstract

Introduction: Cervical lymphadenopathy is a common clinical problem across all age groups. The main cause varies to differentiate reactive (infective) from malignant etiology. Cervical lymphadenopathy poses diagnostic challenge which is important for therapeutic and prognostic significance. Ultrasound elastography is a new imaging technique that can rapidly and noninvasively help to differentiate the benign and malignant lymphadenopathy to a great extent.. The main advantage of this method is its operator independence, reproducibility , high spatial resolution and quantitative assessment of the tissue elasticity without any tissue compression. It is a sensitive method for differentiation of cervical lymphadenopathy.

Aim: The current study was conducted to evaluate the role of ARFI USG elastography in characterization and differentiation of benign from malignant cervical lymphadenopathy.

Material and methods : The cross sectional study was conducted in the department of Radiodiagnosis, Hamdard institute of medical science and research, New Delhi over a period of one year from April 2021 to May 2022.presenting with cervical lymphadenopathy and USG elastography was done. The data gathered included grey scale, color Doppler and ARFI features of enlarged cervical lymph nodes. ARFI measurements of benign and malignant lymph nodes were compared using the student t test. For all tests, a p- value of less than 0.05 was considered to indicate a statistically significant difference.

Result: The mean shear velocity of benign lymph nodes was significantly lower than that of malignant lymph nodes. Shear wave velocity (SWVs) value greater than 2.8m/sec was indicative of malignancy. Median shear wave velocity ranged between 1.7 to 8.4 in malignant lymph nodes and 1.0 to 2.8 in benign lymph nodes.

Conclusion: ARFI technique helps in better differentiation of benign from malignant lymph nodes in conjunction with conventional sonography. The sensitivity and specificity of differentiation between benign and malignant lymph nodes using elastography was 79.1% and 100% respectively

Key words : Lymph nodes, benign, malignant, Shear wave velocity (SWV), tubercular lymphadenitis, lymphoma .

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Introduction

Cervical lymphadenopathy is a common clinical problem across all age groups. There are many causes of lymph node enlargement, cause may vary from infective, reactive, neoplastic, drug induced and many more. In pediatric age group it is mostly reactive (infective**) [1]** whereas in adults, the most common cause for cervical

lymphadenopathy is metastatic**[2].** Cervical lymphadenopathy often appears as the first clinical sign to an underlying malignancy or infection of head and neck. Cervical lymphadenopathy poses a diagnostic challenge to reliably differentiate between benign and malignant lymphadenopathy, which has both therapeutic and prognostic significance. Histopathological and cytological evaluation are the only reliable and gold standard investigations to differentiate benign from malignant lesions, but has invasive nature, causes patient discomfort, adding to the cost. Hence, there was a need for presence of additional reliable methods to complement the existing diagnostic procedures. Gray scale ultrasonography is highly sensitive in detecting the cervical lymph nodes but its specificity in differentiating benign and malignant lymphadenopathy is relatively low **[3].** Benign reactive and tubercular lymph nodes have well defined margins , homogenous echopattern , maintained echogenic fatty hilum and less short axis to long axis diameter ratioand on color Doppler shows central vascularity whereas malignant lymph nodes usually have irregular border , heterogeneous echopattern , loss of fatty hilum and relatively increased short axis to long axis diameter ratio with peripheral or mixed pattern on Doppler**[4,5,6]**

Ultrasound elastography is a new, rapid and noninvasive imaging technique that measures differences in tissue stiffness in various biological tissues**. [7]**

This technique allows for a qualitative and quantitative assessment of the lesions. There are two types of elastography -strain elastography and shear wave elastography. The first is strain elastography imaging, also called free hand real time elastography. It is used to depict relative tissue stiffness or displacement induced by deformation of the tissue. Manual compression is applied by the ultrasound probe and a dedicated software is then used to estimate tissue deformation. Harder area shows less displacement and display dark strain images whereas softer tissues shows more displacement and brighter strain images in response to the same force. **[8]**

The second is shear wave technique including Acoustic radiation force impulse imaging (ARFI) is a technique that can be used to perform both quantitative and qualitative measurements of tissue stiffness and is independent of the amount of tissue compression. ARFI provides true quantitative estimation of tissue stiffness and does not require external compression.**[9,10]**

In this imaging method, a specially designed transducer is used, which produces focused acoustic impulses of high intensity, called push pulses, which are transmitted to the tissue and causing shear wave formation within the region of interest. The velocities of the induced shear waves are tracked by the ARFI imaging using ultrasound correlation methods. The velocity of shear wave propagation is proportional to the square root of the tissue elasticity, based on Young's modulus formula: $E = 3 \rho c2$ where E is stiffness(kPa), c is the shear wave velocity (SWV) (m/s), and ρ is the density (kg/m3) of the tissue. The density of the soft tissue is almost same as the density of water (1000 kg/m3). Thus, by measuring SWV, tissue stiffness is measured quantitatively.[**11].** The main advantage of this method is its operator independence, reproducibility, high spatial resolution and quantitative assessment of the tissue elasticity without any tissue compression **[12]**

Aim and objective

To evaluate the diagnostic role of USG elastography (ARFI) Imaging in characterization and differentiation of benign from malignant cervical lymphadenopathy.

To compare these findings with cyto-histological diagnosis.

Material and methods

This cross sectional study was conducted in the department of Radiodiagnosis, Hamdard institute of medical science and research, New Delhi over a period of one year from April 2021 to May 2022.

Study design: Observational study.

Selection of cases: Eighty patients presenting with clinically enlarged lymph nodes were taken up for the study.

Inclusion criteria: Patients with clinical diagnosis of cervical lymphadenopathy

Exclusion criteria: Patients with suppurative lymphadenopathy

Consent: The procedure was explained to the patients and informed consent in vernacular language was obtained in every case.

Methodology: The clinical history and findings of physical examination were noted in all patients. Each patient was evaluated by grey scale ultrasonography and elastography on ultrasound machine Samsung HS 70 A. Biopsy or FNAC comparison was done for all the lesions. The patients were examined in supine position. Grey and color Doppler findings of lymph nodes included were size (in cms), location/side, short axis diameter, short to long axis diameter ratio, margins, echotexture, calcification, fatty hilum, vascularity on Doppler ultrasound.

High resolution grey scale USG was followed by elastography examination in all patients (largest lymph node was chosen in patients having multiple enlarged lymph nodes) on ACUSON S2000 ultrasound system (Siemens Medical Solutions). The ARFI technique using VTQ (virtual touch quantification) was used to provide quantitative stiffness analysis. The transducer was gently placed in region of interest .After VTQ, in breath hold position, the region of interest (ROI) was obtained which is rectangle with dimension of 0.5cm xo.6cm and maximum depth of 4.0cm. ROI was all included into the enlarged lymph node. The calculation of the shear wave velocity (SWVs) was expressed in m/sec. Five SWVs were obtained from the lesions. The median of SWVs value of the lesions was estimated. The limits for the measurement of the VTQ values for the ACUSON S2000 ultrasound system were in the range of 0.5 to 0.8 m/s. values outside these limits were displayed as X.XXm/s(as per manufacturer) . The results was recorded as 0 when the VTI image appeared bright and 8.4m/s when VTI image appeared dark. Thus, in our study, X.XX measured in the solid lesion was replaced by a value of 8.4m/s. The observations on high resolution grey scale ultrasonography and ARFI measurements were correlated with histopathological diagnosis on FNAC or biopsy of nodes.

Statistical Analysis

Statistical analysis used MedCalc Statistical Software version 13.0.2 (MedCalc Softwarebvba,Ostend,Belgium,http://www.medcalc.org;2014).The ARFI measurements in benign and malignant enlarged lymph nodes were compared using the student t test and receiver operating characteristic curve was used to arrive at the Youden index as well as to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. For all tests a p-value of less than 0.05 was considered to indicate a statistically significant difference.

Result

A total of 80 patients with clinical diagnosis of cervical lymphadenopathy were included in the study. High resolution ultrasonography and elastography using ARFI imaging was done in all cases. Pathological correlation was done in all cases. Of total 80 patients, 56 (70%)were males and 24(30%) were females.(Table 1) 41 lymph nodes were benign while 39 were malignant on FNAC /biopsy correlation (Table 1). Among benign cervical lymph nodes, tubercular was the most common (21/41), while squamous cell carcinoma accounted for majority (18/39) of malignant lymph nodes.

The youngest patient was of 18 years of age and old one was 67 years, mean age was 34.5years. All patients with benign lymphadenopathy were less than 40 years of age (100%). The maximum number of patients of tubercular lymphadenitis (75.6%), were in the age group of 18-30 years 33% (13/39) of patients with malignant cervical lymph nodes were more than 40 years (Table 2). Both benign (29/41) and malignant (27/39) lymph nodes were prevalent in males.

Most of the malignant lymph nodes showed heterogeneous echo pattern on ultrasound. Majority of the malignant lymph nodes showed short axis diameter /long axis diameter ratio >0.5 (35 out of 39 lymph nodes 89.7%). In 37 out of 39 (94.6%) of malignant lymph nodes, fatty hilum was not seen.43.5 % of lymph nodes shows ill-defined border(17 out of 39 lymph nodes).7 out of 39 malignant (18%) showed calcifications in it. These were squamous cell carcinoma, papillary carcinoma of thyroid and Hodgkin's lymphomas in FNAC. (66.3%) of the malignant lymph nodes (26 out of 39) showed presence of both peripheral and mixed vascular pattern. (Table 3)

Most of the benign lymph nodes showed homogenous echo pattern on ultrasound. Majority of the benign lymph nodes showed short axis diameter /long axis diameter ration < 0.5 (38 out of 41 lymph nodes). In 32 out of 41 (78%) of benign lymph nodes , fatty hilum was seen. 100 % of benign lymph nodes shows well defined regular border (41 out of 41 lymph nodes).4 out of 41 benign (9.7%) showed calcifications in it. This was tubercular lymphadenitis on FNAC.(63.3%) of the benign lymph nodes (26 out of 41) showed presence of both central/ hilar and peripheral vascular pattern. 24% (10 out of 41) shows central /hilar vascularity.(table 4)

Median shear wave velocity ranged between 1.7 to 8.4 in malignant lymph nodes. Majority of malignant lymph nodes demonstrated a shear wave velocity values less than 8.4m/sec. 7 out of 39 malignant lymph nodes (20.8%) demonstrated shear wave velocity less than 3m/sec (Table 5). On FNAC /histopathological analysis, these lymph nodes were found to be Hodgkin lymphoma. The mean SWV value (in m/s) in Hodgkin's lymphoma (2.04m/sec) was lower compared to the value in carcinoma (8.15m/s).

Median shear wave velocity ranged between 1.0 to 2.8 in benign lymph nodes. All benign lymph nodes (41/41) demonstrated a shear wave velocity values less than 3m/sec(Table 6). A classical statistical difference was found between benign and malignant lymph nodes ($p<0.0001$) respectively(Table 7).

Discussion

A total of 80 cervical lymph nodes were evaluated of which 39 (48%) were malignant whereas the remaining 41 lymph nodes (52%) were benign. Amongst the malignant lymph nodes, the squamous cell carcinoma was the most common (21%) whereas tubercular lymphadenitis accounted for the majority (27%) of the benign lymph nodes.

The youngest patients in our study was 18 years old and the oldest 67 years, the mean age was 34.5 years. All the patients with benign lymph nodes were less than 40 years (100%) while 33 % of the patients with malignant lymph nodes were more than 40 years old. Our study included 56 males and 24 females.

The sonographic characteristic of all the lymph nodes were evaluated with high resolution grey scale ultrasonography and color Doppler imaging. On ultrasound 35 out of 39 malignant lymph nodes (89.7%) were heterogeneous in echo pattern compared to the benign cervical lymph nodes. 89.7% of the malignant lymph nodes showed short axis /long axis diameter ratio>0.5(35 out of 39 lymph nodes). Majority (37/39) of malignant lymph nodes(94.6%) showed absent fatty hilum.43.5% (17/39) of the malignant lymph nodes showed ill-defined margins on ultrasound .66.3% of the malignant lymph nodes (26/39) showed presence of both peripheral and mixed pattern on Doppler USG.

Our findings were in concordance with **Dayanand SM et al** [13] who demonstrated most malignant lymph nodes have heterogeneous echo pattern.

Dangore SBet al [14] observed central flow pattern in benign and peripheral pattern in malignant lymph nodes

Khanna R et al [15] demonstrated that absent hilum was found in 83 % of metastatic nodes with higher specificity and sensitivity.

.**Norling R et al** [16]concluded statically significant proportion of malignant lymph nodes had heterogeneous pattern, ill-defined border, spherical shape and peripheral vascularity on color Doppler. The SWVs of the malignant lymph nodes in our study were represented by a range of values from 1.7-8.8m/s and SWVs of the benign lymph nodes ranged from 1.0-2.8m/s. the cut off value for malignancy was 2.8m/s. lymph nodes having SWVs greater than 2.8m/s were considered malignant and less than or equal to 2.8m/s were benign. Our findings were in agreement with those given by **Choi YI et al**[17] where SWVs values for malignant lymph nodes were higher than benign nodes. In our study we found that SWVs values were significantly higher in malignant lymph nodes as compared to benign lymph nodes.

Fujiwara T et al [20] also found that shear wave velocity of reactive lymph nodes was 1.52+/-0.48, and that of metastatic /malignant ++lymph nodes was 2.46+/-0.75m/s.

Cui XW et al [21],also demonstrated that shear wave elastography of malignant nodes were homogenously stiffer than benign nodes.

Therefore, ARFI is found to be superior diagnostic performance over conventional USG and color Doppler in characterization and differentiation of benign and malignant lymph does. **Sudhir R, Mohan M V TK et al** [10].

ARFI is a good, non-invasive and cost effective elastography technique that provides quantitative information about the tissue stiffness of cervical lymph nodes in an efficient and reliable manner.

Conclusion

USG elastography (ARFI) is promising new technique that noninvasively and objectively complement the ultrasonography in characterization and differentiation of benign and malignant cervical lymph nodes.

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Tables

Table 1: Age and sex distribution of patients with cervical lymphadenopathy [n=80]

Age group (years)	Male(n=56)	Female (n=24)	Total
≤ 30	20	10	30
31-40	7	5	12
41-50	10	2	12
>50	19	7	26

Table 2: Distribution of cases according to final diagnosis [n=80]

Etiology		No. of lymph nodes	Percentage
Benign		41	52
	Tubercular lymphadenitis	21	27
	Reactive lymphoid hyperplasia	20	25
Malignant		39	48
	Squamous cell carcinoma	18	21
	Hodgkins lymphoma	8	10
	Small cell carcinoma	6	7
	Poorly differentiated carcinoma	5	6
	Papillary carcinoma of thyroid	1	2
	Malignant neurogenic tumor	1	2
Total		80	100

Table 3: Features of malignant cervical lymphadenopathy on high resolution sonography		
Parameter		**Number of lymphnodes (n=39) 48.7%**
Location	Right side Left side	24(62.2%) 15(15.1%)
Echotexture	Homogenous Heterogeneous	5(12.8%) 34(87%)
Short axis/long axis ratio	<0.5 >0.5	4(10.2%) 35(89.7%)
Fatty hilum	Present Absent	2(0.51%) 37(94.6%)
Margins	Well defined Ill defined	 17(43.5%)
Calcification	Present Absent	7(18%) 32(82.0%)
Vascularity pattern	Central Peripheral Mixed(central peripheral)	4(10.2%) 9 26(66%)

Table 4: Features of benign cervical lymphadenopathy on high resolution sonography		
Parameter		**No. of lymph nodes [n=41]**
Location	Right side Left side	18 (56%) 23(44%)
Echotexture	Homogenous Heterogeneous	36(88%) 5(12%)
Short axis/long axis ratio	<0.5 >0.5	38(92%) 3(7.3%)
Fatty hilum	Present Absent	32(78%) 9(21.9%)
Margins	Well defined Ill defined	41(100%) 0
Calcification	Present Absent	4(9.7%) 37(90.3)
Vascularity pattern	Central Peripheral Mixed(central peripheral)	10(24.3%) 5(12.2%) 26(63.3%)

Table 5: Median shear wave velocity values in malignant cervical lymph nodes					
Malignant lymph nodes	**Number**	**Mean shear wave velocity values (in m/s)**			
		<3	**3-6**	**>6**	**Mean±SD**
Squamous cell carcinoma	18	0	3	15	7.982±1.367
Hodgkins lymphoma	8	7	1	0	2.040±0.270
Small cell carcinoma	6	0	0	6	8.40±0
Poorly differentiated carcinoma	5	0	1	4	8.40±0.234
Papillary carcinoma of thyroid	1	0	0	1	8.40±0
Malignant neurogenic tumor	1	0	0	1	8.40±0
Total	39	7	5	27	6.888±2.706

The difference of Mean shear velocity of Hodgkin's Lymphoma is statistically different from rest of the carcinomas with p value of <0.0001.

Table 6: Median shear wave velocity values in benign cervical lymph nodes					
Benign lymph nodes	**Number**	**Median shear wave velocity in m/s**			
		<3	3-6	>6	Mean ±SD
Tubercular lymphadenitis	21	21	0	0	2.057±0.460
Reactive lymphoid hyperplasia	20	20	0	0	2.025±0.441
Total	41	41	0	0	2.042±0.442

Table 7: Comparison of median shear wave velocity values in benign and malignant cervical lymph nodes		
Shear wave velocity (m/s)	**Benign lymph nodes**	**Malignant lymph nodes**
Mean±SD	2.042±0.442	6.888±2.706
Median	2.2	8.4
Range	1.0-2.8	1.7-8.4

A classical statistical difference was found between benign and malignant lymph nodes (p<0.0001) respectively.

Table 8: Sensitivity, specificity, positive predictive value and negative predictive value for malignancy for short axis/long axis ratio>0.5 in cervical lymph nodes

Criteria	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Positive likelihood ratio (95% CI)
Heterogenous echopattern	87.50 (67.6-97.3)	88.46 (69.8-97.6)	87.50 (67.6-97.3)	88.46 (69.8-97.6)	7.58 (2.6-22.2)
Peripheral and mixed vascular pattern	95.83 (78.8-99.9)	69.23 (48.2-85.7)	74.2 (55.4-88.1)	94.7 (74.0-99.9)	3.11 (1.7-5.6)
Ill-defined margins	41.67 (22.1-63.4)	100.0 (86.8-100)	100.0 (69.2-100)	65.0 (48.3-79.4)	8.62 (2.8-24.8)
Absent fatty hilum	91.67 (73.0-99.0)	76.92 (56.4-91.7)	78.6 (59.0-91.7)	90.9 (70.8-98.9)	3.97 (1.9-8.1)
Short axis to long axis ratio>0.5	91.67 (73.0-99.0)	76.92 (56.4-91.0)	78.6 (59.0-91.7)	90.0 (70.8-98.9)	3.97 (1.9-8.1)

Table 9: Diagnostic performance of Acoustic Radiation Force Impulse imaging using shear wave velocity values (based on median shear wave velocity)

Parameter	Result (95% confidence interval)
Area under ROC curve	0.892(0.772-0.962)
Cut –off value (in m/s)	>2.8
Sensitivity (%)	79.17(57.8-92.9)
Specificity (%)	100.00(86.8-100)
Positive predictive value (%)	100(82.4-100.0)
Negative predictive value(%)	83.9(66.3-94.5)
Accuracy	89.9
Youden's index	0.791

Images

Figure 1: on ARFI, the lymph node shows shear wave velocity of 1.69m/s. on cytopathology, there are mixed population of lymphoid cells suggestive of reactive lymphoid hyperplasia

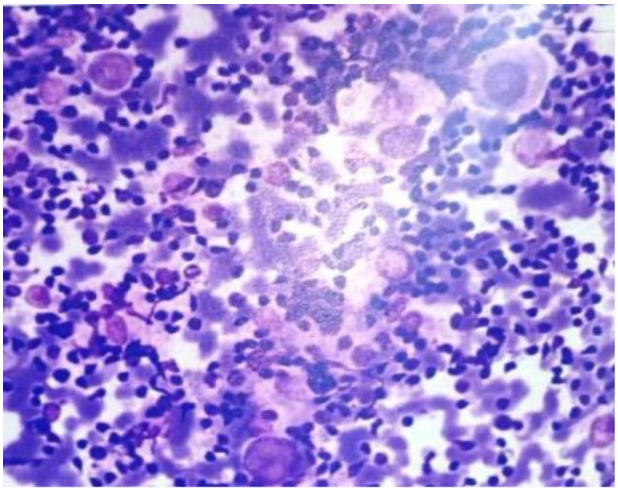
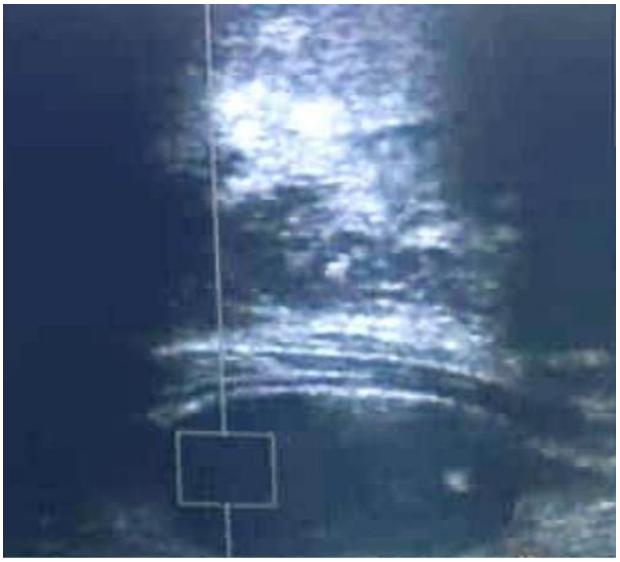
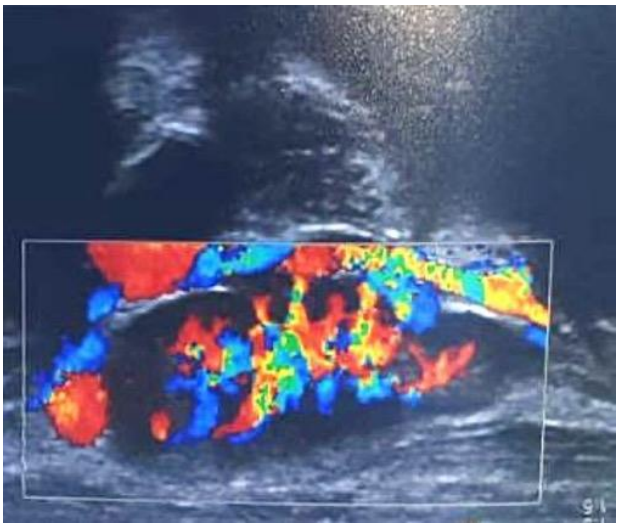


Fig. 2. : Grey scale shows well defined oval homogenously hypoechoic enlarged lymph node with maintained hilum and short/long axis ratio less than 0.5. On color Doppler central hilar vascularity is present





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