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Original Article

Radiology Section

Role of Sonography and Sonoelastography in Characterisation of Cervical Lymphadenopathy with Pathological Association: A Cohort Study

SUMIT KAUSHIK[1], MADHU SHARMA[2], LAL BAHADUR SHARMA[3], ANKUR MALHOTRA[4], DEEPTI ARORA[5], ANSHUL JAIN[6]

ABSTRACT

Introduction: Identification of the nature of lymph nodes is one of the most important parameters for diagnosis in any oncological setting. The lymph nodes help in staging and this directly affects the prognostic outcome and treatment decision. Ultrasound is the preferred imaging method for distinguishing between benign and malignant superficial lymph nodes given ease of availability and its low cost. However, there is no reliable and definitive sonographic criterion in ultrasound to categorise lymph nodes as benign or malignant.

Aim: To evaluate the role of sonography and sonoelastography in characterisation of cervical lymphadenopathy and to associate the imaging findings with cytopathology.

Materials and Methods: This was a prospective cohort study, conducted over a period of one year in Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India, constituting a total of 60 patients with enlarged cervical lymph nodes and evaluated on B-mode ultrasound and elastography in the present study. The ultrasonography was performed using either Acuson S3000 ultrasound system (Siemens Medical Solutions, Mountain View, CA) with a 4 to 9 MHz linear transducer for conventional sonography and Acoustic Radiation Force Impulse (ARFI) imaging. Results of radiological findings were tabulated, evaluated and collated with pathological findings.

Results: ARFI imaging displayed a sensitivity and specificity of 80% and 97.5% respectively with a Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of 94.1% and 90.7% respectively in distinguishing malignant from benign cervical lymphadenopathy with the diagnostic accuracy being 91.67%. Using Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) of 0.925, a cut-off value for shear wave velocity of 2.98 m/s was obtained.

Conclusion: ARFI is a novel technique which can be used to characterise the nature of cervical lymph nodes. Present study demonstrated high diagnostic accuracy (91.67%) in comparison with histopathological findings, ARFI elastography may help in distinction of benign from malignant nodes in adjunct to the gray scale.

Keywords: Lymph nodes, Lymphoma, Metastases, Tuberculous nodes, Ultrasound

INTRODUCTION

Enlarged cervical lymph nodes is a common finding in routine clinical examination, especially head and neck diseases, many-a-times it is the only manifestation. There are numerous causes of cervical lymphadenopathy such as infective (bacterial, viral, protozoal), autoimmune or malignant to list a few. Therefore, identification of nature of lymph nodes is fundamental for diagnosis, especially in any oncological setting as this shall have bearing on the staging and hence, affects the prognostic outcome and treatment decision directly. Currently, the cytology and histopathological assessment is considered to be the standard for differentiation for enlarged cervical lymph nodes into benign and malignant. However, because of invasiveness of the procedure and to minimise patient apprehension, there is need for a non invasive method which could help in reduction of number of avoidable Fine Needle Aspiration Cytology (FNAC) sampling or biopsies [1,2].

Gray scale ultrasound is emerging as the preferred imaging method for distinction between benign and malignant superficial lymph nodes. However, overlapping of features exist and still there is no single definitive criterion to characterise lymph nodes as malignant or benign reliably. Sonoelastography is a novel technique that works on the principle that different kinds of biological tissues have different stiffness and can be measured through it. Strain and shear wave are two varieties of ultrasound elastography [3-5].

In strain elastography mode of compression is operator dependent. Shear wave elasticity, on the other hand, utilises ARFI which instead of applying manual compression, uses transducer induced "pushing pulse" to apply external compression on tissues in the Region Of Interest (ROI) and subsequent serial diagnostic intensity pulses to track tissue micro-displacements. Therefore, it reduces operator dependency and improves reproducibility [6].

Various studies by different authors have been carried out in this regard. For instance, in a study by Rubaltelli L et al., they found that sonoelastography demonstrated a diagnostic accuracy of 77% on comparison with the results of pathological examination [7]. Even still, this is an upcoming diagnostic technique on which several studies are being done. However, more research is imperative. Hence, present study was conducted to assess the role of sonoelastography in characterisation of enlarged cervical lymph nodes with histopathological association.

MATERIALS AND METHODS

This study was a prospective cohort study, was conducted over a period of one year (December 2018-December 2019) after obtaining Institutional Ethical Committee (IEC) (Ethical Certificate Ref. TMMC&RC/IEC/18-19/075) Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India. A total of 60 patients with enlarged cervical lymph nodes who reported during the study duration and fulfilled the eligibility criteria were included.

Inclusion criteria: Patients with enlarged cervical lymph nodes of all age groups were included.

Exclusion criteria: Pathologically proven cases, lymph nodes of <10 mm in diameter, patient on active treatment, post-chemotherapy or post-radiotherapy lymph nodes were excluded.

Methodology

Each patient was evaluated by gray scale or B-mode sonography and later elastographic (ARFI) assessment was done with the help of Siemens Acuson S2000 ultrasound machine using linear 9L4 transducer. Later, final diagnosis correlation was done by histopathology (FNAC) for every lesion.

B-mode US: All the lymph nodes were be evaluated and recorded for the following B-mode characteristics: -

1. Size
2. Side and Level in the neck
3. Short axis and long axis diameter ratio
4. Margins: Well defined or ill defined
5. Echo pattern: Homogeneous or Heterogeneous; Echogenicity- hypo/iso-hyperechoic
6. Presence or absence of calcification
7. Vascular pattern: Mixed (Both central and peripheral) or central or peripheral
8. Presence or absence of fatty hilum.

Sonoelastography: Ultrasound probe was applied vertically to the skin with adequate coupling gel such that a minimal pressure was imparted making a complete contact with the skin over suspected lesion. The patient was then asked to hold the breath so as to minimise any kind of movement. Then, Virtual Touch Tissue Quantification (VTQ) was turned on which showed a box of 0.5×0.6 cm on the screen which was the ROI. The ROI was placed completely within the lymph node. Shear Wave Velocity (SWV) within the ROI was measured which was expressed in metres/second (m/s). There were a few instances where the machine could not display SWV in numericals but rather as "X.XX m/s" as the range provided by the manufacturer is between 0.5 m/s and 8.4 m/s. For these lesions, values of 8.4 m/s were recorded if Virtual Touch Tissue Imaging (VTI) images appeared dark, 0 m/s if the lesion appeared bright. A total of five values for each lesion were taken. The findings of B-mode sonography and elastography were collated with histopathological diagnosis.

STATISTICAL ANALYSIS

Categorical variables were presented in the form of number and percentages while continuous variables were presented as mean±Standard Deviation (SD) and median values. The authors applied following statistical tests for results:

1. Sensitivity, specificity, PPV and NPV was assessed of ultrasound and doppler characteristics and Mean Shear Wave Velocity (MSV) values (in m/s) for predicting malignancy.
2. The association of qualitative variables was analysed using Fisher's-Exact test.

ROC curve was used to find out cut-off point of MSV values (in m/s) for predicting malignancy. Statistical Package for Social Sciences (SPSS) software ver. 21.0 was utilised for the final analysis and $p<0.05$ was considered as significant.

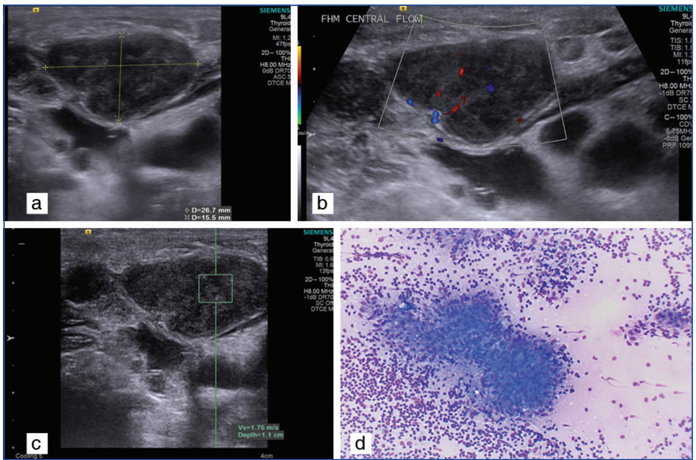
RESULTS

In the present study, out of the 60 lymph nodes that were studied 40 (66.7%) were benign while 20 (33.3%) were classified as malignant on histopathology. The most common aetiology among the malignant lymph nodes was metastatic squamous cell carcinoma (55%) followed by Hodgkin's lymphoma (15%). Amongst benign aetiology, Tubercular Lymphadenitis were reported to be the most common (47.50%) followed by reactive lymphadenopathy (32.50%).

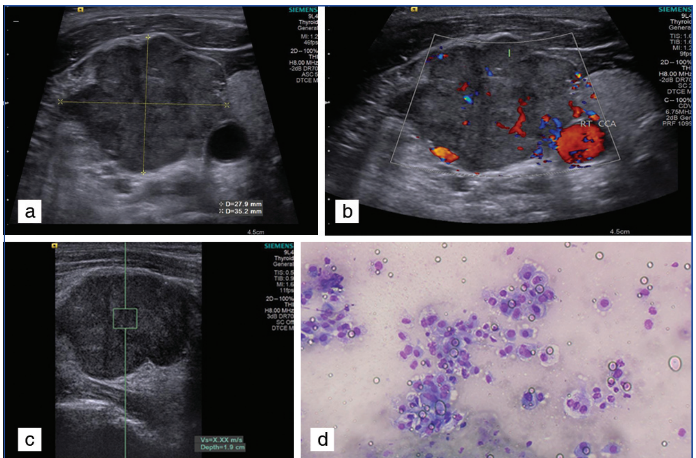
All the patients diagnosed with granulomatous lymphadenitis showed a MSV value <3, 92.31% for reactive lymphadenitis and 100% for tubercular lymphadenitis [Table/Fig-1,2]. The MSV in adenocarcinoma [Table/Fig-3], poorly differentiated metastatic carcinoma and squamous cell carcinoma showed higher MSV values (>6 m/s) [Table/Fig-4]. However, Hodgkin's lymphoma [Table/Fig-5] and non Hodgkin's lymphoma showed lower MSV values (<3 m/s) [Table/Fig-6].

MSV (in m/s)	Granulomatous lymphadenitis (n=8)	Reactive lymphadenitis (n=13)	Tubercular lymphadenitis (n=19)	Total
<3	8 (100%)	12 (92.31%)	19 (100%)	39 (97.50%)
3-6	0	1 (7.69%)	0	1 (2.50%)
Mean±SD	2.37±0.65	2.14±0.48	2.5±0.43	2.36±0.51
Median (IQR)	2.54 (2.042-2.95)	2 (1.905-2.370)	2.67 (2.18-2.865)	2.4 (1.968-2.815)
Range	1.27-2.98	1.5-3.47	1.74-2.98	1.27-3.47

[Table/Fig-1]: Distribution of median shear wave velocity values (in m/s) in benign patients.
SD: Standard deviation; IQR: Interquartile range

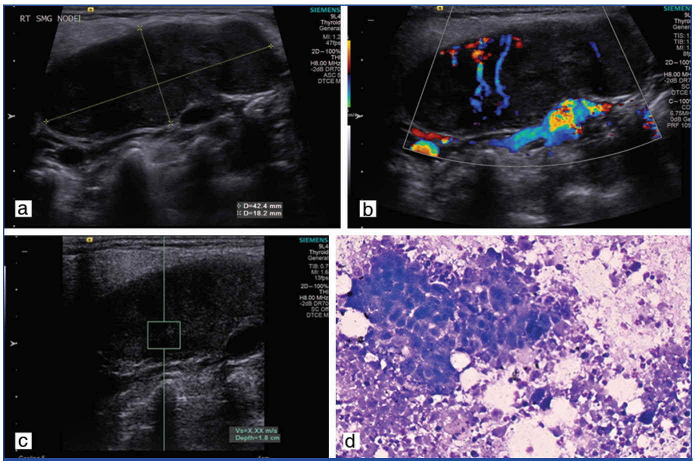


[Table/Fig-2]: a) and b): Gray scale ultrasound shows a well-defined, oval hypoechoic enlarged lymph node with central vascularity pattern on colour doppler imaging; c) On ARFI imaging, lymph node shows a shear wave velocity of 1.75m/s; d) On cytopathology, epithelioid granulomas in a caseous necrotic background were seen suggestive of tubercular lymphadenitis. May Grunwald-Giemsa (MGG) stain (Magnification 100X).

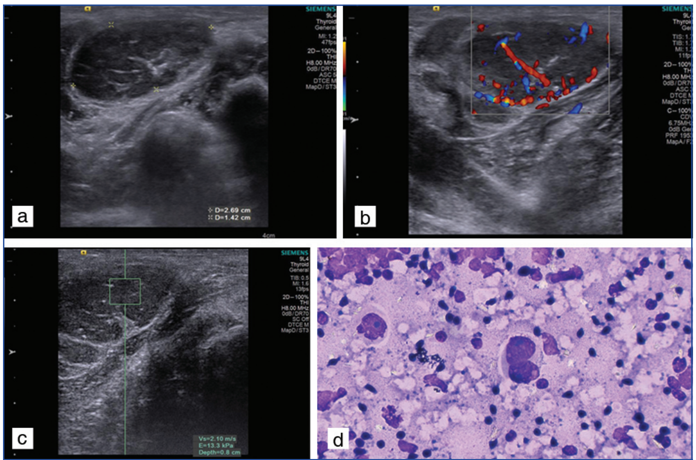


[Table/Fig-3]: a) and b) A well-defined heterogeneously isoechoic enlarged lymph node. It shows absent fatty hilum and short to long axis ratio of 0.5 on gray scale ultrasound. On colour doppler, mixed vascularity (both central and peripheral) pattern was seen; c) Using ARFI imaging, the lymph node showed a SWV of X.XX m/s (>8.4 m/s); d) Cytopathology showed clusters of tumour cells arranged in acinar pattern suggesting it to be a metastatic adenocarcinoma. May Grunwald-Giemsa (MGG) stain (Magnification 400X).

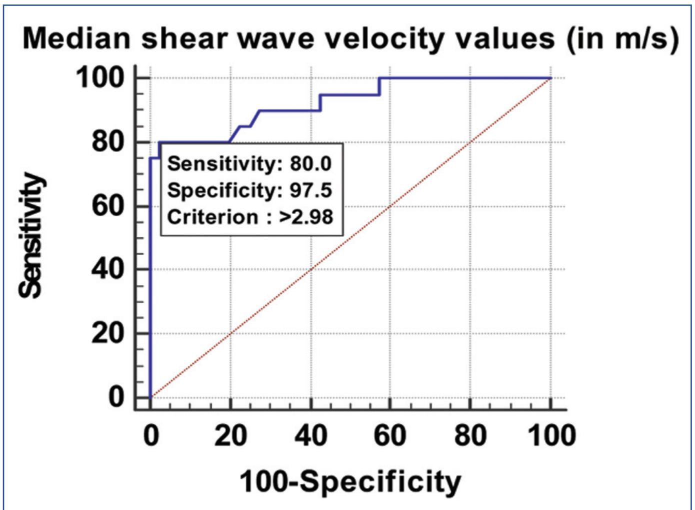
Majority of the patients with malignant aetiology displayed higher MSV values (in m/s) >2.98 as compared to those with benign aetiology ≤2.98 [Table/Fig-7]. Interpretation of the area under the ROC curve showed that the performance of MSV values (in m/s) (AUC 0.925; 95% CI: 0.827 to 0.977) was outstanding. It was observed that among patients who had final diagnosis of benign, 97.50% of patients had MSV (in m/s) ≤2.98 [Table/Fig-8].



[Table/Fig-4]: a) and b) Gray scale ultrasound shows a well-defined, heterogeneously hypoechoic enlarged lymph node with absence of fatty hilum is seen. On colour doppler imaging, it demonstrated peripheral as well as central vascularity (mixed pattern); c) Using ARFI imaging, the lymph node showed a SWV of X.XX m/s (>8.4 m/s); d) Cytopathology revealed a cluster of pleomorphic tumour cells and tumour diathesis in the background suggestive of metastatic squamous cell carcinoma. May Grunwald-Giemsa (MGG) stain (Magnification 400X).



[Table/Fig-5]: a) and b) Gray scale sonography evaluation of the lymph nodes show well-defined, heterogeneously hypoechoic, enlarged lymph nodes with absent fatty hilum and a short to long axis ratio of >0.5; c) ARFI imaging demonstrated the lymph node to have a SWV of 2.10 m/s); c) Cytopathology revealed multiple typical and atypical Reed Sternberg cells with a lymphocytic background suggestive of Hodgkin's lymphoma. May Grunwald-Giemsa (MGG) stain (Magnification 400X).



Malignant	MSV values (in m/s)
Area under the ROC curve (AUC)	0.925
Standard Error	0.039
95% Confidence interval	0.827 to 0.977
p-value	<0.0001
Cut-off	>2.98
Sensitivity (95% CI)	80% (56.3 - 94.3%)
Specificity (95% CI)	97.5% (86.8 - 99.9%)
PPV (95% CI)	94.1% (71.3 - 99.9%)
NPV (95% CI)	90.7% (77.9 - 97.4%)
Diagnostic accuracy	91.67%

[Table/Fig-8]: Receiver operating characteristic curve graph of median shear wave velocity values (in m/s) for predicting malignancy.

MSV values (in m/s)	Adenocarcinoma (n=2)	Hodgkin's lymphoma (n=3)	Non Hodgkin's lymphoma (n=2)	Poorly differentiated metastatic carcinoma (n=2)	Squamous cell carcinoma (n=11)	Total
<3	0	2 (66.67%)	2 (100%)	0	0	4 (20%)
3-6	0	1 (33.33%)	0	0	0	1 (5%)
>6	2 (100%)	0 (0%)	0	2 (100%)	11 (100%)	15 (75%)
Mean±SD	8.4±0	2.8±0.46	2.64±0.23	8.4±0	8.4±0	6.98±2.52
Median (IQR)	8.4 (8.4-8.4)	2.87 (2.585-3.045)	2.64 (2.56-2.72)	8.4 (8.4-8.4)	8.4 (8.4-8.4)	8.4 (7.105-8.4)
Range	8.4-8.4	2.3-3.22	2.48-2.8	8.4-8.4	8.4-8.4	2.3-8.4

[Table/Fig-6]: Distribution of median shear wave velocity values (in m/s) in malignant patients.

MSV values (in m/s)	Benign (n=40)	Malignant (n=20)	Total	p-value
≤2.98	39 (97.50%)	4 (20%)	43 (71.67%)	<0.0001
>2.98	1 (2.50%)	16 (80%)	17 (28.33%)	
Total	40 (100%)	20 (100%)	60 (100%)	

[Table/Fig-7]: Association of median shear wave velocity values (in m/s) with final diagnosis.
Fisher's-Exact test

Discriminatory power of MSV values (in m/s) (AUC 0.925; 95% CI: 0.827 to 0.977) was outstanding. Discriminatory power of sonographic criteria such heterogenous, absent hilum, peripheral and mixed vascular pattern and MSV (in m/s) (AUC 0.89; 95% CI: 0.78 to 0.95) was excellent and discriminatory power of short-axis to long-axis ratio (>0.5) (AUC 0.76; 95% CI: 0.64 to 0.86) and ill-defined margins (AUC 0.61; 95% CI: 0.48 to 0.74) was acceptable. [Table/Fig-9]. Among all the parameters, MSV (in m/s) was the best predictor of malignancy at cut off point of >2.98 with 92.5% chances of correctly predicting malignancy.

DISCUSSION

Acoustic Radiation Force Impulse (ARFI) elastography is a relatively newer technique that provides a quantitative value (in m/s) to measure the hardness of a tissue which in turn helps us to assess the tissue hardness. Therefore, this allows us and helps in distinction between benign and malignant tissues [6]. In present study, gray scale features predicting malignancy were heterogenicity, short to long axis diameter ratio of >0.5, peripheral or mixed vascularity pattern, ill-defined margins and absence of fatty hilum. These were in accordance in with the study conducted by Fang WT et al., who showed a sensitivity of 95% with p-value 0.043 in malignant nodes for short to long axis diameter ratio of >0.5 [8]. Similar statistically significant results were also displayed in the studies by Ariji Y et al., (66% sensitivity, specificity 95%) [9] and Ahuja AT et al., who emphasised that S/L ratio >0.5 was indicative of malignancy [10]. Majority of the malignant nodes showed S/L ratio >0.5 with a high sensitivity (85%) which was similar to as demonstrated by Yadav R et al., (81%). They also exhibited that peripheral vascularity favours malignancy and Colour Doppler Ultrasound (CDUS) had

Malignant	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Diagnostic accuracy
Short axis to long axis ratio (>0.5)	85% (62.11% to 96.79%)	67.5% (50.87% to 81.43%)	0.76 (0.64 to 0.86)	56.67% (37.43% to 74.54%)	90% (73.47% to 97.89%)	73.33%
Heterogenous	100% (83.16% to 100.00%)	67.5% (50.87% to 81.43%)	0.84 (0.72 to 0.92)	60.61% (42.14% to 77.09%)	100% (87.23% to 100.00%)	78.33%
Hyperechoic	5% (0.13% to 24.87%)	100% (91.19% to 100.00%)	0.53 (0.39 to 0.66)	100% (2.50% to 100.00%)	67.8% (54.36% to 79.38%)	68.33%
Absent hilum	85% (62.11% to 96.79%)	80% (64.35% to 90.95%)	0.83 (0.71 to 0.91)	68% (46.50% to 85.05%)	91.43% (76.94% to 98.20%)	81.67%
Peripheral and mixed vascular pattern	100% (83.16% to 100.00%)	67.5% (50.87% to 81.43%)	0.84 (0.72 to 0.92)	60.61% (42.14% to 77.09%)	100% (87.23% to 100.00%)	78.33%
Ill-defined margins	25% (8.66% to 49.10%)	97.5% (86.84% to 99.94%)	0.61 (0.48 to 0.74)	83.33% (35.88% to 99.58%)	72.22% (58.36% to 83.54%)	73.33%
Median shear wave velocity values (in m/s)	80% (56.3%-94.3%)	97.5% (86.8%-99.9%)	0.925 (0.827 to 0.977)	94.12% (71.31% to 99.85%)	90.7% (77.86% to 97.41%)	91.67%

[Table/Fig-9]: Sensitivity, specificity, positive predictive value and negative predictive value of ultrasound and doppler characteristics and median shear wave velocity values (in m/s) for predicting malignancy.

high sensitivity (81-96.3%) and specificity (50-96.3%) which were in agreement with current study [11].

Heterogeneous Echo pattern was the most frequent (positivity rate of 83-88%). In metastatic/malignant lymph nodes in the study conducted by Dayanand Saraswathi M et al., which was in agreement with present study as 100% in malignant nodes. Also, 97.5% benign nodes demonstrated well defined margins. This was in consensus with the findings by Dayanand Saraswathi M et al., who showed a high PPV (93%) for well-defined nodal margins for benign nodes [12]. It was observed in the study that malignant lymph nodes showed higher shear wave velocities and were higher in contrast to benign which were statistically significant. About 80% of patients had MSV/median shear wave velocity values (in metres/seconds) >2.98. Present study found that if MSV values (in m/s) >2.98, then there was 94.10% probability of malignancy and if MSV values (in m/s) ≤2.98, then 90.70% chances of benign. Among benign nodes, 97.50% of patients had MSV values ≤2.98 m/s [Table/Fig-1] and [Table/Fig-6].

In present study, AUC showed that the MSV values was the significant predictor of malignancy at cut-off point of >2.98 with a specificity of 97.5%, sensitivity of 80% and PPV, NPV and diagnostic accuracy were 94.1%, 90.7%, 91.67% respectively [Table/Fig-7]. Findings of contemporary study are in harmony with those published by Vinayagamani S et al., who also reported MSV values to be higher in patients with malignant aetiology as compared to those with benign. They showed that the distinction among non malignant and malignant lymph nodes had a PPV and NPV of 100 and 83.9 respectively with an accuracy of 89.9%; sensitivity and specificity being 79.17 and 100 respectively. Using ROC curve analysis, they derived a cut-off SWV value of 2.8 m/s with value of area under the curve as 0.892 which was statistically significant [13].

Fujiwara T et al., also proved that metastatic/malignant lymph nodes had higher SWV than benign/reactive lymph nodes (2.46±0.75 m/s in comparison to 1.52±0.48 m/s). They derived a SWV cut-off value of more than 1.9 m/s with the AUC of 0.923 (95% CI, 0.842-1.000). This showed a 95.00% specificity, 81.80% sensitivity and 88.00% accuracy [14]. Similarly, Chanda R et al., demonstrated that the mean SWV was higher in malignant nodes (3.7±2.27 m/s) in contrast to benign nodes (2.02±0.94 m/s) and concluded that ARFI exhibited a higher diagnostic performance over gray-scale sonography and CDUS in identification of nature of lymph nodes [15]. It was also observed that mean SWV values for lymph nodes with Hodgkin's (2.8 m/s) and Non Hodgkin's lymphoma (2.64 m/s) were lower from the cut-off value, even though they demonstrated gray scale features of malignant lymph nodes. Therefore, a total of five lymphomatous lymph nodes [Table/Fig-8] showed false negative results which was attributable to the consistency of lymphomatous nodes that are relatively firm in consistency and softer as compared to malignant nodes. These were in accordance to studies by Vinayagamani S et al., and Ahuja AT et al., who also reported that lymphomatous lymph nodes showed lower SWV as compared to malignant lymph nodes in their respective studies [13,16].

Rubaltelli L et al., compared sonoelastography with cytological and/or histological diagnosis, however, demonstrated a sensitivity of 75%, specificity of 80%, and accuracy of 77% which was lower than the current study. The dissimilarity in results could be attributed to the fact that the elastographic study of lymph nodes is affected by the position of the node (superficial or deep) and its relation to nearby structures such as muscles, superficial bones, or large blood vessels. Also, lymph nodes situated at a location below any lump or curved surface, may impart incorect ARFI readings as the impulse becomes non linear and non uniform in such cases [7].

Limitation(s)

There was a scarcity of number and wider variety of cases having malignant lymph nodes in the present study. Present study included only a total of 20 malignant lymph nodes. It is evident that supplementary studies with more number and wider variety of cases (of both benign and malignant aetiology) are essential to substantiate the value of ARFI elastography technique to distinguish benign from malignant lymph nodes.

CONCLUSION(S)

The B-mode ultrasound features that help in prediction of malignancy are short to long axis diameter ratio of >0.5, absence of fatty hilum, heterogeneous echotexture, peripheral and mixed (central as well as peripheral) vascularity. ARFI imaging showed that SWV values were higher for malignant nodes in comparison to benign nodes significantly. The present study also illustrated a high diagnostic accuracy (91.67%) of ARFI imaging in comparison to histopathology. Thus, ARFI can be used in practice to aid in the characterisation of nature of lymph nodes along with gray scale sonography.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Radiodiagnosis, Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India.
2. Professor, Department of Radiodiagnosis, Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India.
3. Consultant, Moradabad, Uttar Pradesh, India.
4. Professor, Department of Radiodiagnosis, Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India.
5. Associate Professor, Department of Pathology, Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India.
6. Junior Resident, Department of Radiodiagnosis, Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sumit Kaushik,
69, Type II, AIIMS Campus, Masjid Moth, New Delhi, India.
E-mail: sk7sk7777@gmail.com

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