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B-MODE ULTRASOUND AND ELASTOGRAPHY TO DISTINGUISH BETWEEN BENIGN AND MALIGNANT CERVICAL LYMPH NODES

Radiodiagnosis

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ABSTRACT

Differentiating benign and malignant cervical lymph nodes is important to institute proper treatment. The status of lymph nodes is also important in staging of malignancy and evaluating the prognosis of the underlying disease. Hence, accurate differentiation of benign and malignant lymph nodes (LNs) is a crucial issue.

The present study was carried out on 100 patients with enlarged cervical lymph nodes, examined with B-mode US, Doppler US and Sonoelastography in the Ultrasound unit of Galaxy Diagnostic Centre, Nagpur (M.S.), India. The aim was to prospectively estimate the diagnostic accuracy of sonoelastography in the differentiation between benign and malignant cervical lymph nodes. Sono-elastography is a new technique of sonography that is noninvasive, available and easy to apply. It evaluates the stiffness of the lesions based on response to the compression and decompression. By applying a mechanical force to the target lesion, an elastogram is obtained. The results appear as red or green indicating softness or blue, indicating hardness of the tissue.[FIG:2] Factors affecting stiffness include types of cell in the lesion, the quantity of cells and micro and macro pathological structures in the vicinity. So, ultrasound-elastography can visualize the hardness of the lesion by reflecting its biological characteristics.

With prior verbal and written consent, patients were examined on gray-scale ultrasound on transverse images and then using elastographic ultrasonography technique. Strain ratio was calculated as the ratio of stiffness between cervical lymph node and surrounding normal muscle tissue. Patients were followed up by fine needle aspiration cytology (FNAC) findings & postoperative histopathology report in cases of inconclusive FNAC . Regarding sonoelastography, relation between elastograph scores and malignant cervical lymph nodes showing sensitivity, specificity and p value was calculated.

RESULTS: Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Inter-rater kappa agreement was used to find out the strength of agreement between various parameters and FNA result. Ultrasound had a sensitivity of 75.00%, a specificity of 87.50%, a positive predictive value of 70.00%, a negative predictive value of 90.00% and diagnostic accuracy of 84.00% in the prediction of malignancy. Ultrasound elastoscore had a sensitivity of 79.00%, a specificity of 94.44%, a positive predictive value of 84.62%, a negative predictive value of 91.89% and diagnostic accuracy of 90.00 % in the prediction of malignancy.

KEYWORDS

Lymph Nodes, Elastography, Sonoelastography, Fatty Hilum, Intranodal vascularity, Strain Ratio.

INTRODUCTION

Evaluation of enlarged lymph nodes (LNs) is important to decide current status, proper treatment and prognosis of patients. It is crucial to differentiate malignant LNs from benign LNs so as to provide appropriate treatment.

The gold standard for evaluating enlarged LNs is pathologic examination of obtained tissue. Although fine-needle aspiration (FNA) is considered as the most efficient method for differentiating benign and malignant LNs, it is considered as an invasive method which is prone to sampling errors and analytic uncertainty.

Different modalities such as ultrasound computed tomography, and magnetic resonance imaging are currently used as imaging techniques for differentiating benign and malignant LNs, but their ability to differentiate malignant and benign LNs is limited.

Ultrasound Elastography is a recently developed ultrasound modality which is based on tissue displacement in response to external forces. Soft tissues show more displacement than stiff ones. A number of previous studies had evaluated accuracy of this modality in differentiating benign and malignant LNs & stated that its sensitivity and specificity ranged from 79% to 100% and 50–96%, respectively. [1,11]

ELASTOGRAPHY [PRINCIPLE]– a) Active external displacement of tissue surface. b) Passive internal physiologically induced. Property displayed Strain (ELASTOGRAM) Measurement Qualitative Imaging Full area image; colour image superimposed on a standard B-mode image (Real-time Tissue Elastography.)

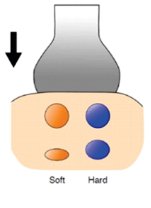


Figure 1 : Schematic representation of **operation of Elastography probe in evaluating Cervical lymph nodes. Strain elastography measures tissue displacement that occurs along the axis of the applied force.**

AIMS AND OBJECTIVES:

1. To determine whether ultrasound elastography (USE) may assist in differentiating benign from malignant cervical lymph nodes.
2. To evaluate the elastography appearances of pathological cervical lymph nodes.

Study setting --- Outdoor patients referred to the Ultrasound section of Galaxy diagnostic centre, Nagpur(m.s.), India.

- **Number of patients ---** 100 (No. of lymph nodes studied =100, most obvious and pathological looking lymph node was selected in cases with multiple lymph nodes)

Place of study --- Ultrasound section, at Galaxy diagnostic centre, Nagpur, india.

- **Duration of study ---** 6 months [from April-2018 to Sept-2018].
- **Equipment ---** GE Voluson ultrasound machine.

MATERIALS AND METHODS

This is a prospective study conducted on sample of 100 patients selected by simple random sampling who attended the Ultrasound section of department Radiodiagnosis at Galaxy Diagnostic Centre, Nagpur [M.S.], India. The selection of patients was done according to the following criteria:

Inclusion Criteria: -

1. Patients with cervical lymphadenopathy referred for ultrasound evaluation.
2. Patients with grey scale ultrasound findings s/o cervical lymphadenopathy referred for FNAC.

Exclusion criteria:
1. Patients not giving consent for procedure.
2. Pregnant patients are excluded from the study.

After history and clinical evaluation, the measurements were taken.

Parameters studied were:
1. Short-to-long axis diameter ratio of the cervical lymph node
2. Abnormal or absence of hilum
3. Microcalcification
4. Intranodal Vascularity
5. Elastographic scores
6. Strain ratio

We tested the sensitivity and specificity of strain elastography in detection of malignant cervical lymph nodes, and compared its results with those of Ultrasound and the Fine Needle Aspiration Cytology [**FNAC**] results which was taken as the **gold standard reference test in this study**. Ultrasound examination was done by using high-frequency linear array transducer (5 to 12 MHz) with compounded B-mode, color Doppler US (CDUS) and real time elastography on the GE VOLUSON PRO Ultrasound System. The elasticity measurements and ratios between cervical lymph nodes and adjacent normal muscle were calculated. The cervical lymph nodes were then classified into benign or malignant based on the elastography results, which were correlated to FNAC results. The subjects were examined in supine position, with pillow placed under their shoulders to hyperextend the neck. US gel was applied over the lymph node region to be examined.

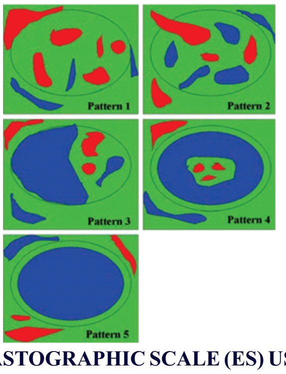


FIGURE 2: ELASTOGRAPHIC SCALE (ES) USED TO ASSESS CERVICAL LYMPH NODES.

[Drawings show typical diagrammatic appearance of five patterns of lymph nodes. Elastographic patterns were determined on distribution and percentage of lymph node area having high elasticity (hard): pattern 1, absent or small hard area; pattern 2, hard area <45% of lymph node; pattern 3, hard area ≥45%; pattern 4, peripheral hard and central soft areas; pattern 5, hard area occupying entire lymph node. Increasing tissue hardness appears in ascending order as red, yellow, green, and blue (Quoted from Alam et al. (1))]

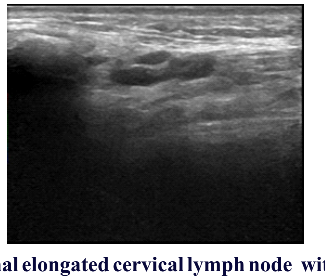


Fig 3 (a): Normal elongated cervical lymph node with fatty hilum.

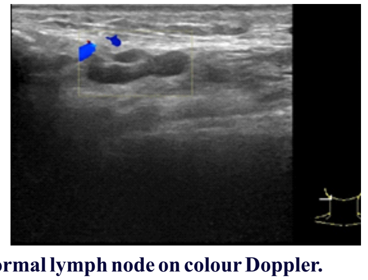
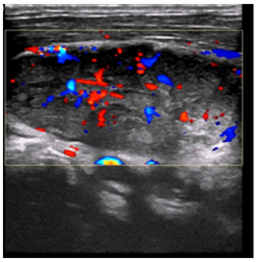


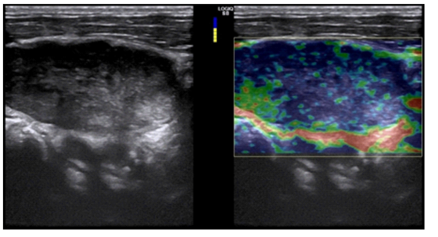
Fig 3(b): Normal lymph node on colour Doppler.

SOME REPRESENTATIVE CASES:

CASE 1: A 48 year old male patient presented with painless lump on right side of neck since one year.

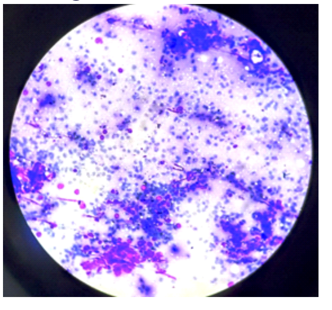


b) Colour Doppler: A large lymph node showing increased peripheral as well as markedly enlarged intranodal vascularity.



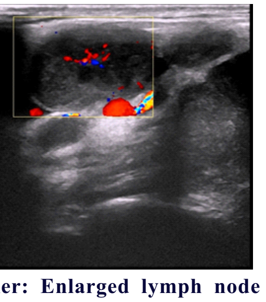
c) Gray scale ultrasound: Enlarged lymph node with irregular borders, increased short to long axis diameter ratio, total loss of fatty hilum, with areas of microcalcifications s/o malignant etiology.

d)Elastogram: showing elastoscore of 4. Strain ratio was 2.3

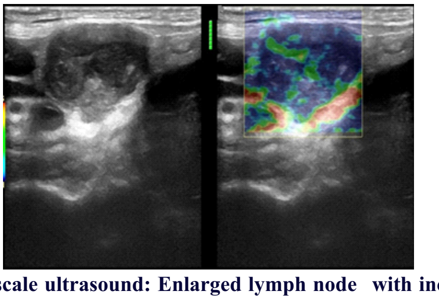


e): FNAC : showing sheets and clusters of atypical epithelial cells with lymphocytes in the background. Features are suggestive of malignancy.

CASE-2: A 45 year old male patient presented with painless lump in neck on left side since 1 year.



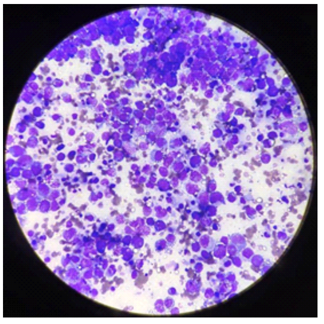
b) Colour Doppler: Enlarged lymph node showing mild peripheral and intranodal vascularity.



c) Gray scale ultrasound: Enlarged lymph node with increased

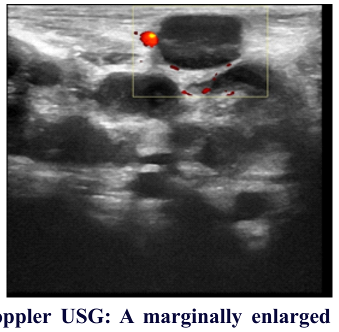
short to long axis diameter ratio (rounded), loss of fatty hilum, with few microcalcifications s/o malignant etiology.

d) Elastogram: showing elastoscore of 4(i.e. malignant). Strain ratio was 2.3

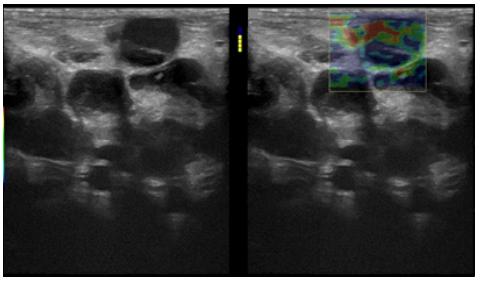


e) FNAC: cellular smears , pleomorphic cells with moderate amount of cytoplasm with cytoplasmic vacuoles and high nucleo-cytoplasmic ratio in a hemorrhagic background s/o- malignant features.

CASE 3: A 8 year old female patient presented with fever, weight loss and small nodular swelling in left side neck since 3 months.

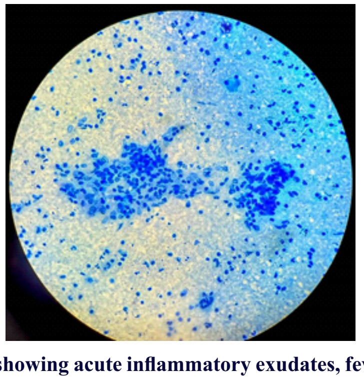


a) Colour Doppler USG: A marginally enlarged (oval shaped) lymph node , without intranodal vascularity.



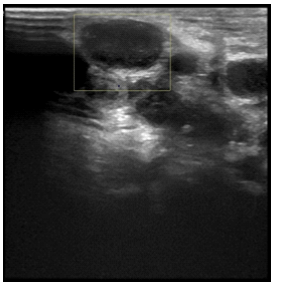
b) Gray scale ultrasound : showed increased short to long axis diameter ratio, presence of thin rim of fatty hilum and without microcalcifications S/O- Benign etiology.

c) Elastogram: showing elastoscore of 2. Strain ratio was 1.2

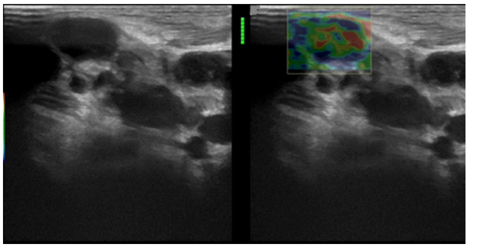


d) : FNAC: showing acute inflammatory exudates, few histiocytes and occasional giant cells in necrotic background with positive AFB stain, features suggestive of Tuberculous infective [Benign] etiology.

CASE 4: A 13 year old female patient presented with relatively painless lump on left side of neck since 6 months.

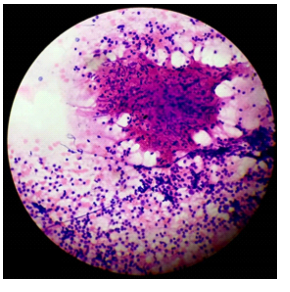


b) Colour Doppler: lymph node without intranodal vascularity.



c) Gray scale ultrasound : A marginally enlarged, (oval shaped) lymph node with increased short to long axis diameter ratio, loss of fatty hilum and without microcalcifications S/O- Benign etiology.

d) Elastogram: showing elastoscore 2. Strain ratio was 1.1



e) FNAC : showing reactive population of lymphoid cells, clusters of epithelial cells and Langerhans type of giant cells, features were suggestive of Granulomatous lymphadenitis(i.e. benign etiology).

RESULTS:

This study included 100 patients who were referred to the ultrasound section. The majority of the sample study were males; **61** patients with percentage of **(61%),** while females were 39 with percentage of **(39%).** Males to Females ratio was approximately (**3:2),** and **28** patients had malignant cervical lymph nodes.

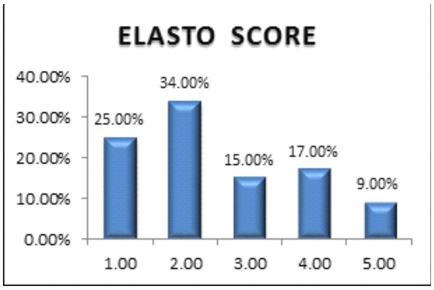
Ultrasound had a sensitivity of 75.00%, a specificity of 87.50%, a positive predictive value of 70.00%, a negative predictive value of 90.00% and diagnostic accuracy of 84.00% in the prediction of malignancy. Ultrasound elastoscore had a sensitivity of 79.00%, a specificity of 94.44%, a positive predictive value of 84.62%, a negative predictive value of 91.89% and diagnostic accuracy of 90.00 % in the prediction of malignancy. The imaging features that were significantly associated with malignant LNs were an increased short-to-long axis diameter ratio, abnormal or absence of hilum, microcalcifications, intranodal vascularity, 4 and 5 elasticity scores, and a high level of strain ratio ($P < 0.05$)

In our study, strain ratio had a sensitivity of 68.00%, a specificity of 86.11%, a positive predictive value of 66.00%, a negative predictive value of 87.00% and diagnostic accuracy of 81.00% in the prediction of malignancy. The cut off value of strain ratio for benign and malignant nodules in present study found to be 2.1.

TABLE 1: Showing percentage of ELASTO SCORES found in the present study in 100 patients with 100 lymph nodes studied:

ELASTO SCORE	Frequency	Percentage
1	25	25.00%
2	34	34.00%

3	15	15.00%
4	17	17.00%
5	9	9.00%
Total	100	100.00%



GRAPH (1): Showing percentage of ELASTO SCORES found in the present study in 100 patients with 100 lymph nodes studied:

Table (2): Strain ratio obtained 100 cervical lymph nodes studied in 100 patients.

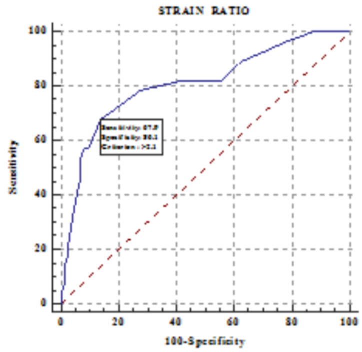
		Benign	Malignant	Total
STRAIN RATIO	<=2.1	62.00%	9.00%	71(71.00%)
	>2.1	10.00%	19.00%	29(29.00%)
Total		72 (72.00%)	28 (28.00%)	100 (100.00%)

Table(3):F.N.A.RESULT

F.N.A. RESULT	Frequency	Percentage
BENIGN	72	72.00%
MALIGNANT	28	28.00%
Total	100	100.00%

Table (4): CROSS TABULATION: ELASTO SCORE * Gold standard [FNAC]

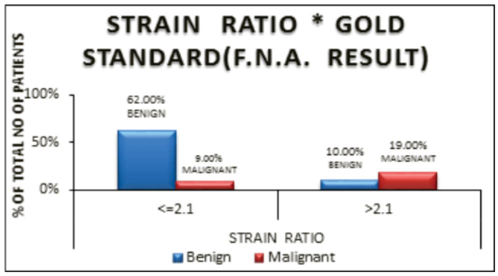
ELASTO SCORE		F.N.A. RESULT		Total	P value	Kappa
		Benign	Malignant			
	Benign	68(68.00%)	6 (6.00%)	74 (74.00%)	<.0001	0.746
	Malignant	4 (4.00%)	22(22.00%)	26 (26.00%)		
Total		72(72.00%)	28(28.00%)	100(100.00%)		



GRAPH (2) : showing sensitivity and specificity of strain ratio.

Table (5): CROSS TABULATION: STRAIN RATIO * Gold standard [FNAC]

		F.N.A. RESULT [GOLD STANDARD]		Total	P value	Kappa
		Benign	Malignant			
STRAIN RATIO	<=2.1	62(62.00%)	9 (9.00%)	71 (71.00%)	<.0001	0.534
	>2.1	10(10.00%)	19(19.00%)	29 (29.00%)		
Total		72(72.00%)	28(28.00%)	100(100.00%)		

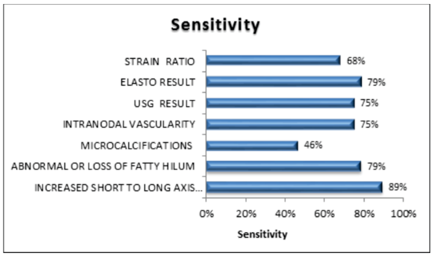


GRAPH (3): Showing STRAIN RATIO * Gold standard[FNAC]

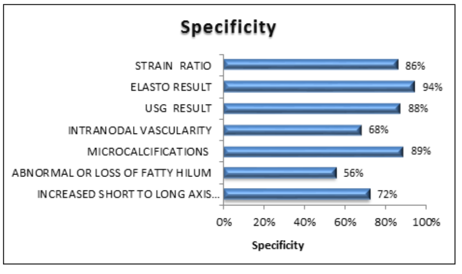
Table (6): Showing predictivity of each parameter studied compared with gold standard test [FNAC] (95% confidence interval [CI]) are as follows:

	Sensitivity	Specificity	AUC	Positive Likelihood Ratio	Negative Likelihood Ratio	Disease prevalence	Positive Predictive Value	Negative Predictive Value	Diagnostic accuracy
INCREASED SHORT TO LONG AXIS RATIO	89.29%	72.22%	0.81	3.21	0.15	28.00%	55.56%	94.55%	77.00%
95% CI	71.77% to 97.73%	60.41% to 82.14%	0.72 to 0.88	2.17 to 4.77	0.05 to 0.44	19.48% to 37.87%	40.00% to 70.36%	84.88% to 98.86%	
ABNORMAL OR LOSS OF FATTY HILUM	78.57%	55.56%	0.67	1.77	0.39	28.00%	40.74%	86.96%	62.00%
95% CI	59.05% to 91.70%	43.36% to 67.28%	0.57 to 0.76	1.28 to 2.44	0.18 to 0.81	19.48% to 37.87%	27.57% to 54.97%	73.74% to 95.06%	
MICROCALCIFICATIONS	46.43%	88.89%	0.68	4.18	0.6	28.00%	61.90%	81.01%	77.00%
95% CI	27.51% to 66.13%	79.28% to 95.08%	0.58 to 0.77	1.94 to 8.98	0.42 to 0.86	19.48% to 37.87%	38.44% to 81.89%	70.62% to 88.97%	
INTRANODAL VASCULARITY	75.00%	68.06%	0.72	2.35	0.37	28.00%	47.73%	87.50%	70.00%
95% CI	55.13% to 89.31%	56.01% to 78.56%	0.62 to 0.80	1.57 to 3.50	0.19 to 0.71	19.48% to 37.87%	32.46% to 63.31%	75.93% to 94.82%	
USG RESULT	75.00%	87.50%	0.81	6	0.29	28.00%	70.00%	90.00%	84.00%
95% CI	55.13% to 89.31%	77.59% to 94.12%	0.72 to 0.88	3.14 to 11.46	0.15 to 0.55	19.48% to 37.87%	50.60% to 85.27%	80.48% to 95.88%	
ELASTO RESULT	78.57%	94.44%	0.87	14.14	0.23	28.00%	84.62%	91.89%	90.00%
95% CI	59.05% to 91.70%	86.38% to 98.47%	0.78 to 0.93	5.35 to 37.38	0.11 to 0.46	19.48% to 37.87%	65.13% to 95.64%	83.18% to 96.97%	
STRAIN RATIO	67.86%	86.11%	0.77	4.89	0.37	28.00%	65.52%	87.32%	81.00%
95% CI	47.65% to 84.12%	75.94% to 93.13%	0.67 to 0.85	2.60 to 9.17	0.22 to 0.64	19.48% to 37.87%	45.67% to 82.06%	77.30% to 94.04%	

	Positive Predictive Value	Negative Predictive Value	Diagnostic accuracy
INCREASED SHORT TO LONG AXIS RATIO	55.56%	94.55%	77.00%
95% CI	40.00% to 70.36%	84.88% to 98.86%	
ABNORMAL OR LOSS OF FATTY HILUM	40.74%	86.96%	62.00%
95% CI	27.57% to 54.97%	73.74% to 95.06%	
MICROCALCIFICATIONS	61.90%	81.01%	77.00%
95% CI	38.44% to 81.89%	70.62% to 88.97%	
INTRANODAL VASCULARITY	47.73%	87.50%	70.00%
95% CI	32.46% to 63.31%	75.93% to 94.82%	
USG RESULT	70.00%	90.00%	84.00%
95% CI	50.60% to 85.27%	80.48% to 95.88%	
ELASTO RESULT	84.62%	91.89%	90.00%
95% CI	65.13% to 95.64%	83.18% to 96.97%	
STRAIN RATIO	65.52%	87.32%	81.00%
95% CI	45.67% to 82.06%	77.30% to 94.04%	



GRAPH 4 : Showing Sensitivity of each parameter in the study.



GRAPH 5 : Showing Specificity of each parameter in the study.

STATISTICAL ANALYSIS:

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Inter-rater kappa agreement was used to find out the strength of agreement between various parameters and FNA result. Receiver operating characteristic curve was used to find out cut off point of strain ratio for predicting malignancy. **A p value of <0.05 was considered statistically significant.**

DISCUSSION:

There are many ultrasound criteria for differentiating benign from malignant cervical lymph nodes. There are multiple US features that are highly suggestive of malignancy in a cervical lymph node including 1. Increased short-to-long axis diameter ratio, 2. Abnormal or absence of hilum, 3. Microcalcification, 4. Intranodal Vascularity.

In this study we have taken FNAC the gold standard [reference] test, with an aim to evaluate the elastographic appearances of pathological cervical lymph nodes and to determine whether ultrasound elastography (USE) may assist in differentiating benign from malignant cervical lymph nodes. In our study, stiffness of individual lymph nodes studied on ultrasound elastography was scored from 1 to 5 based on subjective analysis of the elastogram image. The scoring was classified to differentiate benign and malignant lesions and is based on color pattern with elastography image. Score 1, and 2 included nodules with high elasticity, score 3 was maintained as an intermediate score; and scores 4 and 5 included lymph nodes with low elasticity. Using this score classification, the predictive value of US elastography was highly rewarding. Scores 4 and 5 were associated with malignancy.

In our study, by combining the ultrasound parameters such as 1. Increased short-to-long axis diameter ratio, 2. Abnormal or absence of hilum, 3. Microcalcification, 4. Intranodal vascularity, ultrasound had a sensitivity of 75.00%, a specificity of 87.50%, a positive predictive value of 70.00%, a negative predictive value of 90.00% and diagnostic accuracy of 84.00% in the prediction of malignancy. By combining the scores 1, 2, 3, 4 and 5, **Ultrasound elasto score** had a sensitivity of 79.00%, a specificity of 94.44%, a positive predictive value of 84.62%, a negative predictive value of 91.89% and diagnostic accuracy of 90.00 % in the prediction of malignancy. Our results are close to the findings reported by previous studies conducted by ***ISHIBASHI et al**. [11]* which assessed elastographic scale using a 5-point scale and documented that elastography in combination with conventional US demonstrated sensitivity, specificity, and accuracy values of 90.3%, 80%, and 84.5%, respectively and ***Alam et al. [1]*** which used a 5-point scale for elastography and reported sensitivity, specificity, and accuracy values of 83%, 100%, and 89%, respectively) considering Elastography Score 1 and 2 as benign and Elastography Score 4 and 5 as malignant).

Even more rewarding were the negative predictive values of the elasto scores to exclude malignancy. **In the current study**, scores of **1** or **2** were found in 59 cases, of which 54 were found to be benign on cytology. The low number of false-negative results at USE would allow most patients to be placed in follow-up without significant costs in terms of prognosis. A **score 3** was found in 15 cases with 1 case of malignancy, and 14 cases had benign etiology. In score 3, according to our result, all patients with score 3 were sent to fine needle aspiration cytology (FNAC) for confirmation. A score of **4** and **5** was found in 26 cases. Scores 4 and 5 included lymph nodes with low elasticity. **Our results** are very close to the findings reported by **previous studies of Lyshchik et al.** [8] which published one of the first clinical studies to evaluate the diagnostic promise of strain elastography by examining 141 lymph nodes, of which 98 were confirmed as benign and 43 were confirmed as malignant by histopathology. They classified the nodes according to visualization, brightness compared to the neighboring muscles, and the regularity of the outline. Using a strain ratio cut-off value of >1.5, strain elastography demonstrated sensitivity, specificity, and accuracy values of 85%, 98%, and 92%, respectively. In our study, strain ratio had a sensitivity of 68.00%, a specificity of 86.11%, a positive predictive value of 66.00%, a negative predictive value of 87.00% and diagnostic accuracy of 81.00% in the prediction of malignancy. The cut off value of strain ratio for benign and malignant nodules in present study found to be 2.1.

LIMITATIONS:

Firstly, strain elastography procedure is dependent on personal colour scale and hence it is operator dependent. Secondly, vessel pulsation can affect elasticity change. The lymph node in our study were adjacent to the common carotid artery and internal jugular vein, which can affect the color of the elasticity reading. Thirdly, Strain elastography using freehand compression is dependent on the compression technique, because excessive compression alters tissue stiffness and nonaxial displacement (i.e., displacement that occurs laterally or outside of the imaging plane) can degrade the accuracy of the software's correlation algorithms. Also, the major limitation of FNA cytology is that 10% to 15% of specimens are not diagnostic [7,10]. In the present study, percentage of lymph node FNA specimens with insufficient or inadequate for diagnosis at US (Ultrasound Guided)-FNAC was **8%** and lymph nodes with inconclusive reports were followed up by histopathology.

CONCLUSION:

We found that Ultrasound strain elastography (use) is an easy, non-invasive and rapid technique that can be used routinely in evaluating the cervical lymphadenopathy to select cases for FNAC, and decrease the number of unnecessary biopsies, and consequently decrease its hazards and costs. **In the current study,** the incidence of malignancy in the lymph nodes that were selected for FNAC by real-time ultrasound was **28 %. In the current study**, malignant lymph nodes showed predominantly increased short to long axis diameter(rounded) than benign lesions, presence of microcalcifications and intranodal vascularity, which is in apparent agreement with previous studies.

In conclusion, ultrasound is the modality of choice in evaluation of cervical lymphadenopathy. Ultrasound Strain Elastography is a promising imaging technique that is useful in differentiating between benign and malignant cervical lymph nodes. Further improvements in the technique and the diagnostic criteria are necessary for this examination to provide a useful contribution to diagnosis. Using a combination of criteria increases the likelihood of detecting malignancy.

The use of Ultrasound Strain Elastography is beneficial in differentiating between benign and malignant cervical LNs, thereby guiding decisions on whether to perform a biopsy and/or surgery, and facilitating early proper treatment and follow-up.

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