IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 3 Ver.9 March. (2018), PP 05-10
www.iosrjournals.org

Role of High Resolution UltrasonogramandElastographyIn Cervical Lymphadenopathy

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Abstract:*Cervical lymphadenopathy is one of the common clinical condition which may be due to various causes like infection(especially tuberculosis in our country), inflammation and malignant conditions. The aim of our study is to evaluate the role and diagnostic utility of ultrasonogram and elastography to differentiate the benign and malignant causes of cervical lymphadenopathy as well as differentiating between various benign causes.*

Materials & Methods:
It is a prospective study of 85 patients having cervical lymphadenopathy using Ultrasonogramand Elastography. Biopsy/ FNAC was done for all cases and the results were compared.

Results:*The sensitivity and specificity for diagnostic value of sonography in differentiating the malignant nodes from benign nodes were 88.9% and 98.0% respectively and for elastography they were 88.9% and 89.8% respectively. Tuberculous nodes could not be identified separately by elastography due to overlapping features.*

Conclusion: *The real time strain Elastography can distinguish benign and malignant cervical lymph nodes with high sensitivity and specificity, but it is not much useful in differentiating various etiologies in benign or malignant nodes. It can be used as an adjunct tool with sonography in characterising the lymph node and can be included in the initial workup of the patients with cervical lymphadenopathy, so that more malignancy can be brought into light.*

Key Words*: Cervical lymphadenopathy, Strain elastography, Short to long axis ratio.*

Date of Submission: 02-03-2018 Date of acceptance: 20-03-2018

I Introduction

The management of cervical lymphadenopathy varies with its etiology due to which theevaluation and differentiation ofits causebecomes crucial.

The foremost andinitial investigation of choice used for the evaluation of cervical lymphadenopathy is B-mode ultrasonography along with Doppler study which assess and characterize the nodal morphology and its vascular pattern[1]. Furthermore, it surpasses other modalities in unveiling small lymph nodes [1, 2]. Although it yields adequate and quick diagnostic reference with satisfactory sensitivity as well as specificity, subjectivity is one of the major pitfall which should be reckoned before considering them as universal criteria.And despite the fact that there are various proposed criteria to differentiate benign and malignant nodes, the most specific or meritorious feature is under dispute [3]. Also it is unable to detect micrometastasis in nodes, it may lead to false negative results [4], and so we have to rely upon pathological diagnosis.

Elastography is a novel non-invasive imaging technique which is based on elasticity of the tissue [5,6], rather than anatomy. Elastography has transpired as a new technology for differentiating the lesions by measuring the tissue elasticity [7], which is endorsed by radiologist due to its consistent results.

There exist two types of elastography techniques – strain elastography and shear wave based elastography. Strain elastography is a real time qualitative assessment of the tissue stiffness where displacement of tissue occurs in longitudinal direction. [8].Since the performance is technically easy and less time consuming, it is suitably executed during the routine ultrasonographic examination, allowing dynamic scrutinisation of lesion during compression [9].

The aim of our study is to evaluate the diagnostic utility of B-mode Ultrasonogram and Elastography to differentiate the benign and malignant causes of cervical lymphadenopathy.

II Materials &Methods

It is a prospective study, conducted in our institution over a period of 1 year (September 2016 to September 2017) with a sample size of 85 patients. We studied the patients having cervical lymphadenopathy except those who underwent surgery, radiotherapy or chemotherapy for cervical lymph node malignancy, those who were on or completed treatment like anti-tuberculous drugs and those who had already underwent biopsy from the cervical lymph node.

Conventional B-Mode Ultrasonogram and Doppler study of cervical lymph nodes were done for all patients using SAMSUNG ACCUVIX XG AVXGE30/IN ultrasonogram machine equipped with elastoscan, with compatible high frequency linear probe(7-11Hz). Strain elastography was done using the same machine and same probe.

We studied cervical nodes from level 1 to 6 on both sides. Ultrasonographicdiagnosis was given on the basis of size, shape, short to long axis ratio, echogenicity, fatty hilum and presence of hilar or peripheral vascularity with other ancillary features.

Elastography was done by free hand technique with compression – decompression method using slight pressure until a stable image was obtained. In the elastography image, elastogram appeared in a region of interest box (ROI) which was kept in such a way to include the node with more or less equal depth of surrounding muscle as a reference tissue for strain. Elastic property was given by the colourwhich is unique to the software. In our machine, red indicates more stiffer tissue and blue indicates softer tissues.

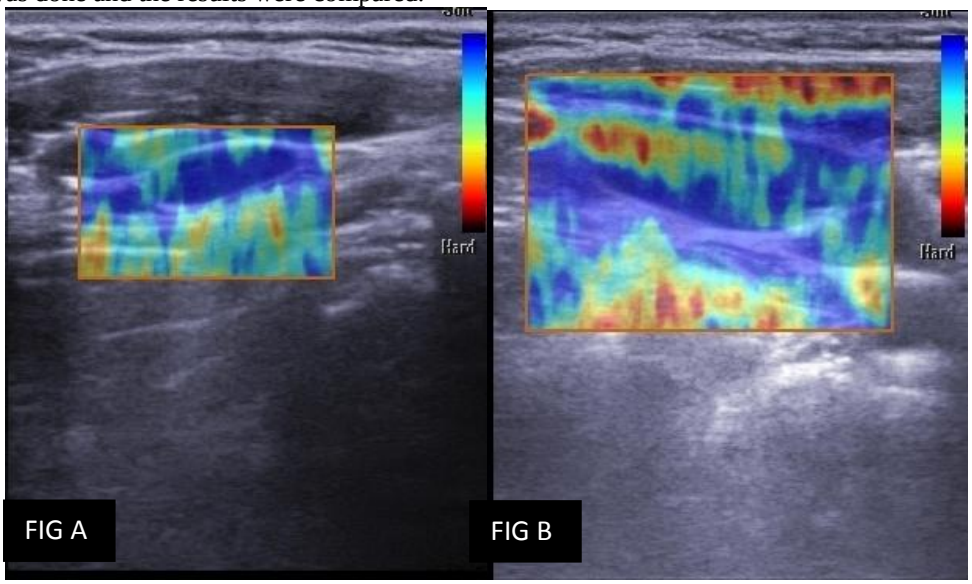
Elastographic patterns were established based on the distribution and area percent of the hard areas within lymph node [10] as5-pattern system of colour scoring as done by Alam et al.

Table 1: Patterns and scoring system on elastographic findings (Quoted from Alam et al. (11)

Pattern	Description	Elastographic diagnosis
1	Absent or very small blue area(s)	Benign
2	Small scattered blue areas, total blue area <45%	Benign
3	Large blue area(s), total blue area ⩾45%	Malignant
4	Peripheral blue area and central green area, suggesting central necrosis	Malignant
5	Blue area with or without a green rim	Malignant

NOTE: Here blue represents hard area and red represents soft area. Intermediate is green.

We selected single node from each patient, with nodal selection criteria being single largest node with other features of malignancy and highest pattern on elastographyforperforminghistopathologicalexamination with ultrasound guided trucut biopsy.In case where there was difficulty in doing biopsy, ultrasound guided FNAC was done and the results were compared.



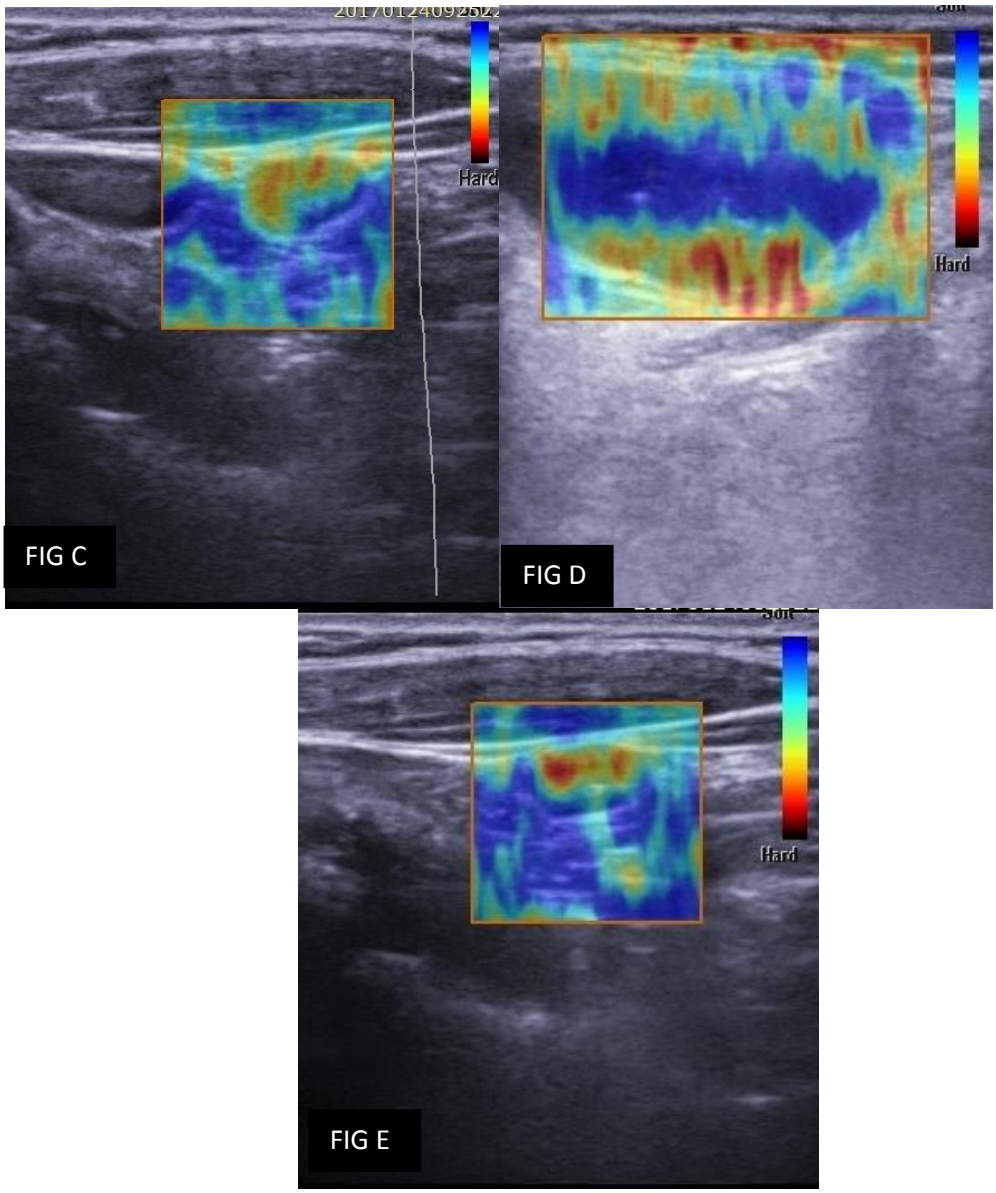


Figure 1 (A-E): Real time strain elastography (A) Blue areas within the node - pattern 1 elastogram, (B) Minimal areas of red – pattern 2 elastogram, (C) >45% of red areas – pattern 3 elastogram, (D) Peripheral red areas with central blue areas – pattern 4 elastogram and (E) Fully red areas – pattern 5 elastogram.

III Statistical Analysis

Categorical variables were analysed by frequency analysis. To find the significance in categorical data, Chi-Square test was used. All statistical tools were carried out at the level of significance of 5% and the probability - p value <0.05 was considered significant. Comparison of ultrasound and elastographic diagnosis with histopathological examination was done by Receiver Operating Characteristic (ROC) curves. Area under the curve was calculated to find the sensitivity, specificity, positive predictive value and negative predictive value.

IV Results

Out of 85 patients, 45 were female and 40 were male. The causes of cervical lymphadenopathy in our patients were distributed as follows:

Table 2: *distribution of cases in our study*

S.NO	ETIOLOGY	NO. OF PATIENTS	CATEGORY	TOTAL
1.	REACTIVE ADENOPATHY	14	BENIGN	25
2.	INFLAMMATORY ADENOPATHY	2		
3.	INFECTIVE – VIRAL/BACTERIAL ADENITIS	9		
4.	TUBERCULOUS ADENITIS	24	GRANULOMATOUS INFECTIVE	24
5.	SECONDARIES FROM ORAL CAVITY MALIGNANCIES	27	MALIGNANT	36
6.	SECONDARIES FROM PAPILLARY CARCINOMA THYROID	4		
7.	LYMPHOMA	5		
	TOTAL	**85**		**85**

Benign lymph nodes tend to be hypoechoic, oval with short axis diameter < 8mm and short to long axis ratio <0.6 with presence of echogenic hilum and hilar vascularity [12,13]. Diagnostic criteria for malignancy include round hypoechoic nodes with S/L ratio >0.6 with absence of echogenic hilum and have peripheral or mixed vascularity. They may have intranodal necrosis and eccentric cortical hypertrophy[13]. On the other hand, tuberculous nodes are large hypoechoic with intranodal necrosis, matting and displaced hilar vascularity [13].

We considered the nodes to be malignant when 3 or more criteria of ultrasonographic features favoured malignancy.

Table 3: summary of sonographic findings of cervical lymph nodes

Sonography Criteria	**Number of patients**	**Percentage %**
B-mode		
S/L axis ratio		
≤ 0.6	32	37.6
> 0.6	53	62.4
Shape		
Round	53	62.4
Oval	32	37.6
Margin		
Sharp	24	28.2
Unsharp	46	54.1
Ill Defined	15	17.6
Hilum		
Present	32	37.6
Absent	53	62.4
Echogenicity		
Hypoechoic	79	92.9
Isoechoic	2	2.4
Hyperechoic	4	4.7
Necrosis		
Absent	48	56.5
Present	37	43.5
Calcification		
Absent	82	96.5
Present	3	3.5
Eccentric cortical hypertrophy		
Absent	75	88.2
Present	10	11.8
Matting/ edema		
Absent	61	71.8
Present	24	28.2
Doppler flow		
Hilar	29	34.1
Peripheral	16	18.8
Both	27	31.8
Displaced Hilar	7	8.2
Absent	6	7.1

According to the sonographiccriterias, among 85 nodes in our study, 26 nodes were benign, 37 nodes were malignant and 22 nodes were reactive constituting 30.6%, 43.5% and 25.9% respectively.

Table 4: Distribution of elastographic pattern of nodes

PATTERN		FREQUENCY	PERCENT %	CATEGORY
1	Very Soft	25	29.4	Benign
2	Soft	23	27.1	48
3	Mildly Hard	9	10.6	Malignant
4	Moderately Hard	16	18.8	37
5	Very Hard	12	14.1	
	Total	85	100.0	85

According to Elastography, 48 nodes were benign (56.5%) and 37 nodes were malignant (43.5%). Tuberculosis could not be diagnosed by elastography since these nodes tend to had multiple overlapping features of both benign and malignant nodes. Among 24 sonographicallylabelledtuberculous nodes, Elastography showed benign pattern in 20 nodes and malignant pattern in 4 nodes.

Table 5: Elastography in sonographically detected tb nodes

PATTERN IN TB NODES	NUMBER
1	5
2	15
3	2
4	1
5	1
TOTAL	**24**

The distribution of etiologies of various category with sonography and Elastography were explained in table 6 and 7.

Table 6: *distribution of etiologies inUltrasonographic diagnosis versus histopathologicaldiagnosis*

		HPE DIAGNOSIS			TOTAL
		BENIGN	MALIGNANT	TUBERCULOSIS	
USG DIAGNOSIS	BENIGN	24	4	0	28
	MALIGNANT	1	32	0	33
	TUBERCULOSIS	0	0	24	24
TOTAL		25	36	24	85

Table 7:*distribution of etiologies inElastographic diagnosis versus histopathological diagnosis*

		HPE DIAGNOSIS			TOTAL
		BENIGN	MALIGNANT	TUBERCULOSIS	
ELASTOGRAPHIC DIAGNOSIS	BENIGN	23	5	20	48
	MALIGNANT	2	31	4	37
	TUBERCULOSIS	0	0	0	0
TOTAL		25	36	24	85

The area under receiver operating characterising curve for sonographuc and elastographic diagnosis are 0.934 and 0.893 respectively. the sensitivity and specificity for both are given in the Table 8.

Figure 1: *Reciever operating characterising curve for comparing radiological and elastographic diagnosis with histopathological examination*

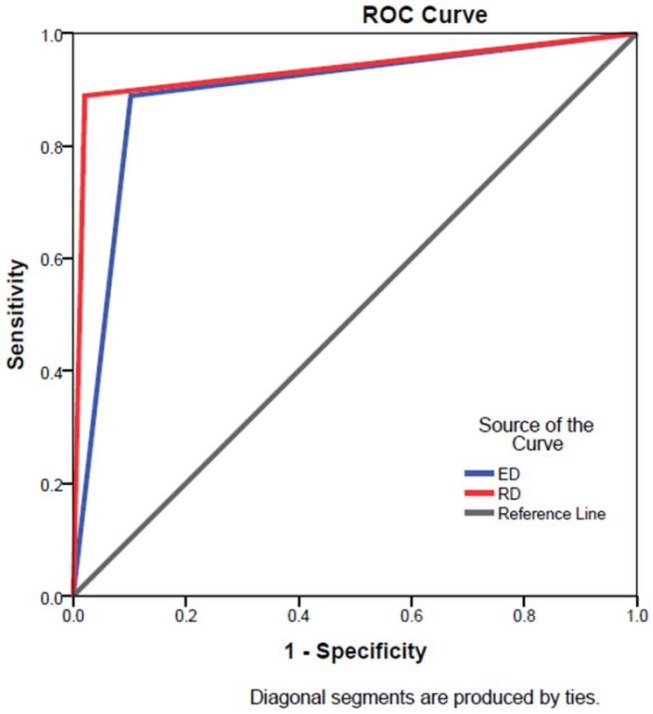


Table 8: *Results of ROC curve*

AREA UNDER THE CURVE								
Test Result Variable(s)	**Area**	**p value**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Asymptotic 95% Confidence Interval**	
							Lower Bound	**Upper Bound**
UD	**.934**	**.0005**	**88.9**	**98.0**	**97.0**	**92.3**	**.869**	**.999**
ED	**.893**	**.0005**	**88.9**	**89.8**	**86.5**	**91.7**	**.816**	**.971**

ED – Elastographic diagnosis UD –ultrasonographic diagnosis

V Discussion

In an attempt to overcome the limitations of other imaging modalities and to decrease negative biopsy rates, elastography has been tested for its ability to differentiate benign and malignant cervical lymphadenopathy and to see if it can be added to the previously available diagnostic armamentarium.

The basic principle of elastography is similar to manual palpation [6,14]. The concept behind it is that benign lesions feel harder than normal tissue but malignant lesions feel even harder than benign lesions [8,14], with exceptions being a few.

In sonographicelastography, a mechanical force either by manual compression or ultrasonic vibration is delivered to the biological tissue, echo data before and after the delivery of force is obtained, digital measurements of tissue hardness is performed and a colourmap of soft-tissue deformation is created [14]. The resultant image is called elastogramwhichappears in ascending order as red, yellow, green, and blue as tissue hardness increases, [11] but the colour can be inverted depending on the machine.

Alam et al. in 2008 [11], conducted a prospective study of 85 lymph nodes using a 5 point elastographic pattern based on the percentage of high and low elastic areas of the node. For grey scale ultrasound they found that sensitivity and specificity were 98%and 59% respectively. For elastographyit was 83% and 100% respectively. We also studied85 lymph nodes using the same 5 point score Elastography. In our study, the sensitivity and specificity for sonographic diagnosis were 88.9% and 98.0% and for elastography were 88.9% and 89.8%.

Rubaltelli et al. [15] studied 53 patients having cervical lymphadenopathy with ultrasonogram and sonoelasography and found a sensitivity of 75%, specificity of 80% and accuracy of 77% which was less impressive, according to him. But he mentioned that the information given by elastography could be a useful adjunct to sonographic findings. Also he noted that in 5 lymph nodes showing sonographic features of malignancy, elastography revealed diffuse elasticity indicative of benign disease, which was confirmed by histopathology. In our study, sensitivity and specificity are quiet higher than that obtained in his study. Also 3 malignant nodes show benign pattern in Elastography and 7 benign nodes show malignant pattern.

Bhatia et al. [16] in 2010 retrospectively studied 74 cervical nodes with real time qualitative sonoelastography. He used receiver operating characteristic curve which gave the area under curve of 0.68 to 0.74 which indicated suboptimal discrimination. Thus he concluded quoting the need of improvement in the real time sonoelastography for it to be adopted as routine investigation. But in our study the area under the curve for Elastography was 0.893 which is well above the value obtained by his study.

A meta-analysis of nine studies related to the diagnostic value of real time strain elastography [17] was conducted in 2012 that included 835 cervical lymph nodes. The conclusion given was elastography has high accuracy in classifying superficial cervical lymph nodes and help potentially to select the suspicious lymph node or biopsy. In our study also, Elastography was used as a guide to select node for biopsy.

VI Limitations

The real time free hand strain elastography was operator dependent, despite the presence of quality scale. So, reproducibility is less for this modality of investigation. Since the study was conducted by a single radiologist, interobserver variation could not be studied.

In patients with multiple lymph nodes, only one node was taken for study. There was difficulty in studying very large lymph nodes, since the region of interest box could include only small amount of adjacent reference tissue.

Since the ultrasound and elastography were done at the same time and ultrasound examination preceded the elastography, the diagnosis was established in ultrasound, so there is observer bias in our study.

Strain elastography gave only qualitative stiffness of the tissue while quantitative measurement could not be done.

VII Recommendations

From our study, we recommend that strain elastography cannot be used alone for assessing malignancy of lymph nodes, but can be used along with the ultrasound and Doppler criteria.

VIII Conclusion

The conclusions derived from our study are:

- The real time strain elastography shows maximum strain over benign lymph nodes and less strain over the malignant lymph nodes. Thus it can distinguish benign and malignant cervical lymph nodes with high sensitivity and specificity.
- But it is not very useful in case of differentiation between various etiologies in benign nodes – like reactive or tuberculosis.
- On combining elastography with B- mode ultrasonogram, the sensitivity to differentiate benign and malignant nodes will increase to 100% and specificity will also be very high.
- Elastography can be included in the initial workup of the patients with cervical lymphadenopathy, so that more malignancy can be brought into light.
- It can be used as an adjunct tool with sonography in characterising the cervical lymph node in the work up of patients with head and neck carcinoma.
- Eventhough it can differentiate the malignant nodes from benign nodes, HPE is needed to confirm the diagnosis since few percent of malignancy can be missed.
- But it can be used as a guide to select the appropriate node for biopsy.

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