

Role of high resolution ultrasound/endosonography and elastography in predicting lymph node malignancy

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ABSTRACT

Objective: The objective of this study is to evaluate the role of high resolution ultrasonography (US) and *endoscopic ultrasound* (EUS)-elastography in predicting malignant lymphadenopathy. **Patients and Methods:** This prospective study included 88 patients who underwent EUS or US examination of different groups of lymph nodes (LNs). The classification as benign or malignant based on the real time elastography pattern and the B-mode US/EUS images was compared with the final diagnosis obtained by EUS or US guided fine-needle aspiration cytology (FNAC), tru-cut biopsy or excisional biopsy and follow-up in benign lesions not indicated for biopsy for at least 12 months. **Results:** Regarding the echogenicity, 98.3% of the benign LNs were hyperechoic, 1.7% was hypoechoic while 89.7% of the malignant LNs were hypoechoic, 3.4% were heterogenous and 6.9% were hyperechoic. With cut-off value of 1.93, the sensitivity of longitudinal to transverse ratio was 73% and the specificity was 100%. Score 1 elastography had specificity of 100% in diagnosis of benign LNs, sensitivity was 76.3%, positive predictive value (PPV) was 100%, negative predictive value (NPV) was 84.7% while score 2 had a sensitivity of 60%, specificity of 31.5%, PPV of 15.3%, NPV of 79.3%. Score 3 had a sensitivity of 70.2%, specificity of 100%, PPV of 13.8%, NPV of 100% in detecting malignancy while score 4 had a sensitivity of 85.5%, specificity of 100%, PPV of 100%, NPV of 65.5%. **Conclusion:** Elastography is a promising diagnostic modality that may complement standard ultrasound and EUS and help guide FNAC during staging of LNs.

Key words: Lymph node, ultrasonography, endoscopic ultrasound, elastography, malignant

INTRODUCTION

Elasticity (hardness) is a mechanical tissue characteristic that prevents tissue displacement under pressure. It varies in different types of tissue (fat, collagen and so forth) and in the same tissue in different pathologic states (inflammatory, malignant). During the past few years, sonographic elastography, magnetic

resonance elastography and some other techniques have performed digital measurements of tissue hardness.^[1] In sonographic elastography, image representation of tissue hardness can be obtained using a conventional sonography machine with special software and a conventional ultrasound probe.^[2,3] In brief, sonographic elastography works in the following steps: First, elastography receives digitized radiofrequency echo lines from the tissue; second, it gives slight compression to the tissue by the transducer along the radiation axis to make some displacement; and third, it receives a second, post compression digitized radiofrequency echo line from the same tissue.^[3] Then the data from these two echo lines undergo processing, and ultimately an elastographic image (elastogram) appears on the

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monitor. Increasing tissue hardness appears in ascending order as red, yellow, green and blue. These colors represent the relative hardness of the tissues in the elastogram.

Sonographic elastography has been used to examine several organs: The breast, thyroid, prostate, cervix, liver and so forth.^[4] The body contains 400-450 lymph nodes (LNs). Differentiation between reactive and metastatic lymphadenopathy is vital and one of the differentiating criteria is hardness (elasticity) of the LN.^[4]

The purpose of this study was to investigate the accuracy of conventional sonography, sonographic elastography and their combined evaluation for the differentiation between benign and malignant LN enlargement.

PATIENTS AND METHODS

Patients

This prospective study included 88 patients referred for either thyroid sonography and elastography where cervical LNs were examined as a part of neck examination or referred for endoscopic ultrasound assessment of pancreatic and gastrointestinal masses where regional and second station LNs were examined and biopsied as a part of staging of the masses.

Inclusion criteria

1. Patients with clinically felt LNs in any part of the body mainly the cervical region;
2. Patients referred for thyroid sonography and elastography where cervical LNs were examined as a part of neck examination; and
3. Patients referred for endoscopic ultrasound assessment of pancreatic and gastrointestinal masses, regional and second station LNs were examined and biopsied as a part of staging of the masses.

Exclusion criteria

Final diagnosis was not settled as in patients with no definite histopathological diagnosis or patients dropping out of follow-up.

Ethical considerations

In all patients, ultrasound or endosonography was done upon request of their consulting physicians. For confidentiality, their names were omitted and replaced by numerical codes.

The ultrasound characteristics of LNs

1. Size
2. Longitudinal/Transverse (L/T) diameter ratio
3. Echogenicity
4. Elastography score. The most common technique used in ultrasound elastography is to apply external pressure using the transducer.

After placing a linear transducer over the region of interest, the ultrasonographer manually applies light pressure with the transducer. For Endoscopic ultrasound (EUS) examinations, the pulsations of nearby major vessels were exerting compression on the intra-abdominal adenopathy. The ultrasonography (US) elastogram was displayed over the B-mode image in a color scale that ranges from red, for components with greatest elastic strain (i.e., softest components), to blue for those with no strain (i.e., hardest components). The US elastographic image was matched with an elasticity color scale present on the side of each image.

US elastography scoring (patterns) system used

1. Pattern 1: 80% or more of the cross-sectional area of the LN is red or green, i.e., soft.
2. Pattern 2: 50% or more and less than 80% is red or green.
3. Pattern 3: 50% or more and less than 80% is blue; and
4. Pattern 4: 80% or more of the cross-sectional area of the LN is blue i.e., hard.^[5]

The LNs had the following distribution:

1. Axillary (1.1%),
2. Perigastric (2.3%), 4 peripancreatic (4.5%), 11 celiac (12.5%), 54 cervical (61.3%),
3. Para-rectal (3.4%), 3 mediastinal (3.4%),
4. Portahepatis (4.5%), and 6 upper para-aortic (6.8%).

All US or EUS elastographic examination was done by a single Gastroenterologist. Ultrasound elastography was done using Hitachi color machine type EUB-7000, with a 10 MHz linear transducer; Hitachi Medical Systems, Tokyo, Japan. Endosonography was done using Pentax[®] machine, EUS EG3830UT connected to a Hitachi sonographic machine EUB-7000.

FNAC specimens were obtained under ultrasound or EUS guidance, smears were wet fixed in 95% ethyl alcohol and stained with hematoxylin and eosin stain for routine cytologic evaluation. Biopsies were taken

either by excision of LNs or using a tru-cut needle biopsy according to circumstances.

Final diagnosis

Final diagnosis was:

1. Histopathological examination of FNAC, tru-cut biopsy or excisional biopsy; and
2. Follow-up in benign lesions not indicated for biopsy for at least 12 months.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Receiver operating characteristic-curve was applied, calculating the area under the curve (AUC), sensitivity and specificity for the tests used. Cut-off values were calculated. Univariate prediction model were performed for calculating predicted probabilities and data were graphically represented. *P* value was considered to be significant if less than 0.05.

RESULTS

Most of the cervical LNs had sonographic criteria suggestive of benign nature and had elastography score of 1 and so biopsy was not indicated and their diagnoses were based on follow-up with the minimum period of 12 months.

Suspicious LNs (perigastric, peripancreatic, celiac, pararectal, mediastinal, portahepatis and upper paraaortic) in patients with malignant masses referred for endosonography were diagnosed based on FNAC from the following LNs groups (perigastric, peripancreatic, celiac, pararectal, mediastinal, portahepatis, upper paraaortic).

There was only one case with celiac lymphadenopathy in which sonographic criteria was suggestive of benign nature so the diagnosis was based also on follow-up and finally the patient had definite diagnosis of acute pancreatitis.

Only one case with axillary LNs was included for a patient with breast adenocarcinoma and it was diagnosed as metastasis based on sonar guided tru-cut biopsy and it had elastography score of 2.

In LNs with score 2, if clinical or sonographic suspicion existed the LN was subjected to histopathological examination, but in case of low

suspicion the follow-up policy was adopted to avoid unnecessary invasive procedures.

All LNs with score 3 and 4 were subjected to histopathological examination either by biopsy or FNAC.

The classification of LNs according to the character was as follows: 59 were benign, 25 metastatic and 4 were diagnosed as lymphoma and the diagnosis was made by biopsy in 17 cases (7 excisional and 10 tru-cut), FNAC in 20 cases and follow-up for at least 12 months in 51 LNs all proved to be benign [Table 1]. Fortunately enough all histopathological diagnosis based only on FNAC (due to technical feasibility) were positive for malignancy so there was no need for further invasive techniques as excisional or tru-cut biopsy.

Regarding the echogenicity, 98.3% of the benign LNs were hyperechoic while the rest were hypoechoic, and 89.7% of the malignant LNs were hypoechoic, 3.4% heterogenous and 6.9% hyperechoic. Patients' number is different.

The mean transverse diameter was much larger in metastatic LNs and so was the longest diameter, there is also a significant positive relation between the transverse diameter and elastography score i.e., the larger the transverse diameter the higher the elastography score. Results of L/T ratio analysis were as follows: AUC = 0.846, *P* = 0.00, cut-off = 1.93, sensitivity = 73%, specificity = 100%. Decreased L/T ratio is associated with increased probability of malignancy [Table 2 and Figure 1].

Elastogram analysis

All cases with score 1 proved to be benign with specificity of 100%, sensitivity of 76.3%, PPV of 100%, NPV of 84.7%, meaning that none of the LNs with score 1 were malignant, so score 1 can be an excellent excluding factor for malignancy [Figure 2a]. The statistical parameters of score 2 in

Table 1. Methods of diagnosis

All patients (N = 88)	Biopsy	FNAC	Follow-up
Benign (n=59, 67%)	8	0	51
Malignant (n=29, 33%)			
Lymphoma (n=4, 4.5%)	2	2	0
Metastasis (n=25, 28.5%)	7	18	0

FNAC: Fine-needle aspiration cytology

detecting benign lesions and the specificity for score 3 in detecting malignancy were shown in Table 3. All LNs with score 4 were malignant with specificity of 100%, PPV 100%, sensitivity 85.5% and NPV 65.5% [Table 4, Figure 2b and c].

Some previous studies grouped the elastography groups into categories, so they combined scores 1 and 2 and also scores 3 and 4. Further analysis to our results revealed that the elastography grouping into scores 1 + 2 then 3 + 4 in differentiating between benign and malignant revealed sensitivity of 79.3%, specificity: 100%, PPV: 100% and NPV: 90.8%. When score 3 +

4 is related to metastatic LNs, only sensitivity becomes 100%, with specificity 95.16%, PPV 88%, NPV 100%.

DISCUSSION

The pathological changes resulting in the enlarged LNs include reactive hyperplasia, lymphoma and tumor metastasis. The findings of B-mode and power Doppler sonography usually overlap and could not accurately reflect the nature of the LNs. Therefore, much more information should be provided to differentiate benign from malignant LNs. The elasticity or stiffness of the tissues is closely related to the biological characteristics. According to this theory, palpation is regarded as valuable for diagnosis in clinical practice. However,

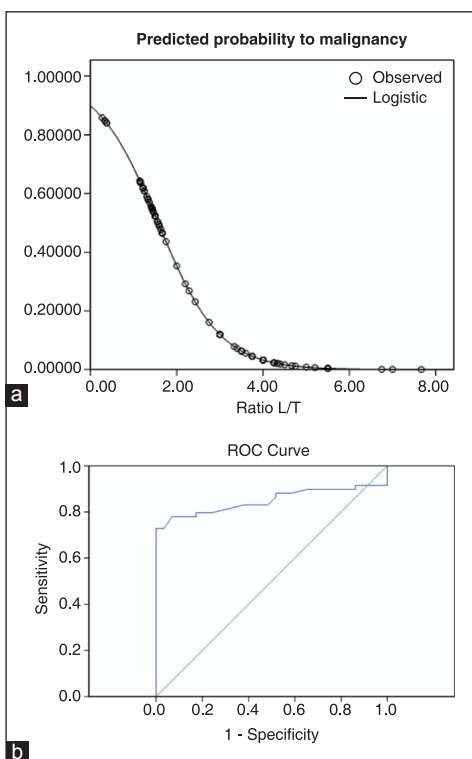


Figure 1. Mentioned in the result section. (a) Prediction of longitudinal/transverse (L/T) ratio for probability of malignancy; (b) Sensitivity and specificity of L/T ratio in detection of malignancy

Table 2. Significance of L/T ratio

Diameters of LNs	Diagnosis	Number	Mean	SD	P value
Transverse diameter	Benign	59	6.322	5.664	0.00
	Metastasis	25	18.44	7.066	
Longest diameter	Benign	59	15.881	7.166	0.00
	Metastasis	25	25.72	9.253	

L/T: Longitudinal/transverse; LN: Lymph nodes; SD: Standard deviation

Table 3. Elastography scoring analysis gave the following results

Statistical data	Score 1	Score 2	Score 3	Score 4
Sensitivity (%)	76.3	60.0	70.2	85.5
Specificity (%)	100	31.5	100	100
Positive predictive value (%)	100	15.3	13.8	100
Negative predictive value (%)	84.7	79.3	100	65.5

Table 4. Elastography score in all studied LNs and their diagnosis

LN diagnosis	Score 1	Score 2	Score 3	Score 4
Number	50	15	4	19
Diagnosis	All were benign	Benign: 9 Malignant: 6	All were malignant	All were malignant

LNs: Lymph nodes; LN: Lymph node

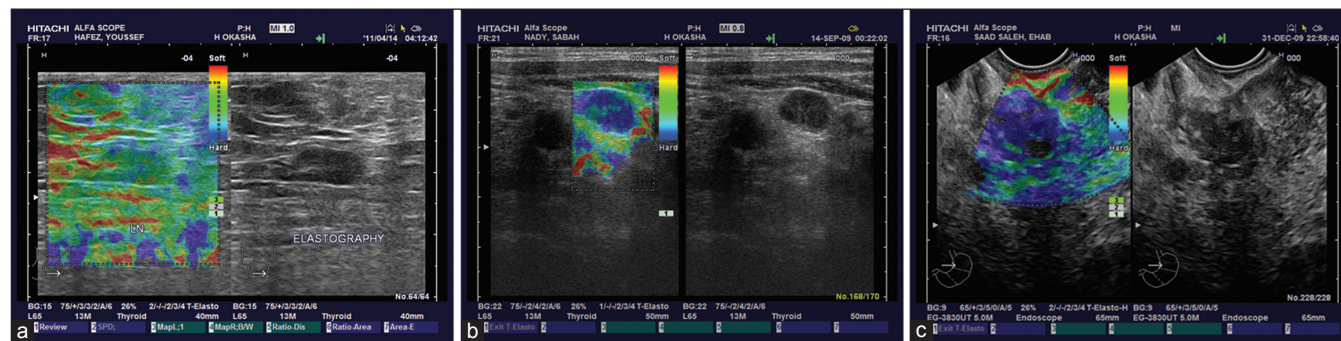


Figure 2. Ultrasound elastography images of a benign cervical lymph node (LN), malignant cervical LN and malignant peripancreatic LN. (a) A benign cervical LN showing elasticity score 1; (b) A malignant cervical LN showing elasticity score 3; (c) A malignant peripancreatic LN showing elasticity score 4

the palpation results vary with the experience of the examiners.^[6] Palpation has less sensitivity than US for detecting enlarged LNs in patients who have suspected regional LN metastases.

Elastography is a new technique with a very high specificity for malignant LNs at score 4 where it had specificity at our study of 100%. In our study, we found that E-score 1 can be a good excluding factor of malignancy so only follow-up is warranted in such cases and E-score of 4 is specific for malignancy and histopathological examination is a must to detect the type of malignancy. Furukawa *et al.*^[5] carried out a study on the LNs and classified the elastographic findings into 4 patterns. Their results revealed that the metastatic LNs were rated as patterns 3 and 4 and the benign ones as patterns 1 and 2. This was similar to our study where most of the benign nodes were classified as score 1 and 2 and most of the malignant ones were classified as score 3 and 4.

According to our results, E-score 3 and 4 has a specificity of 95.16% and sensitivity of 100%, PPV of 88%, NPV of 100% for metastatic LNs. Rubaltelli *et al.*^[7] found score 3 and 4 together 75% sensitive, 80% specific with PPV 80%, NPV 70%, unlike Chaoi *et al.*^[8] at 2011 who found E-score 2 and 3 had a sensitivity of 80.7% and a specificity of 66.7%. This sensitivity dropped to 29% while specificity became 97% in E-score 3 and 4.

At a cut-off value of 1.93, the sensitivity of L/T ratio in our study was 73% and the specificity was 100%. Zhang *et al.*^[6] suggested a cut-off value of 2 below which most LNs are malignant which agreed with Teng *et al.*^[9] in which cut-off value 2 was 78.8% sensitive and 45.9% specific for malignant LNs. These were in contradiction with the older study conducted by Leboulleux who found it to be only 46% sensitive and 64% specific.^[10]

The number of LNs in this study diagnosed as non-Hodgkin's lymphoma (NHL) was only 4, so no significant results could be deduced, however it is worth mentioning that 3 of them had E-score of 3 and one only had a score of 4 suggesting that LNs of NHL might be slightly softer than metastatic LNs. Metastatic LNs are predominantly hypoechoic when compared to

the adjacent soft-tissues except for metastatic nodes from papillary carcinoma of the thyroid, which are commonly hyperechoic.^[11] This agrees with our results in which nearly 90% of the malignant LNs were hypoechoic.

CONCLUSION

Elastography is a promising modality that may complement standard B-mode ultrasound and EUS and help guide FNAC and biopsy during staging of LNs. It is easy, rather cheap, non-invasive and repeatable and offers a strong diagnostic power, so it should be widely implemented into clinical practice. Further studies on a larger number of patients should be done to support the data of this work.

REFERENCES

- Huwart L, Peeters F, Sinkus R, *et al.* Liver fibrosis: Non-invasive assessment with MR elastography. *NMR Biomed* 2006;19:173-9.
- Ophir J, Céspedes I, Ponnekanti H, *et al.* Elastography: A quantitative method for imaging the elasticity of biological tissues. *Ultrasound Imaging* 1991;13:111-34.
- Ophir J, Garra B, Kallel F, *et al.* Elastographic imaging. *Ultrasound Med Biol* 2000;26 Suppl 1:S23-9.
- Alam F, Naito K, Horiguchi J, *et al.* Accuracy of sonographic elastography in the differential diagnosis of enlarged cervical lymph nodes: Comparison with conventional B-mode sonography. *AJR Am J Roentgenol* 2008;191:604-10.
- Furukawa MK, Kubota A, Hanamura H, *et al.* Clinical application of real-time tissue elastography to head and neck cancer – Evaluation of cervical lymph node metastasis with real-time tissue elastography. *Nihon Jibiinkoka Gakkai Kaiho* 2007;110:503-5.
- Zhang Y, Qing LV, Yin Y, *et al.* The value of ultrasound elastography in differential diagnosis of superficial lymph nodes. *Front Med China* 2009;3:368-74.
- Rubaltelli L, Stramare R, Tregnaghi A, *et al.* The role of sonoelastography in the differential diagnosis of neck nodules. *J Ultrasound* 2009;12:93-100.
- Choi JJ, Kang BJ, Kim SH, *et al.* Role of sonographic elastography in the differential diagnosis of axillary lymph nodes in breast cancer. *J Ultrasound Med* 2011;30:429-36.
- Teng DK, Wang H, Lin YQ, *et al.* Value of ultrasound elastography in assessment of enlarged cervical lymph nodes. *Asian Pac J Cancer Prev* 2012;13:2081-5.
- Leboulleux S, Girard E, Rose M, *et al.* Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. *J Clin Endocrinol Metab* 2007;92:3590-4.
- Ying M, Ahuja A, Brook F, *et al.* Ultrasound evaluation of neck lymph nodes. *Australas Soc Ultrasound Med* 2003;6:9-17.

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