Original Article

Diagnostic Performance of Sono-Elastography in Diagnosis of Enlarged Cervical Lymph Nodes: A Comparison with B-Mode and Doppler Ultrasonography at Phramongkutklao Hospital

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Objective: To evaluate diagnostic performance of sono-elastography, B-mode, and Doppler ultrasonography in the differentiation of reactive and malignant enlarged cervical lymph nodes (LNs).

Materials and Methods: The present research was prospectively conducted in all consecutive patients that requested ultrasonography for their enlarged cervical LNs at the Department of Radiology, Phramongkutklao Hospital between January 2018 and November 2018. Informed consents were obtained in all patients. Shear wave sono-elastography, B-mode ultrasonography, and Doppler ultrasonography were performed in all patients.

Results: One hundred nine LNs from 34 patients were studied. One patient with six LNs was lost to follow-up, then only 103 LNs from 33 patients were included in analyses. Fifty-seven LNs (55.4%) were found to be benign and 46 LNs (44.6%) were malignant. B-mode ultrasonography revealed the size criterion was slightly more accurate than the shape criterion. The Doppler ultrasonography assessment provides the highest accuracy compared to the other methods. Sono-elastography assessment at a cut-off point of 45 pKa has high specificity of 98.2% but low sensitivity at 17.4% with an accuracy of 62.1%.

Conclusion: Shear wave sono-elastography is useful for evaluating the cervical LNs. It helped distinguishing malignant from benign LNs. A high specificity may help choose the LNs for biopsy, which avoid the invasiveness of biopsy and save money. However, further study in larger group of patients and use of a combined evaluation (Doppler ultrasonography with shear wave sono-elastography) will help increasing the accuracy.

Keywords: Shear wave elastography, Cervical lymph nodes, Sonoelastography

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Among the 400 to 450 lymph nodes (LNs) in the human body, there are 60 to 70 nodes in the head and neck areas. These LNs may enlarge from inflammation (reactive enlargement) or infection. They can also grow from secondary involvement in the head and neck cancer. Metastatic cervical lymphadenopathy can appear as the first symptom in patients having malignancy in the head and neck, lung, and breast, etc.(1). Differentiation between reactive and metastatic lymphadenopathy is vital for both disease definition and treatment options. The standard diagnosis is pathological biopsy, which is an invasive technique. Radiographic diagnosis is a method that may help to differentiate between benign and malignant LNs using ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), which usually diagnose by size and distribution. Although B-mode and Doppler US are quick and easy screening techniques, with no patient preparation needed, that is less expensive, and that does not have radiation exposure, there are some limitations. Because the information of LNs obtained from these studies is only size, morphology, and distribution along blood vessels, the sensitivity and specificity for differentiation between benign and malignant LNs are not adequate.

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Because of the low accuracy, some malignancy can spread to LNs of less than 5 millimeters in up to 30% of the time. These malignancies can be found in lung cancer, esophageal cancer, gastric cancer, pancreatic cancer, and colorectal cancer[2-8].

Because of the importance to differentiate between benign and malignant LNs[9], ultrasound elastography (USE), a relatively new technique, may be used to evaluate tissue stiffness and elastic property based on the hypothesis that cell density will increase in most tumors and will result in elasticity loss. There have been several pilot studies using USE to find cancer in the LNs at the neck. However, these studies used the USE only to confirm the abnormally enlarged LNs or known abnormality found from B-mode US. These biases resulted in the prevalence of cancer in high rate ranging from 41% to 85%[10].

In addition, the previous published studies usually used a strain-type sono-elastography known to be more operator-dependent. In Phramongkutklao Hospital, the authors used shear wave elastography, which still have very limited information. Therefore, in the present study, the authors would like to evaluate diagnostic performance of sono-elastography, B-mode, and Doppler US, individually, in the differentiation of benign and malignant enlarged cervical LNs.

Materials and Methods

Patients

The present research was conducted as an observational prospective study. Enrollment was performed at the Department of Radiology, Phramongkutklao Hospital between January 2018 and November 2018. Consecutive patients of all ages with level I-VI cervical LN enlargement of unknown cause submitted for diagnostic radiology department for US were included. The ones with level VII cervical LNs enlargement were excluded because of inaccessibility by ultrasound. Written informed consents were received from all patients for undergoing both conventional Bmode sonography, Doppler US, and elastosonography. All patients with history of radiotherapy in the cervical region or patients with scarring or any skin disease involving cervical region were excluded due to potential in interfering with the elastography evaluation.

Sample size estimation

Sample size was calculated based on sensitivity estimation of the sono-elastography for diagnosis of malignant cervical lymphadenopathy by the information obtained from the literature review of Moharram et al[11]. Using the equation: $n = Z^2_{\alpha/2}\, p(1-p) / d^2$, the 'n' was sample size, the 'p' was sensitivity of USE for diagnosis malignant cervical lymphadenopathy (0.86), the 'd' was error, which was 0.07, and the '$Z_{\alpha/2}$' was the standard values from the table Z at α=0.05 (1.96). Then, the number of LNs should be recruited was 94.39. Therefore, the appropriate sample size of this study is at least 95 LNs.

Equipment and scanning process

All patients enrolled in the present study were examined in the supine position using conventional B-mode US, followed by Doppler evaluation, and then shear wave elastosonographic evaluation using Toshiba APLIO 500 (platinum series, Toshiba medical) with the linear transducer at a frequency range of 13 to 6 Hz.

For each LN, conventional B-mode US was performed first to measure both size and shape. Then, Doppler evaluation was performed to access the LN vasculature. Finally, the elastography mode was performed using the same transducer for an additional one to two minutes. USE was done by selecting the target LNs and then a region-of-interest box will be drawn three times to calculate for the average tissue stiffness with avoidance of other tissues and blood vessels. LN stiffness was measured as shear wave velocity (SWV) in m/s or mean EM, which was automatically calculated from the ultrasound software.

Evaluation

B-mode US: B-mode images were evaluated on the criteria of size and shape. Size and shape were evaluated per region. Regional distribution was determined according to the 1997 American Joint Committee on Cancer (AJCC) criteria for LNs. For the size criteria, length in short-axis diameter (in mm) was evaluated. LNs will be determined as normal or reactive when a short-axis diameter was 9 mm or less for sub-digastric and sub-mandibular nodes or 8 mm or less for other cervical nodes. For the shape criteria, the ratio of the length in the short axis divided by the length in the long axis (S/L ratio) was used and the S/L ratio of less than 0.5 will be determined as normal or reactive nodes while the LNs with the S/L ratio of 0.5 or larger will be determined as malignant.

Doppler mode US: Doppler US was performed in each patient and the pattern of vascularity was classified as hilar vascularity, avascularity, peripheral vascularity, or mixed vascularity.

Sono-elastography: LN stiffness was measured as mean EM, which was automatically calculated from

Table 1. Patient characteristics

	Benign (n=21)	Malignant (n=12)
Number of patients*	21 (63.6%)	12 (36.4%)
Number of lymph nodes evaluated	57 (55.4%)	46 (44.6%)
Number of lymph nodes of each patients	1 to 8 (median 2)	1 to 7 (median 3)
Sex	Male 9, female 12	Male 8, female 4
Age (years)	2 to 71 (mean 40.8)	23 to 77 (mean 52.1)
Mode of diagnosis	• Clinical diagnosis (6) • Pathological diagnosis (15)	• Clinical diagnosis (0) • Pathological diagnosis (12)
Final diagnosis	• Granulomatous lymphadenitis (3) • Non-specific lymphadenitis (17) • Submandibular lymphadenitis (1)	• Lymphoma (2) • Metastatic adenocarcinoma from breast cancer (1) • Metastatic adenocarcinoma from pancreatic cancer (1) • Metastatic poorly differentiated CA from nasopharyngeal cancer (1) • Metastatic poorly differentiated CA from thyroid cancer (2) • Metastatic papillary carcinoma from thyroid cancer (3) • Metastatic squamous cell carcinoma from tongue cancer (1) • Metastatic adenocarcinoma from lung cancer (1)

* One patient was lost to follow-up and excluded from an analysis due to uncertain final diagnosis

the ultrasound software. Then the best cut-off value was defined using statistical methods and Receiver Operating Characteristic (ROC) curve.

Final diagnosis

LNs were determined to be benign or reactive nodes on the basis of histopathologic findings or on the basis of clinical findings such as enlarged tender LN, increased C-reactive protein, leukocytosis, or decreasing in size (or disappearance) of the LN after antibiotic treatment in the absence of known malignancy. The LNs were determined to be metastatic nodes on the basis of histopathologic findings or imaging findings suggesting central necrosis which shown as hypodense on contrast-enhanced CT scan or hypointense signal on contrast-enhanced MRI in patients with malignancy. If there were not any histopathology to confirm diagnosis, the patients will be monitored for signs or symptoms or other investigations until the end of the research (December 2018). If there was no conclusion for the final diagnosis, the patient will be excluded from analysis.

Statistical analysis

General data analyses using descriptive statistics including percentage, mean, and standard deviation. The diagnostic performance of each modality will be reported as sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence interval (CI).

Ethical consideration

The present study protocol obtained permission for research by the Ethics Committee at the Institutional Review Board, the Royal Thai Army Medical Department. Informed consents were obtained in all patients. All patients were given the opportunity to disclose confidential information from their treatment history (OPD record), but will be protected by using a code instead of patient name or hospital number (HN) throughout data collection. During the examination, if the patient reported any physical or mental discomfort, the procedure will be stopped immediately, and it will not affect any routine patient care.

Results

During the study period, 34 patients were recruited with 109 LNs evaluated. One patient (2.9%) who carried six LNs was lost follow-up and was excluded from analysis due to uncertain final diagnosis. The characteristics the remaining 33 patients are shown in Table 1. The prevalence of benign LNs was 57 (55.4%) and malignant LNs was 46 (44.6%).

Among benign LNs, 19.6% of nodes (11/56) or 14.3% of patients (3/21) were found to be tuberculous lymphadenitis from histopathological evaluation (Figure 1). For malignant LNs, all of them were histopathologically confirmed (100%) (Figure 2) and

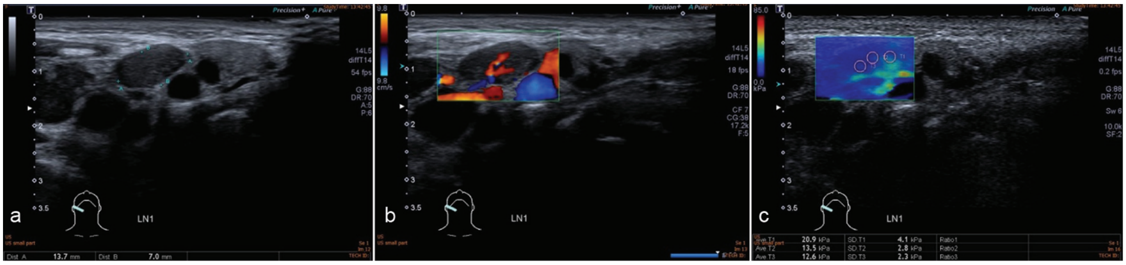

Figure 1. Benign LN. In 28-year-old woman. (a) B-mode US revealed well defined hypoechoic elliptical right cervical LNs, measured size 7 mm in short axis diameter. S/L ratio was 0.51. (b) Doppler US revealed hilar vascularity. (c) The sono-elastography calculated mean EM was 15.6 kPa. Final diagnosis of this patient was cervical lymphadenitis.

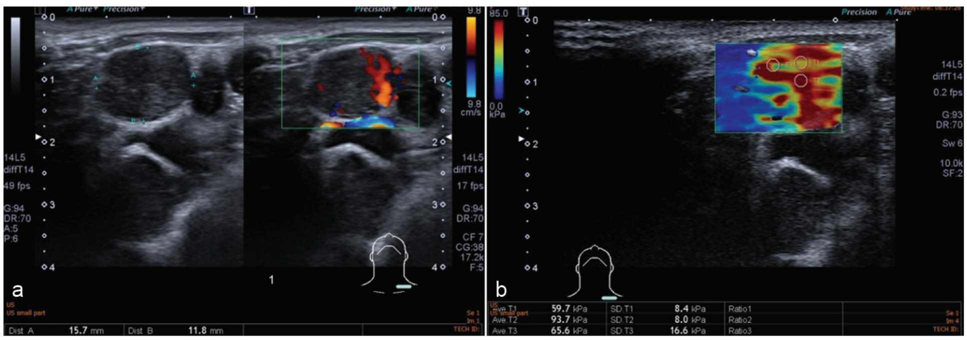

Figure 2. Malignant LN. In 68-year-old woman. (a) B-mode and Doppler ultrasonography revealed well defined hypoechoic right cervical LNs, measured size 11.8 mm in short axis diameter. S/L ratio was 0.75. Doppler ultrasonography revealed peripheral vascularity. (b) The sono-elastography calculated mean EM was 73 kPa. Final histopathological diagnosis was metastatic adenocarcinoma.

list of primary sites are shown in Table 1.

B-mode ultrasonography

It was found that evaluation using size criteria was slightly more accurate than using the shape criterion; however, neither were statistically significant. The detailed findings of B-mode US are demonstrated in Table 2.

The accuracy of using size and shape criteria for differentiating malignant and benign nodes was 57.3% and 53.4%, respectively.

Doppler ultrasonography

Most of benign LNs showed hilar vascularity (79%), which was significantly higher than in malignant LNs. Malignant LNs were categorized at hilar vascularity in three LNs (6.5%), peripheral vascularity in 13 LNs (28.2%), avascular pattern in eight LNs (17.3%), and mixed pattern in 22 LNs (47.8%). The distribution of Doppler findings is shown in Table 2 and Figure 3.

Color Doppler US evaluation of nodal vascular pattern had a 76.1% sensitivity, 89.5% specificity, and 83.5% accuracy for differentiating benign and malignant nodes.

From the final diagnosis, two out of 12 patients with malignancy were lymphoma. There were nine LNs from these two patients. Eight out of nine LNs (88.9%) were categorized as mixed pattern whereas the remaining LN showed a peripheral pattern.

Elastographic finding

The mean EM for malignant LNs (mean was 29.5±24.1 kPa) was greater than that for benign LNs (mean was 16.9±10.0 kPa) (Table 3). ROC was used to examine an optimum stiffness value (mean EM, kPa) that produces maximum specificity in predicting malignant cervical LNs as shown in Figure 4, which area under the curve was 0.68.

At a single cut-off at 45 kPa, the benign LNs show mean EM of 45 kPa or less in 56 LNs (98.2%) and

Table 2. Relationship between final diagnosis and the findings from B-mode ultrasonography and Doppler ultrasonography

Modality	Benign (n=57) n (%)	Malignant (n=46) n (%)	Chi-square	p-value
B-mode sonography				
Size (short-axis diameter)			1.626	0.202
• ≤ cut-off	38 (66.7)	25 (54.4)		
• > cut-off	19 (33.3)	21 (45.6)		
Shape (S/L ratio)			3.172	0.075
• <0.5	14 (24.6)	5 (10.9)		
• ≥0.5	43 (75.4)	41 (89.1)		
Doppler ultrasonography				
Hilar (central)	45 (79.0)	3 (6.5)	53.660	<0.001
Peripheral	0 (0.0)	13 (28.3)	18.436	<0.001
Avascular	6 (10.5)	8 (17.4)	1.022	0.312
Mixed	6 (10.5)	22 (47.8)	17.892	<0.001

Chi-square test

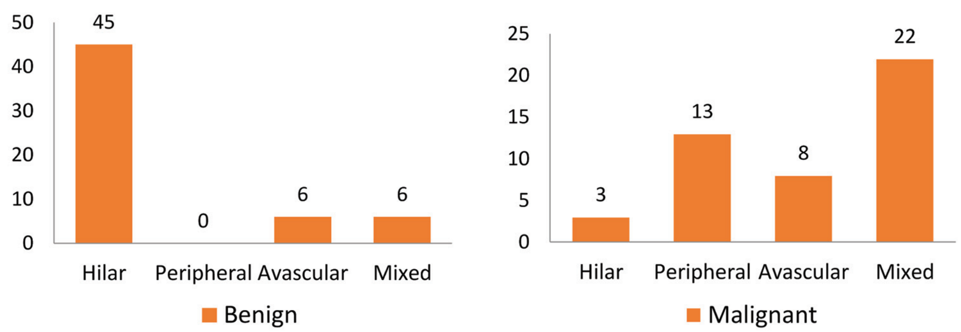

Figure 3. Distribution of vascular patterns.

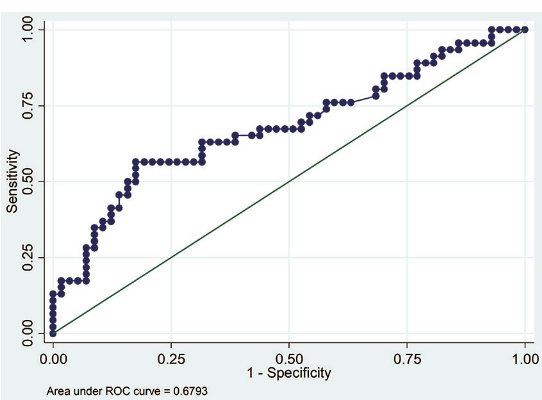

Figure 4. Receiver operating characteristic curve for sono-elastography. Area under the curve was 0.68.

more than 45 kPa in one LN, while malignant LNs show mean EM of 45 kPa or less in 38 LNs and more than 45 kPa in eight LNs (Table 3).

Elastographic sonography evaluation of tissue stiffness had a 17.4% sensitivity, 98.2% specificity, and 62.1% accuracy for differentiating malignant cervical LNs from benign.

Summarized accuracy of all modalities evaluated are shown in Table 4 and Figure 5.

Discussion

Differentiation between benign and metastatic cervical lymphadenopathy is important in both, staging of the disease and choosing the treatment options. The patients were usually taken to biopsy,

Table 3. Comparison between the studied groups as regard mean elastic modulus (EM)

	Benign (n=57) n (%)	Malignant (n=46) n (%)	Chi-square	p-value
Mean EM (kPa)	16.9±10.0	29.5±24.1	7.806	0.010*
≤45	56 (98.2)	38 (82.6)		
>45	1 (1.8)	8 (17.4)		

* Fisher's exact test

Table4. Comparison between the diagnostic performance of B-mode ultrasonography, Doppler, and sono-elastography

Modality	TP	FN	TN	FP	Sensitivity	Specificity	PPV	NPV	Accuracy
B-mode sonography (size criteria)	21	25	38	19	45.7%	66.7%	52.5%	60.0%	57.3%
B-mode sonography (shape criteria)	41	5	14	43	89.1%	24.6%	48.8%	73.7%	53.4%
Doppler ultrasonography	35	6	51	11	76.1%	89.5%	85.4%	82.3%	83.5%
Elastography	8	1	56	38	17.4%	98.2%	88.9%	59.6%	62.1%

TP=true positive; FN=false negative; TN=true negative; FP=false positive; PPV=positive predictive value; NPV=negative predictive value

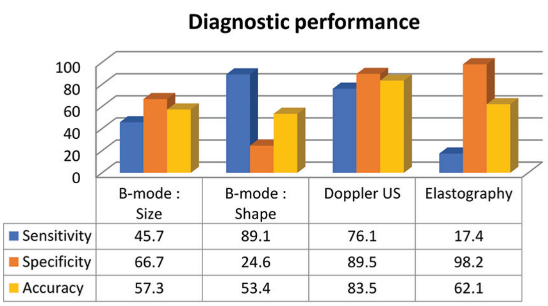

Figure 5. Comparison between the diagnostic performance of B-mode US, Doppler US, and sono-elastography.

which is an invasive procedure. Therefore, the present study evaluated a diagnostic performance to see whether elastography will potentially reduce unnecessary biopsies. Although there have been lots of published studies describing the diagnostic accuracy of elastography in cervical LNs, most are based on strain elastography that was known to be operator dependent. For the shear-wave elastography that the authors used in the present study, while some reports were done about its accuracy, the diagnostic value may be different from the setting in Thailand's population as Tuberculous lymphadenitis is more prevalent. The aim of the present study was to evaluate the diagnostic performance of elastography on cervical lymphadenopathy in Thai population.

B-mode ultrasonography

Nodal size is used as a criterion in distinguishing benign and malignant diseases for a long time. Previous studies reported different cut-off points for the maximum short axis axial diameter to differentiate malignant and benign LNs (5, 8 and 10 mm). At present, there has been no consensus criterion. Van den Brekel et al[12] noted that the optimal cut-off point of nodal size varies with the patient population, and they suggested that for any patient population, the most acceptable size criterion is 9 mm for sub-digastric nodes and 8 mm for other cervical LNs. The present study revealed that malignant LNs tend to have a larger size and larger S/L ratio than benign LNs, however, it was not statistically significant.

The accuracy of using size and shape (S/L ratio) criteria for differentiating malignant and benign nodes was 57.3% and 53.4%, respectively.

As compared to the similar study, Lyshchik et al[13] and Moharram et al[11] used short axis diameter at a cut-off point of 8 mm. The accuracy was found to be 65% and 60%, respectively, which was consistent to the present study.

Alam et al[1] studied the accuracy of both sono-elastography and B-mode US in similar setting to the present study. In contrast, their accuracy was as high as 84%. The possible explanation is that in Alam et al's study[1], 109 LNs of 59 patients were recruited in the study but only 85 LNs of 37 patients were included in analysis. That was because the patients with benign

LNs were self-limited and lead to a lost-to-follow-up events. Thus, twenty-two percent of LNs excluded may have resulted in a higher chance of detectable malignant LNs (62% as compared to 44.6% in the present study).

Another important point to note is the method of diagnosis. While diagnosis of malignancy was made by histopathology in 100% of cases in our study, it was 50% in Alam et al's study[1].

Regarding to the shape criterion, our accuracy was 53.4%, consistent with Alam et al's study[1], with accuracy of 56%.

Doppler ultrasonography

Because the present study was performed in Thailand where tuberculosis is an endemic area, the authors hypothesized that our accuracy of B-mode US and elastosonography may be not as high as in the other studies. Thus, the authors decided to add Doppler US to help distinguishing benign and malignant LNs using vascular pattern. As described above, the present Doppler study showed 83.5% of accuracy. Benign LNs tended to have hilar vascularity pattern (79%) while malignant LNs tended to have mixed (47.8%) or peripheral (28.3%) pattern. In a similar study by Moharram et al[11], the accuracy of Doppler US in evaluation for metastatic LNs was 90%, whereas for lymphomatous LNs was 82.2%. In the present study, because two out of 12 patients (16.6%) diagnosed with malignant LNs were lymphoma, the present study accuracy was assumed to be comparable to the report in the other studies.

Regarding the pattern of vascularity on Doppler US, benign LNs in the present study had a tendency to be hilar vascularity similar to the other reports[14-17], while metastatic nodes tend to have peripheral or mixed vascularity similar to the other reports too[15,16,18,19]. Therefore, the presence of peripheral vessels in LNs is a useful indicator of malignancy. The peripheral vascularity in metastatic nodes is believed to be related to tumor infiltration of the LNs in which the tumor cells produce tumor angiogenetic factor (TAF), which causes angiogenesis and recruitment of peripheral vessels[15,16,19]. Mixed vascularity is seen in malignant nodes because angiogenesis occurs and peripheral vessels are induced, but the pre-existing hilar vessels are preserved until they are destroyed by the tumor cells at a later stage[14].

From the literature review, lymphomatous LNs tend to have both hilar and peripheral vessels (62% to 90%) shown on Doppler US[14,15,19-21]. Unlike metastatic nodes, the presence of peripheral vascularity alone is not common in lymphomatous nodes (5%)[15]. The high incidence of hilar vascularity in lymphomatous nodes is thought to be related to the fact that intranodal necrosis or keratinisation is not common in lymphoma, and therefore the hilar vessels of the nodes are preserved[15,21]. In the present study, eight out of nine LNs (88.9%) from two patients were categorized as mixed pattern whereas the one remaining LN (11.1%) showed peripheral pattern, which is consistent with the previous reports.

Elastosonography

The present study found that malignant LNs were significantly stiffer than benign. A cut-off of 45 kPa attained highest accuracy of 62,1%, corresponding to 17.4% sensitivity, 98.2%, specificity and 0.68 area under the ROC curve. The sensitivity, specificity, and accuracy of elastography from the previous studies ranged widely from 62.2% to 92.5%, 35.1% to 100.0%, and 61.1% to 92.0%, respectively. Possible explanation of these differences was in part due to the technique used (strain elastography), which is an operator dependent technique. In the present study, the authors used a shear wave elastography that depends less on operator. While another study by Bhatia et al[22] was similar to the present study, shear wave elastography could differentiate benign and malignant LNs (median EM; benign was 21.4 kPa, malignant was 25 kPa) and with a cut-off of 30.2 kPa attained highest accuracy of 61.8%, corresponding to 41.9% sensitivity, 100% specificity, and 0.77 area under the ROC curve.

A high specificity in these sono-elastographic studies may help physician choosing the proper LNs to biopsy to lessen unnecessary harmful biopsy and save money. This cut-off point can be used as a baseline value in Thai population for the future study.

Limitations

There were some limitations as followed:

1) There were some factors that may limit proper evaluation using ultrasound, such as the position of the LN that was too deep or located near the blood vessels causing motion artifact, obese patients, or patients having short neck.

2) The sample size was small, using the number of LNs as unit and not the number of patients. For this reason, sub-groups analysis could not be performed in each histologic type of malignant LNs and sub-types of benign LNs (i.e., tuberculous LNs or non-specific lymphadenitis nodes).

3) The prevalence of malignancy in the present

study patients was not high because the LNs included in the analysis were all small in size and more prevalent of tuberculous LNs because of the higher prevalence of tuberculous in Thailand.

4) While Doppler US and sono-elastography were performed at the same time for all patients, the authors did not combine both modalities in distinguishing malignancy or benign LNs, which may result in more accurate diagnosis.

Conclusion

In summary, Doppler US and shear wave sono-elastography are useful tools to evaluate the cervical LNs. It helps in distinguishing malignant from benign LNs. A high specificity seen in this sono-elastographic study may help physician to choose the LNs to lessen unnecessary harmful biopsy and save money. However, due to a few numbers of LNs and patients included in analyses, the authors recommend further study in larger group of patients and use of a combined evaluation (Doppler US with shear wave sono-elastography) to increase the accuracy of study.

What is already known on this topic?

Elasticity of malignant and benign LNs is different. Strain-type sono-elastography can differentiate malignant from benign LNs but its accuracy varied and depended on operators.

What this study adds?

Sono-elastography can differentiate benign and malignant LNs and its high specificity may help us to choose the LNs to lessen harmful biopsies.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Alam F, Naito K, Horiguchi J, Fukuda H, Tachikake T, Ito K. 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.
2. Prenzel KL, Hölscher AH, Drebber U, Agavonova M, Gutschow CA, Bollschweiler E. Prognostic impact of nodal micrometastasis in early esophageal cancer. Eur J Surg Oncol 2012;38:314-8.
3. Prenzel KL, Monig SP, Sinning JM, Baldus SE, Brochhagen HG, Schneider PM, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. Chest 2003;123:463-7.
4. Prenzel KL, Hölscher AH, Vallböhmer D, Drebber U, Gutschow CA, Mönig SP, et al. Lymph node size and metastatic infiltration in adenocarcinoma of the pancreatic head. Eur J Surg Oncol 2010;36:993-6.
5. Jenssen C, Dietrich CF, Burmester E. Malignant neoplasias of the gastrointestinal tract--endosonographic staging revisited. Z Gastroenterol 2011;49:357-68.
6. Moehler M, Al Batran SE, Andus T, Anthuber M, Arends J, Arnold D, et al. German S3-guideline "Diagnosis and treatment of esophagogastric cancer". Z Gastroenterol 2011;49:461-531.
7. Jürgensen C, Dietrich CF. Role of endoscopic ultrasound (EUS) in the staging of rectal cancer. Z Gastroenterol 2008;46:580-9.
8. Jenssen C, Dietrich CF. Endoscopic ultrasound-guided fine-needle aspiration biopsy and trucut biopsy in gastroenterology - An overview. Best Pract Res Clin Gastroenterol 2009;23:743-59.
9. Kurt A, Gunes Tatar I, Ipek A, Hekimoglu B. B-mode and elastosonographic evaluation to determine the reference elastosonography values for cervical lymph nodes. ISRN Radiol 2013;2013:895287.
10. Choi YJ, Lee JH, Baek JH. Ultrasound elastography for evaluation of cervical lymph nodes. Ultrasonography 2015;34:157-64.
11. Moharram MA, Abd-El Maboud NM, Elaziz Ahmed HA. Evaluation of the role of sono-elastography in diagnosis of enlarged cervical lymph nodes. Egypt J Radiol Nucl Med 2017;48:381-91.
12. van den Brekel MW, Castelijns JA, Stel HV, Golding RP, Meyer CJ, Snow GB. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol 1993; 250:11-7.
13. Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, Hiraoka M, et al. Cervical lymph node metastases: diagnosis at sonoelastography--initial experience. Radiology 2007;243:258-67.
14. Na DG, Lim HK, Byun HS, Kim HD, Ko YH, Baek JH. Differential diagnosis of cervical lymphadenopathy: usefulness of color Doppler sonography. AJR Am J Roentgenol 1997;168:1311-6.
15. Ariji Y, Kimura Y, Hayashi N, Onitsuka T, Yonetsu K, Hayashi K, et al. Power Doppler sonography of cervical lymph nodes in patients with head and neck cancer. AJNR Am J Neuroradiol 1998;19:303-7.
16. Wu CH, Chang YL, Hsu WC, Ko JY, Sheen TS, Hsieh FJ. Usefulness of Doppler spectral analysis and power Doppler sonography in the differentiation of cervical lymphadenopathies. AJR Am J Roentgenol 1998;171:503-9.
17. Ying M, Ahuja A, Brook F, Metreweli C. Power Doppler sonography of normal cervical lymph nodes. J Ultrasound Med 2000;19:511-7.
18. Ahuja AT, Ying M. Sonographic evaluation of cervical lymph nodes. AJR Am J Roentgenol 2005;184:1691-9.
19. Steinkamp HJ, Mäurer J, Cornehl M, Knöbber D, Hettwer H, Felix R. Recurrent cervical lymphadenopathy: differential diagnosis with color-duplex sonography.

Eur Arch Otorhinolaryngol 1994;251:404-9.
20. Dragoni F, Cartoni C, Pescarmona E, Chiarotti F, Puopolo M, Orsi E, et al. The role of high resolution pulsed and color Doppler ultrasound in the differential diagnosis of benign and malignant lymphadenopathy: results of multivariate analysis. Cancer 1999;85:2485-90.
21. Steinkamp HJ, Mueffelmann M, Bock JC, Thiel T, Kenzel P, Felix R. Differential diagnosis of lymph node lesions: a semiquantitative approach with colour Doppler ultrasound. Br J Radiol 1998;71:828-33.
22. Bhatia KS, Cho CC, Tong CS, Yuen EH, Ahuja AT. Shear wave elasticity imaging of cervical lymph nodes. Ultrasound Med Biol 2012;38:195-201.