RESEARCH COMMUNICATION

Value of Ultrasound Elastography in Assessment of Enlarged Cervical Lymph Nodes

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Abstract

Background: To investigate the value of ultrasound elastography (UE) in the differentiation between benign and malignant enlarged cervical lymph nodes (LNs). Methods: B-mode ultrasound, power Doppler imaging and UE were examined to determine LN characteristics. Two kinds of methods, 4 scores of elastographic classification and a strain ratio (SR) were used to evaluate the ultrasound elastograms. Results: The cutoff point of SR had high utility in differential diagnosis of benign and malignant of cervical lymph nodes, with good sensitivity, specificity and accuracy. Conclusion: UE is an important aid in differential diagnosis of benign and malignant cervical LNs.

Keywords: Ultrasound - elastography - strain ratio - lymph node - differential diagnosis

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Introduction

The reasons of enlarged cervical LNs can be metastasis, reactivity, primary malignance and tuberculosis. Overall, it can be divided into benign and malignant enlargement. It is very important for the subsequent diagnosis and treatment to make sure the LNs are malignant or not (Kau et al., 2000; Senchenkov and Staren, 2004; Li and Chen, 2012).

Recently, ultrasound elastography is very popular as a novel technique in cancer research. UE works as follows: a mechanical force is applied to soft tissue, such as a lesion and the area around it, to obtain a displacement of the tissue. The degree of stiffness can be analyzed by the displacement. An elastogram obtained with the results of tissue compression appears on the monitor. On the elastogram, soft areas usually appear red or yellow and hard areas appear blue. UE has been used on several organs: breast (Itoh et al., 2006; Thomas et al., 2006), thyroid (Lyshchik et al., 2005), prostate (Taylor et al., 2005), liver (Friedrich-Rust et al., 2007; Thomas et al., 2007) and skin (Iagnocco et al., 2010). But on cervical LNs, there were few researches, such as Lyshchik et al. (2007), Farzana Alam et al. (2008) and Rong Tan et al. (2010). The purpose of this study was to investigate the value of UE in the differentiation between benign and malignant enlarged cervical lymph nodes.

Materials and Methods

Patients

This study was conducted at China-Japan Union Hospital of Jilin University during 6 months from September 2010 to March 2011, 93 patients with 192 enlarged cervical lymph nodes were examined with B-US and PDI. Every multiple lymph node patient was examined by a sonographer who had 25 years experience in cervical sonography, to choose one lymph node which was highly suspicious to be malignant. This highly suspected lymph node will become our research object. All the lymph nodes were examined with ultrasound elastography and underwent ultrasound-guided core needle biopsy to obtain histological pathology results. Except 4 patients lost long-term follow-up, the rest 89 lymph nodes (malignant, n = 52; benign, n = 37) of 89 patients (33 men, 56 women, age rage, 8-78 years) were included in this study. This research had been approved by the hospital's ethics committee, and informed consent had been obtained from each patient before the procedures.

We used Bard automated biopsy device with 18G core needles to obtain the tissue samples 3-4 bars of every lymph node with ultrasound-guided. All final pathologic results were made by a pathologist with more than 20 years of experience performing histological LN diagnosis. A few benign result cases were under suspicion highly to be malignant by clinic. These lymph nodes were taken the ultrasound-guided core needle biopsy again. It was helpful for reducing error in diagnosis caused by sampling error. In addition, all the benign result cases were reviewed for a minimum follow-up period of 3 months to confirm these lymph nodes have no malignant direction.

Equipment and scanning

During the examination, patients remained supine

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position and exposed their necks fully. All the images were acquired by the same sonographer using TOSHIBA-SSA 790A equipped with a linear-array transducer 805A of 5-12 MHz. The sonographer had 25 years neck conventional ultrasound and one year UE experience. These images of every LN contained the length and horizontal diameter, border, shape, hilum, echogenicity and the distribution of the blood flow. If a patient was a single lymph node enlarged, the images of UE were directly acquired after the conventional ultrasound examination. However, for the patients with multiple lymph nodes enlarged, the biopsies to every enlarged LN were more harmful, so the experienced sonographer selected one lymph node as research object which was the most highly suspicious to be malignant based on conventional ultrasound. Then the sonographer obtained UE images of the LN.

In the process of examination, all the original data and images stored in hard disk of ultrasound scanner for further analysis.

In UE examination split-screen mode was used to ensure that the lesions were located in the region of interest (ROI); the complete cervical lymph node of every patient was included in the ROI of elastogram, and the LN should be less than one third of the ROI. Because SR of UE in this study used neck muscles as a reference object, so the ROI should include both the cervical lymph node and neck muscles; in order to avoid carotid artery throb influence test results, carotid artery were not appear in the ROI. The pressure in the process should be stable, uniform and appropriate to insure the elastograms were good enough to be analyzed. The image was scored and than the strain ratio of muscle to LN was calculated. The complete LN should be measured for calculating SR.

Conventional ultrasound

All LNs were examined in B-US as criterions for their short-axis diameter, shape, border, long-to-short-axis diameter ratio in the longitudinal plane (L/T), hilum, and echogenicity. Short-axis diameter < 8 mm was the criterion as benign and ≥8mm as malignant; regular shape was the criterion as benign and irregular sharp as malignant; clear border was considered as benign and unclear border as malignant; L/T ≥ 2 was considered as benign and < 2 as malignant; present of hilum was considered as benign and absent as malignant; homogeneous ehcogenicity was considered as benign and heterogeneous echogenicity as malignant (Solbiati et al., 1992; Takashima et al., 1997; Ahuja and Ying, 2002; Castelins et al., 2003).

According to the report of the Wu et al. (1998), the PDI of lymph node was divided into 5 types as follows: hilar type (type I), defined as branches from center toward the periphery radially or a simple hilar vessel signal only; arboroid or spotted type (type II), defined as scattered segments or spots of vessel signals distributed chaotically; peripheral type (type III), defined as prominent peripheral vascularization distributed; mixed type (type IV), defined as a mixture of more than one type of vascular distribution; and avascular type (type V), barely showing vascularization distributed. Type I and V were the criteria as benign lymph node, and type II, III, IV were the criteria as malignant.

Ultrasonic Evaluation

One kind of UE evaluation methods was the 4 scores of elastographic classification: a score of 1 shows that ≥80% area of the LN section plane is green or red, a score of 2 shows that ≥50% and <80% is red or green, a score of 3 shows that ≥50% and < 80% is blue, and a score of 4 shows that ≥ 80% or more area of the LN section plane is blue. Lesions that present score 1 or 2 are classified as probably benign, while score 3 and 4 are indicative of probable malignancy (Furukawa et al., 2007; Iagnocco et al., 2010). Another kind of UE evaluation methods was the SR of neck muscle to cervical lymph node. The cutoff point of SR was calculated using receiver-operating characteristic (ROC) curve analysis.

Pathology examination

After the ultrasound examination, each lymph node was undergone ultrasound-guided fine core needle biopsy. The lymph node specimens were put in 10% of the formalin, again in paraffin, sliced. Then sections were stained with standard hematoxylin and eosin. Every final pathology diagnosis was given by a pathologist with 20 years of experience. A few benign result cases were under suspicion highly to be malignant by clinic. These lymph nodes were taken the ultrasound-guided core needle biopsy again. It was helpful for reducing error in diagnosis caused by sampling error. Then all benign results were followed at least 3 months to confirm that no malignancy had developed in these lymph nodes subsequently.

Statistical Analysis

SPSS13.0 and Stata11.0 were used for statistical analysis. The unit of analysis was each lymph node and data were registered separately, and then analyzed blindly. Mann-Whitney U test was used for checked differences in continuous measurements. Chi-square test was used for comparing qualitative variables. ROC curve was used to obtain the best cutoff point of SR, according to the following principle: the sensitivity plus specificity had a biggest number. The comparation of area under the curve (AUC) was analyzed by Z test. Parameters with $P < 0.05$ were considered significant and all tests were two tailed.

Results

Pathology

Final pathologic results of all the 89 lymph nodes as

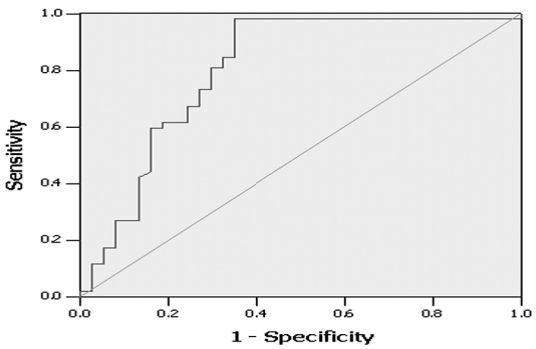

Figure 1. The Best Cutoff Point of SR was 1.78, Which was Calculated by ROC Curve. The LN was considered as malignant with SR ≥ 1.78

Table 1. Results of Conventional Ultrasound

	Sonomorphologic features	Benign	Malignant	P	Contingency coefficient	Odds ratio (95% CI)	Sensitivity	Specificity	Accuracy
Border	Clear	28(31.5%)	30(33.7%)	0.079	0.166	2.28(0.83~6.58)	42.30%	75.70%	56.20%
	Unclear	9(10.1%)	22(24.7%)						
Shape	Regular	23(25.8%)	16(18.0%)	0.003	0.312	3.70(1.39~9.91)	69.20%	62.20%	66.30%
	Irregular	14(15.7%)	36(40.4%)						
Short axis	<8	15(16.9%)	3(3.4%)	0	0.376	11.1(2.68~64.2)	94.20%	40.50%	71.90%
	≥8	22(24.7%)	49(55.1%)						
Echogenicy	homogeneous	23(25.8%)	25(28.1%)	0.189	0.135	1.77(0.69~4.60)	51.90%	62.20%	56.20%
	heterogeneous	14(15.7%)	27(30.3%)						
L/T	≥2	17(19.1%)	11(12.4%)	0.013	0.257	3.17(1.14~8.93)	78.80%	45.90%	65.20%
	<2	20(22.5%)	41(46.1%)						
Hilum	Normal	13(13.5%)	7(7.9%)	0.016	0.232	3.48(1.10~11.6)	86.50%	35.10%	65.20%
	Abnormal	24(27.0%)	45(50.6%)						
PDI	I or V	28(31.5%)	17(19.1%)	0	0.417	6.41(2.27~18.7)	67.30%	75.70%	70.80%
	II,III, or IV	9(10.1%)	35(39.3%)						
UE Score	1 or 2	13(14.6%)	6(6.7%)	0.007	0.254	4.15(1.26~14.9)	88.40%	35.10%	66.30%
	3 or 4	24(27.0%)	46(51.7%)						
Strain Ratio	<1.78	24(27.0%)	1(1.1%)	0	0.66	94.2(12.3~3943.2)	98.10%	64.90%	84.30%
	≥1.78	13(14.6%)	51(57.3%)						

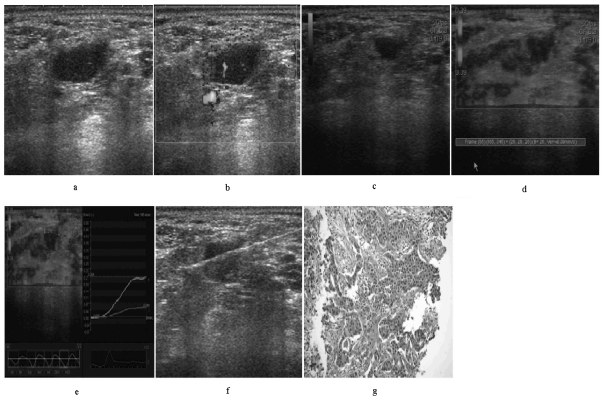

Figure 2. A 61-year-old Woman with Enlarged Cervical LN of Right Neck. (a) the short-axis diameter of this LN was 6.5 mm, less than 8mm. (b) the PDI was typed II; (c, d, e) after compression, the elastogram was obtain. It was scored as 4 point and the SR was 4.22; (f, g) the LN was undergone a biopsy with ultrasound-guided, and the pathology of this LN was adenocarcinoma. Short-axis diameter was misdiagnosis, but UE was correct diagnosis

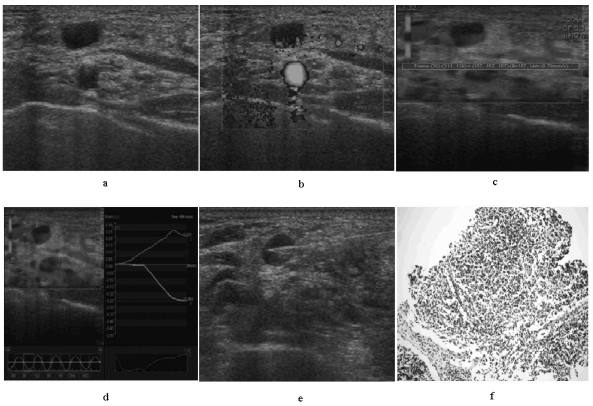

Figure 3. Figures Obtained from a 40-year-old Woman with Left Supraclavicular Fossa Enlarged LN. (a, b) sonogram obtained from conventional ultrasound; (c, d) on the elastogram, the proportion of blue areas in this LN was more than 50%, so it was scored 3 point. But the blue areas in the LN were light blue, the SR was only 1.33; (f, g) the LN was undergone a biopsy with ultrasound-guided, and the pathology of this LN was reactive hyperplasia. 4 scoring method was misdiagnosis, but SR was correct diagnosis

follows: in 37 benign lymph nodes, 5 were Histiocytic Necrotizing Lymphadenitis, 16 were tuberculosis, 16 were hyperplasia; in 52 malignant lymph nodes, 14 were metastatic squamous cell carcinoma, 12 were metastatic adenocarcinoma, 3 were metastatic thyroid papillary carcinoma, 1 was metastatic thyroid follicular carcinoma, 6 were the metastatic small cell carcinoma, 5 were lymphoma (2 non Hodgkin's lymphoma, 1 Hodgkin's Lymphoma, 1 follicular lymphoma, 1 mantle cell lymphoma), 1 was adenosquamors carcinoma, 10 were maligenant lymph nodes can't be distinguish the sources.

Conventional ultrasound

As Table 1 shows, in six B-US evaluation criterions, the highest sensitivity was obtained from short-axis diameter, the lowest from border; the highest specificity was obtained from border, the lowest from hilum; the highest accuracy was obtained from short-axis diameter, the lowest from border and echogenicy. 3 malignant LNs and 22 benign LNs were misdiagnosed by short-axis diameter. 14 of 22 benign LNs misdiagnosed were tuberculosis; 2 of 16 LNs with tuberculosis were correct diagnosis.

28 of 37 benign lymph nodes were type I or V in PDI and only 9 lymph nodes were other types, 35 of 52 malignant lymph nodes were type II, III or IV, only 17 malignant lymph nodes were type I. The statistical analysis shows that the differences are statistically significant (P = 000), the odds ratio is 6.41, contingency coefficient is 0.417. And the sensitivity, specificity and accuracy of PDI in distinguish were 67.3%, 75.7% and 70.8% respectively.

Ultrasonic Evaluation

The results of 4 scoring method and strain ratio were obtained from elastogram. The cutoff point of stain ratio in cervical lymph nodes was 1.78, calculated from ROC curve (Figure 1). Typical examples are illustrated

in Figures 2 and 3. SR≥1.78 was the cutoff point for malignant LNs, SR<1.78 for benign. 13 of 37 benign LNs were scoring as 1 or 2 point in 4 scoring method, 24 were SR<1.78. 46 of 52 malignant lymph nodes were scoring as 3 or 4 point in 4 scoring method, 51 were SR≥1.78. The sensitivity, specificity and accuracy of 4 scoring method were 88.4%, 35.1% and 66.3% respectively. The sensitivity, specificity and accuracy of SR were 98.1%, 64.9% and 84.3%. The sensitivity of SR was statistically significant higher than all the diagnostic criteria examined except short-axis diameter and the accuracy of SR was the highest.

Discussion

Ultrasound elastography was evaluated by stiffness of lesions and surrounding normal tissues to judge the nature of lesions. The stiffness of the lesions was determined by its aspects of pathology character, such as cell types of lesions, the proportion of all kinds of cells and level of metabolic, micro and macro pathological structure, etc. In neck lymph nodes, the source of evalute stiffness of lesion was palpation. It was too subjective to evaluate stiffness accurately. Palpation was less sensitivity than US for detecting enlarged lymph nodes in patients who have suspected regional lymph node metastases. But ultrasound elastography as a special "palpation" can not only show different organization stiffness intuitively, but also be able to calculate the strain ratio of different organizations for every palpable and nonpalpable lymph node. UE is more objective and sensitive. As the results we obtained from this study, UE was a valuable criterion in the differential diagnosis of benign and malignant of cervical lymph nodes (Contingency coefficient 0.658).

UE is a new technique in differential diagnosis of benign and malignant of cervical lymph nodes with excellent sensitivity (98.1%). 51 of 52 malignant lymph nodes were correct diagnosis; only 1 lymph node obtained SR as 0.22, this LN was a metastasis lymph node from thyroid follicular carcinoma. The follicular structure in the lymph node could be the reason of lower SR. The specificity of UE was lower (64.9%). Only 5 of 16 tuberculosis lymph nodes were diagnosed correctly by UE. It could be the structures in tuberculosis lymph nodes were various and often with calcification. The specificity (64.9%) means all lymph nodes with SR≥1.78 need a biopsy (such as ultrasound-guided fine core needle biopsy) or FNAC which was considered as a minimal invasion diagnostic technique (Fatima et al., 2011). However, the sensitivity (98.1%) means 98.1% lymph nodes with SR<1.78 are unnecessary for the invasion diagnostic technique. In SR<1.78 group, this kind of diagnostic technique is just necessary for a few LNs which are highly suspected to be malignant because of the history or other examinations.

Short-axis diameter was the best criterion of conventional ultrasound in our research, but this criterion for malignant LNs was controversial. All of the 3 malignant LNs misdiagnosed with short-axis diameter were correct diagnosis by UE. But for tuberculosis, it seemed that UE had no advantage over other criterions; maybe need further research in this field.

In this study, the SR is better than 4 scoring method in differential diagnosis of benign and malignant of cervical lymph nodes. We considered there were some reasons as follows: 1. SR was more accurate for calculating the different stiffness between lesions and the surrounding tissue. 2. 4 scoring method was scored by the proportion of blue area in lesions. But in the study, we found that there were some differences about the color, light blue and dark blue showed different stiffness of lymph nodes, but the scores could be same. There were 6 benign lymph nodes misdiagnoses, because the proportion of blue area is larger than 50% and scored 3 points. But the blue areas in the lymph nodes were light blue, so the stiffness of entire LN was not high enough. SR could avoid this kind of misdiagnosis.

SR could divide the lymph nodes into benign and malignant with accuracy of 84.3%. But limited by the small sample size of this study, it was not sure whether SR of UE could show significant different in different kinds of disease. With the increase of the sample size, this could be our further research direction. At the same time, we noticed that the diagnoses of benign and malignant could provide a direction of diagnosis, which was helpful for next examination and exact diagnosis.

This study had some limitations: 1.sample size was small. 2. Only lymph nodes difficult to diagnose joined in this study, and some tuberculosis LNs with confirmed diagnosis by conventional ultrasound and Laboratory Examinations were not included in this study. For every multiple lymph node patients, we selected only one lymph node highly suspected to be malignant. 3. The final diagnosis of benign lymph nodes was done based on ultrasound-guided core needle biopsy.

In conclusion, SR with the cutoff point of 1.78 is better than 4 scoring method for UE and conventional ultrasound in differential diagnosis of benign and malignant of enlarged cervical lymph nodes. It potentially can reduce unnecessary biopsy. As conventional ultrasound, UE is expected to an important criterion in differential diagnosis of benign and malignant of enlarged cervical lymph nodes.

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