Original

Comparison of Virtual Touch Tissue Quantification with Strain Ratio in Differentiating Malignant from Benign Cervical Lymph Nodes

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Abstract: The aim of this study was to compare the diagnostic value of virtual touch tissue quantification (VTTQ) and strain ratio (SR) in differentiating malignant from benign cervical lymph nodes (LNs). The local institutional review board approved the study, and all patients provided written informed consent. A total of 144 LNs in 144 patients were examined with ultrasound elastography (UE) to obtain the SR, and with VTTQ technique to obtain the shear wave velocity (SWV) before taking core biopsies for standard reference. A receiver-operating characteristic (ROC) curve was generated to obtain the area under the curve (AUC) and the optimal cut-off point, after which the sensitivity, specificity, and accuracy of the two techniques were compared. In 144 LNs, 52 LNs were benign and 92 LNs were malignant. With ROC curve analysis, the optimal cut-off point was 2.170 for SR and 2.507 for VTTQ. The sensitivity, specificity and accuracy of SR and VTTQ were 78.26 %, 82.69 %, 79.86 % and 89.13 %, 90.38 %, 89.58 %, respectively. Specificity and accuracy were significantly higher for VTTQ than for SR (P<0.05). VTTQ is more accurate than SR in differential diagnosis of benign and malignant cervical LNs.

Key words: Virtual touch tissue quantification, Strain ratio, Lymph node, Differential diagnosis

Introduction

Lymph nodes (LNs) are one of the important immune organs, distributed throughout the entire body and cervical LNs account for around one third of them. Many diseases can lead to cervical LNs enlargement, and it is very important for the subsequent diagnosis and treatment to make sure the LNs are malignant or not so timely and accurate differential diagnosis of malignant and benign cervical LNs is needed to improve the early detection of diseases and guide subsequent treatment. Ultrasound has been the preferred examination for cervical LNs for the past few years. But conventional ultrasound including gray scale and color Doppler flow image (CDFI) is limited in clinical diagnosis for its operator-dependence.

The malignant LNs stiffness were increased for two reasons: 1) Metastatic LNs cortex were damaged and thickened for proliferation and cornification of cancer cells and interstitial cells. 2) The increased stiffness of primary malignant LNs is a result of lymphoid deformation due to infiltration and adhesion to adjacent tissues. Palpation of cervical LNs is based on the different stiffness between malignant and benign cervical LNs, but obviously it is too subjective to evaluate stiffness accurately. Recently, ultrasound elastography (UE) is very popular as a novel technique. Our previous study has reported free-hand compression UE in diagnosis cervical LNs. However, Bhatia et al have shown that the free-hand UE is semi-objective and there is poor concordance among operators. Therefore, a more specific and objective method to differentiate between benign and malignant LNs is needed.

VTTQ is a novel elastography technique which assesses tissue elastic properties by shear wave velocity (SWV) based on acoustic radiation force impulse (ARFI). Unlike the conventional elastography that is performed in an operator-dependent manner, SWV measured with VTTQ is reproducible in an operator-independent manner. This potentially improves the characterization of tissues and focal lesions in an objective way. VTTQ has been used in diagnosis of hepatic disease and breast lesions, but there are few reports about VTTQ technique in LNs examination. Thus we proposed a study to assess the VTTQ technique in differentiating malignant from benign LNs by contrasting with SR.

Materials and Methods

Patients

Between October 2012 and January 2014, 144 enlarged cervical LNs (>2 cm in diameter) in 144 patients were examined.
with conventional gray scale, UE and VTTQ technique. A core biopsy was followed as standard reference. There were 70 women and 74 men (mean age 47.3 years, range 7-76 years) in the study. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jilin University. Written informed consent was obtained from all participants.

Measurement of conventional ultrasound and UE

All patients were scanned in a supine position with their neck slightly extended. Enlarged cervical LNs were examined with conventional ultrasound and UE. Both of them were performed with the Toshiba SSA 790A ultrasound system equipped with a 5-12 MHz linear array probe (Tokyo, Japan). Conventional gray scale provided the shape, border, shorter diameter, echogenicity, hilum, long-to-short-axis diameter ratio in the longitudinal plane (L/T) and the distribution of blood flow of the LNs. In UE examination split-screen mode was used to ensure that the target LN and adjacent neck muscles used as a reference were located in the region of interest (ROI). After a ROI was chosen, 3-5 stable and uniform compressions were applied to the neck and then a sine curve was recorded. The SR was calculated as the mean strain of adjacent neck muscle divided by the mean strain of the target LN.

Measurement of SWV with VTTQ

VTTQ technique was performed with the Siemens Acuson S2000 ultrasound system equipped with a 7-12 MHz linear array probe (Berlin, Germany). When performing VTTQ technique, we centred the ROI in the target LN and avoided internal great vessels, calcified and liquefaction necrosis portions. The patient was then asked to hold the breath and VTTQ technique was then performed. Tissue in the ROI is mechanically excited by using short-duration acoustic pulses with a fixed transmission frequency to generate localized tissue displacement. The displacement results in shear wave propagation away from the region of initial excitation and is tracked by using US correlation-based methods14). By measuring the time to peak displacement at each lateral location, the SWV (m/s) was obtained. The range for the SWV is 0-9 m/s. When measurements were out of the tolerable range of the system, the VTTQ was displayed with “X.XX”. In other words, both extremely hard and soft tissue can be shown as “X.XXm/s”15). The value of “X.XXm/s” was allocated to be 0 m/s or 9 m/s with 0 m/s to cystic LNs and 9 m/s to solid LNs16). The measurement was repeated for 5 times and the mean measurement was then calculated for the following analysis. The best cut-off point for differentiating malignant from benign cervical LNs was obtained using receiver-operating characteristic (ROC) curve analysis.

In all the patients, conventional gray scale, UE and VTTQ examinations were performed by one Sonographer (24 years of experience in superficial organs). This investigator was blinded to the histopathologic diagnosis and the clinical outcome of the patients. Histologic diagnosis from core biopsy was regarded as final diagnosis. Each LN was biopsied three times from three different solid portions.

Statistical analysis

All statistical analyses were performed with SPSS16.0 statistical software. The AUC which indicated the diagnostic performance, and the optimal cut-off point were both obtained using ROC curve analysis. With the cut-off points of UE and SWV were obtained, diagnostic indices (sensitivity, specificity, and accuracy) were both calculated and compared with the χ² test. A two-tailed P<0.05 was considered to indicate significance.

Results

Pathology

Final pathologic results of all the 144 lymph nodes as follows: in 52 benign LNs, 24 were tuberculosis, 8 were histiocytic necrotizing lymphadenitis, 20 were hyperplasia; in 96 malignant lymph nodes, 24 were metastatic adenocarcinoma, 32 were metastatic squamous cell carcinoma, 6 were the metastatic small cell carcinoma, 10 were lymphoma (6 non Hodgkin’s lymphoma, 2 Hodgkin’s lymphoma, 2 follicular lymphoma), 6 were metastatic thyroid papillary carcinoma, 2 was metastatic thyroid follicular carcinoma, 2 was adenosquamous carcinoma, 10 were malignant lymph nodes can’t distinguish the sources.

UE

With ROC curve analysis, AUC was 0.844 (95 % confidence interval: 0.778-0.910, P<0.001) and the best cut-off point is 2.170 for SR (Fig. 1A) which meant SR<2.170 was considered benign and SR>2.170 as malignant. In 52 benign LNs, SR <2.170 in 43 LNs and SR >2.170 in 9 LNs; in 92 malignant LNs, SR <2.170 in 20 LNs and SR >2.170 in 72 LNs. With the best cut-off point 2.170, the evaluation of the ultrasound elastography SR system demonstrated 78.26 % sensitivity, 82.69 % specificity, and 79.86 % accuracy.

VTTQ

The mean SWV of 5 times was calculated for ROC curve analysis. AUC of the ROC was 0. 948 (95 % confidence interval: 0.914-0.982, P<0.001) and the best cut-off point was 2.507 for VTTQ (Fig. 1B) which meant SWV <2.507 was considered benign and SWV > 2.507 as malignant. In 52 benign LNs, SWV < 2.507 in 47 LNs and SWV >2.507 in 5 LNs; in 92 malignant LNs, SWV <.507 in 10 LNs and SWV > 2.507 in 82 LNs. With the the best cut-off point 2.507, the sensitivity, specificity and accuracy of the VTTQ technique was 89.13 %, 90.38 % and 89.58 %, respectively.
Figure 1. The ROC curve for two methods in diagnosis of cervical LNs.
A: ROC curve for SR in differentiation between malignant and benign LNs. AUC was 0.844 and the optimal cut-off point is 2.170; B: ROC curve for VTTQ in differentiation between malignant and benign LNs. AUC was 0.948 and the optimal cut-off point was 2.507.

Figure 2. An enlarged LN in left neck in a 14-year-old girl.
A: Conventional ultrasound showed the LN with clear border, regular shape, abnormal hilum and PDI classification III; B: Strain ratio was calculated as 6.08 > 2.170, so the LN was diagnosed as malignant; C: The same LN was considered benign with VTTQ technique with SWV 1.750 < 2.50.

Figure 3. The histologic diagnosis from biopsy was hyperplasia.
Stain: hematoxylin and eosin.
Fujiwara et al. reported VTTQ technique used for cervical LNs internal calcification which increased the mean tissue stiffness. The other 5 benign LNs achieved SWV >2.507 because of the objective results with VTTQ technique. In our research, 47 in 52 push instead of freehand compression, which result in more of overlap in stiffness between benign and malignant LNs. In accuracy in differentiating cervical LNs due to a certain amount of overlap in stiffness between benign and malignant LNs. The specificity of VTTQ technique had a significantly higher than that of SR (P<0.05) which meant VTTQ had advantages in the diagnosis of benign LNs. In our research, 43 of 52 benign LNs were correctly diagnosed, but 3 in 24 tuberculosis lymph nodes were misdiagnosed. In 92 malignant LNs, 82 were correctly diagnosed with VTTQ technique with sensitivity of 89.13%. We considered there were some reasons as follows: 1. Metastatic LNs cortex were damaged and thickened for proliferation and cornification of cancer cells and interstitial cells, so the LNs stiffness were increased. 2. Microcalcifications in metastatic LNs origining from thyroid papillar carcinoma result in high stiffness and SWV. 3. The increased stiffness of primary malignant LNs is a result of lymphoid deformation due to infiltration and adhesion to adjacent tissues. 4. The fibrous tissue proliferation in LNs after chemical therapy is another reason for increased stiffness and high SWV.

In our research, VTTQ technique had a significantly higher diagnostic performance than SR in distinguishing benign from malignant LNs (P<0.05). We give some reasons as follow: 1. Ultrasound elastography is a newly developed modality of medical imaging examination which assesses tissues depending on the stiffness. The principle of imaging limits the diagnostic accuracy in differentiating cervical LNs due to a certain amount of overlap in stiffness between benign and malignant LNs. In our research, 43 of 52 benign LNs were correctly diagnosed, but other 9 obtained false positive result due to internal hard structures as a result of long-term organization. In 92 malignant LNs, 20 LNs received SR <2.170. The large liquefaction necrosis portions may account for the misdiagnosis.

VTTQ is a novel elastography technique which assesses tissue elastic properties by SWV. When the VTTQ technique is performed, the probe emitted a short-duration acoustic pulse causing slight vibration both in longitudinal and transverse direction which lead to the lateral displacements. The time to peak displacement at each lateral location is defined as SWV, which is the quantitative form of VTTQ. SWV of soft tissue is slower than that of hard tissue, which provided an objective indicator of the tissue stiffness. The lateral displacement is caused by acoustic push instead of freehand compression, which result in more objective results with VTTQ technique. In our research, 47 in 52 benign LNs got correct diagnosis with a high specificity of 90.38%. The other 5 benign LNs achieved SWV >2.507 because of the internal calcification which increased the mean tissue stiffness. Fujiwara et al. reported VTTQ technique used for cervical LNs with a lower cut-off point 1.9 and a higher specificity of 95.0 % because only reactive LNs as benign group were included in their research while a variety of benign ones especially tuberculous lymph nodes. In this research, 3 in 24 tuberculosis lymph nodes were misdiagnosed. In 92 malignant LNs, 82 were correctly diagnosed with VTTQ technique with sensitivity of 89.13%. We considered there were some reasons as follows: 1. Metastatic LNs cortex were damaged and thickened for proliferation and cornification of cancer cells and interstitial cells, so the LNs stiffness were increased. 2. Microcalcifications in metastatic LNs origining from thyroid papillar carcinoma result in high stiffness and SWV. 3. The increased stiffness of primary malignant LNs is a result of lymphoid deformation due to infiltration and adhesion to adjacent tissues. 4. The fibrous tissue proliferation in LNs after chemical therapy is another reason for increased stiffness and high SWV.

In our research, VTTQ technique had a significantly higher diagnostic performance than SR in distinguishing benign from malignant LNs (P<0.05). We give some reasons as follow: 1. It has been reported that the various degrees of freehand compression motions was a major limitation of UE. SR was only a semi-objective outcome for its poor reproducibility and Stability. In our research, there were no much differences among 5 SWVs in the same LN with VTTQ technique, which indicated the reproducibility of VTTQ was satisfactory. With the best cut-off point 2.507, the sensitivity, specificity and accuracy of the VTTQ technique was 89.13 %, 90.38 % and 89.58 %, respectively.

This study had some limitations: 1. The stability of VTTQ technique can be affected by the interference of respiration. 2. Small LNs were excluded on account of unadjustable sample frame size. 3. External pressure caused by carotid pulsation could also bias the results. 4. Sample size was small. 5. The histologic diagnosis was from core biopsies instead of from lymphadenectomy as standard reference.
In conclusion, VTTQ with the best cut-off point of 2.507 is superior to SR in differential diagnosis of benign and malignant cervical LNs, and can provide new insights into the evaluation of cervical LNs.

References