World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i30.4850

World J Gastroenterol 2013 August 14; 19(30): 4850-4860
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

New ultrasound techniques for lymph node evaluation

Xin-Wu Cui, Christian Jenssen, Adrian Saftoiu, Andre Ignee, Christoph F Dietrich

Xin-Wu Cui, Andre Ignee, Christoph F Dietrich, Med. Klinik 2, Caritas-Krankenhaus, 97980 Bad Mergentheim, Germany
Christian Jenssen, Klinik für Innere Medizin, Krankenhaus Märkisch Oderland, 15334 Strausberg, Germany
Adrian Saftoiu, Department of Gastroenterology, Research Center of Gastroenterology and Hepatology, University of Medicine and Pharmacy Craiova, 200349 Craiova, Romania
Author contributions: Cui XW, Jenssen C and Dietrich CF established the design and conception of the paper; Cui XW, Jenssen C, Saftoiu A, Ignee A and Dietrich CF analyzed the literature data; Dietrich CF provided the first draft of the manuscript; Cui XW, Jenssen C, Saftoiu A, Ignee A and Dietrich CF were critically discussed and revised the intellectual content of the manuscript; Jenssen C, Ignee A and Dietrich CF provided figures; all authors discussed the statement and conclusions and approved the final version to be published.
Correspondence to: Christoph F Dietrich, Professor, Head of Med. Klinik 2, Caritas-Krankenhaus, Uhlandstraße 7, 97980 Bad Mergentheim, Germany. christoph.dietrich@ckbm.de
Telephone: +49-7931-582201 Fax: +49-7931-582290
Received: March 4, 2013 Revised: April 4, 2013
Accepted: May 7, 2013
Published online: August 14, 2013

Abstract

Conventional ultrasound (US) is the recommended imaging method for lymph node (LN) diseases with the advantages of high resolution, real time evaluation and relative low costs. Current indications of transcutaneous ultrasound and endoscopic ultrasound include the detection and characterization of lymph nodes and the guidance for LN biopsy. Recent advances in US technology, such as contrast enhanced ultrasound (CEUS), contrast enhanced endoscopic ultrasound (CE-EUS), and real time elastography show potential to improve the accuracy of US for the differential diagnosis of benign and malignant lymph nodes. In addition, CEUS and CE-EUS have been also used for the guidance of fine needle aspiration and assessment of treatment response. Complementary to size criteria, CEUS could also be used to evaluate response of tumor angiogenesis to anti-angiogenic therapies. In this paper we review current literature regarding evaluation of lymphadenopathy by new and innovative US techniques.

Key words: Lymph nodes; Ultrasound; Endoscopic ultrasound; Lymph node metastasis; Lymphoma

Core tip: The differentiation of malignant from benign lymph nodes by ultrasound, computed tomography and magnetic resonance imaging traditionally relies mainly on size measurements and topographic distribution. However, sensitivity and specificity in the differentiation of benign and malignant lymph nodes are disappointing using only size parameters. The presented paper is intended to discuss, comment and illustrate the clinical important work-up of lymphadenopathy with respect of recently introduced imaging techniques including contrast enhanced ultrasound and elastography.

Cui XW, Jenssen C, Saftoiu A, Ignee A, Dietrich CF. New ultrasound techniques for lymph node evaluation. *World J Gastroenterol* 2013; 19(30): 4850-4860 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i30/4850.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i30.4850

INTRODUCTORY CONSIDERATIONS

The differentiation of malignant from benign lymph nodes by ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) traditionally relies mainly on size measurements and topographic distribution[1-3]. However, sensitivity and specificity in the differentiation of benign and malignant lymph nodes are disappointing using only size parameters. Reasons for the low accuracy include that malignant lymph node infiltration occurs in up to 30% in lymph nodes of less than 5 mm which has been shown for lung, esophageal, gastric, pancreatic and rectal carcinoma[4-10]. The evaluation of shape and border often adds no or only little more information

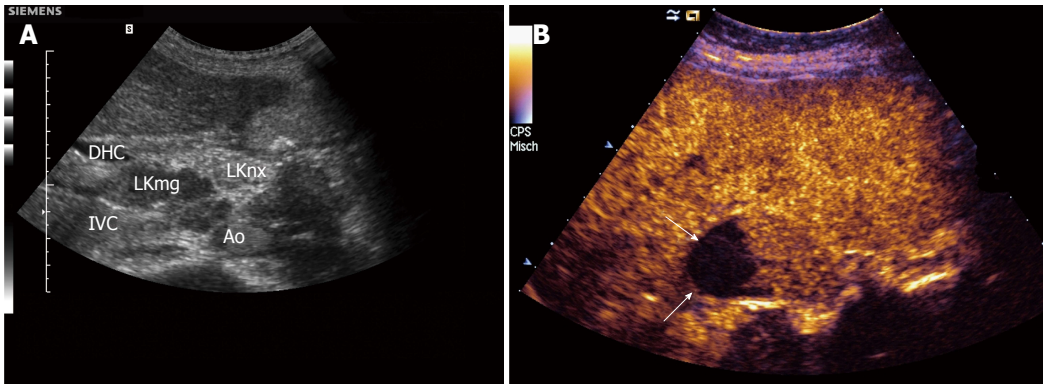

Figure 1 Lymph node infiltration, carcinoma. A: With lymph node (LN) specific contrast agents malignant infiltration can be delineated (LKmg) as focal hypoenhancement in the upper part of this perihepatic LN. The lower part (LKnx) shows normal (physiological) enhancement; B: With SonoVue®. Necrotic (non-enhancing, arrows) areas can be detected within this perihepatic lymph node. Necrotic areas are typically for carcinoma infiltration and tuberculosis. IVC: Inferior vena cava; Ao: Aorta; DHC: Common bile duct.

to exclude malignancy[11,12]. New imaging methods should be able to delineate the early and circumscribed malignant infiltration and to improve ultrasound guided biopsy.

Colour Doppler ultrasound (CDI) adds value for the differentiation of malignant from normal or reactive nodes by displaying the macrovessel architecture. Normal LNs generally show hilar predominant normal vascularity. Inflammatory lymph nodes are typically more vascularised without changes of the predominant hilar vessel architecture. In contrast metastatic lymph nodes present peripheral or mixed vascularity and loss of hilar type of vascularisation[13].

Contrast enhanced CDI has improved the viusalisation of macrovessels (angioarchitecture) but does not allow evaluation of microvessels[14]. Demonstration of malignant neovascularisation, *e.g.*, vessels penetrating the LN capsule, has been used as the characteristic feature of lymph node metastases.

Spectral Doppler ultrasound contributes to differentiation of malignant and benign solid neoplasia[15]. Likewise, normal and inflammatory lymph nodes show lower vascular resistance [resistive index (RI)] as compared to malignant lymph nodes[16] but overall results are disappointing.

Although Doppler ultrasound techniques have extended the opportunities for the differentiation of malignant from benign lymph nodes by displaying changes of macrovascularity and the vascular resistance[13,17,18], they do not improve lymph node detection rate and vascularity is often not detected in small lymph nodes[19]. Therefore, Doppler techniques and contrast enhanced Doppler techniques in general have not significantly improved the diagnostic work up of lymphadenopathy. There is a need for new imaging techniques for better characterisation of lymph nodes with the opportunity to assess also the internal microvessel architecture of lymph nodes and tissue elasticity for detection of early circumscribed malignant infiltration.

In the presented paper we discuss current knowledge about recent advances in ultrasound technology for improved lymph node evaluation.

CONTRAST ENHANCED ULTRASOUND

Contrast enhanced ultrasound (CEUS) is the application of ultrasound contrast agents (UCA) to traditional sonography. The currently used UCA are microbubbles stabilized by a shell which has a high degree echogenicity. Since their physical size is just 1-4 micrometres in diameter (equal to or smaller than red blood cells), UCA allow depiction of both the macrovasculature and the microvasculature[20]. CEUS has been introduced more than ten years ago and guidelines have been published for the liver[20,21] and non-liver indications[22]. Currently 4.8 mL SonoVue® is recommended for imaging superficial LNs with a high frequency probe and for imaging the mediastinal and abdominal LNs with a high frequency endoscopic probe in CE-EUS.

CEUS techniques provide information on vascularisation and perfusion patterns, and exploit the differences in blood flow characteristics between normal and pathological tissue but knowledge about lymph node evaluation is limited[22]. CEUS could be helpful by identifying changes in vascular architecture of macro- and micro-vessels and avascular areas as signs of malignant infiltration.

Carcinoma

Carcinoma infiltration causes the development of pathological vessels (neoangiogenesis) and, therefore, a change of the perfusion pattern with heterogeneous enhancement due to the presence of caliber changes of the neoplastic vessels and arteriovenous shunts[23-27]. Focal hypoenhancement may result from the partial insufficiency of blood-supply due to overpressure in the LN caused by the neoplastic infiltration. Malignant lymph nodes not only have a greater number of peripheral vessels, but also longer contrast enhancement duration than benign lymph nodes[28]. Destructive avascular necroses are an important imaging sign for malignant infiltration (Figures 1-3). Avascular areas are detected by the lack of contrast agent uptake in the necrotic zones and the peripherally located pronounced hyperenhancement (rim enhancement)[29,30]. The contrast enhancement pattern of focal cortical

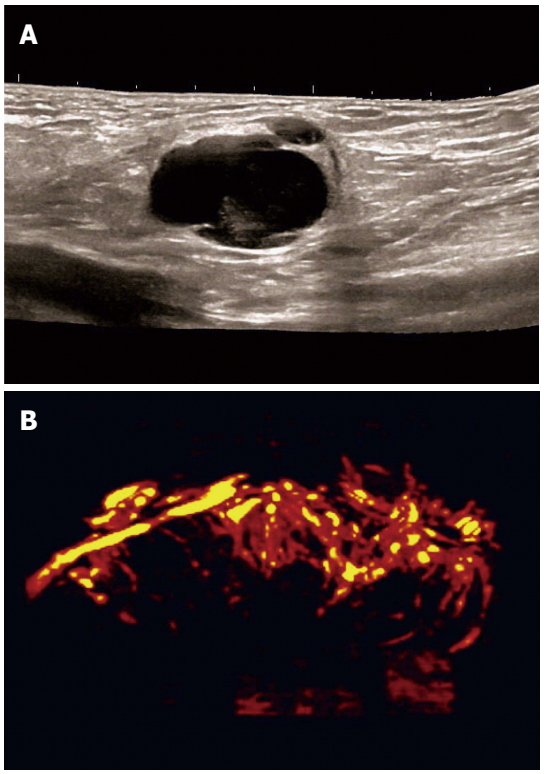

Figure 2 Carcinoma infiltration. Typically vessel destruction with chaotic vessels in the lymph node can be observed. B-mode (A) and 3D angiographic mode (B).

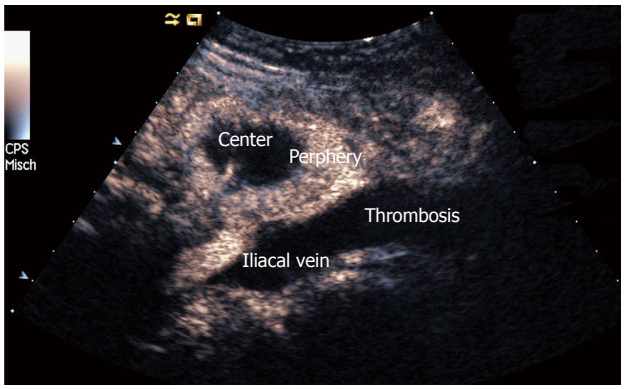

Figure 3 Prostate carcinoma infiltration of the pelvis. Typically vessel destruction with interruption of vessel architecture can be observed in patients with carcinoma. The center of the lymph node is almost non-enhancing except one visible vessel whereas the periphery shows hyperenhancement. Thrombosis of the iliac vein is indicated as well.

thickening has been also identified as an important sign to differentiate benign and malignant lymphadenopathy. In benign lymph nodes contrast enhancement within the cortex is homogeneous, whereas in malignant lymph the cortical thickening is less well vascularized than the adjacent normal lymph node parenchyma[24].

In conclusion, criteria for carcinomatous lymph node infiltration on CEUS are centripetal inhomogeneous enhancement and perfusion defects.

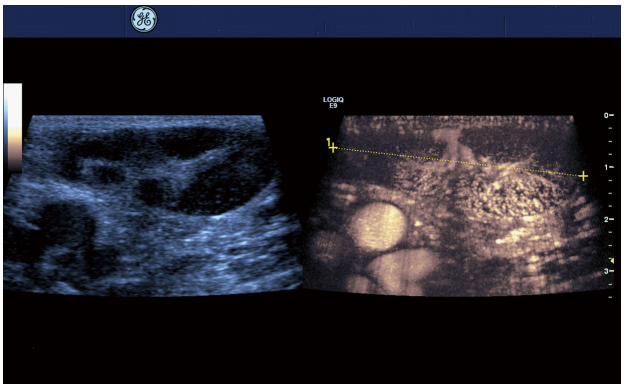

Figure 4 Lymph node infiltration (50 mm), non-Hodgkin's lymphoma. Typically the hilum predominant vessel architecture is preserved (between markers).

Lymphoma

It is essential to consider lymphoma separately because some of its features are different from other LN disease[13,31]. The very few studies published so far showed that in lymphoma contrast enhancement patterns are highly variable. The most often observed pattern is intense homogeneous enhancement, which is not different from reactive inflammatory lymph nodes[25,31] (Figure 4).

In conclusion, there is evidence that the vascular pattern of lymphomatous lymph node infiltration resembles that of non-malignant nodes.

Inflammation

Most inflammatory processes do not change the hilum predominant vessel architecture of lymph nodes. According to the majority of published papers, normal and inflammatory LNs are characterized by a centrifugal and homogeneous enhancement pattern[23-26] (Figure 5). Therefore, inflammation changes the enhancement pattern only by the amount (peak) enhancement but not by changes of distribution. It is worth mentioning that non-destructive necrosis, which is reflected in avascular areas on CEUS, can be also found in granulomatous lymphadenitis, *e.g.*, cat-scratch disease (bartonellosis), tuberculosis and sarcoidosis.

Treatment response

Changes and reduction of intranodal vascularity may be the first sign of response to antineoplastic treatment as shown for gastrointestinal stromal tumors and renal cell carcinoma[22,32]. Since tumour growth depends on neovascularization, CEUS can also help to detect focal nodular tumour recurrence in scars and to guide biopsy[33]. In Hodgkin's disease well demarcated avascular areas have been described as a typical sign of treatment response[34,35].

Dynamic contrast enhanced ultrasound

Quantification software (time intensity curve analysis) has been used for the differential diagnosis of benign and malignant LNs but results so far are conflicting[36]. There

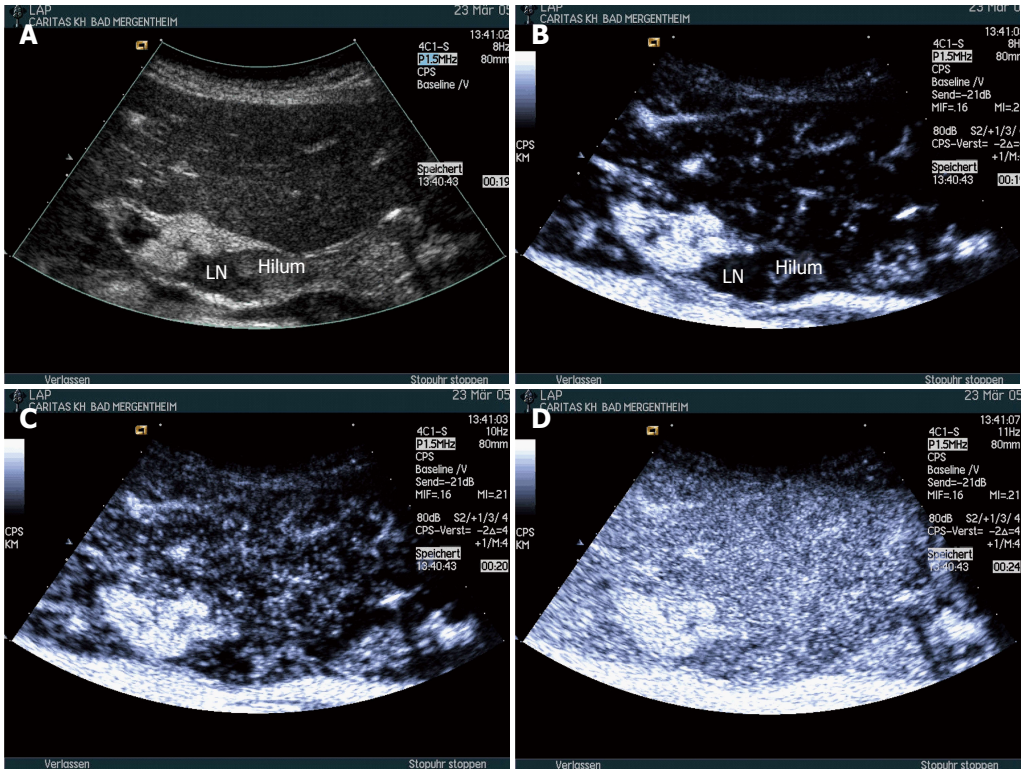

Figure 5 Inflammatory perihepatic lymph node dorsal in the hepatoduodenal ligament. Inflammation most often shows no changes of the symmetric lymph node vascularity and homogenous contrast enhancement (A-D). The hilum is indicated. LN: Lymph node.

are two studies showing that the difference of intensity between the hypervascular and hypovascular regions was significantly higher in metastatic than in non-metastatic LNs[26,37]. Steppan *et al*[38] reported that malignant compared to benign lymph nodes showed higher maximum intensity and duration of enhancement while Yu *et al*[25] reported no significant differences on maximum intensity. Time to peak intensity and area under the curve of malignant lymph nodes and lymphomas were less than that of benign LNs. Ahuja could demonstrate a reduction of vessel density (vascularity) and delay in the time to peak enhancement after treatment. It has to be mentioned that the changes in peak enhancement were operator dependent[33]. Since evidence is inconsistent quantification techniques cannot be generally recommended for clinical use. European Federation for Ultrasound in Medicine and Biology (EFSUMB) has published recommendations on the use of dynamic contrast enhanced ultrasound (DCE-US) discussing the current use and limitations in detail[39].

In conclusion, contrast enhanced techniques compared to conventional ultrasound may improve the differential diagnosis of benign LNs from malignant LNs and provide a more accurate selection of nodes to be submitted to fine-needle aspiration biopsy[25,28].

ELASTOGRAPHY

Elastography is a non-invasive method in which the stiffness of the tissue can be imaged as colour map or shear wave velocity. Two main forms of elastography have been studied for the evaluation of lymph nodes. One form is strain elastography (SE). The ultrasound probe is used to palpate the tissue[40] usually transcutaneously but optionally also intra-operatively or *via* an endoscope[41-45]. The tissue deformation produced (*i.e.*, strain) is assessed by following the way the speckle in the image moves, usually with a tracking algorithm working on the radio-frequency data. The data can then be used to form an image that is coded in colour or grey-scale to show the pattern of strain, which is inversely related to tissue stiffness. Therefore, SE allows assessment and visualization of relative elasticity differences. The area to be evaluated is defined by a ROI in a similar way to CDI[44,46]. New technical developments allow for averaging over several frames to calculate the mean histogram value which corresponds to overall elasticity within a selected area[47]. Comparing two different areas within the ROI allows calculation of the strain ratio. SE is the most commonly used method for the evaluation of lymph nodes. The other forms of elastography are shear wave elastography techniques (SWE) which include transient elastography (TE) (*e.g.*, Fibroscan™, Echosens, France), Acoustic Radiation Force Impulse imaging (*e.g.*, ARFI, Siemens, Germany) and Supersonic Shear Wave Imaging (SSI) (Supersonic, France). In shear wave elastography the "pushing" ultrasound beam causes minute displacements in soft tissue, which depend on the magnitude of tissue stiffness. Using tracking algorithms, the resulting shear waves can be detected sonographically. So far only SSI has been studied for the evaluation of LN. In elastographic images

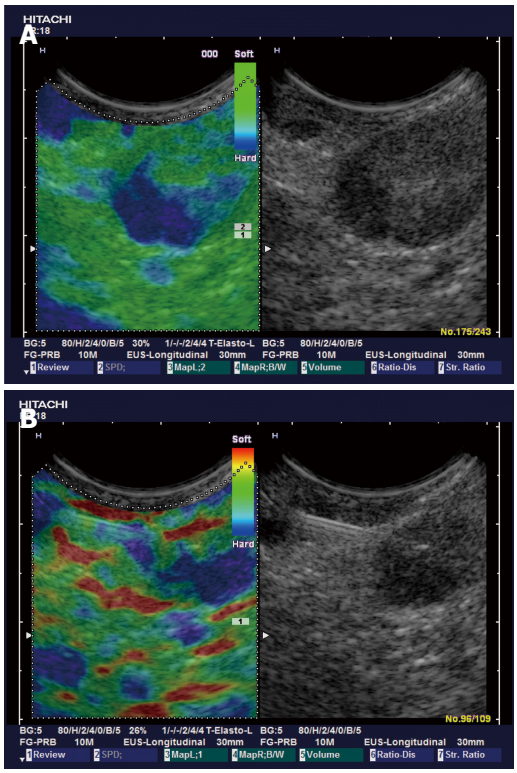

Figure 6 Colorectal carcinoma with presacral circumscribed lymph node metastasis proven by colonic endoscopic ultrasound using Fine Needle Aspiration Cytology. Sonoelastography reliability test evaluation reveals typically harder (blue) area in the lymph node.

of normal lymph nodes the nodal cortex is significantly harder than the medulla and the hilum[48,49].

EFSUMB has prepared recommendations on the use of elastography. In two sets of papers the techniques are explained in more detail[50,51].

Carcinoma

Typically the well differentiated carcinoma at least initially infiltrates lymph nodes in a circumscribed manner (focally stiffer, harder) (Figure 6), whereas the undifferentiated carcinoma leads to a diffuse (stiffer, harder) infiltration.

Suspected cervical LN metastases from hypopharyngeal and thyroid carcinomas have been recently investigated using SE (real time elastography)[39,52]. An elasticity index has been created by comparing the elasticity of the LN with the surrounding head and neck muscle tissue (muscle to LN strain ratio). Using a ratio of > 1.5 as an indicator of malignant infiltration, sensitivity was 82% and specificity 98% which is superior to the best B-mode criteria[52]. These data have been reproduced by Tan *et al*[53]. Moreover, interobserver agreement with SE was very high (kappa 0.828-0.946)[53].

Applying a higher cut-off value for strain ratio (1.78) Teng *et al*[54] at the cost of an only moderate specificity (65%) reported a very high sensitivity (98%) for discriminating malignant from benign suspicious cervical lymph nodes.

Other authors used a scoring system (percentage of blue-coding lymph node area) to differentiate malignant from benign lymph nodes in head and neck cancer patients. A blue coded (hard) area of > 50% of total lymph node area (score 3 and 4) or observation of a central necrosis (score 5) predicted malignant infiltration with high accuracy and added value to traditional ultrasound criteria[55-57].

So far two papers are published for the differential diagnosis of lymph nodes using shear wave elastography on 55 cervical enlarged lymph nodes using SSI. Malignant nodes were homogeneously stiffer than benign lymph nodes. The sensitivity (42%), specificity (100%) and accuracy (62%) were promising defining a cut-off level of 30.2 kPa[58]. The intra- and inter-observer reliability of shear wave elastography using SSI was shown to be fair to excellent for 176 neck lesions according to the intraclass correlation coefficients (0.78-0.85)[59].

In conclusion, elastography seems to be a very promising diagnostic tool for the differentiation between benign and malignant lymph nodes. This is reflected by a recent meta-analysis which reported a pooled sensitivity and specificity for the diagnosis of malignant lymph nodes of 74% and 90% for elasticity scores, and 88% and 81% for strain ratio, respectively[60]. However, to date studies comparing the two techniques of elastography (SE and SWE) are lacking.

Lymphoma

Knowledge of strain imaging in lymphoma is very limited. So far different lymphoma cannot be differentiated. Initial experience suggests that focal lymph node infiltration (Figure 7A) is indicative for low grading of follicular lymphoma whereas diffuse and homogenous lymph node infiltration is typically found in high grade lymphoma (Figure 7B).

Inflammation

Most inflammatory processes do not change the elastographic architecture of lymph nodes. The hilum in normal lymph nodes remains softer than the stiffer cortex also in inflammatory lymph nodes. Circumscribed softer (and stage dependent also stiffer) lymph node areas are found in tuberculosis but this has only been shown in few cases.

ENDOSCOPIC ULTRASOUND

Diagnostic and therapeutic endoscopic ultrasound has been established in the last thirty years[61,62]. The technique can be also applied with colour Doppler imaging as discussed above. Recently CE-EUS and real time endoscopic elastography (RTE-EUS) have been introduced.

Contrast enhanced endoscopic ultrasound

Contrast enhanced endoscopic ultrasound (CE-EUS) is CEUS performed with an endoscopic probe, which can be performed on both Doppler mode with high MI and contrast specific mode with low MI[63] to also guide therapeutic procedures. The dose of the ultrasound contrast agent (UCA) should be 4.8 mL for SonoVue®. CE-EUS

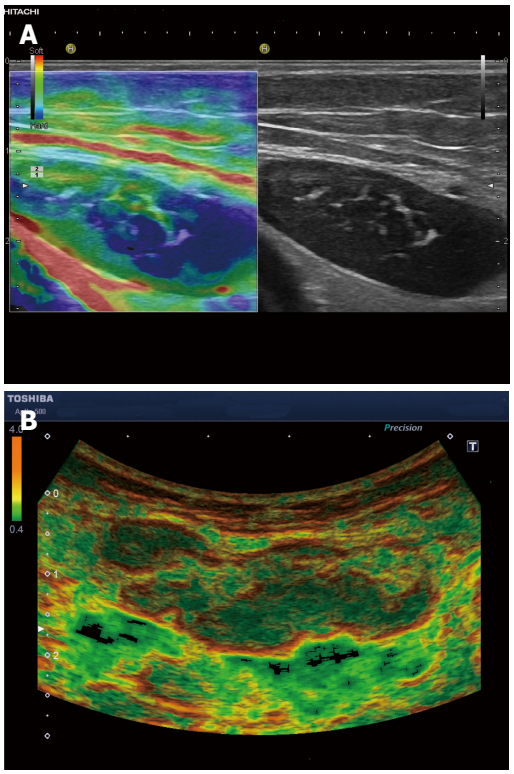

Figure 7 Non-Hodgkin's lymphoma involving the inguinal region. A: Sonoelastography reliability test evaluation reveals typically asymmetric and circumscribed infiltrated harder (blue) lymph node tissue in low grade follicular cell lymphoma; B: Elastography (acoustic structured quantification) reveals mainly homogenous diffuse infiltration in high grade follicular cell lymphoma.

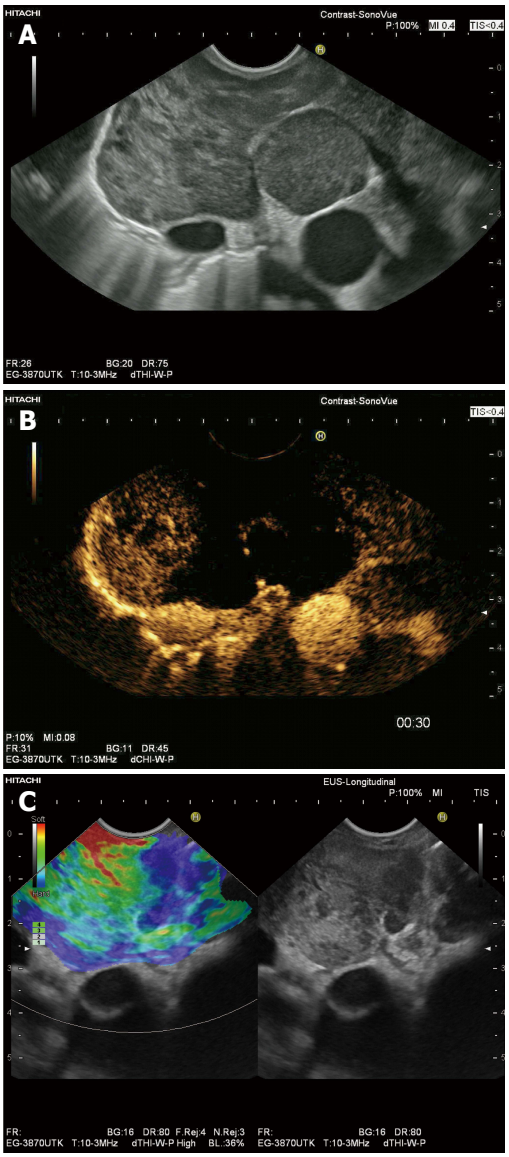

Figure 8 Endosonography of enlarged subcarinal lymph nodes in Non-Hodgkin Lymphoma. A: B-mode reveals two enlarged lymph nodes; B: contrast enhanced endoscopic ultrasound demonstrates extensive avascular (necrotic) areas in the lymph nodes; C: real time endoscopic elastography indicates hard, infiltrated areas (blue color), thus targeting endoscopic ultrasound-guided biopsy.

can improve the detection of small intranodal vessels and thus could be useful in characterization of LNs[3,64] (Figure 8). CE-EUS has improved our understanding of gastrointestinal (subepithelial) tumors[65-67], differential diagnosis of pancreatic neoplasia[15,68-75] and other organ infiltration[74,75] through analysis of perfusion patterns.

There are only a few reports about the usefulness of contrast enhanced endoscopic Doppler ultrasound in the differentiation between malignant and benign lymphadenopathy. Kanamori *et al*[64] performed CE-EUS with high MI on 46 patients in whom EUS revealed LN in the mediastinum or abdominal cavity and suggested that CE-EUS is useful for differentiating benign from malignant LNs by detecting defects of enhancement in malignant nodes. The sensitivity, specificity, and accuracy rate of CE-EUS were 100%, 86.4% and 92.3%, respectively. In another study by Hocke *et al*[3], high MI CE-EUS was performed in 122 patients, and it was found that CE-EUS improved the specificity in diagnosing benign LNs as compared to B-mode EUS by analysing arteries and veins. However, it did not improve the accurate identification of malignant LNs and therefore could not replace EUS-guided fine-needle aspiration[3].

To the best of our knowledge, there is only one report on the application of low MI CE-EUS for the discrimination of benign and malignant abdominal lymph nodes. A Japanese group investigated 43 patients with intra-abdominal lesions of undetermined origin, which were suspected to be malignant lymph nodes, and evaluated the enhancement pattern after injection of the UCA Sonazoid®. Final pathological examination revealed that 35 lesions in fact were lymph nodes. All but one of the malignant lesions showed a heterogeneous enhancement pattern, whereas none of the benign lesion displayed heterogeneous enhancement. Most interestingly the interobserver agreement was very high (kappa 0.953)[78].

Endosonographic elastographic lymph node evaluation (strain imaging)

Endoscopic elastography is real time elastography performed with an endoscopic probe, which has led to further improvement in B mode imaging results for classification of benign and malignant LNs (Figure 8), particularly by

targeting LNs for needle sampling. Janssen *et al*[79] reported on 50 patients, 66 LNs were described elastographically (dominant colour/tissue hardness and guidance for tissue samples) and the elastogram data later compared with the histological findings obtained in the same session from fine needle biopsy. This study revealed that benign LNs exhibited predominantly intermediate homogeneous deformation (yellow/green), while malignant LNs were characterized by a quantitative dominance of hard (blue) units. The accuracy, which could be consistently reproduced by two more reviewers (kappa 0.84), for benign *vs* malignant LNs was about 85%. Intra- and interobserver agreement was also high in one recent study using visual assessment of the elastography image to differentiate between malignant and benign lymph nodes[80]. However, the same group found that EUS elastography did not perform better than EUS morphology in differentiating between malignant and benign lymph nodes in patients with resectable upper gastrointestinal cancer[45]. These findings conflict with the results of two other groups, which showed superior accuracy of EUS elastography strain ratio and histogram analysis, respectively, in comparison with conventional EUS criteria in differentiating malignant and benign lymph nodes in the nodal staging of esophageal cancer[81,82].

Săftoiu *et al*[41] used similar criteria for qualitative analysis in their study. In computer analysis, accuracy for differential diagnosis of malignant *vs* benign LNs increased slightly from 93% to 95%. In a follow-up study[47], they reached an accuracy for differentiation between benign and malignant LNs of 89%, using the computer based histogram analysis of video sequences, while this was significantly superior to the B-Mode image analysis (accuracy 53%). Another recent study with pathological confirmation yielded however lower values for sensitivity, specificity and accuracy, based on strain ratio calculations[45].

A recent meta-analysis calculated a sensitivity of 88% and a specificity of 85%, respectively, of EUS elastography for differentiating between benign and malignant lymph nodes[83].

In conclusion, the sensitivity of an imaging procedure critically depends on spatial resolution, which in elastography is as good as in conventional ultrasound since both depend on the same physical rules. The smallest LN metastases may escape both B-mode diagnosis and endosonographic fine needle biopsy. Elastography can detect the smallest metastasis-related changes in tissue hardness and it is considered to be potentially useful for target selection prior to endosonographic guided tissue sampling[10].

RTE can be recommended for discrimination of benign and malignant lymph nodes by identifying malignant regions that should be targeted for EUS-FNA (Figure 8).

SENTINEL LYMPH NODE EVALUATION

The detection or exclusion of sentinel lymph node (SLN) micrometastases is critical in staging cancer, especially breast cancer and melanoma, because it directly affects patient's prognosis and surgical management. It is well known that conventional US is not able to detect SLN in most cases. However, studies showed that low MI CEUS can be used for detecting SLN, which may become a potential application in clinical routine, like lymphoscintigraphy[32,84-89]. The application of CEUS for the investigation of SLN has shown promising results in animal models but the technique has not been sufficiently evaluated in humans. About 1 mL of contrast agent (*e.g.*, SonoVue®) is injected subcutaneously (intralymphatic) near the tumour site and the enhanced lymphatics are traced to the sentinel lymph node. Initial experience indicates that the method is not toxic and performs as well as blue dye or radioisotope methods. The current literature has been recently reviewed[90] and the topic is not the subject of this paper.

PANORAMIC IMAGING, 3D AND 3D-CEUS

Panoramic imaging, 3D[91] and 3D-CEUS[92,93] have been used for improved anatomic and topographic description of lymphadenopathy but have not gained additional information except improved presentation of results to clinicians.

CONCLUSION

The currently possible lymph node detection rate is limited by a minimal required lymph node size which is between 5-10 mm. Since about one third of malignant infiltrations occur in lymph nodes which are not detectable by all imaging methods, reliable exclusion of malignant lymph node infiltration is almost impossible. Therefore, current imaging methods mainly focus on the improved detection of early malignant infiltration in detectable lymph nodes, *e.g.*, to guide neoadjuvant treatment strategies.

Ultrasound techniques (CEUS, CE-EUS and elastography) demonstrate high spatial resolution which is important for early detection of malignant lymph node infiltration (Table 1). CEUS compared with conventional CDI could improve the visualization of vessels in LNs which is essential for the evaluation of vessel distribution. The visualization of avascular necrotic deposits of neoplastic cells is helpful for the differentiation of benign and malignant lymphadenopathy. The identification of hypoenhancing areas in malignant lymph nodes may guide biopsy for improved early detection of malignant infiltration.

In addition, the strictly intravascular distribution of intravenously injected contrast agents (*e.g.*, SonoVue®) allows the assessment of neoangiogenesis which is of importance for treatment evaluation under antiangiogenetic treatment.

CEUS cannot be recommended for the diagnosis of lymphoma so far. However, CEUS may be a tool to assess the treatment response by indentifying the reduction of vascularisation, *e.g.*, in Hodgkin's disease.

Table 1 Criteria on lymph node characterization using different ultrasound modes

Lymphadenopathy more (most) likely	B-mode	(Contrast enhanced) Colour Doppler	Vascular resistance	CEUS (contrast special imaging mode)	Elastography
Inflammatory	Preserved architectur, homogeneous, thin cortex	Preserved vessel architecture, hilar vascularity with or without tree like branching.	Lower, RI < 0.8, PI < 1.6	Homogeneous enhancement from the hilum, centrifugal enhancement	No data, most often normal architecture (except tuberculosis)
Malignant infiltration (metastasis)	Destroyed architecture (capsule), eccentric hypoechoic cortical thickening, inhomogeneity of the internal structure, loss of echogenic hilum, surrounding edema	Peripheral or mixed vascularity, inhomogeneous vessel density, split arteries, torturous course of vessels	Higher, RI > 0.8, PI > 1.6, often variable at different sites	Centripetal enhancement, different intra-nodal enhancement levels, inhomogeneous wash-out, perfusion defects	Initially circumscribed. SR in diffuse infiltration > 1.5 (1.78)
Lymphoma	Focal or global hypoechoic cortical thickening, usually without echogenic hilum, peri-nodular edema, pseudocystic appearance	Often but not always preserved vessel architecture, rich vascularity	Intermediate RI and PI	Intense homogeneous enhancement, starts with diffuse bright spots, peripheral hypo- or non-enhancement	No data; wide range of appearance applying qualitative criteria

CEUS: Contrast enhanced ultrasound; RI: Resistive index; PI: Pulsatility index.

Elastography is mainly helpful in delineating the very early circumscribed malignant infiltration for improved US- and EUS-guided fine needle aspiration (biopsy). Additionally, normal elastographic architecture of enlarged inflammatory lymph nodes can be helpful to prove a benign inflammatory disease, *e.g.*, sarcoidosis.

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315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
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ISSN 1007-9327