Endoscopic Ultrasound (EUS) Elastography

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Recent developments in ultrasound (US) data processing have made it possible to develop new software. The latest generation of US workstations incorporate a central computer allowing very precise processing of the US image. This has made possible the reconstruction of images like three-dimensional US, second harmonic imaging for detecting contrast agents following intravenous injection, and even more recently, Elastography imaging.

Key Words: Elastography, EUS, Endoscopic Ultrasound, Pancreatic Masses, Lymph Nodes

1. Introduction

The introduction of endoscopic ultrasound (EUS) represented a major advance in the diagnosis and staging of gastrointestinal malignancies. In addition to providing imaging of tumours and enhancing TNM staging, EUS also provides guidance for fine needle aspiration (FNA) and biopsies of undiagnosed masses and lymph nodes (LN) suspicious for malignant invasion, providing further diagnostic and staging information. However, FNA is technically demanding and multiple punctures of LN or masses are sometimes required to obtain sufficient tissue for histologic assessment. In addition, when several lymph nodes appear suspicious, the choice of which to puncture is not always clear. Current sonographic criteria for malignant LN (round, hypoechogenic, diameter >1cm, and distinct margins) are helpful in targeting lesions but problems exist with specificity and overlap of these features with benign LN[1)2)]. For further consideration is the fact that pancreatic masses have a wide differential diagnosis that includes benign and malignant aetiologies and FNA of the pancreas is associated with a small, but not insignificant, risk of pancreatitis[3)]. Hence, the ability to more accurately evaluate masses and lymph nodes prior to their puncture in an effort to aid in targeting lesions for FNA and possibly reduce complications would be welcomed by echo-endoscopists. At least two strategies have been developed with these goals in mind, contrast enhanced endosonography and Elastography.

2. Theory and technique of Elastography

It is well known that some diseases, such as cancer, lead to changes in the hardness of tissue. Elastography, a technique that allows the elasticity of tissue to be assessed during ultrasound examination, provides the ultrasonographer with important additional information that can be used for diagnosis. To date, the majority of clinical research involving Elastography has been focused on the evaluation of breast masses[4)-6)] as described elsewhere.

3. EUS Elastography

As with traditional color Doppler imaging, EUS tissue elasticity imaging is performed with conventional EUS probes and does not require additional instrumentation either for measuring pressure or producing vibrations. The vibrations and compressions are provided physiologically by vascular pulsation and respiratory motion. The calculation of tissue elasticity distribution is performed in real-time and the examination results are represented in colour superimposed over the conventional B-mode image.

We have recently published our preliminary experience on 49 patients[7]. Between March 2004 and April 2005, 49 patients underwent EUS examination with Elastography. Indications for Elastography examination included evaluation of a pancreatic mass (n=24) and assessment of suspicious lymph nodes (n=25). The real-time elasticity imaging described in this study was performed with the Elastography module that was integrated into the platform of the HITACHI EUB-8500 system (HITACHI Medical Systems Europe, Zug, Switzerland). Tissue elasticity imaging was performed with the EUS-scope EG-3830UT (Pentax Europe Gmbh, Hamburg, Germany). The examination results are represented as a colour overlay of the conventional B-mode image with malignant tissue appearing in blue, fibrosis in green, normal tissue in yellow, and fat in red.

An EUS-FNA was performed in all cases using a 22-gauge needle (Wilson-Cook Medical, Winston-Salem, North Carolina).

Masses or lymph nodes which appeared mostly blue (harder) were considered malignant, with other results considered benign. Final diagnosis was based on histology from FNA and surgical specimens when available. Results are presented as mean with standard deviation or median with range, depending on data distribution.

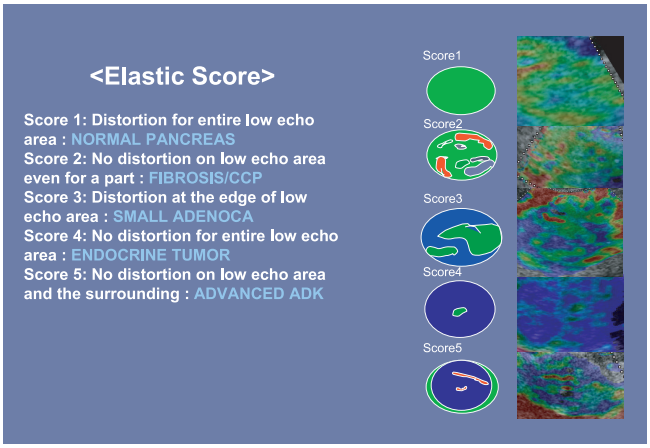
4. Pancreatic Masses

Twenty-four patients (median age 60 years [range 39-88]) underwent EUS examination with Elastography for evaluation of a pancreatic mass (mean diameter 24.7 mm ± 11.1). Masses were located in the pancreatic head (n=12), body (n=6), and tail (n=6). Final histology was based on FNA results in 21 cases and surgical pathology in three cases. Final diagnosis of malignant masses included adenocarcinoma of the pancreas (n=14), metastatic renal cancer (n=2), sarcoma (n=1), and ovarian cancer (n=1). Benign masses consisted of chronic pancreatitis related nodule (n=4), neuroendocrine tumour (n=1), and an intra-papillary mucinous tumour (n=1).

Elastography images of pancreatic masses were interpreted as benign in four cases and malignant in 20. Two masses were misclassified as malignant by Elastography; the first was a neuroendocrine tumour, and in the second case the patient underwent surgical resection and final pathology revealed the mass to be a benign fibromyoblastic tumour of the pancreas. Sensitivity and specificity of Elastography in the diagnosis of malignant lesions was 100% and 67%, respectively.

A subsequent review of our experience with Elastography and pancreatic masses was performed and a more refined classification of pancreatic mass Elastography images has been developed in which EUS Elastography images are differentiated into five scores (Table 1).

Table 1 : EUS Elastography



Score 1 is for a homogenous, soft area (green) and corresponds to the normal pancreatic tissue. For images classified as Score 2, the elastographic image is heterogenous but still in the soft tissue range (green, yellow, and red) and corresponds to fibrosis. Score 3 is for elastographic images which are largely blue (hard) with minimal heterogenicity and corresponds to small, early pancreatic adenocarcinoma (less than 25 mm size). In tumours assigned Score 4 there is a hypoechoic region in the centre of the tumour with green appearance, surrounded by blue or harder tissue and corresponds to a hypervascular lesion such as a neuro-endocrine tumour or small pancreatic metastasis. Finally, Score 5 is assigned to lesions which are largely blue on Elastography but with heterogenicity of softer tissue color (green, red), representing necrosis, and is seen in advanced pancreatic adenocarcinoma (Fig. 1).

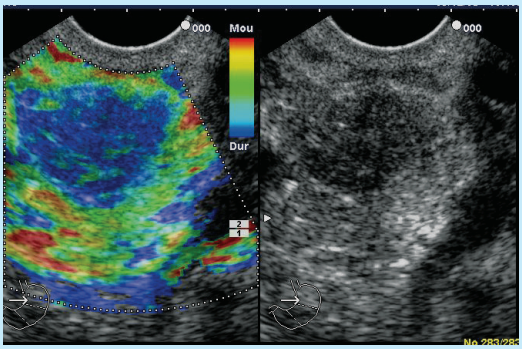


Fig. 1 : Elastography : adenocarcinoma of the pancreas

5. Lymph Nodes

Twenty-five patients (median age 57 years [range 16-76]) underwent EUS examination with Elastography of 31

lymph nodes. The mean diameter of the LN was 19.7mm ± 8.6 and were found in the cervical area (n=3), mediastinum (n=17), celiac arterial trunk region (n=5), and aortocaval region (n=6). Final histology was based on FNA and concluded the lymph nodes to be benign in 14 cases and malignant in 17. Elastography images of the LN were interpreted as malignant in 22 cases (Fig. 2), benign in seven (Fig. 3), and indeterminate in two. While there were no false negatives, there were five false positives. The indeterminate cases were due to the heterogenicity of the Elastography images and were both found to be benign on final histology. The sensitivity and specificity of Elastography in the evaluation of malignant invasion of LN was 100% and 50% respectively. Six patients had Elastography of more than one LN. In two of these cases, one lymph node was benign and the other malignant, and Elastography correctly differentiated between the two.

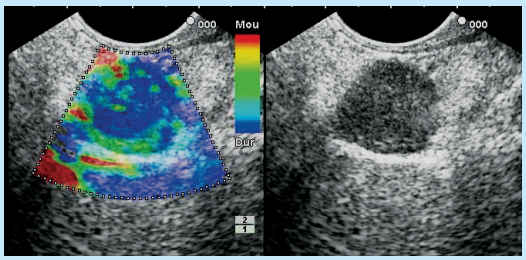


Fig. 2 : Pericaval lymph node Elastography : malignant lymph node : Score 4

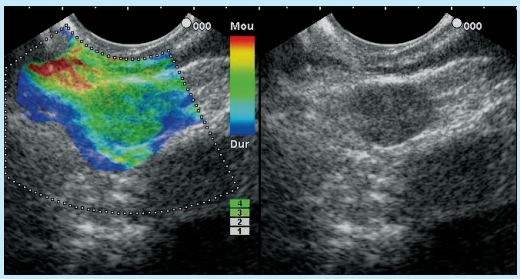


Fig. 3 : Mediastinal lymph node Elastography : Inflammatory lymph node : Score 2

The elasticity of soft tissues depends to a large extent on their molecular building blocks (fat, collagen, etc.), and on the microscopic and macroscopic structural organisation of these blocks. In the normal pancreas, for example, the glandular structure may be firmer than the surrounding connective tissue, which in turn is firmer than the subcutaneous fat. It is known that certain pathologic conditions, such as malignant tumours, often manifest themselves as changes in the mechanical properties of tissue. We believe that the elastic properties of benign lesions are fairly uniform, such as throughout a benign tumour. Cancerous tumours, on the other hand, grow in a very disorganised way. Therefore, within a given malignant tumour, the elastic properties of one area of a tumour may be significantly different from those in another area. The approach used to assess these tissue changes is an extension of the basic principles of traditional medical ultrasound imaging. The principle is based on the fact that tissues are slightly deformed when a small displacement is applied externally[8)-10)].

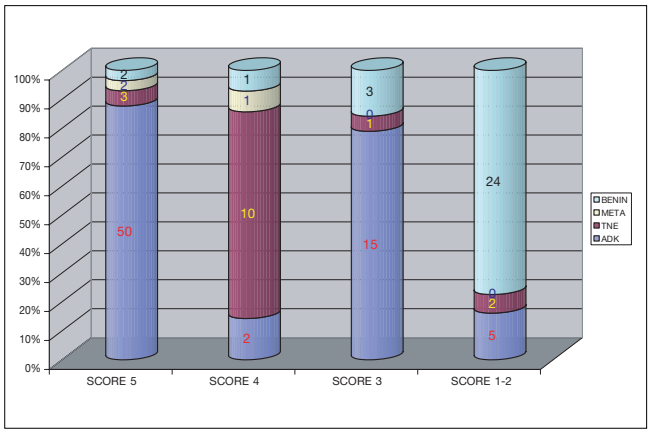
This work represented an extension of our previous results of EUS guided Elastography[11)]. The sensitivity in assessment of both pancreatic masses and lymph nodes was 100%. Although there were false positives in both patient groups, and concerns may exist regarding the specificity of Elastography in both settings (80% in pancreatic group, 50% in LN group) one must recall that the number of benign lesions in this study was relatively small. It is likely that with more experience and refined criteria the specificity will improve. In fact, we have reviewed our experience with Elastography and pancreatic masses and have developed a new, more refined classification of Elastography images. Further assessment of this system is ongoing. The results in the six patients with multiple suspicious lymph nodes highlight the potential utility of Elastography, which is the selection of which lymph node(s) to puncture, thus potentially reducing puncture related risk and reducing procedure time. Although EUS guided FNA has the potential to miss microinvasion of malignancy into lymph nodes, and thus represents a somewhat imperfect gold standard, in the absence of surgical specimens, we feel it is representative of daily practice, particularly when combined with an adequate follow-up period.

6. Results of a prospective multicentre study on Pancreatic masses

Between October 2005 and February 2006, 121 patients (77 M and 44 F), mean age 63 y underwent endoscopic ultrasound (EUS) for a pancreatic mass. The final diagnosis was obtained by EUS-FNA in 82 cases and by surgery in 39 cases. Final histology was pancreatic adenocarcinoma (72 cases), endocrine tumor (16 cases), benign nodule of chronic pancreatitis (30 cases), and pancreatic metastasis (3 cases). Elastography showed malignant aspects (intense blue coloration) for all pancreatic adenocarcinomas, endocrine tumors, pancreatic metastasis and pancreatic sarcoma. All nodules of chronic pancreatitis presented benign aspects (mixed green and low intensity of blue). A score of 1-5 was made using the Elastography classification (table 1). If we considered the scores 1, 2 as benign and 3-5 as malignant, the sensitivity, specificity, positive

and negative predictive values of EUS Elastography to differentiate benign from malignant pancreatic masses were respectively 80.6%, 92.3%, 93.3% and 78.1% with an overall accuracy of this new technology of 89.2%. The negative predictive value for malignancy of scores 1-2 was 77.4% and the positive predictive value for malignancy of scores 3, 4 and 5 was 92.8% (table 2). An interobserver study of 30 patients showed a good concordance (kappa score = 0.7) for the diagnosis of malignant pancreatic masses using Elastography.

Table 2 : SCORE/HISTOLOGY



7. Results of a prospective multi centre study on Lymph nodes staging

Between October 2005 and February 2006, 101 patients (56M and 45F), mean age 61.1 years underwent EUS-FNA of lymph nodes for staging of lung cancer (26 cases), esophageal carcinoma (25 cases), gastric cancer (13 cases), pancreatic cancer (12 cases), of a breast cancer (8 cases) and for a suspicion of LN relapse of a kidney cancer (2 cases). An EUS-FNA was also performed in 15 cases for isolated LN. LN were located in the mediastinum (51 cases), in the cervical area (4 cases), in the celiac or mesenteric area (44 cases) and in perirectal space (2 cases). The mean size of the lesion was 20.1 mm (range: 7-50 mm).

Final histology was malignant LN (55 cases including 35 metastasis by an adenocarcinoma, 13 by a squamous cell carcinoma, 3 by an endocrine tumor, 1 melanoma and 5 lymphomas) and inflammatory LN (44 cases including 3 cases of sarcoidosis). The Elastography classification was made as a score from 1 to 5. If we consider score 1, 2 and 3 as benign and score 4 and 5 as malignant, the sensitivity, specificity, positive and negative predictive values of EUS Elastography to differentiate benign from malignant LN were respectively 100%, 83.3%, 100% and 75%. But, if we consider score 1, 2 as benign and score 3, 4 and 5 as malignant, the sensibility, specificity, positive and negative predictive values of EUS Elastography to differentiate benign from malignant LN were respectively 88.10%, 88.13%, 91.22% and 84.10% with an accuracy of this new technique of between 88 and 89.10%.

EUS Elastography is a new application in the field of the endosonography and seems to be able to differentiate fibrous and benign tissue from malignant lesions. While our results are very encouraging further research will be needed to further define the place of this new technique and should be aimed at further defining criteria for accurate Elastography as well as subsequently assessing the technique using multiple operators in a blinded setting. EUS guided Elastography has the potential for further guiding the diagnosis and therapy of gastrointestinal related tumours.

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