

Real-time Sonoelastography - a New Application in the Field of Liver Disease

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Abstract

Ultrasound elastography is a new imaging technique that allows a noninvasive estimation and imaging of tissue elasticity distribution within biological tissues using conventional real-time ultrasound equipment with modified software. Elastography has been reported to be useful for differentiation and characterization of various malignant tumors, such as breast, prostate, thyroid, pancreas, lymph nodes, gastrointestinal stromal tumors, hepatocellular carcinoma and liver metastasis. Transient and, more recently, real-time elastography has been proved to be useful for noninvasive assessment of liver fibrosis in patients with diffuse liver diseases. Elasticity imaging promises to make an important contribution to ultrasound practice.

Key words

Real-time sonoelastography – liver tumors – hepatitis.

Introduction

In the past decade, an important field that has emerged as complementary to ultrasound imaging is that of elasticity imaging. Sonoelastography is an ultrasound technique that allows the tissue mechanical properties to be estimated in vivo and imaged using conventional ultrasound systems with modified software. Ultrasonic elastography is an ideal imaging modality for assessing the bioelasticity distribution in biologic tissues because of its low cost and low risk. Introduced by Ophir et al in 1991 [1], it subsequently evolved into a real-time imaging tool. The mechanical properties of biologic tissues depend on their constituent

macromolecules (parenchyma, fat, collagen, etc.) and on their structural organization. Tissue elasticity is characterized by the amount of tissue's displacement or distortion in response to the application of an external load (elastic or Young's modulus). In many cases, in spite of the difference in stiffness or mobility, the small size of a pathological lesion and/or its deep location impedes the detection and/or evaluation by palpation [2]. Because the echogenicity and the mechanical attributes of the tissue are generally not correlated, it is expected that imaging tissue stiffness or strain will provide new information related to tissue structure and/or pathology [3].

Elasticity imaging has been reported to be useful for the diagnosis and characterization of various tumors, which are usually stiffer than normal tissues [4]. To date, extensive sonoelastography research has been focused on the evaluation of the breast masses [5-8], prostate cancer [9, 10] and thyroid nodules [11, 12]. Preliminary data in breast tissue elastography have shown that the technique allows correct differentiation of most benign and malignant masses [8]. A qualitative assessment of the tumoral pattern according to Ueno classification and an elasticity score 1 to 5 were developed for breast lesions (Fig. 1); the higher the score (4 or 5), the stiffer the tissue and the higher the probability of a malignant lesion [5]. Further applications of elastography emerged for high-intensity focused ultrasound (HIFU), treatment evaluation and follow-up of prostate lesions [13], as well as for monitoring of thermal lesions after radiofrequency ablative (RFA) therapy of liver or kidney lesions [14, 15], being well known that heat-ablated tissues are more elastic than untreated tissues.

Giovannini et al [16] brought elastography imaging in the field of gastroenterology. They explored for the first time the potential add-on endoscopic ultrasound (EUS) elastography for differentiating between benign and malignant pancreatic lesions and lymph nodes. Saftoiu et al have recently confirmed that real-time EUS elastography represents a reliable method for differentiating between benign and malignant lymph nodes, adding complementary information to conventional EUS imaging by qualitative and quantitative pattern analysis [17]. Furthermore, different solid tumors

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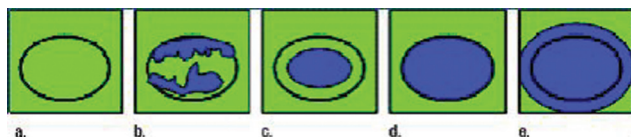


Fig 1. Diagram depicting general appearance of lesions for elasticity scores a) 1, b) 2, c) 3, d) 4, and e) 5. Black circle indicates outline of hypochoic lesion (i.e. border between lesion and surrounding breast tissue) on B-mode images (5).

located into the wall or nearby gastrointestinal tract might be also visualized and characterized by EUS elastography. Recently, our group highlighted the complementary role of EUS elastography for differentiating the benign or malignant nature of GISTs locating into the wall of the gastrointestinal tract [18]. Transient and, more recently, real-time elastography has proved to be useful for noninvasive assessment of liver tissue stiffness and for characterization of liver fibrosis in patients with diffuse liver diseases such as viral hepatitis or liver cirrhosis [19-21].

As a result of these data, elasticity imaging with its ever increasing number of applications and demonstrated accuracy in a typical, clinical ultrasound setting promises to make an important contribution to the ultrasound practice [22].

Theoretical principles and technical aspects

The principle of the elastography technique is based on slight external tissue compression on the structures examined, that produces strain (displacement) within the tissue, with subsequent calculation of the strain profile along the axis of compression. The strain profile is converted into an elastic modulus image (i.e. the tissue elasticity distribution) called elastogram. By measuring the tissue strain induced by compression, it is possible to estimate the tissue hardness and to differentiate benign from malignant lesions.

Basically, tissue elasticity imaging methods based on ultrasound examination fall into three main groups:

1) methods where a quasi-static compression is applied to the tissue and the resulting components of displacement or of the strain tensor are estimated. These methods include elastography, based on a global compression of the medium and acoustic radiation force imaging that uses localized compression [1];

2) methods based on a monochromatic low-frequency vibration such as sonoelasticity [23], which uses Doppler signals to estimate tissue displacement, and vibroacoustography which uses ultrasound-stimulated acoustic emission;

3) transient elastography [24], which relies on the observation of the propagation of a transient (pulsed) shear wave to determine the visco-elastic properties of the tissues. This method offers the advantage of producing a spatially and temporally localized excitation, independent of boundary conditions, that propagates through the medium so that a whole volume can be scanned rapidly.

Real-time sonoelastography is carried out with a conventional Hitachi 8500 or 6500 ultrasound system with an embedded Sono-Elastography module (Hitachi Medical Systems Europe Holding AG, Zug, Switzerland), a dedicated software with a complex algorithm that is able to process in a very short time all the data coming from the lesion as radiofrequency impulses and minimizes the artifacts due to lateral dislocation, allowing accurate measurement of the degree of tissue distortion. Real-time elastography can be performed with the linear L54M probe (for transabdominal examination) or with the conventional EUS probes (when coupled with the linear endoscope EG3870UT) (Pentax, Hamburg, Germany) during EUS examination, without any need for additional equipment. The linear probe is set to a frequency of 6.5 MHz for the transabdominal examination of liver and at 7.5 MHz for EUS examination during the performance of sonoelastography in our department. The transabdominal examination was performed with this kind of transducer in order to obtain the maximum penetrability and to be able to include as much as possible the tissues surrounding the liver.

The compression is provided physiologically by spontaneous respiratory motion or vascular pulsation, as well as by the slight compression obtained with the linear probe or the endoscope tip. Calculation of the tissue elasticity distribution is carried out in real time and displayed in color superimposed over the conventional B-mode imaging. The color scale includes the following colors: red (soft tissue), blue (anelastic, hard tissue) and green (intermediate, normal tissue). The system also displays a compression threshold which has to be set up between 3 and 4 (adequate compression).

Elastography is performed by using a two panel image with the usual conventional gray-scale B-mode image on the right side and with the elastography image on the left side. A region of interest (ROI) for the elastography calculations is manually selected and should include the targeted lesion, as well as the soft surrounding tissues. The ROI needs to be set to include sufficient surrounding tissue because elasticity values are displayed relative to the average strain inside the ROI.

Real-time ultrasound elastography for liver diseases

Hepatocellular carcinoma, liver metastasis and benign liver tumors

Small dysplastic nodules (1-2 cm) detected on US in cirrhotic patients represent the most challenging category for radiologic diagnosis of HCC. In these patients, contrast-enhanced US, dynamic computed tomography (CT) and magnetic resonance imaging (MRI) may lead to major problems due to the false-positive (in the presence of arteriovenous shunts and in patients with macroregenerative nodules with dysplastic liver cells) [25] and false-negative results (smaller than 2 cm nodules are hypovascular due to the low number of unpaired arteries in the tumor, which

increase in parallel with increasing size of the tumor and to incomplete vascularization of the tumoral sinusoid-like blood spaces) [26]. Due to their hypovascularization, in nodules smaller than 2 cm, real-time sonoelastography by transabdominal or EUS approach may be a better alternative to contrast-enhanced US, or even dynamic CT or MRI. Transabdominal elastography shows the HCC nodule as an inhomogeneous hard (blue) structure (Fig. 2); due to abrupt change in mechanical properties of the malignant area, tumoral borders are well visualized and characterized by abrupt color change, as well. The liver is imaged at EUS from the proximal stomach or gastroesophageal junction to view the left lobe and from the gastric antrum or duodenal bulb to view the right lobe. EUS/EUS-guided fine needle aspiration (FNA) has been recently proved to be a safe and accurate test for the diagnosis of HCC in a small series of patients [27]. Examination of the entire liver requires close attention and systematic “pull-through” views. In addition, EUS at 5 MHz generally will allow imaging of the entire depth of the liver, i.e. to the abdominal wall or lung, depending on position. EUS can detect focal lesions that are missed by conventional imaging modalities (CT and MRI) and it should be considered as an alternative in patients with liver cirrhosis and HCC who are candidates for liver transplantation or curative liver resection. EUS elastography can add more accuracy to the diagnosis of small HCC, eliminating the need of FNA, as well (Fig. 3). Our group already published the case of a patient with small hypervascular cirrhotic nodule showing an intense blue pattern indicating the hardness of a malignant nodule [28].

Not only small HCC nodules, but also liver metastases, even the occult ones, can be accurately detected by sonoelastography (Fig. 4). Elasticity imaging technique can also accurately characterize other types of focal liver lesions such as adenoma, focal nodular hyperplasia, hemangioma, lipoma, sarcoidosis [27, 29, 30] (Figs. 5 and 6).

Real-time sonoelastography provides also important additional information during the follow-up after therapy (follow-up examination after local ablative therapy using radiofrequency or ethanol injection, as well as follow-up examination for fibrosis assessment after antiviral therapy of chronic hepatitis B or C) (Fig. 7).

Hepatitis

An aspect of granulomatous hepatitis is shown in Fig. 8. The elastogram corresponding to the hyperechoic lesion is heterogeneous, but still within the soft-tissue range. The first report regarding chronic hepatitis evaluated by real-time elastography included both HCV and HBV infection [21]. An area under curve (AUC) value of 0.75 was obtained using real-time elastography (elasticity score) for the diagnosis of significant fibrosis ($\geq F2$). In comparison, other recent studies [19, 20] analyzing the noninvasive assessment of liver fibrosis with FibroScan (transient elastography) revealed AUCs between 0.75 and 0.84 for the diagnosis of significant fibrosis ($\geq F2$). Both methods have been proved to be useful for noninvasive evaluation of liver fibrosis, regardless of etiology of liver disease. Figs. 9 and 10 reveal

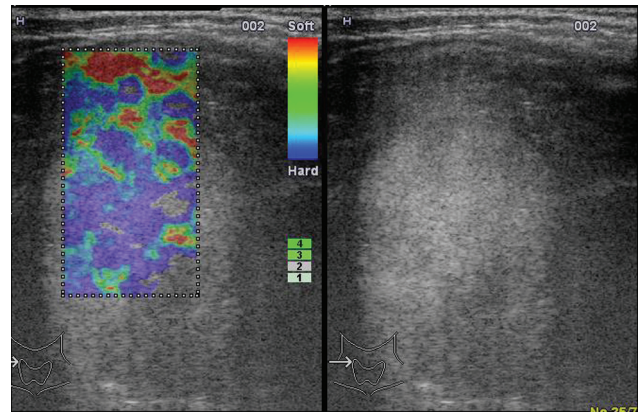


Fig 2. Real-time transabdominal sonoelastography showing a 34 mm HCC nodule of the right lobe, with an inhomogeneous blue-green pattern due to the hardness of malignant tissue, in a patient with decompensated HBV liver cirrhosis.

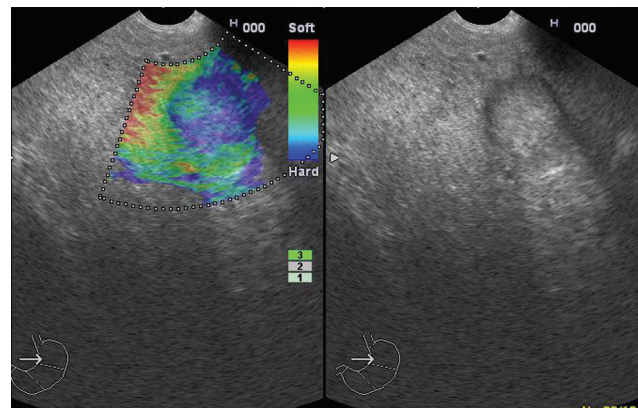


Fig 3. EUS elastography showing a 14 mm HCC localized in the right hepatic lobe, visualized as an inhomogeneous hard focal lesion (blue-green), in a patient with compensated HCV liver cirrhosis.

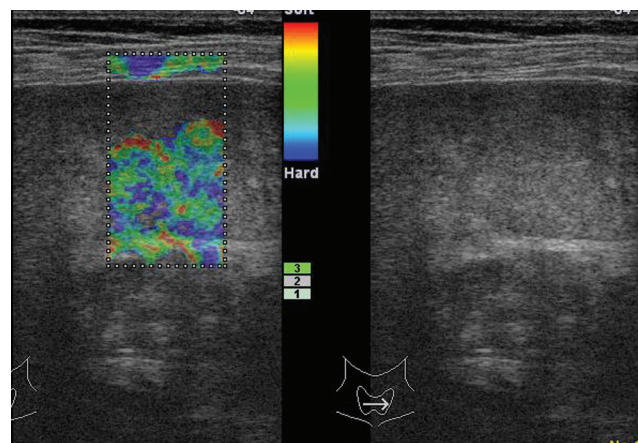


Fig 4. The same appearance is noted for liver metastasis originating, in this case, from gastric cancer (inhomogeneous hard tissue mixed with “soft areas” suggesting necrosis within the tumor).

sonoelastographic aspects of chronic hepatitis F2 on liver biopsy (Fig. 9) and compensated liver cirrhosis (Fig. 10) in patients with HCV infection. There are recent studies

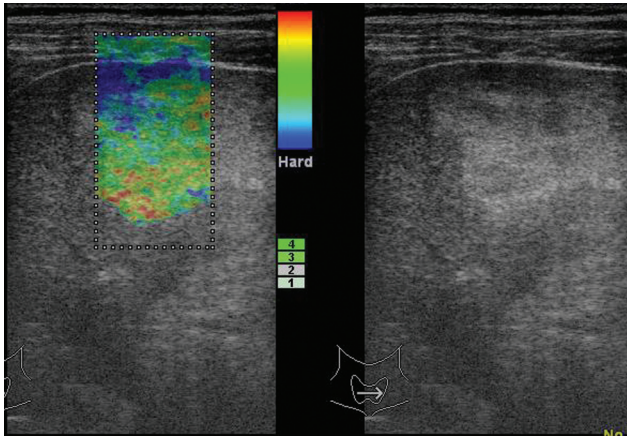


Fig 5. Hepatic hemangioma depicted as a hyperechoic mass by conventional US and a soft red-green image by sonoelastography.

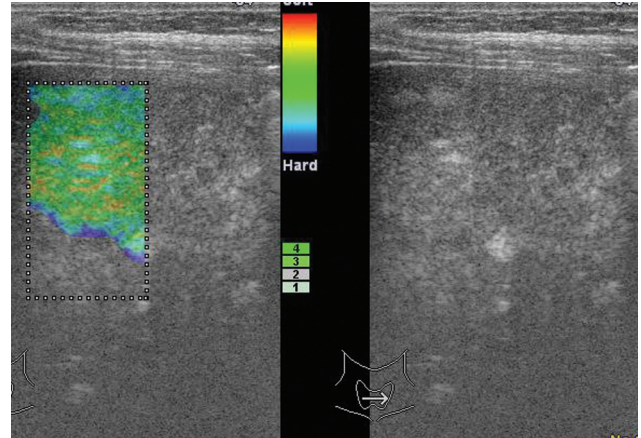


Fig 8. Sonoelastography image of granulomatous hepatitis (“soft” aspect of the granulomas).

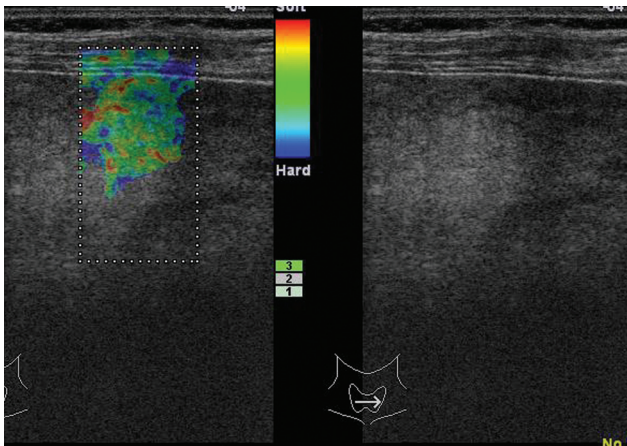


Fig 6. Inhomogeneous pattern of an adenoma mass depicted as a hyperechoic mass by conventional US and a soft green area with blue foci and bands by sonoelastography.

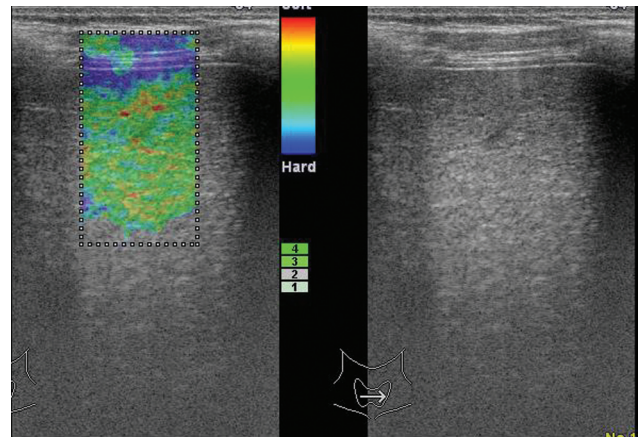


Fig 9. Sonoelastography aspect of HCV chronic hepatitis (F2 on liver biopsy).

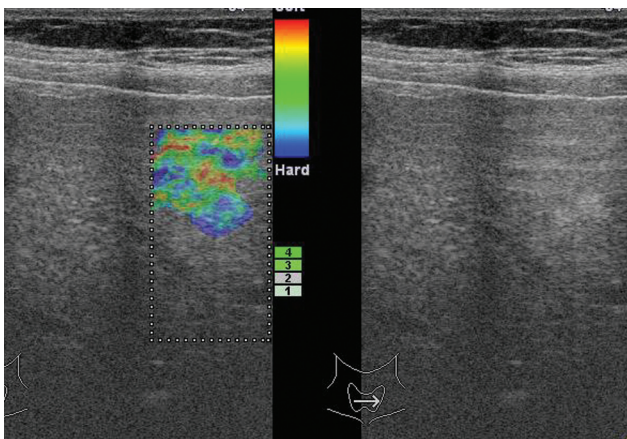


Fig 7. Follow-up imaging of an HCC nodule after radiofrequency ablation (“softer” green appearance of the nodule depicting therapeutic necrosis).

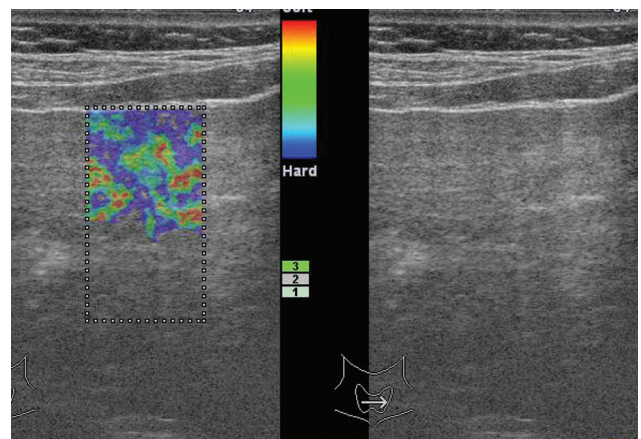


Fig 10. US elastography of compensated HCV macronodular liver cirrhosis.

showing that the efficacy of liver stiffness measurement for the assessment of liver fibrosis was superior in patients with chronic hepatitis C as compared to patients with chronic hepatitis B [31] and different models should be considered for different etiologies of liver disease.

Real-time sonoelastography for liver diseases: drawbacks and limits

The major drawback for transabdominal elastographic examination of the liver is the absence of the SonoElastography

module available for convex transducer in order to allow adequate visualization of the whole liver and good penetrability. This can be surpassed by echo-endoscopic examination, but this is an invasive method that requires sedation increasing also the cost of the procedure. On the other hand, pitfalls of EUS elastography are represented by the impossibility to control tissue compression by the EUS transducer, as well as by the induction of motion artifacts determined by respiratory or heart movements, which can not be adequately eliminated or quantified. On external US elastography it is much easier to control compression, but also in this case the application of strong pressure can lead to misdiagnosis [5]; this is probably much more expressed in superficial tumors like breast or thyroid than in liver tumors where intercostal approach permitted to apply micrometer compressions only. Usual breathing does not produce motion artifacts because each elastography image is obtained in a few milliseconds. Anyway the patient is not sedated during transabdominal ultrasound, so he is able to hold his breath. Also, during transabdominal approach, the ROI can be selected in order to avoid large blood vessels.

There is no yet adequate quantitative measurements to perfectly characterize the mixture of tissue hardness depicted by elastography images. Either a qualitative assessment of the tumoral pattern according to Ueno classification for breast lesions, or a quantitative histogram analysis of the fundamental colours (red-green-blue) in images recorded during real time transabdominal or EUS Elastography (Adobe PhotoShop 7.0; Image J) may be used.

Computer-enhanced dynamic analysis based on hue histograms of the EUS elastography movies [17] represents a method that permits a better characterization of lesions. Anyway this depends on a movie that has to include only elastography colored images and not gray-scale images such as those often obtained during transabdominal examination especially in localized intrahepatic lesions. A high number of static images chosen by an experienced ultrasound examiner can surpass the bias induced by still images instead of dynamic sequence. The qualitative pattern analysis of the elastography images is clearly subject to errors due to inter and intra-observer variability. Anyway, the quantitative analysis (histogram) with mean values of the color intensity obtained during elastography can be a good indicator of malignancy.

The diagnostic accuracy of real-time elastography of the liver should be further improved by optimization of the images using different ultrasound probes, by combining transabdominal and EUS examination of the liver, by refining selection of the analyzed area of liver tissue, and by a more adequate statistical assessment of the elasticity images for a larger data set or a larger number of images or movies for each patient.

Conclusion

Real-time sonoelastography is a promising technique in the field of liver diseases and appears to be capable of

distinguishing between benign tissue and malignant focal lesions, on the one hand, and assessing the amount of fibrosis in diffuse liver diseases, on the other hand. Adding routinely elastography imaging to conventional US, a better noninvasive characterization of small focal lesion of the liver is possible, decreasing the number of unnecessary bioptic procedures in patients scheduled for curative treatment. Further advances in elastography technology, as well as large prospective studies to gain adequate statistical power will better delineate the usefulness of elastography in the field of liver diseases.

Conflicts of interest

Nothing to declare.

References

- Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging* 1991; 13: 111-134.
- Ophir J, Garra B, Kallel F, et al. Elastographic imaging. *Ultrasound Med Biol* 2000; 26 Suppl 1: S23-S29.
- Gao L, Parker KJ, Lerner RM, Levinson SF. Imaging of the elastic properties of tissue- a review. *Ultrasound Med Biol* 1996; 22: 959-977.
- Skovoroda AR, Klishko AN, Gusakyan DA, et al. Quantitative analysis of the mechanical characteristics of pathologically changed soft biological tissues. *Biophysics* 1995; 40: 1359-1364.
- Itoh A, Ueno E, Tohno E, et al. Breast disease: clinical application of US elastography for diagnosis. *Radiology* 2006; 239: 341-350.
- Thomas A, Fischer T, Frey H, et al. Real-time elastography – an advanced method of ultrasound: first results in 108 patients with breast lesions. *Ultrasound Obstet Gynecol* 2006; 28: 335-340.
- Céspedes I, Ophir J, Ponnekanti H, Maklad N. Elastography: elasticity imaging using ultrasound with application to muscle and breast in vivo. *Ultrason Imaging* 1993; 15: 73-88.
- Garra BS, Céspedes EI, Ophir J, et al. Elastography of breast lesions: initial clinical results. *Radiology* 1997; 202: 79-86.
- Cochlin DL, Ganatra RH, Griffiths DF. Elastography in the detection of prostatic cancer. *Clin Radiol* 2002; 57: 1014-1020.
- Miyayama N, Akaza H, Yamakawa M, et al. Tissue elasticity imaging for diagnosis of prostate cancer: a preliminary report. *Int J Urol* 2006; 13: 1514-1518.
- Rago T, Santini F, Scutari M, Pinchera A, Vitti P. Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. *J Clin Endocrin Metab* 2007; 92: 2917-2922.
- Lyshchik A, Higashi T, Asato R, et al. Thyroid gland tumor diagnosis at US elastography. *Radiology* 2005; 237: 202-211.
- Souchon R, Rouviere O, Gelet A, et al. Visualisation of HIFU lesions using elastography of the human prostate in vivo: preliminary results. *Ultrasound Med Biol* 2003; 29: 1007-1015.
- Varghese T, Zagzebski JA, Lee FT Jr. Elastographic imaging of thermal lesions in the liver in vivo following radiofrequency ablation: preliminary results. *Ultrasound Med Biol* 2002; 28: 1467-1473.
- Pareek G, Wilkinson ER, Bharat S, et al. Elastographic measurements of in-vivo radiofrequency ablation lesions of the kidney. *J Endourol* 2006; 20: 959-964.
- Giovannini M, Hookey L, Bories E, Pesenti C, Monges G, Delpero JR. Endoscopic ultrasound elastography: the first step towards virtual biopsy? Preliminary results in 49 patients. *Endoscopy* 2006; 38:

- 344-348.
17. Saftoiu A, Vilman P, Ciurea T, et al. Dynamic analysis of EUS used for the differentiation of benign and malignant lymph nodes. *Gastrointest Endosc* 2007; 66: 291-300.
 18. Gheorghe L, Gheorghe C, Cotruta B, Carabela A. CT aspects of gastrointestinal stromal tumors: adding EUS and EUS elastography to the diagnostic tools. *J Gastrointest Liver Dis* 2007; 16: 346-347.
 19. Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005; 41: 48-54.
 20. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (Fibroscan): a prospective study. *Gut* 2006; 55: 403-408.
 21. Friedrich-Rust M, Ong MF, Herrmann E, et al. Real-time elastography for noninvasive assessment of liver fibrosis in chronic viral hepatitis. *AJR Am J Roentgenol* 2007; 188: 758-764.
 22. Konofagou EE. Quo vadis elasticity imaging? *Ultrasonics* 2004; 42: 331-336.
 23. Krouskop TA, Wheeler TM, Kallel F, Garra BS, Hall T. Elastic moduli of breast and prostate tissues under compression. *Ultrason Imaging* 1998; 20: 260-274.
 24. Sandrin L, Catheline S, Tanter M, Hennequin X, Fink M. Time resolved pulsed elastography with ultrafast ultrasonic imaging. *Ultrason Imaging* 1999; 21: 259-272.
 25. Bolondi L, Gaiani S, Celli N, et al. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. *Hepatology* 2005; 42: 27-34.
 26. Kojiro M. Focus on dysplastic nodules and early hepatocellular carcinoma: an Eastern point of view. *Liver Transpl* 2004; 10(2 Suppl 1): S3-S8.
 27. Singh P, Erickson R, Mukhopadhyay P, et al. EUS for detection of the hepatocellular carcinoma: results of a prospective study. *Gastrointest Endosc* 2007; 66: 265-273.
 28. Gheorghe L, Iacob S, Gheorghe C, et al. Ecoendoscopic elastography for the diagnosis of hepatocellular carcinoma in small cirrhotic nodules. *Archives of the Balkan Medical Union* 2007; 42: 186-188.
 29. Prasad P, Schmulewitz N, Patel A, et al. Detection of occult liver metastases during EUS for staging of malignancies. *Gastrointest Endosc* 2004; 59: 49-53.
 30. Rustemovic N, Hrstic I, Opacic M, et al. EUS elastography in the diagnosis of focal liver lesions. *Gastrointest Endosc* 2007; 66: 823-824.
 31. Seo YS, Kim ES, Kwon YD, et al. Liver stiffness measurement in patients with chronic hepatitis B is not as useful as that in patients with chronic hepatitis C for the assessment of liver fibrosis. *Hepatology* 2007; 46 (Suppl 1): 842A.