ABSTRACT Fibrosis is the liver’s scarring response to injury, culminating in cirrhosis and its complications. Percutaneous liver biopsy with connective tissue stain is considered more likely a “silver”, rather than a “gold standard” for assessing the degree of hepatic fibrosis. That’s why new modalities were recently developed to accurately assess the stage of the liver disease. The term “elastography” describes an imaging technique that conveys information about a tissue’s relative firmness in response to compression, meaning it is more akin to palpation than inspection. Real-time transabdominal elastography represents a new technology for measurement of tissue elasticity integrated in ultrasound systems and can be performed with conventional ultrasound probes during a routine sonography examination. Some of its limitations are that it cannot explore neither all the patients, nor a sufficient size of the liver. In order to overcome these, now that the technology exists, we propose an endoscopic approach from the “inside”.

KEY WORDS chronic liver disease, elastography, endoscopic ultrasound elastography

Introduction

Fibrosis is the liver’s scarring response to injury that occurs in almost any chronic liver injury, representing in fact accumulation of extracellular matrix, which, when progressive, culminates in cirrhosis and its complications.

Assessing liver fibrosis: liver biopsy, the reference standard?

Percutaneous liver biopsy with connective tissue stains is still considered the “gold standard” for assessing the degree of hepatic fibrosis, but several studies reveal that this approach is far from being perfect, due to the fact that it is subjected to both sampling errors and interobserver variability\(^1\)\(^2\)\(^3\)\(^4\). Moreover, liver biopsy is associated with significant complications in approximately 1% of patients\(^5\).

This is the reason why other modalities of determining the stage of liver disease are currently under investigation, generally following two directions: serum markers of liver fibrosis and imaging tests\(^6\).

Imaging tests used for the assessment of liver fibrosis

Harder tissues deform less than softer tissues, while ultrasound echoes carry information about tissue location and density, both of which change slightly with deformation. Therefore, it is possible to estimate the tissue hardness, which might be useful for the evaluation of the amount of fibrosis present in organs such as the liver.

Recently, the characteristically increased “stiffness” of a fibrotic liver, which is caused by the increased and abnormal extracellular matrix, has been exploited to develop a technology known as “transient elastography” (FibroScan; EchoSens, Paris, France)\(^7\). The principle of the method is that a vibration transmitted into the liver tissue induces an elastic shear wave that propagates through the organ. Pulse-echo ultrasound acquisitions are performed to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness: the harder the tissue, the faster the shear wave progresses\(^8\). Disadvantages of this method include the uncertainty whether FibroScan can differentiate intermediate levels of fibrosis with adequate sensitivity or specificity, although it is quite accurate in detecting cirrhosis\(^9\). Furthermore, testing obese individuals is difficult using current versions of the technology, because, on one hand, the signal penetrates only 25 to 65 mm, and on the other, the fat in the thoracic wall attenuates elastic and ultrasound waves, making measurement of liver stiffness impossible in this subset of patients\(^10\). Moreover, FibroScan cannot clearly differentiate fibrosis from steatosis, and its sensitivity and precision are not yet validated for tracking changes in fibrosis in response to treatment\(^6\).

Transabdominal real-time sonoelastography represents a newly developed
technology for the measurement of tissue elasticity, being integrated in current ultrasound systems. Thus, echo signals before and under slight compression are compared and analyzed, using conventional ultrasound probes. The tissue elasticity distribution can be calculated by the strain and stress of the examined tissue. The reported diagnostic accuracy expressed as areas under receiver operating characteristic (ROC) curves were 0.75 for the diagnosis of significant fibrosis (fibrosis stage according to METAVIR scoring system \[F \geq F2\]), 0.73 for severe fibrosis \((F \geq F3)\), and 0.69 for cirrhosis\(^{16}\). In our limited experience with the technique, liver steatosis has a distinct appearance on real-time sono-elastography images, with low mean hue histogram values\(^{15}\). This means that the method might differentiate between fibrosis and steatosis, which Fibroscan cannot. One limitation of this approach is that the higher frequencies used for examination might be too high to examine correctly and consistently the right liver lobe. Manual application of pressure is another limitation, because a small deformation (below 2%) of the tissues is needed, and this is quite difficult to obtain through the thoracic wall.

Another important limitation is the impossibility to correctly depict elastography information inside the liver in a significant proportion of the patients, due to the limited penetration of real-time elastography (only 3–4 cm)\(^{15}\). This is particularly evident in the presence of a large body habitus, as well as an increased width of the thoracic wall.

Real-time endoscopic ultrasound (EUS) elastography. Why not from inside?

EUS elastography is a recent imaging procedure used for the calculation and visualization of tissue elasticity during usual EUS examinations\(^{11}\). EUS elastography is using the same principle as the above mentioned real-time transabdominal elastography, and allows the assessment of elasticity distribution within tissues. As an advantage, it compares the echoes simply obtained over several seconds of normal breathing and blood circulation, thus overcoming the need for applying manual pressure\(^{12}\), with the images being represented in transparent color superimposed on the conventional gray-scale B-mode scans\(^{12}\).

EUS elastography equipment includes a Hitachi 8500 ultrasound system with an embedded Sono-Elastography module (Hitachi Medical Systems Europe Holding AG, Zug, Switzerland), coupled with the EG 3830 linear endoscope or the EG 3630 radial endoscope (Pentax, Hamburg, Germany). Real-time EUS elastography can be thus performed with the conventional EUS probes, being relatively simple to use.

To the best of our knowledge, there are no published reports of EUS elastography used for the assessment of liver hardness in chronic liver diseases, although there is at least one report about using this method in the diagnosis of focal liver masses\(^{13}\).

---

**Fig. 1.** EUS elastography examination in a patient with a normal liver.

To visualize tissue elasticity patterns, different elasticity values are marked with different colors (on a scale of 1 to 255) and the sono-elastography information is shown superimposed on the conventional gray-scale image. The system is set-up to use a hue color map (red-green-blue), where hard tissue areas are marked with dark blue, medium hard tissue areas with cyan, intermediate tissue areas with green, medium soft tissue areas with yellow and soft tissue areas with red. In this case, note the green ("soft") characterization of a large explorable portion of the liver. A branch of a liver vessel is depicted in red, as being soft and easily compressible.

**Fig. 2.** EUS elastography examination in a patient with advanced liver fibrosis. Note the predominantly blue ("hard") appearance of the ultrasound section.

The great advantage of the EUS technique is that it provides excellent images of the medial two-thirds of the liver\(^{14}\), with minimal distance between the transducer and the liver (Fig. 1 and 2). However, the method is minimally invasive (with risks derived from patient sedation and its
theoretical risks of gastro-intestinal perforation or pulmonary aspiration, etc.) and is quite expensive. These drawbacks, coupled with the current conception that the liver is an organ largely explorable from the “outside”, not from the “inside”, concurred to leave this method behind in this field.

Conclusion

At present, no single test for diagnosing liver fibrosis is optimal. Therefore new, more accurate and minimally invasive modalities to diagnose and monitor liver fibrosis are needed in this context, especially for the “gray zone” of intermediate stages of fibrosis, because these are the patients most likely to benefit from antiviral or other specific therapies.

Although studies on the utility of EUS elastography are currently ongoing, mapping of the tissue elasticity distribution might be useful to accurately estimate the stage of different chronic liver diseases. The potential advantages of real-time EUS elastography as compared with Fibroscan are that it allows estimation of liver stiffness in all the patients (either obese or not), that it has the potential of differentiating between fibrosis and steatosis, and that, most importantly, can evaluate a large volume of the liver.

Further developments in the field of EUS elastography technology, as well as prospective studies with blinded examiners and adequate statistical power will probably establish more clearly the clinical impact of dynamic elasticity imaging, and just how pressed we will be to adopt elastography as a standard adjunct to EUS will undoubtedly depend upon the firmness of future data.

Acknowledgement

This paper was supported through the research grants no. 2076/2007 (SONOFIBROCAST) and 320/2007 financed by the Romanian Ministry of Education, Research and Innovation – National Authority for Scientific Research (NASR), and Executive Unit for Financing Higher Education and Scientific University Research (UEFISCUS), respectively.

References


