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WFUMB GUIDELINES AND RECOMMENDATIONS FOR CLINICAL USE OF ULTRASOUND ELASTOGRAPHY: PART 3: LIVER

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Abstract—The World Federation for Ultrasound in Medicine and Biology (WFUMB) has produced these guidelines for the use of elastography techniques in liver disease. For each available technique, the reproducibility, results, and limitations are analyzed, and recommendations are given. Finally, recommendations based on the international literature and the findings of the WFUMB expert group are established as answers to common questions. The document has a clinical perspective and is aimed at assessing the usefulness of elastography in the management of liver diseases. (E-mail: m-kudo@med.kindai.ac.jp) **© 2015 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.**

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INTRODUCTION

Diffuse liver disease is a major health problem worldwide. A wide range of liver insults (chronic viral hepatitis, alcoholic and non-alcoholic fatty liver disease, autoimmune hepatitis drug-induced liver injury, primary biliary cirrhosis and several rarer causes) set up a common pathway of fibrosis, which, if the damage continues, progresses and leads to cirrhosis which may be complicated by portal hypertension, liver failure and the development of hepatocellular carcinoma.

Accurate staging of the degree of fibrosis is essential in planning therapy (including antiviral therapy) and predicting response to treatment and malignant potential. Although liver biopsy has long been the gold standard, it is an invasive procedure with potential complications such as bleeding and severe pain (Bravo et al. 2001; Cadranel et al. 2000). In addition, sampling error is an intrinsic problem because of the small sample size taken from a heterogeneous organ (Cholongitas et al. 2006), and diagnostic consistency may be influenced by interobserver variability (Maharaj et al. 1986; Bedossa et al. 2003; Regev et al. 2002).

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Therefore, there has been great interest in the development of noninvasive techniques for the diagnosis of liver fibrosis. There are many reports on the use of blood markers for liver fibrosis, such as platelets, hyaluronic acid, type IV collagen, aminotransferase/platelet ratio index (APRI), and algorithm-based serum models (such as Fibro Index, FIB-4, and Fibro Test) (Martinez et al. 2011a). However, these methods can be affected by factors unrelated to the liver.

As chronic liver damage results in hepatic fibrosis characterized by an increase of extracellular matrix produced by fibroblast-like cells, the liver becomes stiffer than normal.

Elastography can be used to assess liver stiffness noninvasively. It measures tissue behavior when a mechanical stress is applied using ultrasound (US) or magnetic resonance imaging.

Several US-based elastography techniques are available and have been extensively described in Part 1. Table 1 lists those that are in clinical use. They differ in the physical properties used.

SHEAR WAVE-BASED techniques measure the speed of shear waves in tissues. The shear waves can be generated by an external push (transient elastography) or by ultrasound radiation force enabling a single measurement (point shear wave speed measurement) or an image (shear wave speed imaging). The main difference between these techniques is that shear wave speed, being linked with stiffness, can be measured and converted into kPa, the unit of Young's modulus whereas strain elastography gives relative estimates only.

STRAIN IGING measures the deformation of tissue.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) has recently issued guidelines and recommendations on the clinical use of ultrasound elastography (Bamber et al. 2013; Cosgrove et al. 2013). Accordingly, our objectives are to determine based on the evidence whether elastography is useful and reproducible in the evaluation of diffuse liver disease, in particular, in terms of the accuracy and limitations of the available techniques depending on the indications and etiologies. The impact of elastography on liver biopsy (reduction and/or replacement) for diffuse liver disease will be discussed. Finally, we discuss the potential role of elastography in the characterization of focal liver diseases.

Table 1. Elastography methods in clinical use for the liver.

1- Shear wave speed techniques	Transient elastography Point shear wave speed measurement Shear wave speed imaging
2- Strain/displacement techniques	Strain elastography

TRANSIENT ELASTOGRAPHY

Procedure

Transient elastography (TE) is performed on a patient lying supine, with the right arm elevated to facilitate access to the right liver. The tip of the probe is in contact with the intercostal skin through a coupling gel in the 9th to 11th intercostal space at the level where a liver biopsy would be performed. The operator, assisted by a time-motion image, locates a liver portion at least 6 cm deep and free of large vascular structures. The operator then presses the probe button to start the measurements ("shots"). TE measures the liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 mm and 65 mm below the skin surface (Figure 1). The software determines whether each measurement is successful or not. When a shot is unsuccessful, the instrument does not return a value. The entire procedure is considered to have failed when no values are obtained after ten shots. Successful measurements are validated using the following criteria: 1) number of valid shots $\geq$ 10; 2) ratio of valid shots to the total number of shots $\geq$ 60%; and 3) interquartile range (IQR, reflecting the variability of measurements) less than 30% of the median liver stiffness measurement (LSM) value (IQR/LSM $\leq$30%) (Castera et al. 2008).

TE is a user-friendly procedure: it only requires a short time (<5 minutes) and can be performed at the bedside or in an outpatient clinic. The results, expressed in kilopascals (kPa) and ranging from 2.5 to 75 kPa, are available immediately. Finally, it is not a difficult procedure to learn and can be performed by a nurse after minimal training (about 100 examinations) (Boursier et al. 2008a). Nevertheless, the clinical interpretation of TE results should be always in the hands of an expert clinician and should be made with full knowledge of the patient demographics, disease etiology and essential laboratory parameters.

Reproducibility. Two independent groups (Boursier et al. 2008b; Fraquelli et al. 2007) have evaluated its reproducibility. In the earlier study (Fraquelli et al. 2007), the reproducibility of TE was excellent for both inter-observer and intra-observer agreement, with an intraclass correlation coefficient (ICC) of 0.98. However, interobserver agreement was significantly lower in patients with lower degrees of hepatic fibrosis (ICC for F0-F1 0.60 vs. 0.99 for F $\geq$ 2), with hepatic steatosis (ICC for steatosis $\geq$ 25% of hepatocytes 0.90 vs. 0.98 for <25%) and those with increased body mass index (ICC for BMI $\geq$ 25 kg/m^2 0.94 vs. 0.98 for <25 kg/m^2). Consistent results were reported by Boursier et al. (2008) in a series of 46 patients examined by 4 different operators, suggesting that the ideal candidate for TE is a lean patient with severe fibrosis.

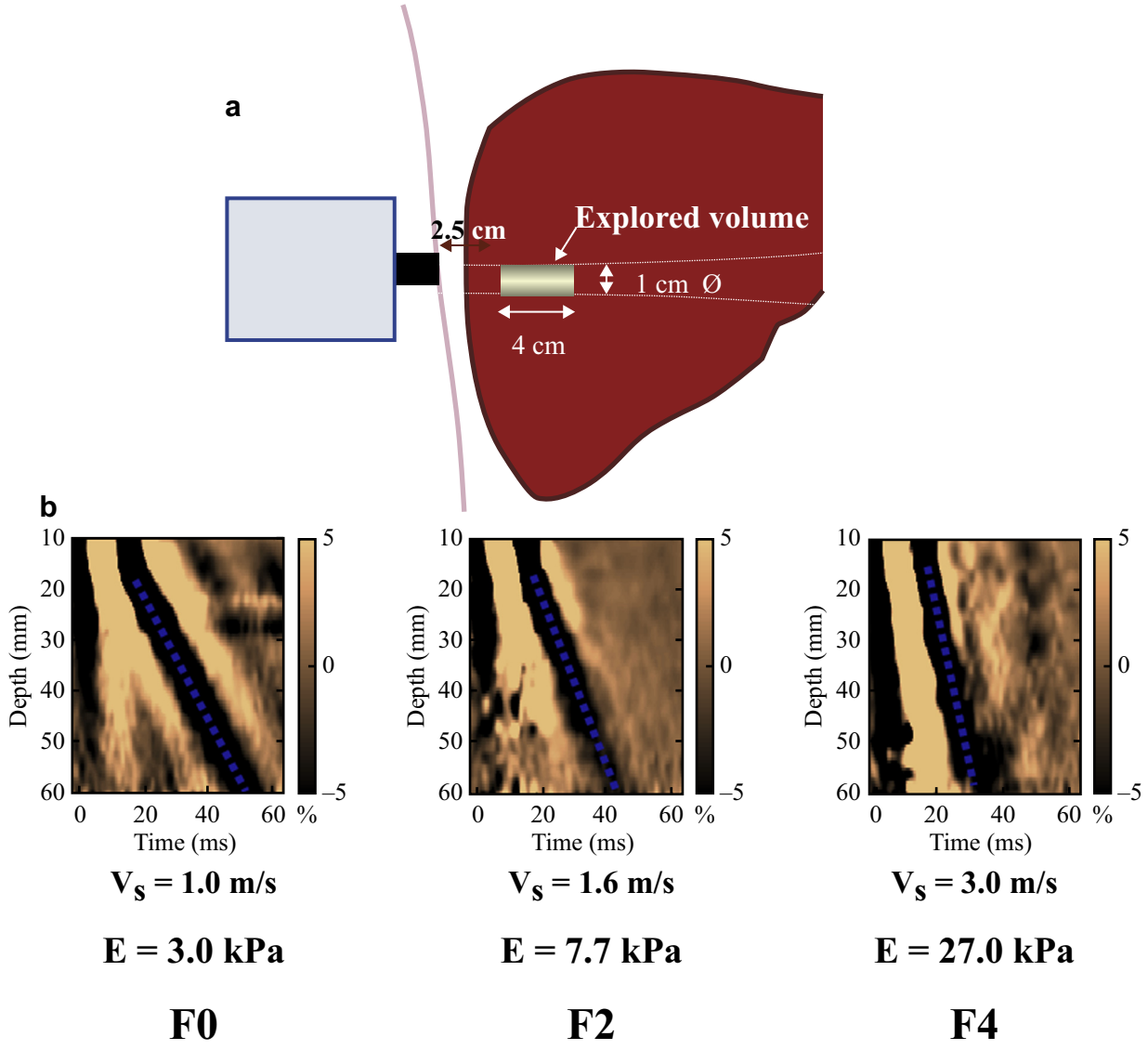

Figure 1. (Adapted from Castera et al. 2008).
a. Position of probe and explored volume (Imaging from Echosens).
b. Shear wave propagation according to the severity of hepatic fibrosis (Metavir score). The elastic modulus E expressed as $E = 3\rho V^2$, where V is the shear velocity and ρ is the mass density (constant and close to 1 kg/m^3 for tissue): the stiffer the tissue, the faster the shear wave propagates. In the absence of fibrosis (F0), the velocity is 1.0 m/s and elasticity is 3 kPa whereas with cirrhosis (F4), the velocity is 3.0 m/s and elasticity is 27 kPa.

Normal values. "Normal" liver stiffness values have been examined in 429 healthy subjects without overt causes of liver disease and normal liver enzymes, who were undergoing a medical check-up (Roulot et al. 2008). The mean liver stiffness value in these patients was 5.5±1.6 kPa. Age had no influence but, as suggested previously (Corpechot et al. 2006a), liver stiffness values were higher in men than in women (5.8±1.5 vs. 5.2±1.6 kPa, p=0.0002) and in subjects with BMI>30 kg/m^2 (6.3±1.9 vs. 5.4±1.5 kPa, p=0.0003). However, even after adjustment for gender and BMI, liver stiffness values remained higher in 59 subjects with the metabolic syndrome (6.5±1.6 vs. 5.3±1.5 kPa, p<0.0001). In a more recent study of 746 Italian subjects analyzed according to the absence (602) or presence of fatty liver (144) at ultrasonography, liver stiffness was significantly lower in normal livers without steatosis than in fatty livers (median 4.4 vs. 5.3 kPa, p<0.001), and male gender was associated with increased liver stiffness (Colombo et al. 2011). However, all these studies were conducted in developed countries. Recent data from India, using a populations-based approach in 437 healthy subjects,

suggest that in healthy individuals, undernutrition and leanness (lower BMI), increase liver stiffness values in a similar way to obesity, providing a U-shaped distribution of normal liver stiffness values (Das et al. 2012).

Results

1. Diagnostic performances for staging liver fibrosis. ***Viral hepatitis and HIV coinfection.*** Two index studies suggest the value of TE in the assessment of liver fibrosis in patients with chronic hepatitis C (Castera et al. 2005; Ziol et al. 2005). Liver stiffness values correlated strongly with Metavir fibrosis stages. However, despite high area under the receiver operator characteristic curve (AUROC) values, a substantial overlap in liver stiffness between adjacent stages of hepatic fibrosis was observed, particularly for lower stages. Many other groups have confirmed these results (Arena et al. 2008a; Degos et al. 2010; Lupsor et al. 2008; Zarski et al. 2012), also in hepatitis B (Chan et al. 2009; Coco et al. 2007; Degos et al. 2010; Marcellin et al. 2009; Oliveri et al. 2008) and HIV-HCV coinfection (de Ledinghen et al. 2006; Kirk et al. 2009; Pineda et al. 2009; Vergara et al. 2007).

TE accurately discriminates cirrhosis from significant fibrosis (AUROC 0.87–0.98; correct classification 85% to 94%) (AUROC 0.75–0.93; correct classification from 57% to 90%). Several meta-analyses (Friedrich-Rust et al. 2008, Shaheen et al. 2007, Talwalkar et al. 2007, Tsochatzis et al. 2011) have confirmed the better diagnostic performance of TE for cirrhosis than for fibrosis, with mean AUROC values of 0.94 and 0.84, respectively (Friedrich-Rust et al. 2008). In a meta-analysis of 40 studies (32 papers and 8 abstracts), sensitivity and specificity values were 0.83 and 0.89 for patients with cirrhosis and 0.79 and 0.78 for patients with significant fibrosis. However, only 9 studies (1364 patients) had acceptable standards for both liver biopsy and TE, which limits the conclusions (Tsochatzis et al. 2011).

The performance of TE is similar in patients with HBV and HCV infection (Cardoso et al. 2012).

In the metanalysis of Chon et al. (2012), 18 studies comprising 2,772 patients with chronic hepatitis B were analyzed. The mean AUROC values for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were 0.86, 0.89, and 0.93, respectively. The estimated cutoffs for F2, F3 and F4 were 7.9 kPa (sensitivity, 74.3%; specificity, 78.3%), 8.8 kPa (sensitivity, 74.0%; specificity, 63.8%), and 11.7 kPa (sensitivity, 84.6%; specificity, 81.5%), respectively.

Serum aminotransferases should be considered in interpreting the results from TE in patients with hepatitis B because elevated enzymes are associated with increased stiffness readings (Fraquelli et al. 2011). To avoid false positive results, some authors have proposed using modified TE cut-offs based on ALT levels (Chan et al. 2009) - a strategy that might not apply to patients with fluctuating levels of ALT or hepatitis flares. Conversely, in hepatitis B e antigen negative patients with normal ALT levels, non-invasive methods, particularly TE, could be used as adjuncts to HBV DNA measurements, to follow inactive carriers or better identify patients who require liver biopsy (those with ongoing disease activity or significant fibrosis, despite normal ALT levels) (Castera et al. 2011; Maimone et al. 2009; Ngo et al. 2008; Oliveri et al. 2008).

NAFLD. So far, the number of studies that have investigated TE in NAFLD patients remains limited (Gaia et al. 2011; Nobili et al. 2008; Petta et al. 2011; Wong et al. 2010; Yoneda et al. 2008; Wong et al. 2012; Kumar et al. 2013). TE results should be interpreted with caution because these studies have been conducted either in particular populations (Asian with low BMI or pediatric population) or with small sample size. Nevertheless, TE could be useful to confidently exclude severe fibrosis and cirrhosis with a high negative predictive value (approximately 90%) in these patients (Wong et al. 2010). In a very recent meta-analysis, 9 studies including 1,047 NAFLD patients were compared. The analysis was performed only on the data obtained with the M probe in 854 patients. The overall results suggest that TE is good in diagnosing $F \geq 3$ (sensitivity, 85%; specificity, 82%) and $F=4$ (sensitivity, 92%; specificity, 92%) and has moderate accuracy for $F \geq 2$, (sensitivity, 79%; specificity 75%) (Kwok et al. 2014).

Other liver diseases. TE has also been evaluated in cholestatic liver diseases (Corpechot et al. 2012, Corpechot et al. 2006b), in a variety of chronic liver diseases (Foucher et al. 2006a; Fraquelli et al. 2007; Ganne-Carrie et al. 2006) as well as in alcoholic liver disease (Nahon et al. 2008; Nguyen-Khac et al. 2008). In the study of Corpechot et al. (2012), there was a significant association between TE and histological fibrosis stage ($P < 0.0001$), but no correlation with necroinflammatory activity grade or the presence of ductopenia. It has been suggested by several groups that the presence of alcoholic hepatitis may influence the liver stiffness results (Bardou-Jacquet et al. 2013; Mueller et al. 2010; Trabut et al. 2012) and thus TE should be performed after alcohol withdrawal to improve accuracy.

Cut-offs. TE appears as a reliable method for the diagnosis of cirrhosis, better at excluding than at predicting cirrhosis. For instance, in a population of 1,007 patients with different chronic liver diseases, a cut-off

value of 14.6 kPa yielded positive and negative predictive values of 74% and 96%, respectively (Ganne-Carrie et al. 2006). Interestingly, proposed cut-off values for cirrhosis ranged from 11 kPa in patients with hepatitis B to 22.7 kPa in patients with alcoholic liver disease. Some researchers have proposed cut-off values based on the causes of liver disease (Ganne-Carrie et al. 2006). However, differences among cut-off values could result from differences in the prevalence of cirrhosis among the study populations (ranging from 8% to 25%). A cut-off value for one population might not be applicable to another with a different prevalence of disease. Most studies used single cut-off values for patients with cirrhosis or advanced fibrosis, but more information can be obtained when values are interpreted as a continuum. For example, when liver stiffness values range from 2.5 to 7 kPa, fibrosis is likely mild or absent, whereas when values are above 12.5 kPa, cirrhosis is likely (Castera et al. 2008) (Figure 2).

2. Monitoring disease progression and prognosis. ***Portal hypertension.*** TE results can identify patients most likely to develop clinically significant portal hypertension, but are not able to identify patients with esophageal varices (Castera et al. 2012). Given its likely prognostic value for patients with cirrhosis, TE could be used to discriminate among patients at different stages of progression of compensated cirrhosis, and stratify them in different risk categories.

TE has recently been used to evaluate the stiffness of the spleen. Colecchia et al. (2012) have reported that in patients with compensated liver cirrhosis spleen stiffness correlates with portal pressure gradient and is accurate in predicting esophageal varices. However, the accuracy of spleen stiffness in ruling in or ruling out clinically significant portal hypertension or esophageal varices needs to be validated. A recent meta-analysis including 12 studies performed with either TE, PSWSM or magnetic resonance elastography, has concluded that the accuracy is still limited to allow its use in clinical practice (Singh et al. 2013).

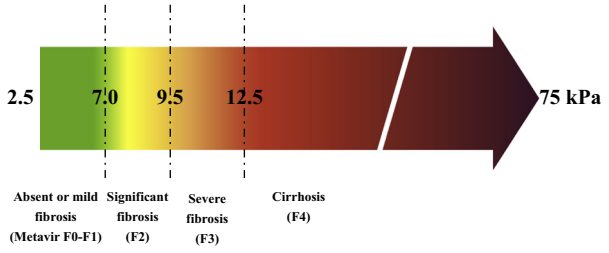

Figure 2. (Adapted from Castera et al. 2008). Clinical significance of liver stiffness cut-offs in chronic liver diseases. When liver stiffness values range between 2.5 and 7.0 kPa, mild or no fibrosis is likely, whereas when liver stiffness values are greater than 12.5 kPa, cirrhosis is likely.

Hepatocellular carcinoma. Large, prospective cohort studies in Asia of patients with hepatitis B or C correlated liver stiffness values with HCC occurrence (Fung et al. 2011a; Jung et al. 2011; Masuzaki et al. 2009). Among 866 Japanese patients with HCV infection, the cumulative incidence of HCC within 3 years was as high as 38.5% among those with baseline liver stiffness values >25 kPa, compared with 0.4% among subjects with values ≤10 kPa (Masuzaki et al. 2009). Although the measurements of liver stiffness could be used to identify patients at risk of developing HCC, more data are needed before they can be integrated into a HCC surveillance program.

Prognosis and survival. Recently, it has been suggested that TE could be used to predict the prognosis of patients with chronic liver disease related to viral hepatitis or other causes (Robic et al. 2011; Vergniol et al. 2011; Merchante et al. 2012). When compared with serum biomarkers, TE had the highest 5-year predictive value to predict survival and liver-related death in 1,457 patients with HCV infection, and this did not change after adjustment for treatment response, patient age, or estimates of necroinflammatory grade (Vergniol et al. 2011). Similarly, in a cohort of 600 patients with chronic hepatitis B, the 5-year overall survival was 97.1% in patients with liver stiffness <9 kPa, and 61.5% in patients with liver stiffness >20 kPa. At 5 years, no liver-related death was observed in inactive carriers, and the association of liver stiffness with survival persisted after adjustment for potential confounders (age, treatment, and estimate of necroinflammatory activity) (de Ledinghen et al. 2013).

Monitoring the response to antiviral treatment. In patients already receiving antiviral therapy, TE can be used to monitor the response and evaluate the regression of fibrosis. Significant histologic improvements have been documented in studies of paired liver biopsies from patients with chronic hepatitis C who achieved sustained viral eradication (Poynard et al. 2002; Shiratori et al. 2000) and patients with chronic hepatitis B who received long-term antiviral therapy (Chang et al. 2010; Hadziyannis et al. 2006). Several studies reported a significant decrease in liver stiffness values, compared with baseline values, in patients with HCV who achieved sustained viral eradication (Fontana et al. 2009; Hezode et al. 2011; Martinez et al. 2011b; Ogawa et al. 2009; Vergniol et al. 2009; Stasi et al. 2013; Casado et al. 2013), as well as in HBV-infected patients treated with nucleoside analog drugs (Enomoto et al. 2010; Fung et al. 2011b; Lim et al. 2011; Ogawa et al. 2011; Osakabe et al. 2011; Wong et al. 2011; Kim et al. 2013; Kuo et al. 2014).

Despite these encouraging results, following the progress of treated patients with TE can be confounded

by changing levels of ALT and inflammation. Similarly, a decrease in liver stiffness could result from reductions in inflammatory activity, rather than fibrosis. However, in the only study (Hezode et al. 2011) that assessed liver stiffness kinetics at multiple time points during (weeks 4 and 12) and after therapy (week 24), liver stiffness decreased significantly with treatment among all patients but only continued to decrease significantly after the end of treatment in those patients with sustained viral eradication.

Limitations

Applicability: failure and unreliable results. TE can be difficult in obese patients or those with narrow intercostal space and cannot technically be performed in patients with ascites (Sandrin et al. 2003).

In an initial trial of 2114 examinations, failure occurred in 4.5% of cases (Foucher et al. 2006b). In a multivariate analysis, the only factor associated with failure was obesity (body mass index $>$ 28 kg/m^2 (OR 10.0 (95% CI 5.7-17.9), p=0.001). Updating this experience with more than 13,000 examinations in 7,261 patients seen over a 5 years period, failure to obtain any measurement was observed in 4% of examinations and unreliable results in 17% (Castera et al. 2010). Thus, TE was not successful in almost 20% of cases. In the multivariate analysis, failure and unreliable results were associated with obesity and limited operator experience. However, a fatty thoracic belt, not a fatty mass index, was a limiting factor for the success rate. Indeed, when metabolic syndrome and waist circumference were taken into account in a subgroup of 2,835 patients, waist circumference was the most important determinant of unreliable results and LSM failure.

Whether unreliable results translate into decreased accuracy is an important question in clinical practice. It has been suggested that among the recommendations, the IQR/LSM >30% is the most important for good diagnostic accuracy (Lucidarme et al. 2009; Myers et al. 2010). In 1165 patients with chronic liver diseases (798 with chronic hepatitis C), Boursier et al. (2013) found no difference in the overall diagnostic accuracy. In a multivariate analysis, they found that fibrosis staging was independently associated with the median liver stiffness and IQR/LSM for all stages and proposed new reliability criteria: very reliable: IQR/M $<$ 0.10; reliable: IQR/M 0.10–0.30 or IQR/M >0.30 and median liver stiffness <7.1 kPa; and poorly reliable: IQR/M >0.30 and median liver stiffness >7.1 kPa. Using these new criteria, only 9.1% of the examinations were unreliable. These results warrant further validation.

Confounding factors. The liver is encapsulated in a distensible but stiff envelope (Glisson's capsule), such that additional space-occupying changes, such as edema, inflammation, extra-hepatic cholestasis, or congestion, can increase its stiffness and elevate the measurements, independently of fibrosis. The extent of necro-inflammatory activity has been shown to influence TE measurements in patients with viral hepatitis, with a steady increase of liver values in parallel with the degree of histological activity (Arena et al. 2008b; Chan et al. 2009; Fraquelli et al. 2007). Consistent with these results, overestimation of liver stiffness has been reported during ALT flares in patients with acute viral hepatitis or chronic hepatitis B (Arena et al. 2008b; Coco et al. 2007; Sagir et al. 2007) as well as in cases of extrahepatic cholestasis (Millonig et al. 2008) or congestive heart failure (Millonig et al. 2010). The influence of steatosis is still a matter of debate because of conflicting results: some studies suggest a detrimental effect (Gaia et al. 2011) whereas others do not (Wong et al. 2010).

Influence of food intake. Food intake increased liver stiffness values in patients with cirrhosis and portal hypertension, and in healthy controls (Mederacke et al. 2009; Arena et al. 2013, Berzigotti et al. 2013), thus patients should fast before TE (and all liver elastography) examinations.

Recommendations

- The interpretation of TE results should always be in the hands of an expert clinician and should be made in light of the patient demographics, disease etiology and key laboratory findings, as well as according to the manufacturer's recommendations, particularly the IQR/M ratio, which should be less than 30%.
- The main limitation to the use of TE in clinical practice is its limited applicability in obese patients. The use of the XL probe reduces the failure rate in obese patients but results in a high rate of unreliable results (approximately 25%). The clinical value of unreliable results remains a matter of debate.
- TE cannot be performed in patients with ascites.
- Several factors, including acute hepatitis, cholestasis, liver congestion, and food intake, increase the liver stiffness. Therefore, TE should be performed in fasting patients, and avoided or interpreted cautiously in patients with elevated transaminases (>5 x upper limit of normal), cholestasis, congestive cardiac failure, ongoing alcohol intake or alcoholic hepatitis.
- TE has been well validated in chronic viral hepatitis (C better than B) and can confidently be used as first line method for staging liver fibrosis. This strategy remains to be validated for other liver diseases.

- Combining TE with serum biomarkers of fibrosis increases the diagnostic accuracy for significant fibrosis in patients with chronic hepatitis C, a strategy that needs to be validated for other liver diseases, such as hepatitis B or NAFLD.
- TE offers better performance for detecting cirrhosis than significant fibrosis and is currently the standard among non-invasive methods.
- In patients with cirrhosis, liver stiffness has a prognostic value for the occurrence of portal hypertension. However, TE cannot replace upper GI endoscopy for the detection of esophageal varices.
- Current evidence suggests that TE could be used for monitoring the response to antiviral treatment and for predicting the prognosis of patients with chronic liver disease.

POINT SHEAR WAVE SPEED MEASUREMENT (PSWSM) AND SHEAR WAVE SPEED IMAGING (SWSI)

Procedure

All technologies are implemented in a conventional US system under direct visualization using a curved array broadband transducer. A sample box is positioned on B-mode image of the liver and elastography measurements are obtained by pressing a button.

Optimal conditions include:

- Fasting;
- Dorsal decubitus position, with the right arm elevated above the head for optimal intercostal access;
- Resting respiratory position (breath-hold without deep inspiration);
- ROI placement beneath Glisson's capsule by 1.5-2.0 cm to avoid reverberation artifacts and increased subcapsular stiffness;
- ROI placement to avoid large liver vessels;
- The median value of 5-10 measurements is considered with PSWSM, and the mean value of 4 measurements with SWSI.

Specific recommendations include:

- For SWSI, the sample box size should be large enough to reduce the variation between measurements. This provides a cumulative value that is the average of stiffness at several points, thus being more representative of the heterogeneous stiffness in abnormal and normal livers.
- For PSWSM, the ROI should be placed perpendicular to the center of the transducer surface as the angle of insonation may have a slight but significant influence on the result.

Results

Point Shear Wave Speed Measurement. As of today, there are two techniques: Virtual Touch Tissue Quantification (VTTQ®) technique that expresses the results in m/sec (Figure 3) and ElastPQ® that gives the results in m/sec or in kPa (Figure 4). There are numerous reports of studies performed using the VTTQ® technique, which has been commercially available since 2009, but only a few using ElastPQ®, which was introduced in 2012.

The reproducibility of the VTTQ® technique is excellent, with an intraclass correlation coefficient ranging from 0.84 to 0.87 (Bota et al. 2012; Boursier et al. 2010; D'Onofrio et al. 2010; Guzman-Aroca et al. 2011). Operator training does not appear to be necessary (Boursier et al. 2010). Similarly, the ElastPQ® technique is highly reproducible, with an interobserver agreement ranging from 0.83 for comparison of single measurements to 0.93 for the median value of 10 measurements (Ferraioli et al. 2014).

In healthy volunteers, the values of PSWSM performed with VTTQ are available in several publications (D'Onofrio et al. 2010; Friedrich-Rust et al. 2009a; Goertz et al. 2012; Grgurevic et al. 2011; Kaminuma 2011; Karlas 2011; Kim 2010; Kircheis 2012; Osaki 2010; Piscaglia 2011; Rifai 2011; Rizzo et al. 2011; Son et al. 2012; Sporea et al. 2011; Takahashi et al. 2010). In all studies, the values were lower ($<$ 1.2 m/sec) than in patients with chronic hepatitis. Food intake significantly increases the liver stiffness values (Goertz et al. 2012; Popescu et al. 2013).

The median value of PSWSM obtained with ElastPQ in healthy volunteers is 3.5 kPa (Ling et al. 2013; Ferraioli et al. 2014).

Chronic viral hepatitis. The range of cut-offs for each fibrosis stage is quite large with overlap between consecutive stages. The range of cut-offs for the fibrosis stage ranges from 1.13 to 1.55 m/sec for F$>$2; from 1.43 to 1.81 m/sec for F$>$3; and from 1.36 to 2.13 m/sec for F4. The largest series comprises more than 600 patients with mixed etiologies of chronic liver disease (Kircheis et al. 2012). Using TE as the reference method, the investigators obtained cut-off values of 1.32 m/sec for F2 and 1.62 m/sec for F4. Similar cut-offs were obtained in the meta-analysis of Friedrich-Rust et al. (2012a), in which nine studies were analyzed. Patients with chronic liver disease of several etiologies were included, and the cut-off values were 1.34, 1.55 and 1.80 m/sec, for significant fibrosis, severe fibrosis and cirrhosis, respectively. PSWSM showed accuracy similar to that of TE for the diagnosis of severe fibrosis, whereas a slightly but significantly higher diagnostic accuracy of TE with respect to PSWSM was found for the diagnosis of significant

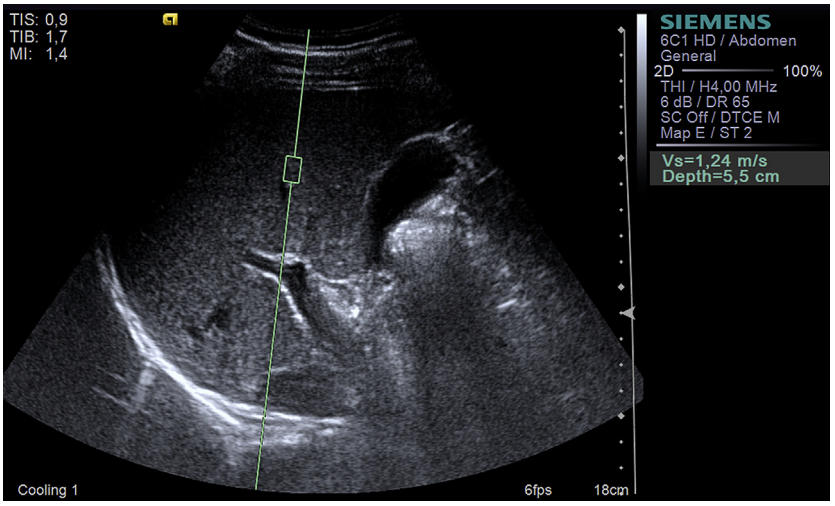

Figure 3. VTTQ technique in a healthy subject. Measurements of liver stiffness are given in m/sec; the sample box is shown.

fibrosis and liver cirrhosis. In the more recent meta-analysis of Bota et al. (2013), in which thirteen studies were included, PSWSM showed a predictive value similar to TE for significant fibrosis and cirrhosis.

In an international multicenter study comprising 1,095 patients (181 with chronic hepatitis B and 914 with chronic hepatitis C), the correlation of PSWSM with histological fibrosis was significantly higher in patients with chronic hepatitis C compared with those with chronic hepatitis B ($r=0.653$ *vs.* $r=0.511$, $p=0.007$), whereas both groups showed similar PSWSM values for each fibrosis stage (Sporea et al. 2012).

In the study of Rizzo et al. (2011), using the PSWSM cut-offs of 1.3 m/sec for the diagnosis of significant fibrosis ($F \geq 2$), 1.7 m/s for severe fibrosis ($F \geq 3$), and 2.0 m/sec for cirrhosis ($F = 4$), the highest concordance was obtained for the diagnosis of mild fibrosis. TE may overestimate the fibrosis stage in cases with severe liver inflammation (Sagir et al. 2008; Arena et al. 2008). The same limitation has been observed in some studies with PSWSM (Takahashi et al. 2010; Yoon et al. 2012; Chen et al. 2012), but not in others (Friedrich-Rust et al. 2009a; Palmeri et al. 2011; Rizzo et al. 2011; Nishikawa et al. 2014).

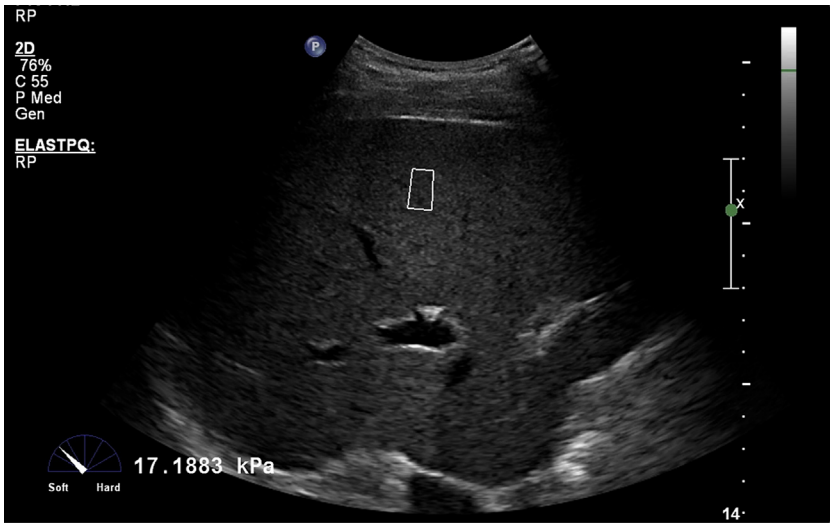

Figure 4. ElastPQ in a patient with chronic hepatitis C of F4 Metavir stage on liver histology. The values of liver stiffness are expressed in kPa. Bottom left corner of the image: the stiffness is estimated and displayed by using a scale that ranges from soft to hard.

The grade of liver steatosis appears not to influence PSWSM (Friedrich-Rust et al. 2009a; Rizzo et al. 2011; Rifai et al. 2011).

Measurement failure with PSWSM is reported in less than 3% of patients (Friedrich-Rust et al. 2012a). No invalid measurement occurred in the series of Rizzo et al. (2011) and in the study of Crespo et al. (2012). PSWSM provided valid results in all patients whereas TE failed in 11% of cases. In the series of Bota et al. (2014), reliable measurements were obtained in 93.3% of cases. Older age, higher BMI and male gender were associated with the risk of failed and unreliable measurements.

A recent meta-analysis, which included either full papers or abstracts for a total of 36 studies, has shown that BMI has a significant influence for the diagnosis of significant fibrosis (F $\geq$ 2) (Nierhoff et al. 2013). In this meta-analysis, the diagnostic accuracy expressed as the area under the ROC curve was 0.84, 0.89 and 0.91 for the diagnosis of significant fibrosis, advanced fibrosis, and cirrhosis, respectively. Measurements are not limited by ascites because the US push beam, which generates the shear waves, propagates through fluids and appears not to be influenced by clinical and biochemical variables (Rizzo et al. 2011).

The possibility to evaluate several areas of the liver parenchyma could be another advantage of PSWSM. Indeed, histological studies have shown that liver fibrosis is not homogeneously distributed within the liver, and can be missed when performing liver biopsy at one site only, thus leading to underestimation of liver fibrosis (Bedossa et al. 2003; Maharaj et al. 1986). It should be noted that D'Onofrio et al. (2010) reported significant differences between intercostal and subcostal scans, and Kaminuma et al. (2011) found that PSWSM were more reliable when performed in a deep portion of the right lobe. In their series of patients with chronic hepatitis, Toshima et al. (2011) obtained significantly higher values in the left lobe of the liver than the right lobe. It has been suggested that oscillation of the left liver by cardiac activity may interfere with stiffness measurements (Osaki et al. 2010).

Karlas T et al. (2011) found that, in healthy individuals, the shear wave speed was higher in the left liver than in the right, but no difference in speed was observed in patients with advanced fibrosis and cirrhosis. The authors suggest that the absence of differences between the two sides could be a criterion for the diagnosis of advanced liver disease.

Preliminary results of PSWSM using ElastPQ® in 102 patients with chronic hepatitis C have shown that the accuracy of the method for staging liver fibrosis is similar to that of TE and the best cut-off value for significant fibrosis (F $\geq$ 2) is 5.7 kPa (Ferraioli et al. 2014). In a series of 291 patients with chronic hepatitis B, the AUROCs for significant fibrosis and cirrhosis were 0.94 and 0.89, respectively (Ma et al. 2014).

Monitoring disease progression and prognosis. Very few studies regarding disease progression and prognosis have been published with conflicting results. In the cohort of Vermehren et al. (2012), the diagnostic accuracy of PSWSM of the liver and the spleen for the prediction of esophageal varices was not significantly different from that of TE and the Fibrotest; however, the AUROCs of all methods were fairly low, ranging from 0.50 to 0.58. In the series of Morishita et al. (2013), a cutoff value of 2.39 m/s had a sensitivity of 81% and a specificity of 82% for detecting high-risk esophageal varices.

In a recent study, a spleen stiffness value $<$3.3 m/s ruled out the presence of high-risk varices in patients with compensated or decompensated liver cirrhosis (negative predictive value, 99.4%). Regardless of the etiologies of liver disease, spleen stiffness was highly accurate for the detection of esophageal varices (Takuma et al. 2013).

Nonalcoholic fatty liver disease (NAFLD). Only few studies in small series of patients are available (Yoneda et al. 2010; Osaki et al. 2010; Palmeri et al. 2011; Friedrich-Rust et al. 2012b; Fierbinteanu Braticevici et al. 2013).

In 172 patients diagnosed with NAFLD, a cutoff of 4.24 kPa distinguished low (fibrosis stage 0–2) from high (fibrosis stage 3–4) fibrosis stages with a sensitivity of 90% and a specificity of 90% (AUROC 0.90) (Palmeri et al. 2011). In a study on 61 patients with NAFLD/NASH, the paired comparison of diagnostic accuracies between TE and PSWSM for the diagnosis of significant fibrosis, severe fibrosis and liver cirrhosis were similar (Friedrich-Rust et al. 2012). In 64 patients with histologically proven NAFLD, the diagnostic performance of PSWSM in predicting significant fibrosis and cirrhosis had an AUROC of 0.94 and 0.98, respectively (Fierbinteanu Braticevici et al. 2013).

Shear Wave Speed Imaging. SWSI expresses the results in m/sec or kPa (Figure 5). Ferraioli et al. (2012b) found ICCs of 0.95 and 0.93 for expert and novice operators when comparing measurements performed on the same day, and 0.84 and 0.65 for measurements performed on different days. The interobserver agreement was 0.88. These results have been confirmed in the recently published study of Hudson et al. (2013). Like conventional US, SWSI technology may be user dependent, so it is recommended that at least 50 supervised scans and measurements should be performed by a novice to obtain consistent measurements (Ferraioli et al. 2012b).

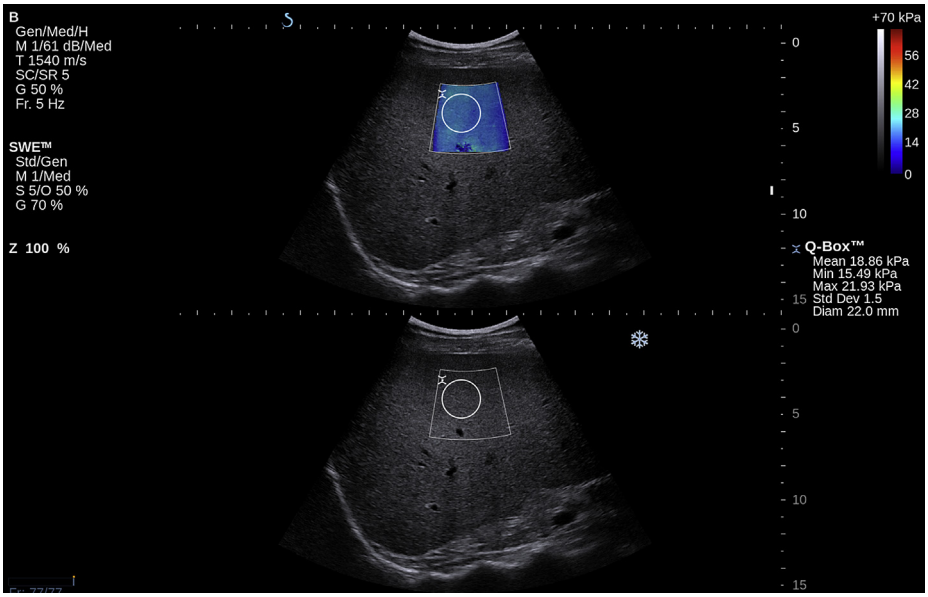

Figure 5. SWSI technique in a patient with decompensated liver cirrhosis. Measurements of liver stiffness are given in kPa. The mean value along with the minimum and maximum values and the standard deviation are shown.

Values ranging from 2.6 to 6.2 kPa have been reported for histologically proven normal livers (Suh et al. 2013).

In patients with chronic hepatitis C, cut-off values for SWSI are reported in two publications based on 4 (Ferraioli et al. 2012c) or 5 (Bavu et al. 2011) measurements from an intercostal space. Bavu et al. (2011) evaluated 113 patients with chronic hepatitis C, comparing the results to those obtained with TE; liver biopsy was not performed. The results showed a good agreement between fibrosis staging and elasticity assessment. SWSI showed a higher accuracy in assessing mild and intermediate stages of fibrosis. The diagnostic accuracy of SWSI in the assessment of liver fibrosis in patients with chronic hepatitis C was evaluated in a pilot study on 121 patients (Ferraioli et al. 2012c). The optimal cut-off values of SWSI were 7.1 kPa for significant fibrosis ($F \geq 2$), 8.7 kPa for advanced fibrosis ($F \geq 3$), and 10.4 kPa for cirrhosis ($F=4$). Areas under the ROC curves were 0.92 for $F \geq 2$; 0.98 for $F \geq 3$ and 0.98 for $F=4$. A better performance of SWSI compared to TE has also been observed in 226 patients with chronic hepatitis B (Leung et al. 2013). In a study that evaluated liver fibrosis in a cohort of 422 patients without a gold standard, Poynard et al. (2013) report that the applicability of SWSI is lower than that of TE whereas the performance of the two methods is similar. In the same study, the applicability of SWSI was higher than that of TE in patients with ascites.

It has been reported that stiffness values are not correlated with liver steatosis (Ferraioli et al. 2012c; Suh et al. 2013) or with necro-inflammation (Ferraioli et al. 2012c).

Limitations

- SWSI accuracy has only been assessed in the right lobe through intercostal access. Interlobe variations of liver stiffness have been reported with PSWSM. Body habitus (obesity, narrow intercostal spaces) may hamper the results.
- Because of the frequency-dependency of the elasticity properties of tissue, great care and consideration must be used when comparing quantitative results among these techniques.
- Results in kilopascals are not comparable between SWSI, PSWSM and TE.
- The majority of the studies has been performed in patients with chronic hepatitis C, therefore these cut-offs may not be applicable to other viral etiologies or to NAFLD. Only small series of patients with NAFLD have been studied, therefore the cut-offs in these patients need further assessment.
- Readings may be higher in patients with ALT levels greater than five times the upper limit of normal; thus, the effect of inflammation should be taken into account, and the results should always be evaluated in the clinical setting. As with TE, it is likely that congestive heart failure, and feeding will be associated with a stiffer liver.

Recommendations

PSWSM and SWSI can be used to assess the severity of liver fibrosis in patients with chronic viral hepatitis, best evidenced in patients with hepatitis C. Nonetheless, the evidence that is available is still limited, particularly

for SWSI. Like TE, PSWSM and SWSI are more accurate in detecting cirrhosis than significant fibrosis.

STRAIN ELASTOGRAPHY

Procedures

Scanning method. Successful real-time strain elastography (SE) depends on the clarity of B-mode images - the fundamental US images - and therefore, B-mode images need to be of good quality and free from artifacts.

- Visualize the right liver through a right intercostal space with the patient supine and the right arm elevated to widen the intercostal spaces;
- Place the probe lightly on the skin without moving it, since the method relies on intrinsic, mainly cardiac, movement to displace the tissue;
- Select a region of interest in which B-mode images are free from interfering structures;
- Obtain images displaying axial, not lateral, movement by pointing the probe towards the heart;
- With a transient breath hold, make sure that SE images are displayed consistently. (Fujimoto et al. 2013, Morikawa et al. 2011, Tatsumi et al. 2010, Tatsumi et al. 2008, Yada et al. 2013)

Region of Interest (ROI) placement. The manufacturer recommends that the ROI should be placed deep to the liver capsule (Fujimoto et al. 2013, Morikawa et al. 2011, Tatsumi et al. 2010, Tatsumi et al. 2008, Yada et al. 2013). Some researchers include the surrounding tissues, such as the subcutaneous and muscle layers (Kanamoto et al. 2009, Saftoiu et al. 2007); however, placing the ROI entirely inside the liver is the key to generate uniform images (Ferraioli et al. 2013, Morikawa et al. 2011, Tatsumi et al. 2010, Yada et al. 2013). To avoid large blood vessels, imaging using a 2.5 × 2.5cm ROI is recommended (Fujimoto et al. 2013, Yada et al. 2013).

Elimination of artifacts requires attention to technique. The ROI should not include large blood vessels to eliminate anechoic areas. It should not be placed close to ribs or the liver capsule, or too deep in the parenchyma as acoustic shadows, reverberation artifacts, and lack of sufficient penetration will generate incorrect higher readings. Experimentation with placement of the transducer between the ribs will lead to the optimal positioning.

When an examination is difficult, it is recommended to try another intercostal space, selecting one that is softer and has a thinner subcutaneous layer. Other subcutaneous structures, such as ribs and lungs, should not be included in the image.

For the analysis, frames with strain generated in the depth direction with no artifacts should be selected. Good images may be obtained at the end of diastole with electrocardiographic gating or at the largest downward wave on a strain graph.

Results

Reproducibility of the technique. The intra-observer variability and intra-observer agreement of SE for the assessment of liver fibrosis have been criticized in several studies (Friedrich-Rust et al. 2009b; Saftoiu et al. 2007; Ferraioli et al. 2007). In a recent study, a Japanese group (Koizumi et al. 2011) used a semi-quantitative method (elastic ratio) and found that the measurements obtained from four separate locations had no observed variation between the two operators (ICC 0.97).

Chronic hepatitis. In chronic hepatitis, the liver tissue hardens unevenly as fibrosis advances. Accordingly, if the ROI is placed only over the liver, it will highlight the color variation of the SE images, emphasizing areas with relatively low strain (blue areas). This generates images with a mottled appearance (Fig. 6) (Tatsumi et al. 2008, Yada et al. 2013).

Evaluation methods. The examiner's experience and subjectivity influence the outcome of visual assessments. To overcome this, various quantitative methods have been developed to assess tissue stiffness objectively.

- Image pattern recognition

Indices obtained by adjusting grayscale, histogram, and binarization are called feature values, and are used in pattern recognition. In SE imaging, feature values given by the scanner or by separate imaging software can be used to calculate correlations with liver fibrosis. The strain estimate is converted to numerical values using color gradations, with blue being 0 and red being 255.

Tatsumi et al. and Morikawa et al. have reported that mean strain values inversely correlated with liver stiffness and fibrosis in patients with chronic hepatitis C. On the other hand, the standard deviation of mean values of strain, the percentage of area of low strain and its complexity were positively correlated with liver stiffness and fibrosis (Morikawa et al. 2011, Tatsumi et al. 2008).

Calculation of function values

a. Liver Fibrosis (LF) Index

For the calculation of the LF index, nine features - mean and standard deviation of the relative strain value, complexity and ratio of the blue area in the ROI, skewness, kurtosis, entropy, inverse difference moment, angular second moment – are extracted (Fujimoto et al. 2013).

In a validation study of the LF Index using 245 patients with cirrhosis and chronic hepatitis B and C,

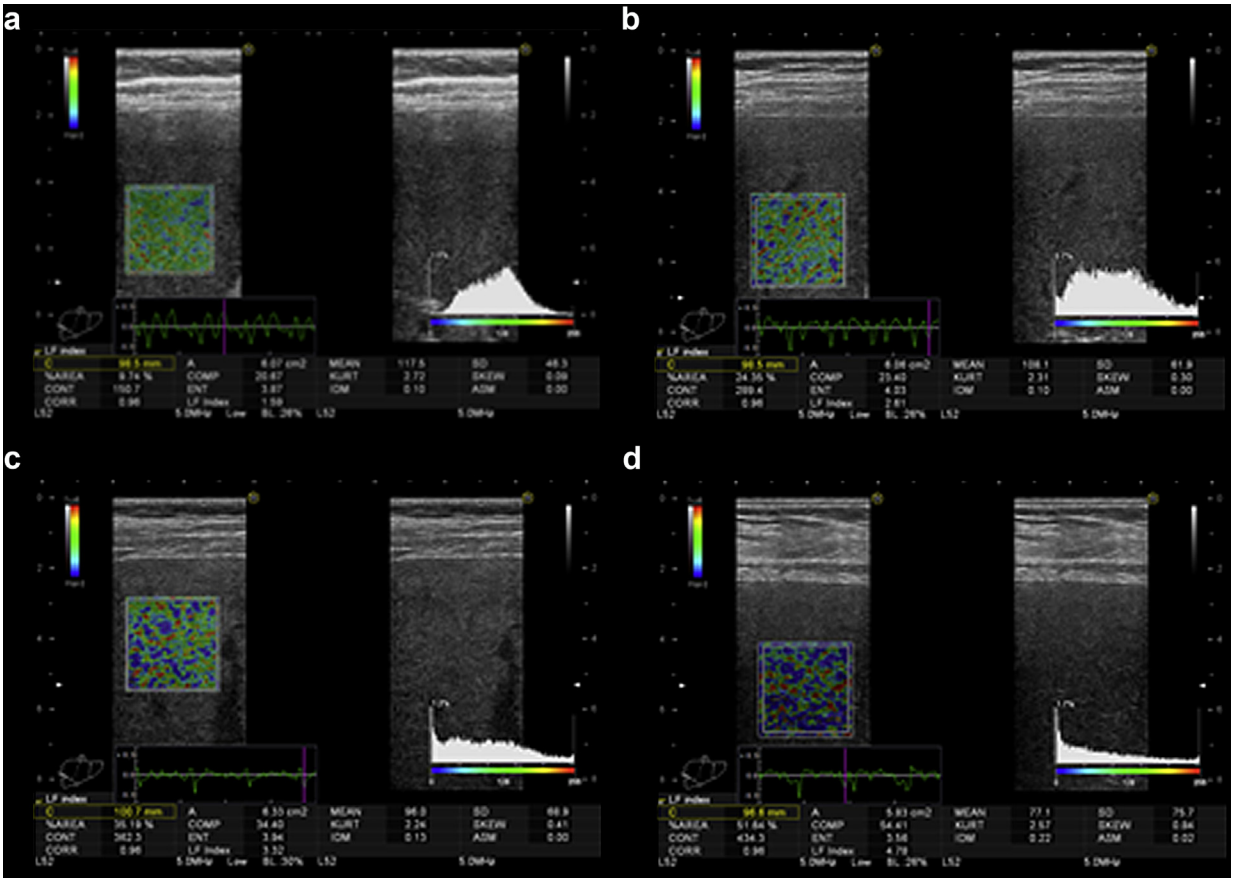

Figure 6. SE images of different stages of liver fibrosis in patients with chronic hepatitis C. The histogram displays the color dispersion in the region of interest. The x-axis shows the color scale of the elastogram, coded from 0 (dark blue) to 255 (dark red); the y-axis shows the percentage of each color. LF index can be calculated on the ultrasound device. F1 (a), F2 (b), F3 (c) and F4 fibrosis stage (d).

Yada et al. observed significant differences between advanced fibrosis and cirrhosis (AUROC 0.80) but not between other consecutive stages of liver fibrosis (Yada et al. 2013).

LF index is a company-recommended standard analytic method.

The positive results obtained in the Japanese series were not confirmed in other series (Ferraioli et al. 2012a).

b. Strain ratios

There are two types of evaluation methods that use the strain ratio for analysis. The mainstream method places the ROI only in the liver parenchyma for analysis and calculates the ratio between the parenchyma and a blood vessel. In another method, the ROI includes the liver parenchyma and the surrounding tissue, and the strain ratio between the two tissues is used in the analysis.

Koizumi et al. (2011) imaged 70 chronic hepatitis C patients with the ROI placed only in the liver parenchyma; they used the strain ratio (elastic ratio) between the liver parenchyma and a peripheral hepatic vein for evaluation. The elastic ratio increased with the progression of liver fibrosis and was not affected by inflammation.

In patients with NAFLD, Ochi et al. (2012) observed a significant correlation between the elasticity ratio and liver fibrosis. In addition, there was a significant difference in elasticity ratios between patients with NAFLD activity score ≤ 4 and those with scores ≥ 5.

The elasticity ratio is not the manufacturer-recommended technique for SE.

c. Other methods

In patients with hepatitis B and C, Friedrich-Rust et al. calculated the tissue elasticity from every pixel in SE images and performed multivariate analysis to obtain a unique formula (Friedrich-Rust et al. 2007). Elasticity scores calculated using that formula showed a significant correlation with liver fibrosis. These results were not confirmed in a more recent study by the same group (Friedrich-Rust et al. 2009b).

- Influences other than liver fibrosis

SE can evaluate liver fibrosis without being affected by inflammation, jaundice, and blood congestion. SE evaluation is possible in patients with ascites (Hirooka et al. 2011).

Limitations

Various SE imaging and analysis methods are currently available, and they all show a clear correlation with liver fibrosis. However, a comparative study is needed to reveal the best method. Although the technique that uses cardiac activity as the driving force is most popular today, weak pulsation can adversely affect the quality of SE images. Moreover, even though SE can be applied to most cases because it can assess patients with ascites and narrow intercostal spaces, it is difficult to generate clear SE images in severely obese patients. It is also necessary to learn to avoid artifacts. The experience and skill of examiners can influence the accuracy of ultrasonography; however, variability among examiners with proper training is reportedly low (Koizumi et al. 2011). To expand the use of liver SE and further improve accuracy, the imaging and analysis methods need to be standardized and an effective SE training system needs to be established. The current standard analytic method of SE is the LF index (Fujimoto et al. 2013, Yada et al. 2013).

Lastly, negative results should not be neglected (Ferraioli et al. 2012a; Friedrich-Rust et al. 2009b).

Recommendations

Objective assessment can be made only by the use of the LF index.

Multicenter studies are currently being performed and the results are anticipated.

FOCAL LIVER MASSES

Diagnosis of focal liver masses is needed to identify patients with malignant liver disease, to determine the correct management and to differentiate these patients from those with benign and insignificant pathology. Although historically, these diagnoses were obtained with liver biopsy, today we live in an era of noninvasive diagnosis. For many years, contrast enhanced CT and MR scans, and more recently contrast enhanced ultrasound (CEUS), have shown their value and ability to provide correct diagnoses without the requirement for surgery or biopsy.

Currently, the use of elastography for characterization of focal liver masses remains investigational. It is hoped that elastography may supplement imaging to give more specific diagnoses in selected patients.

RECOMMENDATIONS

- **Is elastography useful in the evaluation of diffuse liver disease?**

Liver elastography is useful for the evaluation of diffuse liver diseases. The level of evidence is high for TE, moderate for PSWSM, and still low for SWSI and SE. Some methods have been used for more than ten years while others have been introduced more recently, resulting in large variability in the number of published manuscripts on different techniques.

The majority of studies have evaluated patients with viral chronic hepatitis and results obtained in this setting may not be applicable to other clinical situations as the critical cut-offs are strongly dependent on the etiology.

Values with shear wave-based elastography and with strain techniques vary between manufacturers.

Thus, the cutoffs are both system and etiology dependent.

Elastography is capable of distinguishing significant fibrosis (F2 or greater) from non-significant (F0 - F1) fibrosis. However, more data are needed to confirm its use to distinguish between consecutive stages of early fibrosis.

It is also important to note that each method may provide different values expressed in different units (meters per second, kilopascals) or indices.

Several confounding factors have been identified, such as liver inflammation, liver congestion and biliary obstruction.

Elastography results should be interpreted in the full clinical context of the patient, taking into account the method used to obtain the results.

Elastography can be used for follow-up of patients with chronic liver diseases.

- **Is the method reproducible?**

Generally, the reproducibility of elastography techniques is good. However, manufacturer recommendations should be followed. Dedicated training is required for all elastography methods.

- **What is its accuracy in a range of pathologies?**

The accuracy of elastography methods improves with the severity of fibrosis. The most studied etiology is chronic viral hepatitis. The body of evidence is highly dependent on the method for other etiologies.

- **What are the limitations?**

Obesity is a common limitation of all ultrasound-based elastography methods. Other limitations are narrow intercostal spaces and, for transient elastography, the

presence of ascites. Most methods show higher values when the levels of aminotransferases are elevated.

Some manufacturers do not recommend the use of liver elastography in pregnancy.

- **To what extent can elastography reduce the use of liver biopsies?**

In some countries, where liver elastography is used in clinical practice, the number of liver biopsies has decreased significantly. When elastography results are consistent with other clinical findings, liver biopsy may be avoided.

- **Can elastography provide additional information for focal liver lesions?**

Currently, the body of evidence concerning the use of elastography in focal liver lesions is not strong enough to recommend its use in clinical practice.

These recommendations are based on the international literature and on the findings of the WFUMB expert group.

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