

## Liver elastography, comments on EFSUMB elastography guidelines 2013

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**Core tip:** The presented paper is intended to comment the "European Federation of Societies for Ultrasound in Medicine and Biology Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography" and discuss the multivariate factors that have an influence on liver stiffness, and the current techniques of ultrasound elastography as well as magnetic resonance elastography.

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## INTRODUCTION

Non-invasive methods for liver stiffness (LS) assessment have been researched over decades, often mirroring the development of new drugs in the treatment of chronic liver disease. So far, two main forms of elastography have become established in clinical practice. The first is known as quasi-static or strain elastography (SE). Imaging of strain and elastic modulus distributions in soft tissues based on external tissue compression, with subsequent computation of the strain profile along the transducer axis, was first described by Ophir *et al*<sup>[1,2]</sup>. Strain imaging can be applied to the liver by inducing probe pressure<sup>[3]</sup>. The temporal derivative of strain, *i.e.*, the strain rate, is a measure of the rate of deformation<sup>[4]</sup>. Strain Rate Imaging is a Doppler-based method that can be used to mea-

## Abstract

Recently the European Federation of Societies for Ultrasound in Medicine and Biology Guidelines and Recommendations have been published assessing the clinical use of ultrasound elastography. The document is intended to form a reference and to guide clinical users in a practical way. They give practical advice for the use and interpretation. Liver disease forms the largest section, reflecting published experience to date including evidence from meta-analyses with shear wave and strain elastography. In this review comments and illustrations on the guidelines are given.

sure strain of moving tissue<sup>[5,6]</sup>. The second form is shear wave elastography (SWE). Shear waves are generated in the tissues when a directional force is applied to the tissue which causes shear deformation. Shear waves are rapidly attenuated by tissue, they travel much more slowly (between 1 and 10 m/s) and they are not supported by liquids of low viscosity<sup>[7]</sup>.

The use of different ultrasound methods to estimate liver fibrosis have been published, such as transient elastography (TE) (FibroScan<sup>TM</sup>)<sup>[8-10]</sup>, strain elastography (*e.g.*, Hitachi Aloka Medical)<sup>[11-14]</sup> and SWE using acoustic radiation force impulse (ARFI) (Siemens *et al.*)<sup>[14-16]</sup>. Other techniques including 2D-SWE (Supersonic, Siemens) and 3D-SWE (Supersonic) have since been introduced<sup>[17-19]</sup>.

Recently the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines and Recommendations have been published assessing the clinical use of ultrasound elastography<sup>[7,20]</sup>. The document is intended to form a reference and to guide clinical users in a practical way. The guidelines also give practical advice on its use and interpretation. Liver disease forms the largest section, reflecting the published experience to date, including evidence from meta-analyses with shear wave and strain elastography. This article comments on the EFSUMB elastography guidelines, discusses the multivariate factors that have an influence on LS, and the current techniques of ultrasound elastography as well as magnetic resonance elastography (MRE).

## LS AS A DYNAMIC AND MULTIFUNCTIONAL PROCESS

LS (elasticity) is a dynamic and multifunctional process. This means that factors influencing the stiffness and elasticity of a healthy liver are different to the factors in advanced fibrosis. However, many studies have examined the grade of liver fibrosis as the sole indicator of LS<sup>[21-25]</sup> (Table 1); a few others have evaluated more factors<sup>[26-29]</sup> (Table 1).

In patients with chronic liver disease, the assessment of the patient should include age, liver-related comorbidity, aetiology and duration of the liver disease, grading (inflammation), fatty infiltration, risk of malignant transformation, fibrosis, general comorbidity and many other factors. Such factors are important as they guide management and indicate prognosis. Therefore, the assessment of liver fibrosis is only one of many other important factors to determine before treatment. However, the focus on the assessment of liver fibrosis seems to be overstated and many studies lack the design of multivariate analysis.

Factors influencing liver elasticity in healthy subjects depend mainly on blood volume and perfusion parameters that are reported by surgeons during daily routine. Studies have reported a positive correlation of LS with central venous pressure<sup>[30]</sup>, therefore knowledge of co-existing cardiac and pulmonary disease is necessary for interpretation of results.

In addition, it is also reported that food intake could

significantly increase the LS in adults<sup>[31,32]</sup>, children<sup>[33]</sup> and the patients with chronic or resolved hepatitis C virus (HCV) infection<sup>[34]</sup>, therefore, elastography should be performed in fasting conditions. However, there is controversy on the influence of respiration on LS. Yun *et al.*<sup>[35]</sup> reported that LS was significantly elevated during expiration especially in patients without liver cirrhosis while Goertz *et al.*<sup>[32]</sup> did not find differences on the LS in deep inspiration, deep expiration and during Valsalva maneuver.

In liver cirrhosis, the degree and architecture of fibrosis is presumed to be the most important factor influencing LS (elasticity). The factors influencing liver elasticity in intermediate (significant) fibrosis are still not known in detail.

The factors influencing liver elasticity in patients with inflammatory disease (at least to some degree), independent of fibrosis, are acute hepatitis, any flare of transaminase values, acute-on chronic hepatitis<sup>[36,37]</sup>, cholestasis<sup>[38]</sup> and acute liver failure<sup>[39]</sup>. In a recent study of 104 patients with chronic hepatitis B (CHB) and 453 patients within chronic hepatitis C (CHC), histological necro-inflammatory activity was found to be an independent risk factor for the overestimation of LS in HCV and hepatitis B virus (HBV), while histological steatosis was a risk factor in HCV patients only<sup>[40]</sup>.

Other factors influencing liver elasticity in patients with fatty liver (hepatic steatosis) with or without inflammatory activity, with or without fibrosis, have also been described<sup>[41-47]</sup>.

The multivariate intercorrelation of factors influencing liver elasticity under different circumstances is not known. Since multiple factors have shown to influence LS measurements, interpretation of results has to be performed taking into account all these risk factors.

## DIAGNOSIS OF LIVER FIBROSIS

### Liver biopsy

Liver biopsy (LB) has been considered the “gold-standard” for grading and follow-up of necro-inflammatory activity and staging of fibrosis for more than fifty years<sup>[48,49]</sup>.

However, substantial limitations are obvious. Firstly, it is an invasive method with a significant complication rate<sup>[50]</sup>. A review of the literature regarding possible complications has recently been published<sup>[51]</sup>. Secondly, LB has shown some sampling variability<sup>[52]</sup>. The specimen obtained by LB represents a very small part of the liver (about 1/50000) but inflammatory and fibrotic activity is known to be patchy within the liver. The sampling variability can be reduced by mini-laparoscopic guided biopsy with the ability to evaluate the liver surface<sup>[53-57]</sup>, however, it has been shown that the sampling error using mini-laparoscopic guided biopsy is still about 30%<sup>[58]</sup>. LB has also shown some intra- and inter-observer variability<sup>[58,59]</sup>. Thirdly, there is a high inter-observer variability during microscopic evaluation<sup>[58]</sup>.

Therefore, one difficulty for the evaluation of non-

Table 1 Examples of studies

Title	Comment	Ref.
Univariate approach		
Elastographic assessment of liver fibrosis in children: A prospective single center experience	Pearson's correlation	[21]
Is it better to use two elastographic methods for liver fibrosis assessment?	Spearman rank correlation	[22]
Is ARFI elastography reliable for predicting fibrosis severity in chronic HCV hepatitis?	Spearman rank correlation	[23]
Factors that influence the correlation of acoustic radiation force impulse, elastography with liver fibrosis	Spearman rank correlation	[24]
Liver stiffness measurement using acoustic radiation force impulse elastography and effect of necroinflammation	Pearson product-moment correlation	[25]
Multivariate approach		
Liver stiffness measurements in patients with different stages of non-alcoholic fatty liver disease: Diagnostic performance and clinicopathological correlation	Spearman's correlation (no attention paid to Bonferroni or alpha correction) 6 factors (higher age, serum albumin, serum AST, serum cholesterol, diabetes mellitus, LSM), LSM is the only independent predictor of advanced fibrosis (odds ratio = 1.47, 95%CI: 1.23-1.77, $P < 0.001$ )	[26]
Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease	Spearman's correlation (with Bonferroni test). In multivariate analysis including fibrosis, HAH, and steatosis, fibrosis was the only histological parameter significantly correlated with LSM	[27]
FibroScan and ultrasonography in the prediction of hepatic fibrosis in patients with chronic viral hepatitis	Pearson correlation (no attention paid to Bonferroni or alpha correction) 12 factors. Multivariate analysis showed that LSM positively correlates with hepatic fibrosis, necro-inflammatory activity and ultrasound scores	[28]
Performance of unidimensional transient elastography in staging non-alcoholic steatohepatitis	Spearman's correlation (no attention paid to Bonferroni or alpha correction) 4 factors (fibrosis, ballooning, Lobular inflammation, steatosis). Multivariate analysis found fibrosis as the only factor influencing independently liver stiffness in NASH patients	[29]

LSM: Liver stiffness measurement; HAH: Hepatic abscess of hydatid origin; AST: Aspartate aminotransferase; NASH: Non-alcoholic steatohepatitis.

invasive markers of fibrosis is the use of LB as a reference method. Taking into account the limitations of LB, a perfect non-invasive method cannot be distinguished from an unacceptable fibrosis marker. Thus a new reference marker is needed. Studies have shown that non-invasive tests for liver fibrosis with FibroTest, enhanced liver fibrosis (ELF) and TE can predict 5-10 year survival of patients with CHC<sup>[60-64]</sup>. However, more studies using liver related mortality as the endpoint are still awaited to identify the best non-invasive methods<sup>[3]</sup>.

### Serum marker of liver fibrosis

One important non-invasive method for assessment of the severity of fibrosis includes serum markers<sup>[65-68]</sup>. So far, many serum biomarkers, both direct and indirect, have been evaluated for their ability to stage liver fibrosis<sup>[69-71]</sup>. Direct serum markers, reflecting either the deposition or the removal of extracellular matrix in the liver, include: (1) collagens such as type IV collagen, procollagen III N-peptide, collagenases; (2) inhibitors of collagens such as matrix metalloproteases and tissue inhibitory metalloprotease-1; and (3) glycoproteins such as serum hyaluronate, laminin, and YKL-40. So-called indirect markers include factors that can be measured from routine blood tests, such as platelet count, prothrombin index, and aspartate aminotransferase/alanine aminotransferase (AST/ALT), which indicate alterations in hepatic function. The usefulness of these markers has been assessed mostly in patients with CHC<sup>[70-72]</sup> and hyaluronate has been the most extensively studied direct marker<sup>[73,74]</sup>. These direct and indirect markers, when

used individually, are useful for the diagnosis or the exclusion of cirrhosis but have limited accuracy for the diagnosis of clinically significant fibrosis<sup>[75]</sup>. Therefore, more sophisticated algorithms or indices combining the results of groups of markers have been developed to improve the diagnostic accuracy. The FibroTest™ (proprietary formula; Biopredictive, Paris, France) was the first algorithm that combined these data<sup>[76]</sup>. Thereafter, several other indices, such as Fibrosure™ in the United States (LabCorp, Burlington, NC, United States), the Fibrometers™ (BioLiveScale, Angers, France), the FibroSpect II™ (Prometheus Laboratory Inc., San Diego, CA, United States), the ELF™ (Enhanced Liver Fibrosis Test, iQor Ltd, Southampton, United Kingdom) and the Hepascore™ (PathWest, University of Western Australia, Australia), have been developed. They are mainly for patients with CHC<sup>[77-80]</sup>, but can also be used in patients with hepatitis B<sup>[81,82]</sup> and human immunodeficiency virus (HIV)-HCV co-infection<sup>[83,84]</sup>. Among these indices, Fibrotest has been the one most extensively studied<sup>[69]</sup>.

In a prospective cohort of 537 HCV-infected patients, Fibrotest had a 5 year prognostic value (HCV-related complications and death) similar to that of LB<sup>[61]</sup>. In a meta-analysis<sup>[85]</sup> which included 6378 subjects with both FibroTest and biopsy (3501 HCV and 1457 HBV), the mean standardized area under the receiver operator curve (AUROC) for diagnosing significant fibrosis was 0.84 (95%CI: 0.83-0.86), without differences between HCV, 0.85 (95%CI: 0.82-0.87) and HBV, 0.80 (95%CI: 0.77-0.84). ELF has been evaluated in a recently published study<sup>[86]</sup> that included 196 patients. The ELF panel

had an AUROC of 0.90 for distinguishing severe fibrosis, 0.82 for moderate fibrosis, and 0.76 for no fibrosis, and it was improved to 0.98, 0.93 and 0.84, respectively, by the addition of simple markers. The clinical utility model showed that 82% and 88% of liver biopsies could potentially be avoided for the diagnosis of severe fibrosis using ELF and the combined panel, respectively<sup>[62,64]</sup>.

### Advantages and limitations

The practical advantages of analysing serum biomarkers to measure fibrosis include their high applicability and high inter-laboratory reproducibility<sup>[87,88]</sup>. However, the direct markers of liver fibrosis are not routinely available in most hospital settings, and none of the serum markers are liver specific-their results can be influenced by comorbidity. For example, FibroTest and Hepascore produce false-positive results in patients with Gilbert's syndrome or haemolysis as these patients have hyperbilirubinaemia<sup>[89]</sup>. Similarly, acute hepatitis can produce false-positive results in the marker measuring the level of aminotransferases, such as aspartate-to-platelet ratio index (APRI), Forns index, FIB-4, or Fibrometer tests.

### Magnetic resonance elastography

In recent years, magnetic resonance elastography (MRE) has been developed as a non-invasive functional magnetic resonance imaging (MRI) method for assessing and staging liver fibrosis, using a modified phase-contrast method to image the propagation characteristics of shear waves in the liver<sup>[90,91]</sup>. Elasticity is quantified by MRE and expressed in kilopascals (kPa) using a formula that determines the shear modulus, equivalent to one-third of the Young's modulus which is estimated with TE<sup>[72,92]</sup>. So far, there is only limited data on the accuracy of MRE. Several studies<sup>[92-96]</sup> have evaluated the usefulness of MRE for the assessment of LS among patients with chronic liver disease and have shown that increased shear stiffness measured on MRE is associated with increased severity of the fibrotic process. In addition, MRE has relatively high sensitivity and specificity for predicting the stage of hepatic fibrosis. It has shown at least equivalent diagnostic performance in fibrosis staging compared with TE with fewer limitations regarding its application in patients with a large amount of ascites or who are obese<sup>[92-95]</sup>. Yin *et al.*<sup>[95]</sup> reported sensitivity of 86% and 78%, and specificity of 85% and 96%, with cut-off values of 4.89 and 6.47 kPa, respectively. Huwart *et al.*<sup>[93]</sup> showed similarly high sensitivity of 98% and 95%, and specificity of 100% and 100%, for discrimination, but lower cut-off values of 2.5 and 3.1 kPa were used. The reason for the difference in cut-off values obtained in the two studies may potentially be explained by the differently manufactured scanners used for MRE acquisition, case mixes, imaging protocols, and post-processing procedures. A meta-analysis has been recently published<sup>[97]</sup>.

### Advantages and limitations

Compared with TE, dynamic MRE has the potential

to assess larger volumes (almost the entire liver) and to provide full three-dimensional information about the viscoelastic properties of tissues<sup>[98]</sup>, moreover, due to the theoretical advantages, MRE is capable of application to patients with obesity or ascites. However, MRE cannot be performed on the liver of patients with iron overload because of signal-to-noise limitations and it is too costly and time-consuming to use in routine practice<sup>[72]</sup>.

## INTRODUCTION TO ULTRASOUND ELASTOGRAPHY

### TE

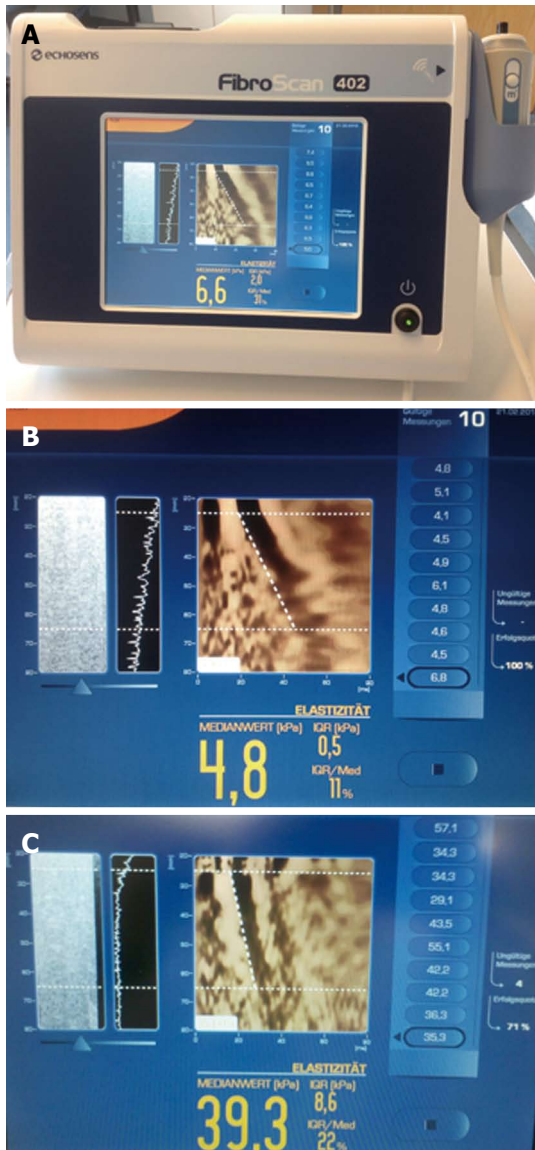
TE (FibroScan<sup>®</sup>) was the first tool introduced for routine clinical use (Echosens, Paris, France) (Figure 1). TE does not display a conventional ultrasound image. TE has been mainly evaluated in patients with chronic viral hepatitis C and also in a few patients with HIV/viral hepatitis C co-infection and some other liver diseases (see below)<sup>[99]</sup>.

### Technique

**Basic principles:** TE is an ultrasound-based non-invasive method. It is characterized by the material's strain response to external stress according to the principle of Hooke's law<sup>[9]</sup>. Briefly, an ultrasound transducer probe is mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency (50 Hz) are transmitted by the transducer from a right intercostal space, inducing an elastic shear wave that propagates through the liver. Pulse-echo ultrasound acquisition is used to follow the propagation of the shear wave and to measure its speed. This speed is proportional to the tissue stiffness, with faster wave progression occurring through stiffer material. The elastic modulus  $E$  is expressed as  $E = 3qV^2$ , where  $V$  is the shear wave speed and  $q$  is the material density (assumed constant for tissues): the stiffer the tissue, the faster the shear wave propagates<sup>[100]</sup>. TE measures LS in a cylindrical volume approximately 10 mm wide and 40 mm long, between 25 and 65 mm below the skin surface with the standard M-probe, and between 35 and 75 mm for the recently developed XL probe, recommended for obese patients<sup>[101,102]</sup>. This volume is at least 100 times bigger than a biopsy sample and it has been suggested, therefore, that the results compared to LB are more representative of the hepatic parenchyma. However, TE does not work for the left liver lobe or from a subcostal approach and the measurement is only feasible *via* a few intercostal spaces. Therefore, the technique is limited. Inter- and intra-observer variability depend on the intercostal space used, the presence of ascites, musculoskeletal habitus, depth of subcutaneous tissue, position of the patient, and many other factors<sup>[47,103]</sup>.

**How to perform?** The measurements with FibroScan<sup>®</sup> are taken from the right liver lobe *via* an intercostal space, while the patient lies flat on his/her back, with the right arm tucked behind the head to facilitate access to the liver parenchyma. The tip of the probe is covered with





**Figure 1** Transient elastography (FibroScan®, A) for the evaluation of normal liver (B) and liver cirrhosis (C).

coupling gel and placed on the skin between the ribs at the level of the right lobe where LB would be performed. Once the measurement area has been located, the operator presses the probe button (shot) to start an acquisition. When a shot is unsuccessful, the machine does not give a reading. Measurement of LS is measured in kilopascals (kPa) (range is between 2.5 and 75 kPa)<sup>[100]</sup>.

**Advantages:** TE with FibroScan® is a rapid procedure (less than 5 min), painless, and easy to perform even in the outpatient clinic or at the bedside. The results are immediately available<sup>[103]</sup>. The examination can be performed by a nurse after a short learning curve (about 100 examinations)<sup>[104]</sup>. In addition, TE analysis has excellent inter- and intra-observer agreement, which makes it suitable for widespread application in clinical practice<sup>[103,105,106]</sup>.

**Limitations:** TE provides only a regional elasticity measurement (determined by the width of the ultrasound beam and depth of the shear wave penetration), but no anatomical images or elastograms. Other drawbacks include limited depth (several cm), the inability of the shear wave to propagate beyond fluid collections (ascites) and difficulty in obtaining sufficient signal in obese patients. Recently, a new probe (XL probe; Echosens, Paris, France) has been proposed for overweight and obese patients<sup>[107]</sup>, and a so-called S-probe has been developed for patients with narrow intercostal spaces, especially children<sup>[108]</sup>. However, it remains impossible to obtain TE results from patients with ascites<sup>[105]</sup>.

The validity of the TE result also depends on two important parameters: (1) the success rate (the ratio of the number of successful measurements to the total number of acquisitions) should be at least 60%; and (2) the interquartile range (IQR), which reflects the variability of the validated measurements, should not exceed 30% of the median value<sup>[109]</sup> (Figure 1). Both the feasibility and reproducibility of the TE measurement may be affected by high body mass index (BMI). In a study with 13369 TE measurements, a failure rate of 3.1% was reported. Unreliable results were reported in 15.8% of measurements and were associated with a BMI > 30 kg/m<sup>2</sup>, age > 52 years, female sex, operator experience and type 2 diabetes<sup>[47]</sup>.

The clinical interpretation of TE results should always be made by an expert clinician and with reference to the patient's history, disease aetiology and essential laboratory parameters Castera *et al.*<sup>[110]</sup>.

**Intra- and inter-observer variability:** Several studies<sup>[103,105,106]</sup> have shown that the intra- and inter-observer reproducibility of TE measurements are good, at least in non-obese subjects. In the study by Sandrin *et al.*<sup>[105]</sup> intra- and inter-observer variation in TE was investigated in 15 patients and was around 3%, but with a wide variation (2%-18%). The sample size of this study was small, and therefore inadequate to draw firm conclusions on host- and disease-related co-variables that may interfere with TE performance. Another study by Fraquelli *et al.*<sup>[103]</sup> with a larger sample obtained similar results; 800 TE examinations were performed by two operators in 200 patients with various chronic liver diseases. Both inter- and intra-observer agreement was high and TE reproducibility was excellent, with an intraclass correlation coefficient (ICC) of 0.98. However, inter-observer agreement was significantly reduced in patients with mild hepatic fibrosis, and hepatic steatosis.

The probe location during the TE measurement may affect its reproducibility. In a recent study<sup>[111]</sup> TE was performed on 625 consecutive patients with chronic liver disease at three different sampling sites. Sampling variability according to probe location was seen in approximately 30% of patients and it was suggested that TE should be performed from various sites to minimize the sampling error.

### Review of the literature

**Chronic viral hepatitis:** For patients with CHC, LS values  $> 6.8$ – $7.6$  kPa are indicative of significant fibrosis ( $F \geq 2$ ) using the gold standard of LB, and the cut-off values for predicting complete cirrhosis ( $F = 4$ ) range between 11.0 and 13.6 kPa<sup>[20,112,113]</sup>. TE is able to distinguish mild fibrosis from advanced liver fibrosis and cirrhosis, which is important for decision making<sup>[114]</sup>. In contrast, TE does not allow differentiation between the contiguous stages of liver fibrosis. In a meta-analysis including 40 studies<sup>[114]</sup>, the pooled sensitivity and specificity of TE was 79% and 78% for the diagnosis of significant fibrosis; 82% and 86% for diagnosing severe fibrosis; and 83% and 89% for the diagnosis of liver cirrhosis.

It might be of interest to remember that conventional ultrasound techniques can also distinguish between liver cirrhosis and early liver disease in approximately 70% of patients with high specificity but low sensitivity<sup>[115-124]</sup>. However, TE had an acceptable diagnostic accuracy for detecting early compensated cirrhosis in patients with CHB who did not fulfil the clinical and ultrasound criteria for cirrhosis<sup>[125]</sup>. Conventional ultrasound techniques are helpful in the detection of complications of liver cirrhosis including portal hypertension<sup>[126,127]</sup> and can also give important information about fatty infiltration<sup>[128-132]</sup> and inflammation<sup>[133-136]</sup>. In a study with 90 patients with suspected liver cirrhosis, liver surface nodularity on conventional ultrasound and TE showed comparable results for diagnosis and exclusion of liver cirrhosis, with the best results when both methods were combined. Liver surface nodularity was better for the diagnosis of liver cirrhosis, while TE was better at ruling out cirrhosis<sup>[137]</sup>.

The performances of TE, when compared, have been shown to be similar between patients with HBV and HCV<sup>[138]</sup>. Several studies have investigated the performance of TE in an Asian population with CHB<sup>[125,139-144]</sup> and concluded that TE is a promising and accurate tool for the early detection of cirrhosis. It is demonstrated that the optimal cut-off values for diagnosing HBV-related cirrhosis were between 9.0 and 10.1 kPa in the Asian population<sup>[125,140,142,145]</sup>, which is lower than that in patients with CHC<sup>[146,147]</sup>. Since there is an increasing number of evidence on the usefulness of TE in patients with CHB, especially in the Asian population, TE should also be recommended in patients with CHB, though the evidence is more limited compared to CHC. Future and updated guidelines have to include this recommendation.

It would be interesting to know in what percentage of patients TE can give important additional information which is of relevance to the treatment, over and above sophisticated ultrasound technology in the hand of an expert hepatologist<sup>[43,148]</sup>.

### EFSUMB recommendations

TE can be used to assess the severity of liver fibrosis in patients with chronic viral hepatitis, provided that confounding factors are taken into account, and especially to distinguish patients with nil/mild fibrosis from those with

significant fibrosis, and to identify those with cirrhosis. TE is useful for assessment of liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD), alcoholic liver diseases, and in patients co-infected with HIV and HCV. Other types of chronic liver disease might also have been investigated, but the evidence is more limited. TE is useful for assessment of liver fibrosis in patients with post-transplant recurrence of CHC. TE has some value for predicting the occurrence of complications of liver cirrhosis, portal hypertension, hepatocellular carcinoma (HCC) and liver-associated mortality. It cannot replace upper gastrointestinal endoscopy for identifying patient with varices<sup>[20]</sup>.

## POINT SHEAR WAVE ELASTOGRAPHY WITH ACOUSTIC RADIATION FORCE IMPULSE IMAGING

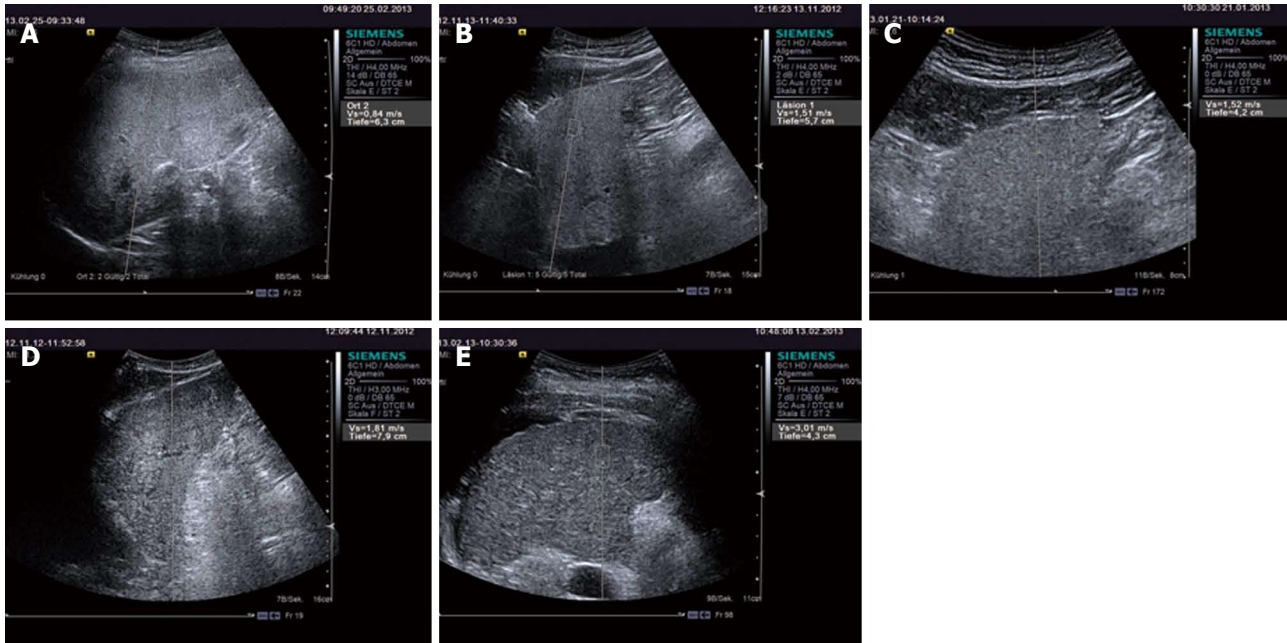
Point shear wave elastography (pSWE) has been introduced by different companies, each currently at different stages of development<sup>[7,20]</sup>. Acoustic radiation force impulse (ARFI) was the second method to be introduced as a tool for liver fibrosis assessment in a clinical setting. ARFI has a significant advantage over TE in that it simultaneously displays a conventional ultrasound image. The accuracy of both methods has been shown to be similar in the differentiation of normal liver parenchyma from liver cirrhosis<sup>[15,149,150]</sup>. ARFI has been mainly evaluated in patients with chronic viral hepatitis C and in a few other liver diseases.

### Technique

**Basic principles:** ARFI quantification has been developed by two companies (Siemens and Philips) according to the guidelines<sup>[7,20]</sup>, almost all reported studies were done with a conventional high-end ultrasound machine (Siemens S2000). It uses a region of interest (ROI) cursor to interrogate the elastic properties of a specific anatomic region, while real-time B-mode imaging of the abdomen being performed. Short-duration acoustic pulses with a fixed transmit frequency of 2.67 MHz, are generated in the vicinity of the ROI and the subsequent mechanical excitation of the tissues results in tissue displacement and the formation of shear waves that propagate away from the region of excitation. Ultrasound tracking beams laterally adjacent to the single push-beam are used to estimate the shear wave speed in the tissue by the measurement of the time to peak displacement at each lateral location<sup>[151]</sup>. The shear wave speed is estimated in the central window 5 mm long by 4 mm wide within a graphically displayed ROI of size 10 mm long by 6 mm wide. The results are expressed in meters per second (m/s) (range: 0.5–4.4 m/s with  $\pm 20\%$  accuracy over the range), the shear wave propagation speed being proportional to the square root of the tissue elasticity<sup>[152,153]</sup>. The ARFI imaging examination takes approximately 5 min. Unlike FibroScan®, ARFI can be utilized in patients with ascites. No limitations

**Table 2** Mean shear wave velocities (VirtualTouch values) of the left and right liver lobes (mean  $\pm$  SD)

Ref.	n	Subjects	Left lobe (m/s)	Right lobe (m/s)
Karlas <i>et al.</i> <sup>[158]</sup>	50	Healthy individuals	1.28 $\pm$ 0.19	1.15 $\pm$ 0.17
Karlas <i>et al.</i> <sup>[158]</sup>	23	Patients with F1, F2 fibrosis	2.1 $\pm$ 0.73	1.75 $\pm$ 0.89
Toshima <i>et al.</i> <sup>[159]</sup>	103	24 healthy volunteers, 79 patients with chronic liver disease	1.90 $\pm$ 0.68	1.61 $\pm$ 0.51
Piscaglia <i>et al.</i> <sup>[157]</sup>	14	Healthy individuals	1.29 (1.00-1.60)	1.15 (0.80-1.74)
Piscaglia <i>et al.</i> <sup>[157]</sup>	114	Patients with chronic liver disease	1.79 (0.80-4.00)	1.67 (0.45-3.76)

**Figure 2** Point-shear wave elastography with acoustic radiation force impulse for the evaluation of histologically proved liver fibrosis and cirrhosis. A: F0; B: F1; C: F2; D: F3; E: F4 = cirrhosis.

concerning measurement are known<sup>[154]</sup>.

**Tips and tricks:** When scanning the right lobe (especially segment VIII), an optimal window should be used. To reduce the variance of the measurement, it is recommended to apply minimal scan pressure and for the patient to minimize breathing, the influence of cardiac motion should also be avoided. In general, the best and most consistent results will occur when the “normal” state of the liver is measured. When scanning intercostally, no pressure should be applied to the liver and the patient should be asked to just stop breathing for a moment (instead of deep inspiration and breath hold).

In difficult patients, several measurement attempts are needed to “average” out the readings, and data that varies significantly should be excluded. It is recommended to put the patient in a left lateral decubitus position with right arm behind the head in order to get better access to the liver without excessive pushing or the need for breath holds<sup>[155]</sup>. However, it may still not be possible to get reliable readings in 5.3 % of patients<sup>[156]</sup>.

**Intra- and inter-observer variability:** Reproducibility of ARFI is also an important pre-requisite for its widespread application in clinical practice. Good inter-observer vari-

ability has been reported<sup>[157]</sup>. Since ARFI allows different measurement sites, comparison of measurements in the right and left liver lobes have been made, and have shown a trend toward higher values in the left lobe<sup>[157-159]</sup>. However, results in the right lobe revealed higher diagnostic accuracy compared to the left (AUROC: for diagnosis of F1, F2, F3, F4, right lobe: 0.92; 0.83; 0.86; 0.80; left lobe: 0.77; 0.71; 0.78; 0.84; sensitivity, specificity, positive predictive value and negative predictive value of right lobe: 0.88; 0.81; 0.74; 0.92; left lobe: 0.80; 0.75; 0.87; 0.68)<sup>[159]</sup> (Table 2).

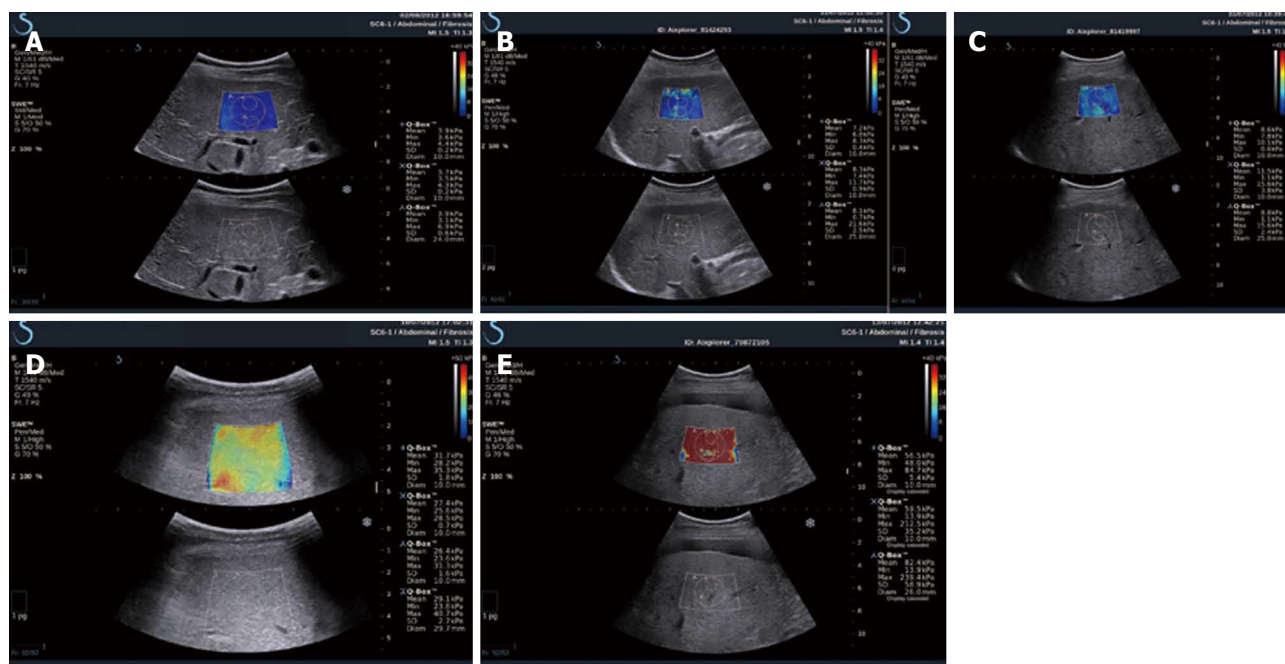
### Clinical applications

**Chronic viral hepatitis:** In patients with significant fibrosis ( $F \geq 2$ ) the ARFI cut-off values published have been between 1.21-1.34 m/s (AUROCs 0.85-0.89)<sup>[23,149,150]</sup> and in patients with cirrhosis, 1.55-2 m/s (AUROC's 0.89-0.93)<sup>[15,23,149,160]</sup> (Figure 2). Similar to TE, SWE has not proved accurate enough to distinguish between contiguous stages of fibrosis<sup>[20]</sup>.

**Other liver diseases:** ARFI has also been evaluated in patients with NAFLD and NASH<sup>[161,162]</sup> and in patients after liver transplantation<sup>[163]</sup>.

**Meta-analysis:** Friedrich-Rust *et al.*<sup>[154]</sup> published a meta-





**Figure 3** 2D-shear wave elastography with supersonic shear imaging for the evaluation of histologically proved liver fibrosis and cirrhosis. A: F0; B: F1; C: F2; D: F3; E: F4 = cirrhosis.

analysis which included 9 studies with a combined total of 518 patients with chronic liver disease and evaluated the diagnostic performance of ARFI imaging for the staging of liver fibrosis. The diagnostic accuracy of ARFI quantified by the AUROC was 87% for predicting significant fibrosis ( $F \geq 2$ ), 91% for the diagnosis of severe fibrosis ( $F \geq 3$ ) and 93% for the diagnosis of liver cirrhosis. The meta-analysis revealed good diagnostic accuracy for ARFI in the diagnosis of significant liver fibrosis and excellent diagnostic accuracy for the diagnosis of liver cirrhosis.

It was also shown that a comparison of ARFI with TE in the four studies that included 312 patients, resulted in comparable diagnostic accuracies for both methods in the diagnosis of severe fibrosis, and slightly, but significantly, higher diagnostic accuracies of TE for the diagnosis of significant fibrosis and liver cirrhosis. However, a recent study showed superior results for ARFI elastography<sup>[150]</sup>. Future multicentre studies are necessary to compare the different methods before any conclusions can be drawn.

### Advantages and limitations

In contrast to TE, ARFI has been shown to be less influenced by obesity and ascites<sup>[151]</sup>. One study showed that valid LS measurement (LSM) were obtained in all 23 patients with morbid obesity (mean BMI was higher than 44 kg/m<sup>2</sup>)<sup>[164]</sup>. In addition, it can be easily added to a commercial ultrasound machine.

However, in contrast to TE values, ARFI values have a narrow measurement range (0.5-4.4 m/s), which limits the definition of cut-off values required for decisions on patient management. In addition, inflammatory activity

and elevated aminotransferase levels may lead to overestimation of ARFI-LS values<sup>[15,25]</sup> as has been shown for TE. Moreover, since this is a new technique, the quality criteria are not yet well-defined.

### EFSUMB recommendations

pSWE with ARFI can be used to assess the severity of liver fibrosis in patients with chronic viral hepatitis, especially with hepatitis C. pSWE with ARFI is promising for liver fibrosis assessment in patients with NAFLD, and post-transplant patients<sup>[7,20]</sup>.

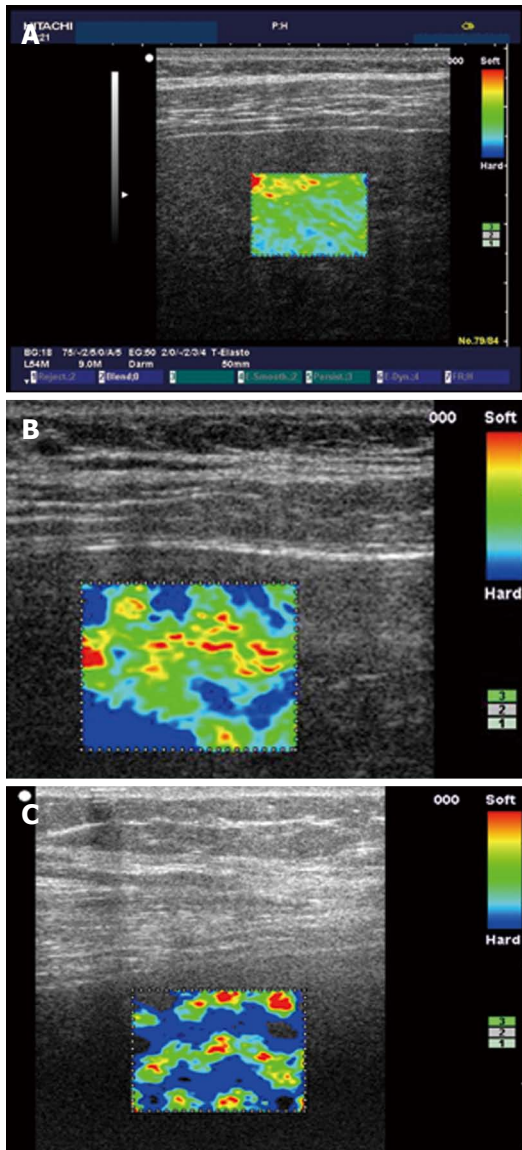
## 2D SWE

SWE [Aixplorer®, SuperSonic Imagine (SSI), France] has been introduced as a 2D and also 3D-technique. So far, only 2D-SWE has been evaluated in studies on the liver. The studies of 3D-SWE have mainly focused on the breast<sup>[165,166]</sup>.

### Technique

This technique is based on the combination of a radiation force induced in the tissues by focused ultrasonic beams and very high frame rate (up to 5000 f/s) ultrasound imaging capable of catching, in real time, the transient propagation of the resulting shear waves<sup>[167,168]</sup>. The local shear wave speed is recovered using a dedicated time-of-flight estimation technique and enables the 2-D quantitative mapping of elasticity. This imaging modality can be performed using a conventional ultrasound probe, during a standard intercostal ultrasound examination. Three supersonic shear wave imaging sequences are applied successively to the left, middle and right parts of





**Figure 4** Strain elastography for the evaluation of histologically proved liver fibrosis and cirrhosis. A: F0; B: F2; C: F4 = cirrhosis.

the 2-D ultrasound image. The resulting elasticity images in the three regions are concatenated to provide the final image covering the entire region-of-interest. The ability of the SWE technique to provide a quantitative and local estimation of liver shear modulus with a millimetric resolution has been proven in a pilot study in 15 healthy volunteers<sup>[18]</sup>. Liver moduli extracted from *in vivo* data from healthy volunteers, were consistent with those reported in the literature (Young's modulus ranging from 4 to 7.5 kPa). Moreover, LSM using the SWE mode was fast (less than one second), repeatable (5.7% standard deviation) and reproducible (6.7% standard deviation)<sup>[3]</sup>.

**Intra- and inter-observer variability:** To date, there has only been one study<sup>[169]</sup> aimed at assessing the intra- and inter-observer precision of 2D-SWE measurements in the evaluation of liver elasticity. It was reported that the

reproducibility was good with high intra- and inter-observer agreement. In this study, 2D-SWE was performed on 60 volunteers (42 cases with 10 consecutive measurements, 18 cases with 2 measurements) on 2 different days by 2 operators (one expert and one novice). The intra-observer agreement between measurements performed in the same subject on the same day (day 1 or day 2) showed intraclass correlation coefficient (ICC) values of 0.95 and 0.93 for the expert operator and novice, respectively, and the ICC values for intra-observer agreement between measurements performed in the same subject on different days were 0.84 and 0.65, respectively. The inter-observer agreement was 0.88. Therefore, real-time 2D-SWE has been shown to be a reproducible method to measure liver elasticity, but the novice operator showed lower measurement reproducibility over time than the expert operator.

### Clinical application

**CHC:** 2D-SWE might be used in assessing liver fibrosis for patients with CHC, as has been proved in two large studies. Ferraioli *et al.*<sup>[170]</sup> assessed the accuracy of 2D-SWE in comparison with transient elastography in 121 patients with CHC using LB as the reference standard, and found that LS values increased in parallel with the degree of liver fibrosis both with 2D-SWE and TE. The AUROC was 0.92 for 2D-SWE and 0.84 for TE ( $P = 0.002$ ); 0.98 for 2D-SWE and 0.96 for TE ( $P = 0.14$ ); 0.98 for 2D-SWE and 0.96 for TE ( $P = 0.48$ ), when comparing F0-F1 *vs* F2-F4, F0-F2 *vs* F3-F4, and F0-F3 *vs* F4, respectively (Figure 3). Therefore, the real-time 2D-SWE was more accurate than TE in assessing significant fibrosis ( $\geq F2$ ). In the other study which included 113 hepatitis C virus patients, a good agreement was shown between 2D-SWE and TE, the AUROC for elasticity values assessed by 2D-SWE were 0.948, 0.962 and 0.968 for patients with predicted fibrosis levels  $F \geq 2$ ,  $F \geq 3$  and  $F = 4$ , respectively. However, LB was only available in 39 patients<sup>[17]</sup>.

### EFSUMB recommendations

2D-SWE can be used to assess the severity of liver fibrosis in patients with chronic viral hepatitis, especially with hepatitis C<sup>[7,20]</sup>.

## STRAIN ELASTOGRAPHY

Strain elastography (SE), also termed as quasi-static strain imaging, has been developed by several manufacturers, however, only Hitachi ultrasound system has been evaluated for use in liver.

### Technique

SE is based upon the fact that soft tissue can be more easily compressed than hard tissue. When subtle compression is applied with probe, SE shows the relative degree of tissue strain, but not demonstrates the physical elasticity directly. SE calculates the strain response of the tissue

**Table 3** Advantages and disadvantages of non-invasive methods to evaluate liver fibrosis

Parameters	Transient elastography	ARFI	2D-SWE	MR Elastography	Serum biomarkers
Advantages	High and rapid performance Reproducibility Easy to learn	High and rapid performance Reproducibility Easy to learn	High and rapid performance Reproducibility Easy to learn, large ROI	High performance (applicability) Reproducibility Examination of the whole liver Combined with conventional MRI obesity and ascites are not limiting	Availability Reproducibility Low cost
Disadvantages	Technical requirements (equipment) without additional use Intermediate cost Limited recognition of intermediate stages of fibrosis Blind selection of region of interest Restricted value in obese patients and ascites False positive values in patients with acute hepatitis, cholestasis, and heart failure	Combined with conventional ultrasound Obesity and ascites are not limiting Technical requirements (ultrasound equipment) Intermediate cost Limited recognition of intermediate stages of fibrosis Narrow range of values, small ROI Quality criteria not well defined	Combined with conventional ultrasound Ascites are not limiting Technical requirements (ultrasound equipment) Intermediate cost Limited recognition of intermediate stages of fibrosis Quality criteria not well defined	Technical requirements (MRI equipment) Extremely high cost, time consuming Limited recognition of intermediate stages of fibrosis Not applicable in case of iron deposition	Non-specific (hyperbilirubinemia, hemolysis, inflammation, others) Relatively high cost, limited availability (patent) Limited recognition of intermediate stages of fibrosis Results not immediately available

ARFI: Acoustic radiation force impulse; SWE: Shear wave elastography; ROI: Region of interest; MRI: Magnetic resonance imaging.

to stress (relative tissue elasticity) and displays it as a colour overlay [ranges from red (soft) to blue (hard)] on the B-mode image<sup>[171]</sup>. The echo signals could be captured in real-time by incorporating a high speed algorithm, in addition, both the B-mode image and corresponding tissue elasticity image could be simultaneous displayed<sup>[172]</sup>. Semi-quantitative elastography techniques are based on quantification of the strain distribution within a defined ROI.

Because the pressure generated by the operator's compression may influence both the image of elasticity and the resulting elasticity score, Hitachi medical system has recently developed an elastography method that did not require extra external stress. The required liver distortion for future analysis would be achieved from the rhythmic pulsations of the abdominal aorta or the heart.

### Clinical application

In 2007, Frederick-Rust *et al*<sup>[11]</sup> reported the clinical application of SE in the liver. They developed an elasticity score by assessing the colour-coded strain image using the computer program Matlab. The diagnostic accuracy for F2, F3 and F4 were 0.75, 0.73 and 0.69, respectively. In 2009, the same group<sup>[173]</sup> compared SE with TE (Fibroscan) and serum fibrosis marker (Fibrotest), and concluded that SE in its evaluated format could not replace TE for non-invasive assessment of liver fibrosis at the time of the study. After the software for elastography was developed by Hitachi medical systems, good results were published by several studies. Morikawa *et al*<sup>[174]</sup> transferred the pixel data in the ROI into a histogram and a binary

image for semi quantification with a devised system, and found that the mean value on the histogram and the percentage of hard tissue may directly represent liver elasticity. The diagnostic accuracy of SE for liver fibrosis was also compared with TE, the author felt SE compared favourably with TE and suggested SE could potentially be used as a routine imaging tool to evaluate liver fibrosis. A Chinese group<sup>[175]</sup> utilized a new Hitachi ultrasound system (HI VISION Preius) and concluded that there was a strong positive correlation ( $r = 0.81$ ) between the elasticity index and fibrosis stage. Diagnostic accuracies of SE for the diagnosis of F1, F2, F3, F4 were 0.93, 0.92, 0.84 and 0.66, respectively. Koizumi *et al*<sup>[176]</sup> performed a semi-quantitative analysis using the elastic ratio method (ratio of strain distribution in two selected ROI) on 70 patients with CHC and with the hepatic vein as the internal control and found that the AUROC curves for elastic ratio were superior to serum fibrosis markers and scores of fibrotic change based on blood results (Figure 4).

More studies including meta-analysis about the use of SE for the evaluation of liver fibrosis are required to establish a protocol for accurate imaging and to standardize analysis.

### Advantages

The main advantage of this technique is the relatively large region of interest that can be interrogated in the right liver lobe, plus the quantification method that can measure the change from the diffuse soft uniform architecture of the liver to a patchy hard pattern as hepatic

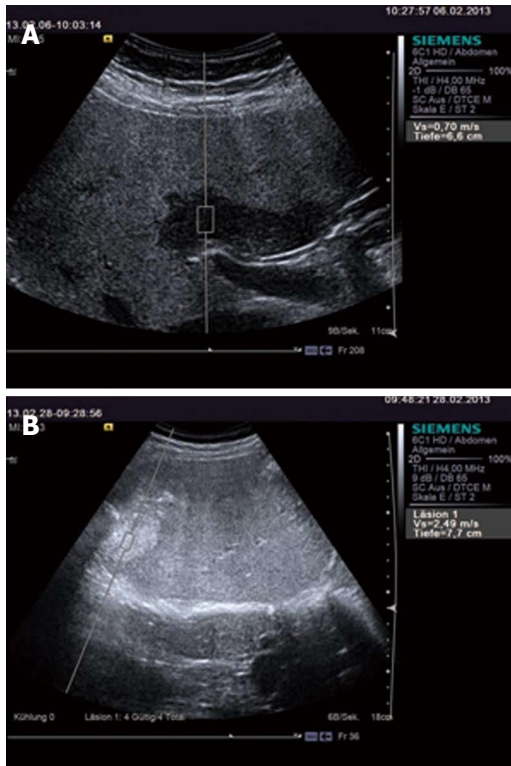


Figure 5 Point-shear wave elastography with acoustic radiation force impulse for evaluation of focal liver fatty lesion (A) and liver metastasis (B).

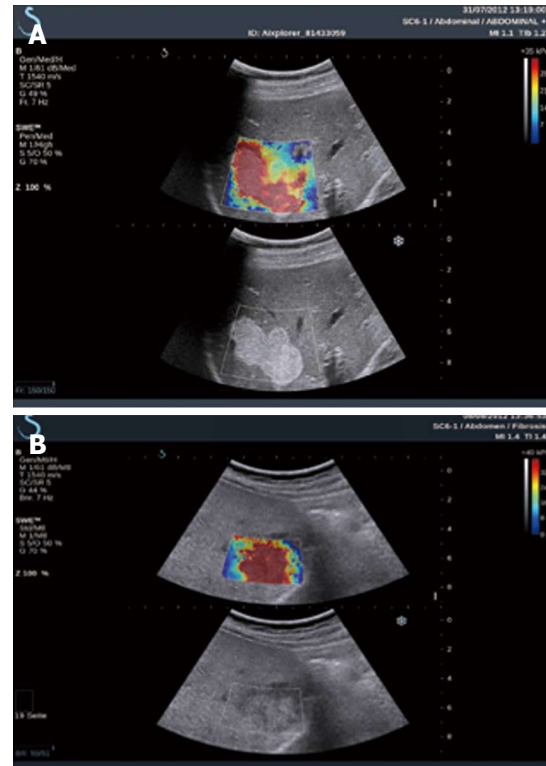


Figure 6 2D shear wave elastography with supersonic shear imaging for the evaluation of liver hemangioma (A) and metastasis (B).

Table 4 Performance of acoustic radiation force impulse in the identification of malignant focal liver lesions

No. of FLL	Rate of malignancy	Reference standard	Lesion types	ARFI cut-off (m/s)	QUADAS score	Ref.
105	64.8%	Biopsy, imaging	Haemangioma, FNH, focal fatty sparing, focal fat deposits adenomas, HCC, metastasis	2.7	11	[182]
60	71.7%	Biopsy, CT/MRI	haemangioma, HCC, CCC, metastasis	2	10	[183]
128	53.1%	Biopsy, surgery, imaging	Haemangioma, FNH, focal fatty change, abscess, adenoma, solitary necrotic nodule, HCC, metastasis, CCC	2.2	10	[184]
42	64.3%	Biopsy	Haemangioma, lymphoma, FNH, sarcoid, abscess, focal fatty sparing, HCC, metastasis	2.5	12	[185]
45	22.2%	Biopsy, CT/MRI	Haemangioma, metastasis	2.5	8	[186]

QUADAS: Quality assessment of diagnostic accuracy studies; HCC: Hepatocellular carcinoma; FNH: Focal nodular hyperplasia; CCC: Cholangiocarcinoma; FLL: Focal liver lesions; CT: Computed tomography; MRI: Magnetic resonance imaging.

fibrosis progresses.

#### ***Intra- and inter-observer reproducibility***

The intra-observer variability and intra-observer agreement of SE for the assessment of liver fibrosis have been criticized in several studies<sup>[173,177,178]</sup>. In a more recent study, a Japanese group<sup>[176]</sup> 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 ( $K = 0.835$ ,  $ICC = 0.966$ ).

#### ***EFSUMB recommendations***

The evidence with this approach is still too limited to allow recommendation for its clinical use, at least in European patients<sup>[7,20]</sup>.

### **ADVANTAGES AND DISADVANTAGES OF CURRENT NON-INVASIVE METHODS IN EVALUATING LIVER FIBROSIS**

Advantages and disadvantages of currently available non-invasive methods in patients with chronic viral hepatitis C are summarized in Table 3.

### **ELASTOGRAPHY FOR DETECTION AND CHARACTERIZATION OF FOCAL LIVER LESIONS**

Elastography methods have been also applied for detection and characterisation of focal liver lesions (FLL).



Although the method so far cannot be applied to all segments and the limited depth of penetration is so far disappointing, several studies have evaluated the performance of ARFI to differentiate FLL, and the results are encouraging. ARFI has shown a high accuracy for the identification of malignant FLL. In a meta-analysis by Ying *et al.*<sup>[179]</sup> including 590 lesions in eight studies, the summary sensitivity and specificity for identification of malignant liver lesions were 0.86 and 0.89, respectively. The hierarchical summary receiver operating characteristic (HSROC) was 0.94. However, one paper showed that ARFI did not permit differentiation between benign and malignant FLL because high ARFI values occur in benign as well as in malignant lesions<sup>[180]</sup>. In another study by Gallotti A, the mean shear wave speed of HCC, haemangioma, adenoma, metastasis, FNH was 2.17, 2.30, 1.25, 2.87, 2.75 m/s, respectively. Adenoma showed similar stiffness to the surrounding liver, and was significantly softer than the other four types of lesion. FNH showed different stiffness to HCC and metastasis, however, haemangioma showed no difference to HCC, metastasis and FNH<sup>[181]</sup> (Figures 5 and 6). The performance of ARFI is summarized in Table 4.

### EFSUMB recommendations

Although promising results have been reported, more research is needed, especially in comparison to CEUS, before recommendations on its use in clinical practice can be made. So far, elastography cannot be recommended for the differential diagnosis of benign from malignant liver lesions<sup>[7,20]</sup>.

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