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Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement[1]

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The Society of Radiologists in Ultrasound convened a panel of specialists from radiology, hepatology, pathology, and basic science and physics to arrive at a consensus regarding the use of elastography in the assessment of liver fibrosis in chronic liver disease. The panel met in Denver, Colo, on October 21–22, 2014, and drafted this consensus statement. The recommendations in this statement are based on analysis of current literature and common practice strategies and are thought to represent a reasonable approach to the noninvasive assessment of diffuse liver fibrosis.

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Online supplemental material is available for this article.

Chronic liver disease is a substantial worldwide problem. Its major consequence is increasing deposition of fibrous tissue within the liver, leading to the development of cirrhosis with its consequences, portal hypertension, hepatic insufficiency, and hepatocellular carcinoma (HCC). Different histologic stages of progressive liver fibrosis have been described, from no fibrosis (METAVIR stage F0) to the cirrhotic stage (METAVIR stage F4). As fibrosis progresses, there is increasing portal hypertension, loss of liver function, and higher risk of HCC. The stage of liver fibrosis is important to determine prognosis and surveillance and to prioritize for treatment and potential for reversibility. The process of fibrosis is dynamic, and studies have shown that a regression of fibrosis is possible with treatment of the underlying condition (eg, antiviral therapy in viral hepatitis and immunosuppression in autoimmune hepatitis) (1–3). Previously, the only method of staging the degree of fibrosis was liver biopsy. Liver biopsy is considered the reference standard for fibrosis assessment and stage classification and also allows grading of steatosis, necrosis, and inflammatory activity. However, biopsy is invasive, with potential complications that can be severe in up to 1% of cases (4,5). Further, tissue obtained via biopsy represents roughly only 1/50000 of the liver volume, which may result in sampling error (6) and is associated with considerable interobserver variability at microscopic evaluation (7). Therefore, noninvasive methods for liver fibrosis assessment have been an intense field of research, including elastographic methods involving ultrasonography (US) and magnetic resonance (MR) imaging.

The Society of Radiologists in Ultrasound convened a panel of specialists from radiology, hepatology, pathology, and basic science and physics to arrive at a consensus regarding the use of elastography in the assessment of liver fibrosis in chronic liver disease. The panel met in Denver, Colo, on October 21–22, 2014, and drafted this consensus statement. The recommendations in this statement are based on analysis of current literature and common practice strategies and are thought to represent a reasonable approach to the noninvasive assessment of diffuse liver fibrosis.

The goals of the consensus conference were to *(a)* understand the variability of elastography measurements (intrinsic and patient factors); *(b)* review factors that can affect measurements; *(c)* provide guidance on how to perform the examinations, interpret the results, and report the findings; *(d)* determine where US elastography can be used in clinical practice; and *(e)* set an agenda for further research.

Methods and Conference Preparations

The comoderators of the conference (R.G.B. and D.L.) designed the schedule for the consensus conference and invited the speakers. M.L.P. has intellectual property rights without a financial interest in acoustic radiation force impulse (ARFI) technology. R.E., who is noted in the acknowledgment, has intellectual property rights and a financial interest in MR elastography technology and participated as a consultant to the panel. Final recommendations in this publication are the consensus opinions of the panel members, who do not have a financial interest in the technologies reviewed.

We limited the discussion to diffuse liver disease, as our goal was to determine how elastography could be best used to evaluate patients at risk for liver fibrosis and to manage patients with known fibrosis. Speakers were requested to provide a summary of their talks and a short list of relevant references (8–42) that were made available to the panelists before the meeting. The panel consisted of the two comoderators and 10 additional speakers with expertise in US elastography, MR elastography, hepatology, and basic physics. An audience of invited representatives from various medical societies and industry was also present.

Background

Clinical Importance of Chronic Liver Disease and Cirrhosis

Once a patient with chronic liver disease develops cirrhosis, complications such as portal hypertension, liver insufficiency,

Advance in Knowledge

■ In a consensus conference, it was decided that the best use of elastography is to identify patients with no or minimal fibrosis (METAVIR stages F0 and F1) and those with severe fibrosis or cirrhosis (METAVIR stages F3 and F4).

Implications for Patient Care

■ In select patients, elastography may eliminate the need for liver biopsy for staging fibrosis.

■ Elastography can be used to monitor disease progression and treatment response.

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and HCC can occur. The presence of cirrhosis changes the prognosis of any chronic liver disease and, once it is diagnosed, different algorithms regarding screening for the presence of varices and monitoring for the development of HCC need to be implemented. For example, diagnosis of nodules larger than 1 cm shown at any imaging examination (by means of either assessment with another imaging modality or biopsy) is mandated when cirrhosis is present (43). Furthermore, priority for antiviral therapy in patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) is currently driven by the presence or absence of moderate to severe fibrosis (METAVIR stage F3 and higher).

Predisposing Conditions

Essentially, any chronic liver disease may lead to liver fibrosis and progress to cirrhosis. This includes infections with HBV and HCV, alcohol abuse, and nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis, cholestatic liver disease (eg, primary biliary cirrhosis), iron or copper deposition, and autoimmune causes. Understanding the different causes of fibrosis is important when assessing a screening tool such as elastography, since disease prevalence affects measures of performance.

These diseases can also lead to necrosis, inflammation, and fat deposition (steatosis) that may affect elastographic measurements. In addition, comorbidities, such as acute and chronic disease or vascular congestion, can affect liver stiffness. Patient factors such as obesity, ascites, medications, and prandial state can also affect elastography measurements. Pretest probabilities according to age, sex, ethnicity, and laboratory tests also affect the cutoff values used for stage of liver fibrosis in patients with liver disease from different origins. Owing to these varied factors (Table 1), thresholds obtained from specific populations may have limited generalizability for other populations.

The U.S. Centers for Disease Control give the following global statistics

Table 1	
Sources of Variability in Elastography	
Category	Examples
Origin of the underlying disease	Hepatitis B, hepatitis C
Patient comorbidities	Acute chronic liver disease (44), congestive heart failure (45), extrahepatic cholestasis (46)
Modality being used	MR imaging, transient elastography (TE), shear wave elastography (SWE), point quantification SWE (pSWE)
System-specific factors	Depends on the manufacturer
Machine-specific factors	Machines and probe variability from individual manufacturers
Measurement variability	Location in the liver, intra- and interobserver variability
Patient physical factors	Obesity, ascites
Indication for study	Thresholds will be different, depending on the need for the study (fibrosis detection, staging, or follow-up) to optimize characterization of certain populations
Disease prevalence	Will affect measures of accuracy, positive predictive value, and negative predictive value
Patient sex	Male vs female (47)
Postprandial state	Fasting vs nonfasting (48,49)
Breath-hold technique	Valsalva maneuver can increase stiffness values (50)

for hepatitis (51): There are an estimated 240 million people with chronic HBV infection with high incidence in Asia and Africa. There are up to 1.4 million people in the United States with chronic HBV infection. Even within a given geographic area, the distribution of HBV can be variable. Asian and Pacific Islanders make up less than 5% of the total population in the United States but account for more than 50% of Americans living with chronic HBV infection. In 2011, the prevalence for the male population in the United States was approximately 1.7 times higher than that for the female population. In 2011, the highest prevalence was among persons aged 30–39 years (2.00 cases per 100000 people), and the lowest was among adolescents and children up to 19 years old (0.04 cases per 100000 people). Five to 10 percent of acute HBV infections become chronic in adult-acquired disease.

Hepatitis C has a prevalence of 2.4% of the worldwide population, an estimated 160 million individuals. In the United States, the overall incidence of acute HCV increased from 2010, with the largest increases among persons aged 0–19 years (from 0.05 to 0.10 cases per 100000 people) and 20–29 years (from 0.75 to 1.18 cases per

100000 people). Hepatitis C affects approximately 3.2 million U.S. residents. HCV infections progress to chronicity in 75%–85% of acute cases.

The worldwide prevalence of being overweight (body mass index > 25 kg/m²) is 42%, while that of obesity (body mass index > 30 kg/m²) is 12% (52). This varies greatly on the basis of geography; the prevalence of obesity in Southeast Asia is 2%, compared with 33% in the Americas. The prevalence of NAFLD (directly linked to being overweight or obese and having diabetes and dyslipidemia) is estimated at 27%–34% in the United States and 20%–30% in Europe. In morbidly obese individuals, the prevalence is estimated to be 75%–92%. The prevalence of nonalcoholic steatohepatitis in the general population of the United States is 10%–20% and 37% in patients with severe obesity.

Staging of Fibrosis

Fibrosis is defined as an abnormal increase in collagen deposition and other components of the extracellular matrix in response to chronic injury. Cirrhosis is a diffuse process, characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules (53). There are several
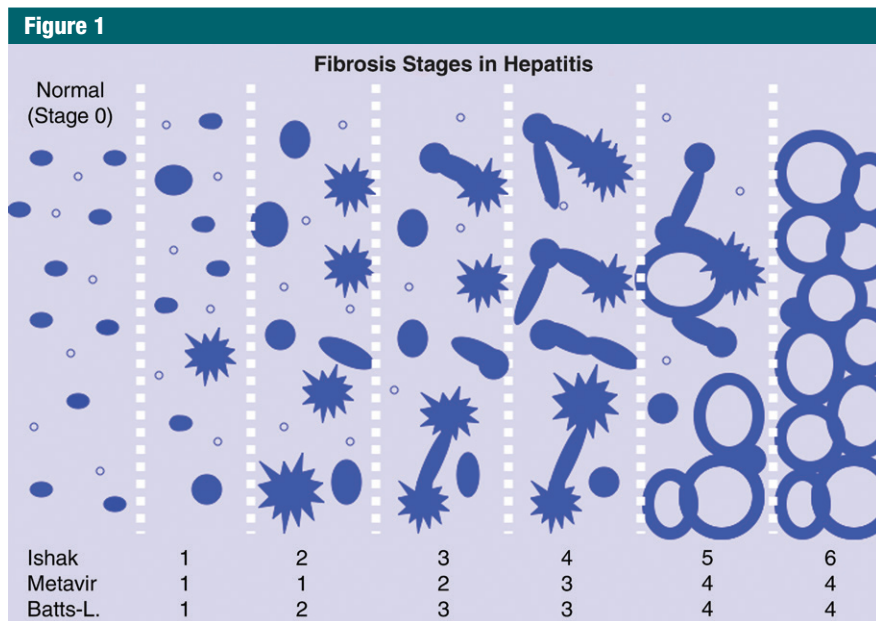
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Figure 1: Diagram of the comparison of the various staging systems for liver fibrosis. Stars represent periportal fibrosis, lines represent bridging fibrosis, and circles represent nodularity. This chart shows the four stages of the METAVIR system, the six stages of the Ishak system, and the four stages of the Batts-Ludwig *(Batts-L.)* system. Note how each system has one "extra" stage 0 that describes a normal liver. While each stage ends with a stage 4 or 6 cirrhotic nodular liver, the actual descriptions of the stages between normal liver and cirrhosis differ. The Ishak system discriminates between early (stage 5) cirrhosis and established or advanced cirrhosis (stage 6), which differ in prognosis and incidence of clinical events. Four-stage (five if including normal liver) systems such as METAVIR and Batts-Ludwig do not take into account the fibrosis spectrum of a cirrhotic liver. (Reprinted, with permission, from reference 7.)

liver fibrosis staging systems routinely used by histopathologists. These include the Ishak, METAVIR, and Batts-Ludwig systems (7,54) (Fig 1). These staging systems are used to evaluate the location and the degree of portal and periportal fibrosis, bridging fibrosis, and nodularity to assess the stage of fibrosis. The METAVIR system is the most often used. Although developed primarily for use in viral hepatitis, these systems have been adapted to other liver diseases.

These fibrosis staging systems correlate with clinical outcomes in liver disease. In all systems, it is cirrhosis (METAVIR stage F4, Batts-Ludwig stage 4, Ishak stages 5–6) that is most strongly associated with liver-related morbidity and mortality and is therefore the most important stage to identify noninvasively (55). This is important when evaluating studies in which thresholds are assessed in the diagnosis

of specific stages of fibrosis, since sensitivity and specificity thresholds can then be optimized for the most severe forms of the disease. With the development of new antiviral medications, those who have moderate to severe fibrosis (METAVIR stage F2–F3, Batts-Ludwig stage 3, Ishak stages 3–5) and are at risk for progression of the fibrosis, dependent on the origin of the fibrosis (eg, HCV-infected individuals), may be candidates for specific treatments and are another important group to identify noninvasively (56,57).

For the clinician, the most important question in a patient with chronic liver disease is whether or not the patient has cirrhosis. Because the diagnosis of decompensated cirrhosis (defined by the presence of clinical complications, such as ascites, variceal hemorrhage, jaundice, and/or encephalopathy) can be assigned clinically (on the basis of patient history, physical

examination, and laboratory tests), the diagnosis of compensated cirrhosis is more challenging. Although some findings, such as low platelet count and a nodular liver surface on images, can indicate the presence of cirrhosis, these findings are often absent in a patient with compensated cirrhosis; thus, a noninvasive study to confirm or exclude the presence of cirrhosis is needed.

Portal hypertension is an important prognostic factor in patients with chronic liver disease and is the pathophysiological basis of most complications of cirrhosis. Upper gastrointestinal bleeding from esophageal varices, ascites, and encephalopathy are among the most important clinical manifestations of increased portal venous pressure. Additionally, increased portal venous pressure induces morphologic changes in the spleen, including increased red and white pulp volume, hyperplasia of splenic histiocytes, lengthening of arterial terminals, and fibrosis of splenic trabeculae.

Currently, the reference standard for the evaluation of portal hypertension is direct measurement of the hepatic venous pressure gradient by using invasive angiographic techniques. In patients with cirrhosis, substaging can be performed on the basis of the degree of portal hypertension; patients with compensated cirrhosis and a hepatic venous pressure gradient of more than 10 mm Hg (clinically significant portal hypertension) are at a higher risk of varices, decompensation, and HCC. Noninvasive means to evaluate liver function in association with portal hypertension include serologic markers, clearance tests (eg, indocyanine green), liver stiffness, and spleen stiffness (35).

Clinical Indications for Elastography

The main clinical indication for liver elastography is fibrosis staging of chronic liver disease (eg, chronic viral hepatitis and screening patients with NAFLD to rule out nonalcoholic steatohepatitis), with a main objective of determining the presence or absence of advanced fibrosis. As mentioned previously, determining the presence of cirrhosis is important, since this

will trigger screening and/or monitoring procedures and establish priority for therapy. Other indications for liver elastography include follow-up of previously diagnosed fibrosis, assessment of patients with known cirrhosis (by establishing whether there is clinically significant portal hypertension), and evaluation of patients with unexplained portal hypertension. With new treatments that can actually decrease fibrosis in patients with viral hepatitis, another indication is follow-up to assess response to treatment and potentially to tailor further follow-up and therapy (1,2). One study performed in patients with HBV infection who were undergoing antiviral therapy showed that histologic regression of fibrosis occurred in

91% of them, with cirrhosis regression occurring in 74% of patients after 5 years of therapy (1).

The (Imperfect) Histologic Reference Standard

Although histologic evaluation of a liver biopsy sample has been considered the reference standard for staging liver fibrosis, it is an imperfect reference standard. In addition to its invasive nature, some degree of sampling variability is inevitable because of the irregular distribution of fibrosis in chronic liver disease, but obtaining good-quality, adequate-sized biopsy samples can minimize this. Specimens that contain 11 or more portal tracts are as accurate as

larger tissue samples, whereas biopsies with fewer than 11 portal tracts tend to be understaged (58). The American Association for the Study of Liver Diseases practice guideline (53,59) recommends that biopsy samples for fibrosis staging be obtained with a 16-gauge needle and be at least 2 cm long because 94% of such biopsies contain 11 or more portal tracts and are therefore nearly as accurate as larger specimens (58). The excellent concordance of MR elastography results with adequate liver biopsy findings (32) confirms the accuracy of both techniques.

Another drawback of liver biopsy is the relatively limited number of stages (5–7) in most staging systems. Fibrosis in liver disease is actually a continuous spectrum, rather than discrete categories. It is possible to measure fibrosis precisely on a continuous scale in histologic specimens by using morphometric methods and digital image analysis (54), but this is not currently practical for routine use. The limited number of stages is especially problematic in patients approaching end-stage liver disease. The Ishak system allows discrimination between early cirrhosis (stage 5) and established or advanced cirrhosis (stage 6), which differ in prognosis and incidence of clinical events. Four-stage (five if including normal) systems such as METAVIR and Batts-Ludwig do not take into account the fibrosis spectrum of a cirrhotic liver (Fig 1), whereas liver stiffness measurements present a continuous and wide range of values that correlate with clinical parameters of advanced cirrhosis (7,60).

In addition to the sampling error, variability of histologic interpretation may be a problem, particularly for inexperienced pathologists. In several studies, interobserver agreement on the staging of liver fibrosis by pathologists as expressed with the κ statistic varied from 0.4 (moderate agreement) to 0.9 (almost perfect) (7). Consequently, when noninvasive methods are compared with histologic findings as the reference standard, a perfect concordance will be impossible to achieve, since histologic examination itself is an imperfect reference standard.

Figure 2

Figure 2: TE image in a 50-year-old woman with chronic hepatitis C. The left image is in time motion mode, the middle image is in amplitude mode, and the right image is the elastographic image. The elastogram is the representation of the shear wave as a function of time. The slope of the white line decreases with the increase in stiffness. The value of 5.2 kPa obtained is in the normal range. The interquartile ratio (IQR) is 0.3, with an IQR/median value of 5%, confirming that the 10 measurements obtained are of high quality (only one is shown). The controlled attenuation parameter is a measure of the US attenuation that corresponds to the decrease in the amplitude of ultrasound waves as they propagate through the liver; in this case, the controlled attenuation parameter is 198 dB/m, which is within the normal range.

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Despite the drawbacks of liver biopsy, histologic examination can serve to identify the common confounders that result in increased liver stiffness unrelated to fibrosis (61). Inflammation, hepatic vascular congestion, and cholestasis can cause increased liver stiffness in the range associated with cirrhosis.

Noninvasive Methods for the Assessment of Liver Fibrosis

There are four main methods for noninvasive tissue stiffness–based assessment of liver fibrosis: TE, pSWE, two-dimensional (2D) SWE, and MR elastography. Both pSWE and 2D SWE involve the use of ARFI technology. Although the measurements obtained from each are correlated with each other and with pathologic stage of fibrosis, they each have inherent strengths and weakness, and the measurements provided by each differ (Table 2). Strain elastography assessment for liver fibrosis has been reported, but the literature is limited and therefore, it was not discussed in this consensus panel (65). A glossary of terms is provided in Appendix E1 (online). The European Federation of Societies for Ultrasound in Medicine and Biology (66) and World Federation for Ultrasound in Medicine and Biology (65) have produced guidelines for the use of elastography for evaluation of liver stiffness (Table 3) but do not give specific thresholds for the evaluation of fibrosis and/or cirrhosis. Clinical organizations such as the European Association for the Study of the Liver (56,67), Canadian Association for the Study of the Liver (57), and National Institution for Health and Care Excellence (68–70) have mentioned elastography for the assessment of liver fibrosis in clinical guidelines. For all of the guidelines, the use of US elastography is agreed upon in the evaluation of liver stiffness, with the comment that there is sufficient literature to recommend the technique for HCV, but other disease origins have been studied less. For all guidelines, it has been commented that the literature

is more substantial for the use of TE than ARFI (pSWE and 2D SWE) techniques, owing to the longer period of time that TE has been available. The physics behind these tools is discussed in depth in reviews by multinational US societies (24,71).

Technical Aspects of Performing Elastography

In each of the US-based methods of elastography, the patient is imaged in the supine or slight (30°) left lateral decubitus position (Table 4). The right arm is raised overhead to increase the intercostal acoustic window. The probe is placed in an intercostal position. The B-mode image should be optimized for the "best acoustic window" to provide the best results. The amount of displacement of the liver is optimized when the ARFI pulse is perpendicular to the liver capsule to limit refraction of the pulse. Although liver fibrosis is a heterogeneous process, the "best" accuracy of stiffness value is from multiple measurements in the same location. The site selected should be the best location for "most accurate" measurement, taking acoustic window and depth into consideration.

The measurement is performed while the patient holds his or her breath. It was the consensus of the panel that breath hold (a few seconds) during quiet breathing led to the most optimal results. Taking a deep breath or using a Valsalva maneuver or deep expiration changes hepatic venous pressures that can affect the stiffness measurements (72,50).

The literature suggests that 10 measurements should be obtained and the median reported. More than 60% of the measurements should be "good" measurements; if not, a value should not be reported. A "good" measurement is one where a numerical result is obtained, not an "x.xx" or "0.00." In some studies, investigators suggest that a smaller number of measurements may have similar accuracy (36,73). Further study is required to determine if a smaller number of measurements would be as accurate.

The IQR should be used to assess quality of the data. The interquartile range, also called the "middle fifty," is a measure of the statistical dispersion being equal to the difference between the upper and lower quartiles. An IQR/median value of less than 0.30 suggests that a data set is good. In patients with TE values less than 7.1 kPa, the IQR does not affect accuracy (74). This can be used to monitor sonographer quality, as well as laboratory quality. However, this method needs verification as the most appropriate manner in which to ensure quality.

The ARFI push pulse energy deposition for current U.S. Food and Drug Administration–approved vendor systems is within current Food and Drug Administration diagnostic limits for livers in adults. Off-label use for other organs and for use during and immediately after the use of US contrast materials should be avoided until further investigation (75).

TE Technique

TE is a US-based technique, but it is used without direct image guidance. A 3.5-MHz "M" probe, a 2.5-MHz "XL" probe (for obese patients), or a 5.0-MHz probe (for children) is placed in the region dullest to percussion, typically in the 9th–11th intercostal space, and a portion of liver about 6 cm deep is interrogated. An image is provided that shows the propagation of the shear wave over time in the ROI (Fig 2). The image should be evaluated for a uniform background and a linear shear wave propagation. The software determines whether each measurement is valid or not. When a data acquisition is unsuccessful, the machine does not return a stiffness value. The entire procedure is considered to have failed when no value is obtained after at least 10 attempts. Validation of the measurements is performed by means of the following criteria: *(a)* number of at least 10 valid shots; *(b)* ratio of valid shots to the total number of shots of at least 60%; and *(c)* IQR (reflecting the variability of measurements) less than 30% of the median liver stiffness measurements value (IQR/liver stiffness

Table 2

Comparison of Elastography Modalities

Parameter	TE	pSWE	2D SWE	MR Elastography
Advantages	Point of care for clinician, technique well defined, rapid learning curve, repeatable, presently not recommended for spleen measurements	Can be an independent procedure or an add-on during liver US, direct visualization of liver region being insonated, quantitatively possibly less variability than 2D SWE, can be used to assess the spleen	Can be an add-on during liver US, direct visualization of the liver region being insonated, color display of a larger field of view, can be used to assess the spleen	Closest correlation to adequate liver biopsy, large sample of liver allows for assessment of spatial pattern of disease, no depth dependence of measurement, can be used to assess the spleen, can be performed in patients with obesity or ascites, cross-vendor standardization
Expense	Inexpensive	Inexpensive	Inexpensive	Expensive, unless performed as a limited MR elastography–only examination
Frequency for shear wave generation	40–50 Hz ("S," "M," "XL" probe dependent)	100–500 Hz	100–500 Hz	60-Hz standard, other frequencies possible.
Limitations	Needs dedicated machine, probe needs recalibration every 6–12 months depending on probe, failures due to ascites and obesity (obesity failures may be overcome with the use of extra-large probe), no grayscale image of liver (A-mode images are available), lower performance compared with ARFI techniques (36,55,56,57)	Less published material than TE owing to shorter time in use	Less published material than TE owing to shorter time in use	Failures due to iron overload (newer sequences will reduce these), failures due to claustrophobia, not as widely available as TE, higher charges for examination
Measurement location	Right intercostal space (dullest area of percussion)	Most often segment VII or VIII	Most often segment VII or VIII	Right lobe of the liver in four sections
Region of interest (ROI) size	About 4 cm³	About 0.5–1.0 cm³	About 20 cm³	About 250 cm³
Value reported	Median of 10 measurements, check IQR/median value < 0.3	Median of 10 measurements*, check IQR/median value < 0.3 if the stiffness value is > 1.5 m/sec (7.1 kPa)	Median of 10 measurements*, check IQR/median value < 0.3 if the stiffness value is > 1.5 m/sec (7.1 kPa)	Mean or median of ROI measurements in four sections
Defining a good measurement	Machine does not report value if inadequate	Not "x.xx" or "0.00"	ROI area not colored	Confidence map shows areas that are above a threshold

* Each vendor has a recommended number of acquisitions. The listed number is the consensus recommendation.

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Table 3

Current Guidelines on the Use of Elastography

Source	Patient Population	Threshold
World Federation for Ultrasound in Medicine and Biology (65)	Can be used as first-line assessment of hepatitis C staging of liver fibrosis to monitor response to antiviral treatment and predict prognosis	Combining TE with a serum biomarker of fibrosis increases diagnostic accuracy; validation in other liver diseases is needed
European Federation of Societies for Ultrasound in Medicine and Biology (66)	Can be used to assess the severity of liver fibrosis in patients with chronic viral hepatitis, providing that confounding factors are taken into account	Can be used to distinguish patients with no or mild fibrosis from those with clinically significant fibrosis and identify those with cirrhosis; cutoff values vary with the manufacturer

Table 4

Best Practice for Performance of US-based Elastography

Suggested Technique	Comments
Fasting for 4–6 hours	The normal liver is very compliant, so a nonfasting patient with a normal liver will likely have normal elastography findings. However, the fibrotic liver is less compliant and in the nonfasting state can have falsely increased elastography values. Six hours of fasting is likely longer than necessary but corresponds to what we typically ask for when scanning the gallbladder. Four hours is likely sufficient.
Specific positioning	Supine or slight (30°) left lateral decubitus position
Right arm elevated above the head	Improves intercostal access
Shallow breath hold	The patient only needs to hold his or her breath for a few seconds; it may be helpful to practice the breath hold with the patient prior to initiating elastography; obtaining a measurement in deep inspiration or with a Valsalva maneuver can give inaccurate measurements
ROI placement in the right lobe of liver (typically segment VII or VIII) about 2 cm beneath the Glisson capsule, perpendicular to the liver capsule	Use intercostal transducer placement; avoid reverberation artifacts; avoid increased subcapsular stiffness (1.5 cm); the transducer-specified lens focus is typically about 4–5 cm below the transducer, thus best measurements are in this region; maintain the ARFI pulse perpendicular to the liver capsule; find a location with best B-mode image without shadowing
ROI placement to avoid large liver vessels and/or bile ducts and rib shadows	The ROI actually extends 1 cm above and below the in-plane ROI, so check the liver in these areas prior to initiating the elastography measurement for large vessels and focal lesions
Acquisition of measurements	Ten measurements obtained in the same location

measurements ≤ 30%) (76). TE shear wave speed measurements are typically expressed as the Young modulus in kilopascals (Appendix E1 [online]).

Strengths of the TE approach are that it is widely available (at hepatologists' offices) and used at the time of assessment of patients by staff in the hepatologists' office. The technique has excellent reproducibility, with an intraclass correlation coefficient of 0.96 (77,78). Weaknesses are the lack of grayscale image guidance to determine where the measurement is being obtained, inability to access masses and large vessels at the site of measurement, the need for recalibration of the spring in the device at 6–12-month intervals (depending on the type of probe), and inability to use it in patients with ascites. Like

liver biopsy, it cannot be used to assess the nonuniformity of the disease distribution in the liver.

pSWE Technique

In pSWE, an ARFI pulse is used to generate shear waves in the liver in a small (approximately 1-cm³) ROI. B-mode imaging is used to monitor the displacement of liver tissue due to the shear waves. From the displacements monitored over time at different locations from the ARFI pulse, the shear wave speed is calculated in meters per second. Assumptions can then be made that can convert the shear wave speed in meters per second to the Young modulus in kilopascals: $E = 3(vS^2 \cdot \rho)$, where E is the Young modulus, vS is the shear wave speed, and ρ is the density of the tissue in homogeneous

isotropic tissues. The assumption is made that the density is 1 g/mL. The panel believed that for comparison between modalities and machines, industry should strive for standard reporting based on meters per second. A strength of the technique is that it is performed with real-time imaging, so masses and large vessels can be identified and avoided (Fig 3), and it can be used to systematically select different parts of the liver to sample.

2D SWE

In 2D SWE, multiple measurements with ARFI technology are performed over a large field of view. This can be done as a single image or performed in real time. Within this large field of view, an ROI can be placed to obtain measurements from that location (Fig 4).
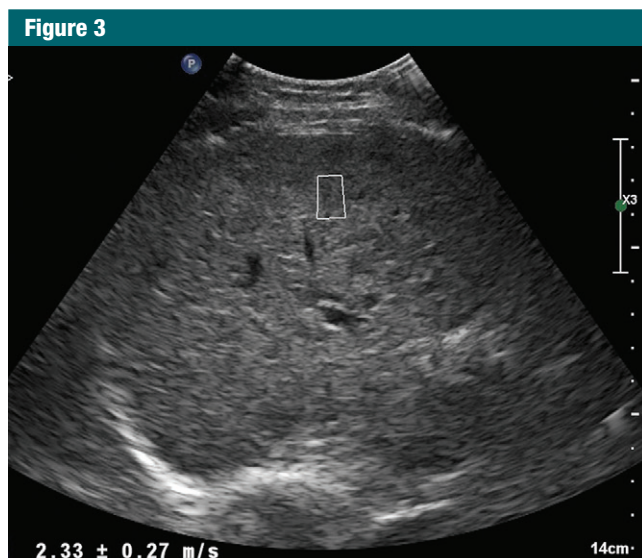
Figure 3: pSWE image in a 59-year-old woman with a history of hepatitis C. Note the white box that is the ROI where the measurement is obtained. Image demonstrates one of the 10 measurements obtained in the same location. The median stiffness measure is 2.38 m/sec, consistent with cirrhosis. Diagnosis of METAVIR stage F4 was confirmed at liver biopsy.

The mean, maximum, minimum, and standard deviation of the shear wave speed (in meters per second) or the Young modulus (in kilopascals) within the ROI are displayed. A strength of this technique is that it is performed with real-time imaging, so masses and large vessels can be avoided and areas with artifacts can be identified. It can also be used to assess multiple regions of the liver. The larger area of measurement allows for a larger ROI for the averaging of measurements. Further, real-time 2D SWE allows the operator to see the generation of the elastographic measures in a color display as they are accumulated.

MR Elastography

MR imaging systems are equipped for MR elastography via installation of a device to generate shear waves in the body, a special MR imaging sequence to image the mechanical waves, and processing software to produce color-scaled quantitative images ("elastograms") depicting tissue stiffness in units of kilopascals (Fig 5). MR elastography can be performed as an add-on sequence in an abdominal MR imaging examination or as a short MR elastography–only examination. The acquisition is performed during suspended respiration at full expiration and takes 12–15 seconds. This acquisition is typically repeated four times, for a total acquisition time of less than 1 minute. Processing to generate the elastograms occurs automatically after the acquisition. Current U.S. Food and Drug Administration–cleared versions of MR elastography use algorithms to calculate the magnitude of the complex shear modulus in kilopascals. For most tissues, shear modulus values can be compared with Young modulus values (calculated with TE) by dividing by a factor of three. The region of the liver that is typically assessed with MR elastography is the right lobe of the liver and thus represents a much larger volume of tissue than that assessed with US-based elastography methods. In addition, the algorithm provides anatomic images that correspond to each of the elastograms and "confidence images" that provide a measure of the reliability of the tissue stiffness measurement at each image location.

Variability in Noninvasive Assessments of Liver Fibrosis

As mentioned previously, the US-based modalities used to assess liver fibrosis involve varied technologies, and the measurements that they provide are not equivalent. Even systems that use similar techniques but are made by different manufacturers can have different measurement values and can provide the measurement with different standards (a measurement in meters per second, the speed of the shear wave, and the kilopascal measurement of the Young or shear modulus). This means that results from different studies are not always directly applicable in other settings. In contrast, the three U.S. Food and Drug Administration–cleared versions of MR elastography use standardized shear wave driver systems, processing algorithms, and display conventions. As a result, measurements obtained from examinations with these different MR imaging systems can be directly compared (79).

Efforts to quantify the differences between commercial systems in tissue-mimicking phantoms are being undertaken by the Ultrasound Shear Wave Speed technical committee of the Radiological Society of North America Quantitative Imaging Biomarker Alliance, or QIBA. These efforts have demonstrated that the differences in measurements between machines and observers can vary on the order of 12% (80). Clinical studies need to be performed to validate if the 12% change is clinically relevant. QIBA efforts will hopefully lead to standardization of US-based hardware and software that will allow for decreased measurement variability in the future. This has important implications if measurements are to be used to follow patients over time.

The ARFI push pulse is attenuated as it traverses the patient and reaches a point where adequate shear waves are not generated for accurate measurement. On most US systems, this occurs between 6 and 8 cm in depth. The attenuation is higher with a stiffer liver, which leads to more variable measurements in cirrhotic patients. The ARFI pulse is also attenuated in patients with more
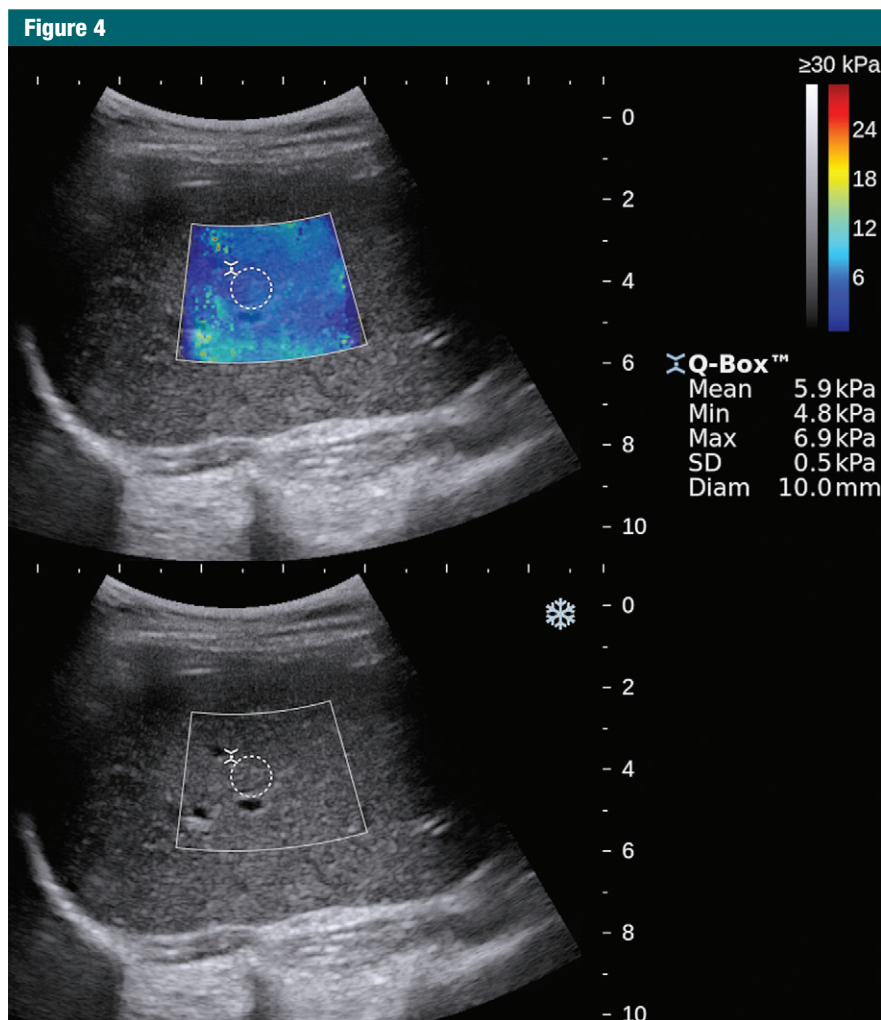
Figure 4: A 2D SWE image in a 48-year-old woman who had abnormal liver function tests at presentation. Note the split-screen image with the rectangular box, which is the field of view where shear wave measurements are obtained and color coded. The round circle is the ROI where the measurement is obtained. The system provides the maximum, median, minimum, and standard deviation of the stiffness measurements within the ROI. In this case, the mean value is 59 kPa.

subcutaneous tissue. The ARFI pulse has a sweet spot at 4–5-cm depth with most equipment. Measurements obtained in this location may have less variability (Fig 6).

In addition, as mentioned previously, there are population-specific issues that need to be addressed. There are varied predisposing factors for the development of cirrhosis and fibrosis, which vary worldwide. Thus, cutoff values for specific fibrosis stage can vary for a variety of different reasons (Table 1). Most patient-related confounding factors

increase the stiffness value; therefore, a normal value of elastography can be accepted as normal, whereas an increased value must be taken in clinical context.

Gaia et al have reported that in patients with NAFLD, the cutoffs for advanced fibrosis and cirrhosis with TE are lower than that observed in patients with chronic viral hepatitis (81). Yoneda et al have reported that TE and pSWE showed similar diagnostic performance in patients with NAFLD (82). The panel felt that there is a preponderance of evidence that fat content within the liver

does not substantially affect the degree of measured liver stiffness. However, this is an area that will require further research, since most studies have been underpowered to test for this effect.

Comparative Accuracy of Elastography Methods

TE Usefulness

Multiple studies and meta-analyses have demonstrated that liver stiffness values correlate strongly with histologic stage of fibrosis in chronic HCV (83–92). However, despite high area under the receiver operating characteristic curve (AUROC) values (cirrhosis, AUROC of 0.87–0.98 and correct classification of 85%–94%; significant fibrosis, AUROC of 0.75–0.93 and correct classification of 57%–90%), there is a substantial overlap between stages of hepatic fibrosis, particularly at the lower stages. Investigators have found similar results in HBV (93–97) and human immunodeficiency virus–HCV coinfection (86,98,99). Early studies were limited in patients with obesity. In more recent studies, investigators used probes specific for body habitus (86).

Fewer investigators have studied TE in patients with NAFLD (77,81,100–102). Early studies suggest that TE could be useful to confidently exclude severe fibrosis and cirrhosis with a high negative predictive value (around 90%) in these patients (101).TE has also been evaluated in cholestatic liver diseases (103,104) and in a variety of other chronic liver diseases (78,105–107), including alcoholic liver disease (108).

In most studies, a single cutoff value is determined for each stage of fibrosis; however, there is substantial overlap between fibrosis stages, and considering the stiffness values as a continuum may be more appropriate. For example, when liver stiffness values range from 2.5 to 7 kPa, fibrosis is likely mild or absent, whereas when values are higher than 12.5 kPa, cirrhosis is likely (76).

pSWE Techniques

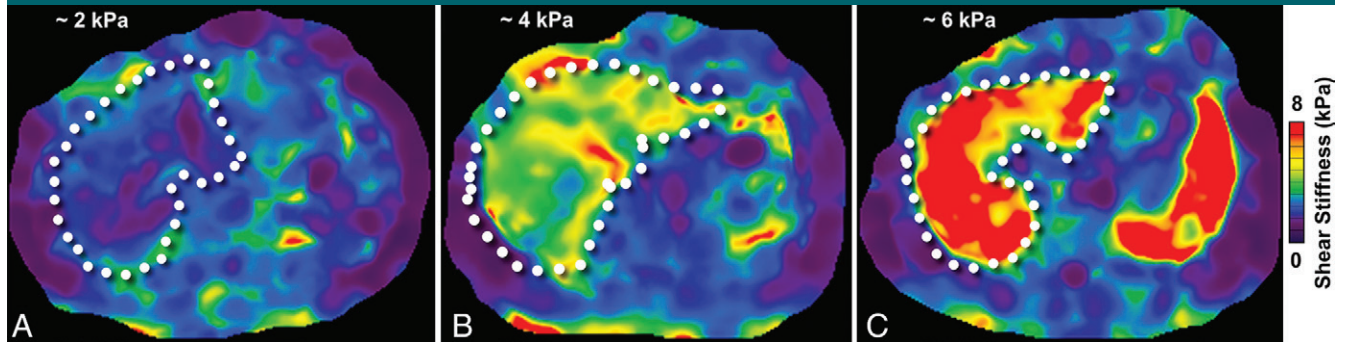Two pSWE techniques are commercially available: Virtual Touch Quantification,

Figure 5

Figure 5: MR elastograms in three patients. *A,* MR elastogram in a 63-year-old woman with a history of autoimmune hepatitis shows that the liver (outlined) has no evidence of hepatic fibrosis, with a normal stiffness value of approximately 2 kPa. *B,* MR elastogram in a 52-year-old woman with chronic cholestatic hepatitis demonstrates increased hepatic stiffness with approximately twice the normal value at 4 kPa, indicating the presence of significant hepatic fibrosis. *C,* MR elastogram in a 46-year-old man with chronic hepatitis C infection demonstrates markedly increased hepatic stiffness, averaging over 6 kPa, as is consistent with the presence of advanced hepatic fibrosis (cirrhosis).

or VTQ (Siemens Healthcare, Mountain View, Calif), and ElastPQ (Philips Healthcare, Bothell, Wash). Several investigators have shown that VTQ and ElastPQ are highly reproducible methods (109–111). In a meta-analysis that included nine studies, the optimal cutoff values were 1.34, 1.55, and 1.80 meters per second, respectively, for staging clinically significant fibrosis, severe fibrosis, and cirrhosis (38). Bota et al, in a meta-analysis that included 13 studies with 1163 patients affected by chronic liver disease, found that VTQ elastography shows a higher rate of reliable measurements and similar predictive value to that of TE for significant fibrosis and cirrhosis (62). In a series of 102 consecutive patients with chronic HCV, it has been shown that, for staging liver fibrosis, ElastPQ compares favorably with TE and that healthy volunteers show significantly lower values of both ElastPQ and TE compared with patients with nonsignificant fibrosis (109).

2D SWE

There are presently four systems clinically available from the following manufacturers: SuperSonic Imagine, Aix-en-Provence, France; Siemens Healthcare, Mountain View, Calif; Toshiba Medical Systems, Tochigi Otawara, Japan; and GE, Waukesha, Wis. Bavu et al evaluated the performance
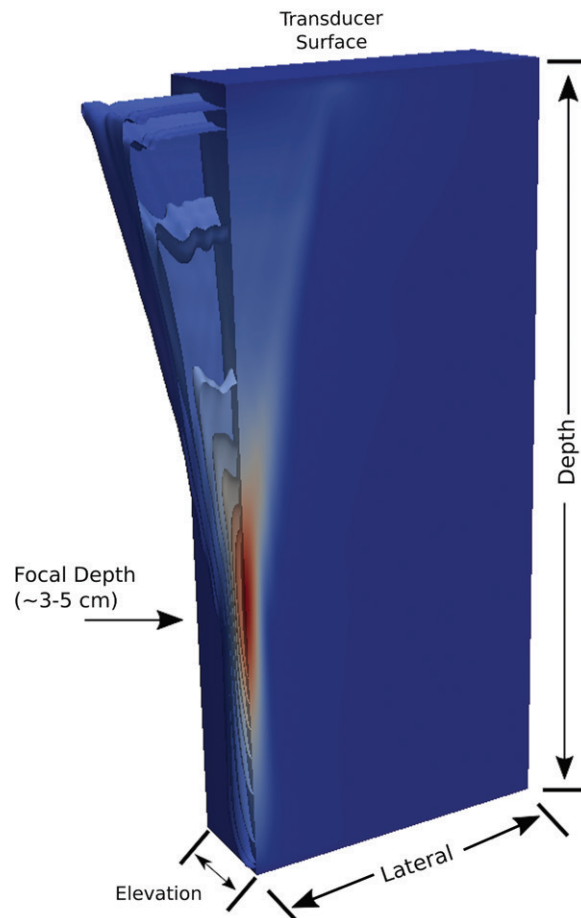
Figure 6

Figure 6: Diagram of a slice profile of an ARFI pulse. Note that the pulse has a focus usually at 3–5-cm depth.

of real-time 2D SWE and TE in 113 patients with chronic HCV and found that 2D SWE showed a higher accuracy in the assessment of mild and intermediate stages of fibrosis in hepatitis C (112). In a study of 2D SWE and TE (36), liver stiffness values were linearly correlated with the degree of liver fibrosis with both 2D SWE and TE, but 2D SWE was more accurate than TE in the assessment of significant fibrosis (fibrosis stage ≥ 2). In a study in which the diagnostic performance of 2D SWE, VTQ, and TE were compared, 2D SWE had higher accuracy than TE for the diagnosis of severe fibrosis (P = .002) and higher accuracy than VTQ for the diagnosis of clinically significant fibrosis (63). One potential limitation of studies in which TE is compared to SWE is absence of the "XL" probe with the TE device, particularly in earlier studies, which allows for better measurements in obese patients.

MR Elastography

Multiple studies have shown strong correlation between MR elastography–measured hepatic stiffness and the stage of hepatic fibrosis at histologic examination (30). An MR elastography–based measurement of hepatic stiffness that is in the normal range (<2.5 kPa) has a very high negative predictive value for hepatic fibrosis of any stage. In one meta-analysis, investigators concluded that the sensitivity, specificity, and AUROC of

MR elastography for the diagnosis of advanced hepatic fibrosis and cirrhosis (≥F3) from less-advanced disease are 92%, 96%, and 0.98, respectively (31). These metrics are probably at the limit of what is realistic to achieve, given the previously mentioned limitations of using biopsy as a reference standard. Another pooled meta-analysis of 12 published studies (113) that encompassed 697 patients found that the sensitivity, specificity, and AUROC diagnostic performance for diagnosis of stage F3 fibrosis and higher were 85%, 85%, and 0.93, respectively.

Several investigators have compared the diagnostic performance of MR elastography and TE. In a study of 141 patients, the AUROC values for TE were found to be 0.80 for fibrosis stage of at least F1, 0.84 for fibrosis stage of at least F2, 0.91 for fibrosis stage of at least F3, and 0.99 for F4, while with MR elastography, the AUROC values were 0.96 for fibrosis stage of at least F1, 0.99 for fibrosis stage of at least F2, 0.99 for fibrosis stage of at least F3, and 0.99 for F4 (32). The technical failure rate was 16% for TE and 6% for MR elastography. A comparative study being completed at the Mayo Clinic has shown the following preliminary results in a series of 113 patients: For TE and MR elastography, respectively, the AUROC values for the detection of clinically significant fibrosis (fibrosis stage ≥ 2) were 0.79 and 0.90, respectively (114). Technical failure rates were similar.

Nonetheless, in spite of clear performance advantages, the cost and accessibility of MR elastography are considerations.

Consensus Statement: Best Practices for Elastography for Diffuse Liver Disease

It was the consensus of the panel that a stepwise approach to the diagnosis of liver fibrosis would be helpful. Patients with decompensated cirrhosis can receive diagnoses clinically. In patients without overt decompensated cirrhosis, an assessment with elastography can be helpful. Elastography can be performed with either a US-based technique or MR elastography. The panel believed the literature suggests that TE and ARFI (pSWE and 2D SWE) techniques are at least equivalent, with a few investigators suggesting that ARFI techniques may be more accurate (36,62,63,64). Patients can then be grouped into three categories (Table 5): those with normal elastography values who have a low likelihood of cirrhosis (stage F0 or F1) and may not require additional follow-up, those with high elastography values who have a high likelihood of cirrhosis, and those in between who have moderate to severe fibrosis (stages F2 and F3) and are at risk for progression of the fibrosis, depending on the origin of the fibrosis.

On the basis of discussion herein, it is the recommendation of the consensus panel to interpret results by using

Table 5

Consensus of Suggested Thresholds in Patients with Hepatitis C

Device	No Clinically Significant Fibrosis: METAVIR Stage ≤ F2, Unlikely to Need Follow-up	Advanced Fibrosis and/or Cirrhosis: METAVIR Stage of F4 and Some Stages of F3—Clinically Significant Fibrosis	References
TE FibroScan (Echosens)	<7 kPa (1.5 m/sec)	>15 kPa (2.2 m/sec)	42,91,92,95,64,115–117
Siemens pSWE	1.2 m/sec (Siemens suggests <1.34 m/sec, <5.6 kPa)	>2.2 m/sec (>15 kPa)	38,91,45
Philips pSWE	<5.7 kPa (1.37 m/sec)	>2.2 m/sec (>15 kPa)	109
2D SWE (SuperSonic Imagine)	<7 kPa (1.5 m/sec)	>2.2 m/sec (>15 kPa)	36
MR elastography (GE, Siemens, Philips)	<3.0 kPa* (27–30)	>5.0 kPa*	29–32

Note.—The location for Echosens is Paris, France.

* MR elastography is reported as shear modulus, while US elastography techniques are reported in Young modulus. The Young modulus is three times the shear modulus.

two cutoff values: one to select patients that are at low risk for clinically significant fibrosis who would not require additional follow-up and another cutoff value to select patients at high risk for advanced fibrosis or cirrhosis (some F3 and F4) who require different management and prioritization for therapy. Between these two cutoff values, there is substantial overlap of fibrosis stages (Fig 7), and it may be that likelihood ratios will be a better tool for documenting risk. Additional tests (blood tests, liver biopsy, or MR elastography) and clinical evaluation will be needed to determine appropriate follow-up when values are in the indeterminate range. The suggested thresholds for elastography measurements of liver stiffness in hepatitis C on the basis of published literature for each manufacturer are presented in Table E1 (online).

Report Elements

The report for US-based elastography should provide the median value, as well as the IQR/median value as a measure of quality. The report should indicate whether these patients are at minimal risk of having clinically significant fibrosis (stage F0 or F1, no follow-up required), moderate risk of having clinically

significant fibrosis (stage F2 and some F3, additional testing appropriate), or high risk of having clinically significant fibrosis (some stage F3 and F4, follow-up advised). To allow for improved reproducibility of serial measurements, the patient position and equipment used (both machine manufacturer and transducer frequency) should be reported, so that similar equipment and technique are used in subsequent studies.

Future Research Questions

Basic Questions

1. What are the sources of variability between commercial SWE systems? In particular, how does the frequency component affect measures of stiffness?

2. Are 10 measurements in one location necessary when good-quality measures of stiffness are obtained? Are existing methods (IQR/median values) optimal for determining the values to report?

3. Should we measure in more than one location?

4. What are appropriate tissue-mimicking phantom materials for the liver?

Clinical Questions

1. What thresholds should be used to optimize patient care with respect to different causes of cirrhosis and different patient populations? How can these be combined with other non-invasive techniques to optimize patient care?

2. Can fibrosis be distinguished from other forms of disease that increase shear wave speed, such as congestive liver disease or hepatitis?

3. How can US elastography complement hepatic venous pressure measurements in the assessment of portal hypertension and in the assessment of changes in portal venous pressure in patients with liver disease?

4. Inflammation is an important process to document in the evolution of liver disease. Histologic assessment of biopsy specimens can only be used to identify the cellular component of inflammation and is essentially blind to the fluid component. Quantitative elastography, in contrast, seems to be sensitive to the effects of the fluid component of inflammation. How can this capability be exploited for diagnostic purposes?

5. Can we use elastography and measures of loss modulus to differentiate nonalcoholic steatohepatitis from simple steatosis?

Follow-up of Patients

1. What is a minimal clinically important difference in stiffness measurements over time? How often should these measures be obtained?

2. How should the use of elastography change the screening interval in patients at risk for HCC?

3. Focal lesions can lead to erroneous results. What changes will be needed to mitigate problems with anisotropic and heterogeneous tissues?

Conclusions

The literature indicates that elastography techniques can be used to distinguish patients with no or minimal (METAVIR stages F0 and F1) fibrosis
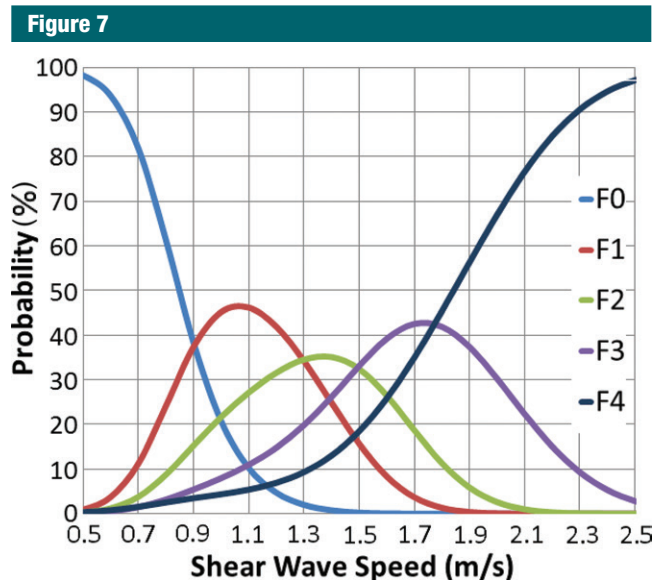

Figure 7: Graph of shear wave stiffness measurements for METAVIR stages based on the meta-analysis (38) in which median and IQR data were used.

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and differentiate them from those with severe fibrosis or cirrhosis (METAVIR stages F3 and F4), with no need for biopsy in these groups unless there are other factors that would lead to biopsy, such as risk of acute flares in chronic hepatitis that would not be appropriately assessed noninvasively. A middle group between these cutoff values requires additional data to determine follow-up. A consensus of best practices is presented. Additional research is needed in the areas of population differences, disease differences, spleen measurement, steatosis, and incidence of HCC related to liver fibrosis grade.

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