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LIVER (B BACON, SECTION EDITOR)

Utilization of FibroScan in Clinical Practice

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Abstract The evaluation of liver fibrosis is critical, particularly to rule out cirrhosis. Novel non-invasive tests such as transient ultrasound elastography are widely used to stage liver fibrosis as an alternative to liver biopsy, and this technology has recently been approved in the US. In this review, we discuss the performance characteristics of elastography for a variety of liver diseases and highlight practical appropriate suggestions for how to incorporate this technology into clinical practice.

Keywords Liver fibrosis · Cirrhosis · Viral hepatitis · Liver stiffness · Ultrasound elastography

Introduction

The search for a noninvasive method to assess liver fibrosis has encouraged the development of a number of new approaches. Recently, the FDA has vibration controlled transient elastography (VCTE) approved transient elastography measurement of shear velocity as a test for the evaluation of liver disease. This review will evaluate the clinical data on the efficacy of transient elastography to stage liver fibrosis.

Liver biopsy, the gold standard for assessment of liver fibrosis, is invasive and expensive and the accuracy is sometimes questionable due to sampling variations, inadequate specimen size, and observer variability [1].

The limitations of biopsy and patient and physician preferences have led to extensive evaluation of non-invasive tests to stage liver fibrosis. The perfect non-invasive marker of liver fibrosis should be liver-specific, easy to perform, reproducible, accurate, and inexpensive. In addition, it should both stage liver fibrosis and also monitor disease progression and treatment efficacy [2].

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The Principle of Vibration Controlled Transient Elastography

A vibration of mild amplitude and low frequency (50 Hz) is transmitted through the intercostal space using a vibrator at the skin surface. The vibration induces an elastic shear wave that propagates through the hepatic tissue. Using pulse echo ultrasound acquisition, the velocity of the shear wave can be determined. This shear wave velocity is directly related to tissue stiffness; the harder the tissue, the faster the shear wave propagates. The liver stiffness is calculated from velocity and expressed in kilopascal (kPa) [3].

Probes and Equipment: Making an Accurate Measurement of Liver Stiffness

The feasibility and accuracy of liver stiffness measurement (LSM) using the FibroScan device are heavily influenced by anthropometric factors. Numerous studies have shown that obesity and other associated factors (e.g., thoracic fold thickness, waist circumference, and the distance between the skin and liver capsule) are important determinants of FibroScan failure and unreliable results, which occur in approximately 5 and 15 % of patients, respectively. Moreover, subcutaneous adipose tissue may lead to overestimation of liver stiffness [4••, 5]. As a result, a novel FibroScan probe (the 'XL' probe) is approved for use in obese patients. This probe has a greater vibration amplitude and measurement depth compared with the standard M probe. The XL probe allows for accurate

measurement of LSM in a significantly greater number of obese patients than the M (9-mm probe) probe [6, 7, 8•]. Also, in smaller adults, the standard FibroScan M probe (with a 9-mm tip diameter) may inaccurately assess liver stiffness because the narrow intercostal spaces in these patients may make it difficult to obtain an unobstructed window for LSM. Thus, a smaller probe, the S2 probe, has been developed for pediatric use and, in a recent published trial by Prahda et al. [9], the S2 and M probes were comparable with respect to reliability and accuracy of stiffness measurements. However, the S2 probe may overestimate liver stiffness in some patients, particularly those with a larger distance between the skin and liver capsule, and should be reserved for smaller, lean patients or children.

A reliable scan has an inter quartile range (IQR) of less than 30 %, at least 10 measurements with a 70 % success rate and no major clinical confounding variables that could lead to an inaccurate liver stiffness measurement. Important factors that can falsely elevate liver stiffness are shown in Fig. 1 and include acute inflammation, right heart failure with hepatic congestion, and cholestasis [10–13]. Also, when measuring stiffness, there can be minor but potentially significant changes with moderate hepatic inflammation and post-prandially, all of which should be considered in individual patients. We recommend that a correction is made for ALT > 100 IU in chronic hepatitis and for scans performed within 2 h of a meal [14•].

Since fat affects the propagation of the ultrasound wave, the FibroScan can also be used to estimate liver fat content. This novel parameter, named Controlled Attenuation Parameter (CAP), measures the ultrasound attenuation at the center frequency of the FibroScan M probe. In a preliminary retrospective study [15••], CAP assessment in 112 patients with chronic liver disease from various etiologies has shown good performances for the detection and semiquantification for steatosis, and will be further discussed in the section on non-alchoholic fatty liver disease (NAFLD).

Hepatitis B and C

The current guidelines for HBV recommend that treatment is based on ALT elevation, HBV DNA levels, and, where indicated, liver histology [16]. Histologically, both liver inflammation and fibrosis are an indication for treatment particularly in E-negative patients over the age of 50 with normal ALT levels in whom 30 % may have significant injury [17].

The first study on HBV was published by Cardoso et al. [18], where 202 consecutive patients with chronic hepatitis B admitted for liver biopsy were enrolled from five different French hospitals. Liver stiffness measurement was performed with Fibroscan. All biopsy specimens were analyzed by two experienced pathologists who were blinded to the results of LSM and clinical data.

This prospective study showed that transient elastography is an efficient technique for the assessment of fibrosis in patients with chronic hepatitis B. LSM was well correlated with the histological METAVIR and Ishak scores, and discriminated between patients with METAVIR F0–F1 versus F2–F4 (ROC curves 0.81, 0.73–0.86) and even better for

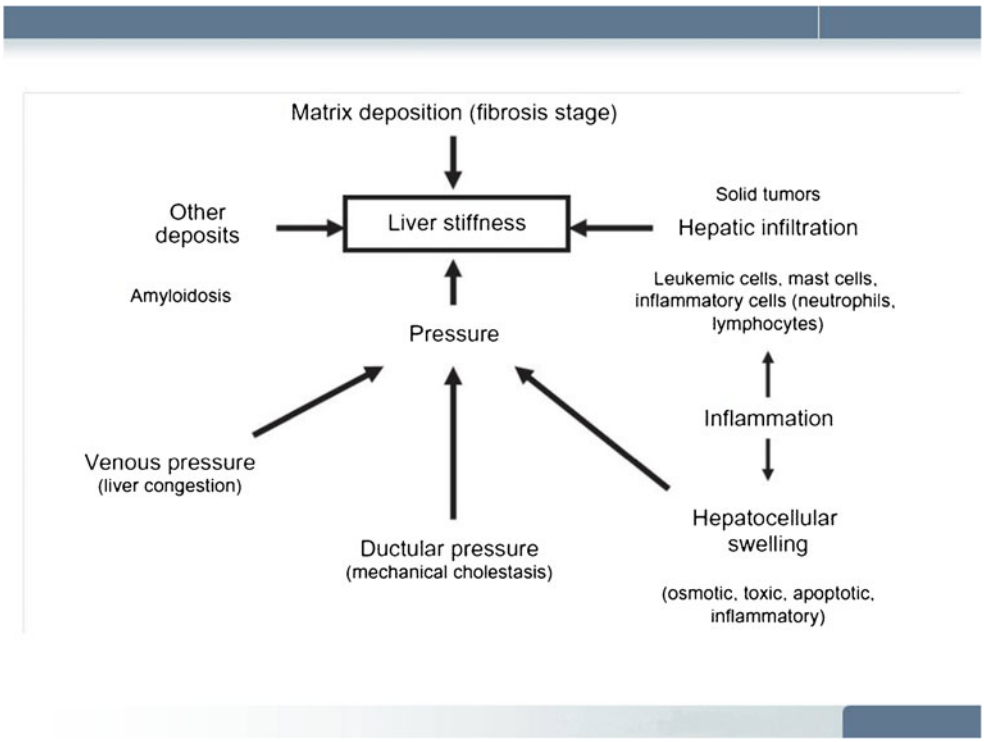

Fig. 1 Factors affecting liver stiffness

patients with F0–F2 versus F3–F4 (ROC curves 0.93, 0.82–0.98).

This study also showed that the performance of LSM in predicting liver fibrosis stage in patients with chronic hepatitis B is comparable to that observed in patients with chronic hepatitis C (studies published by Ziol et al.). The ROC curves were 0.82 for F0–F1 versus F2–F4 and 0.90 for F0–F2 versus F3–F4. LSM was very accurate for the diagnosis of bridging fibrosis or cirrhosis (90 %).

These results suggest that elastography accurately reflects the amount of fibrosis, with the obvious limitation of an inability to diagnose the grade of necroinflammatory activity, which is of importance in decision making for HBV treatment. We can recommend elastography as an effective tool for staging liver fibrosis in HBV, but biopsy may still be necessary to evaluate hepatic inflammation. In particular, in patients with normal ALT and low HBV DNA levels, liver stiffness can be extremely useful to rule out fibrosis.

Ziol et al., in 2005 [19], published the first multicenter prospective study of 327 consecutive patients with HCV who also underwent liver biopsy. Inclusion criteria were the presence of HCV RNA in serum and at least transiently elevated serum alanine aminotransferase levels. Patients with ascites were excluded from the study. LSM was performed within 6 months of the liver biopsy. These investigators generated cutoff values with greater accuracy for higher stages of fibrosis and a relatively narrow range of total values; cutoff values for F $\geq$2 (6.6 kPa), F $\geq$3 (10.3 kPa), and F4 (14.6 kPa).

Several US studies have confirmed these findings particularly for cirrhosis. Gara et al. [20] from the National Institutes of Health confirmed that transient elastography can be used to diagnose cirrhosis reliably and accurately in HCV patients. Perhaps the most important finding is that, with a cutoff value of 13 kPa, there was a negative predictive value of 1.0 for the diagnosis of cirrhosis. Interestingly, the specificity at 0.89 resulted in a positive predictive value of 0.58, but 7 of 10 patients with increased liver stiffness consistent with cirrhosis, but a noncirrhotic biopsy result also had other clinical and radiologic features of cirrhosis, suggesting that the liver biopsy may have understaged the disease. Malik et al., in a larger series [21] including cirrhosis from all causes, confirmed the excellent correlation of liver stiffness with cirrhosis. In this study, 124 patients were included with cirrhosis and yielded a negative predictive value of 0.9 with an optimum cutoff for transient elastography of 12 kPa. Interestingly, in patients with Child's Pugh A status and no clinical, biochemical, or radiologic features of cirrhosis, Fibroscan was highly diagnostic for clinically occult cirrhosis. In our practice, we use liver stiffness of 12–15 KPa as high probability of cirrhosis and >15 KPa as definite cirrhosis.

The interaction of liver stiffness in patients with increased necroinflammatory activity has been evaluated in HCV. In a recent study, Tapper et al. [14•] studied a large cohort of patients with F0–F2 fibrosis and showed that inflammation significantly increased the odds of receiving a liver stiffness score indicative of more advanced fibrosis and cirrhosis. In patients with F0–F2 fibrosis who were diagnosed as cirrhotic on TE, 40–50 % of patients had grade 3 histologic inflammation and 18.8–28.1 % of patients had an ALT level >120 IU/L. The authors concluded that an increase in levels of necroinflammation is positively correlated with liver stiffness even at the lowest strata of fibrosis (F0–F2) in patients with chronic inflammation.

Overall liver stiffness is an accurate modality for staging liver fibrosis in viral hepatitis and in particular for excluding the presence of cirrhosis. Since this is a very important endpoint in the evaluation of HCV and HBV patients, we would recommend a LSM in all patients with chronic viral hepatitis at baseline. An algorithm for the use of LSM in the evaluation and screening of patients with HCV has been proposed by Bonder et al. [22].

HCV-HIV Co-Infected Patients

During recent years, the natural history of HIV-related diseases has changed, and chronic liver disease and HCV coinfection have become an important and growing cause of morbidity and mortality in HIV-infected patients [23]. Cohort studies have shown that the progression of liver fibrosis to cirrhosis is faster in HIV co-infected patients than in HCV mono-infected patients [24].

Sanchez-Conde et al.] in 2010, [25], published a prospective study of 100 patients with documented HIV/HCV coinfection undergoing liver biopsy and TE. Based on the AUROC curves, three cutoff values were chosen to identify F 1 (<7 kPa), F3 (>11 kPa), and F4 (>14 kPa). Using these best cutoff scores, the NPV to exclude F2 was 81.1 % and the PPV to confirm F2 was 70.2 %. Likewise, the NPV to exclude F3 was 96.3 %, and the PPV to confirm F 3 was 60.0 %. Finally, the NPV to exclude F4 was 100 %, and the PPV to confirm F4 was 57.1 %. This study confirmed TE as an efficient technique for the exclusion of advanced liver fibrosis and cirrhosis.

Both the cutoff values and the accuracy of TE for the diagnosis of advanced fibrosis and cirrhosis found are within the ranges published for HCV-monoinfected patients and HIV/HCV-coinfected patients.

Cholestatic Liver Disease

Transient elastography has also been studied for the evaluation of fibrosis and histological stages in chronic cholestatic diseases. Corpechot et al. [26] studied 101 patients, 73 patients with PBC and 28 with PSC. Areas under curves (95 % CI)

were 0.88 (0.81-0.95), 0.91 (0.85-0.97), and 0.96 (0.93-1.00) for fibrosis stage 2, 3 and 4, respectively, and 0.92 (0.87-0.98), 0.95 (0.91-0.99), and 0.96 (0.93- 1.00) for fibrosis stage >2, >3 and = 4, respectively. Optimal cutoff values were 7.1 kPa, 11.1 kPa, and 17.3 kPa for histological stage > 2, > 3, and = 4, respectively, and 7.3 kPa, 9.8 kPa, and 17.3 kPa for fibrosis stage >2, >3 and = 4 respectively.

There was a significant positive relationship between liver stiffness values and histological and fibrosis stages on liver biopsy. The diagnostic performance of the test was similar to, or even better than, that previously reported in patients with chronic hepatitis C but the cutoff levels particularly for cirrhosis were higher than those reported for viral hepatitis. Despite the relatively small number of patients, results suggest that transient elastography is an efficient and simple method for assessing biliary fibrosis in patients with chronic cholestatic diseases.

Non Alcoholic Fatty Liver Disease

About 70 million individuals in the US over the age of 18 have steatosis, accounting for 20 % of all new office visits being related to NAFLD [27]. Cross-sectional and longitudinal studies in HCV confirm the importance of steatosis as a variable associated with more rapid progression of fibrosis and worse SVR rates secondary to interferon-based treatments [28]. Therefore, the diagnosis of steatosis and its quantification is also useful in HCV patients.

In an initial study of 112 patients by de Ledinghen et al. [29], AUROCs of liver stiffness in patients with NAFLD and HCV as measurements for the diagnosis of liver fibrosis were 0.79 (0.71–0.88) for F2F3F4, 0.89 (0.83–0.95) for F3F4 and 0.96 (0.92–1.0) for F4. Seventy-one patients had CAP measurement and ultrasonography within 1 month to evaluate the degree of steatosis. Steatosis was graded as follows S1 < 10 %, S1 11 = 33 %, S2 34 = 66 %, S3 > 67 %. For the diagnosis of steatosis grade S1, the performance of CAP (maximum accuracy cutoff) was significantly better than ultrasonography (P=0.003): sensitivity 0.91 versus 0.59, specificity 0.79 versus 0.90, positive predictive value (PPV) 0.78 versus 0.83, negative predictive value (NPV) 0.91 versus 0.73, and accuracy 0.85 versus 0.76, respectively. For the diagnosis of steatosis grade S2, the performance of CAP (maximum accuracy cutoff) was significantly better than ultrasonography (P=0.001): sensitivity 0.86 versus 0.68, specificity 0.86 versus 0.84, PPV 0.73 versus 0.65, NPV 0.93 versus 0.85, and accuracy 0.86 versus 0.79, respectively. For the diagnosis of steatosis grade S3, the performance of CAP (maximum accuracy cutoff) was significantly better than ultrasonography (P=0.002): sensitivity 0.67 versus 0.92, specificity 0.97 versus 0.80, PPV 0.80 versus 0.48, NPV 0.93 versus 0.98, and accuracy 0.92 versus 0.82, respectively.

In conclusion, CAP can be used for steatosis detection and semi-quantification and can be performed at the same time as the liver stiffness measurement, making possible the simultaneous evaluation of both fibrosis and steatosis. CAP is not yet FDA-approved for use in the United States but is undergoing clinical evaluation in NAFLD and HCV patients.

Because of the increasing prevalence of childhood obesity, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in children in industrialized countries, with a natural history similar to that seen in adults.

Alkhouri et al. [30] studied 67 consecutive children with biopsy-proven NAFLD (46 male subjects and 21 female subjects), age range from 5.5 to 11.3 years. A TE score less than 8.6 kPa provided a 100 % (23/23) accurate prediction of early liver fibrosis (F0–F1) indicating no need for liver biopsy; while a TE score >8.6 kPa, predicts significant fibrosis (F2–F3) with a 100 % accuracy which can aid the clinician in deciding whether a liver biopsy is warranted.

Portal Hypertension

The prognosis and management of chronic liver diseases strongly depend on the presence of portal hypertension and its complications. Hepatic venous pressure gradient (HVPG) has been shown to be a prognostic marker for variceal bleeding, risk of liver decompensation, liver failure after surgery, and death.

Bureau et al. [31] evaluated the correlation between liver stiffness and an increase in portal pressure. The optimal cutoff value was found to be 21 kPa (this correlates with HVPG of >10 mmHg) with an accurate prediction of significant portal hypertension in 92 % of the 144 patients for whom LS was successful. LS is highly correlated with HVPG and accurately predicts the presence of significant portal hypertension in patients with chronic liver disease. In this study, liver diseases from different causes were included even though most patients had chronic alcoholic or chronic viral liver disease.

Fibroscan has also been used for the prediction of esophageal varices, Kazemi et al. [32] evaluated 175 consecutive patients with cirrhosis who were undergoing endoscopy for variceal screening. A variety of liver diseases were included in the study: HCV in 98 patients, alcohol in 37, hepatitis B in 17, hemochromatosis in 5, non-alcoholic steatohepatitis in 5, and cryptogenic in 3. The primary objective of the study was the diagnosis by LSM of “presence of esophageal varices” compared to “absence of varices”. Area under the ROC curve was 0.84 (95 % CI: 0.78–0.90). The cutoff value defined by higher total of sensitivity and specificity was 19.0 kPa. The overall sensitivity and specificity for a cutoff of 13.9 were 95 and 92 %, respectively. In a US study, Pritchett et al. [33] determined if there was an optimal cutoff of liver stiffness that

Table 1 Recommended values for different stage of fibrosis

Disease	F0–F1 (Kpa)	F2 (Kpa)	F3 (kpa)	F4 (kpa)
Hepatitis B	≤6.0	≥6.0	≥9.0	≥12.0
Hepatitis C	≤7.0	≥7.0	≥9.5	≥12.0
HCV–HIV coinfection	≤7.0	≤10	≥11.0	≥14.0
Cholestatic liver disease	≤7.0	≥7.5	≥10.0	≥17.0
NAFLD/NASH	≤7.0	≥7.5	≤10	≥14.0

could predict the presence of large (grade 2 or 3) esophageal varices and whether this was disease-specific. A total of 222 patients with all cause cirrhosis (Child class A) were screened and 211 had successful elastography, while 132 had no or small grade 1 varices and 79 had large varices. Liver stiffness of 19.8 kPA had a negative predictive value of 91 % and a positive predictive value of 55 % with an AUROC of 0.73 in differentiating between small and large varices. Seven patients with large varices would have been incorrectly classified. In the 157 patients with hepatitis C as the etiology of cirrhosis, the negative predictive value was 98 % and only 1 patient was misclassified. Liver stiffness was superior in diagnostic accuracy to platelet count in all patients. A liver stiffness of >19.8kPa could be utilized as a cutoff for endoscopy and beta blocker utilization, particularly in patients with hepatitis C.

We would recommend that all patients with a liver stiffness in the cirrhosis range (>15 kPA) be screened for varices and that in those with stiffness >20 kPa a beta blocker be started while patients are waiting for endoscopy.

Liver Stiffness and Clinical Outcomes

Klibansky et al. [34••] evaluated 667 patients with chronic liver disease of various etiologies and followed them for 3 years to see if any patients developed liver failure, liver cancer, death, or transplantation. In this study, 8.1 % of patients with chronic liver disease experienced a clinical event and using a cutoff of 10.5 kPa, TE demonstrated a sensitivity of 0.947 and a negative predictive value of 0.992 of developing a complication.

Liver stiffness has also been used in the prediction of outcomes for patients with HCC undergoing liver resection. This study by Cescon et al. [35] showed that perioperative liver failure (PLF) occurred in 26 patients (28.9 %). Patients with LS value higher than or equal to 15.7 kPa were at higher risk of PLF while those with LS value lower than 14.8 kPa had no liver failure after surgery. LS values higher than 12.6 kPa and higher than 19.6 kPa were correlated with the presence of cirrhosis (AUC = 0.880; $P<0.001$) and of PH (AUC = 0.786; $P<0.001$), respectively.

Singh et al. [36], in a recent meta-analysis, reviewed 17 prospective cohort studies on 7,058 patients with cirrhosis, and showed that non-invasive measurement of liver stiffness may be a useful tool for identifying patients at risk for progression to clinical events. The meta-analysis confirmed that LSM was an independent marker of severity of liver disease and hepatic synthetic function and was able to predict future risk of hepatic decompensation, HCC, and overall mortality. Each unit of LSM is associated with an incremental 7 and 11 % increased risk of decompensation and HCC, respectively.

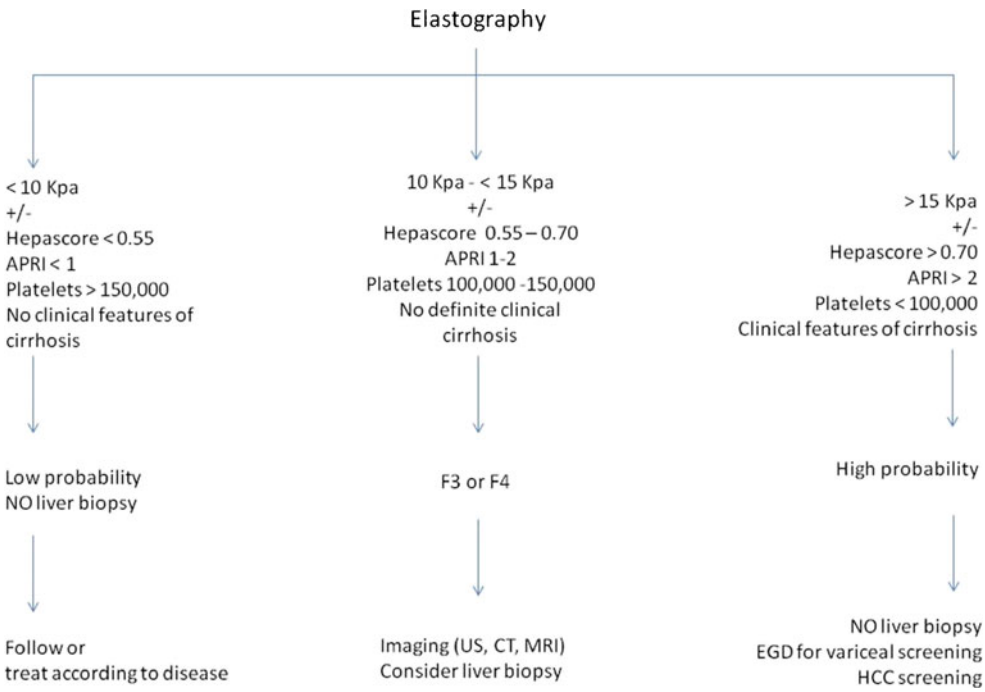

Fig. 2 Clinical algorithm for exclusion of cirrhosis

Putting it all Together; How to use Transient Elastography in Clinical Practice

Currently, we utilize FibroScan elastography extensively as a point of contact test in our liver clinics. We recommend a baseline elastography in all patients at the initial visit to establish the baseline stiffness for each patient and to assist in management decisions. Table 1 illustrates the ranges we use for approximate disease staging which are based on over 3,000 scans performed at BIDMC. The key clinical parameter in patient management is the diagnosis or exclusion of advanced fibrosis (F3) and cirrhosis. The FibroScan is an adjunct to clinical, radiological, and biochemical evaluation and we do not merely use it to replace liver biopsy. When elastography does not correlate well with clinical findings, we use serological tests such as APRI, Hepascore [37], and FibroSure/FibroTest and will also consider liver biopsy. A scheme for the management algorithm we suggest is shown in Fig. 2. Utilizing this approach, we have reduced the number of staging liver biopsies we perform by 65 %. We also utilize elastography to follow patients over time with a suggested frequency of scans at least every 2 years but not more than annually. Increases in liver stiffness by more than 30 % or up 2 stages will prompt a re-evaluation of the patient for cirrhosis.

In summary, transient elastography is a new adjunctive test for the evaluation of liver stiffness and fibrosis in US patients and is a useful addition to the diagnostic armamentarium of the practicing clinician.

Conclusions

We recommend staging and monitoring of liver fibrosis be individualized. Elastography provides a non-invasive and reproducible tool which can be easily utilized for patient care as an adjunct to clinical evaluation for the staging of liver fibrosis. Continued ongoing longitudinal studies will further define the optimal use of elastography in managing patients with chronic liver disease.

Compliance with Ethics Guidelines

Conflict of Interest Nezam Afdhal has received research support from Merck, Glaxo Smith Kline, Vertex, Gilead, Abbott and BMS. Nezam Afdhal is a consultant/advisory board member for Merck, Gilead, Echosens, Glaxo Smith Kline, Vertex, Novartis, Boehringer Ingelheim, Ligand, Springbank, Medgenics and Kadmon. Afdhal has stock options in Springbank and Medgenics, and is Editor for the Journal of Viral Hepatitis. Alan Bonder has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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