



Elastography for Longitudinal Assessment of Liver Fibrosis after Antiviral Therapy: A Review

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Abstract

Chronic hepatitis B or C viral infection is a common cause of liver cirrhosis and hepatocellular carcinoma. Fibrosis regression can be achieved after long-term antiviral therapy (AVT). Monitoring of dynamic changes in liver fibrosis after treatment is essential for establishing prognosis and formulation of a follow-up surveillance program. Routine surveillance of fibrosis after AVT by liver biopsy, the gold standard for fibrosis assessment, is hindered by its invasive nature, sampling error and observer variability. Elastography is a noninvasive quantitative alternative that has been widely used and validated for the staging of liver fibrosis prior to treatment. Recently, increasing research interest has been focused on the role of elastography in longitudinal assessment of liver fibrosis after AVT. In this review, the basic principles, acquisition techniques, diagnostic performances, and strengths and limitations of ultrasound elastography and magnetic resonance elastography are presented. Emerging evidence regarding the use of elastography techniques for the monitoring of liver fibrosis after AVT is summarized. Current challenges and future directions are also discussed, designed to optimize the application of these techniques in clinical practice.

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Introduction

Liver fibrosis is a progressive disease that can evolve into cirrhosis, ultimately resulting in liver failure or the development of hepatocellular carcinoma.^{1,2} The main etiologies of liver fibrosis include chronic hepatitis B or C (CHB or CHC) viral infection, alcoholic steatohepatitis, nonalcoholic steato-

hepatitis, and autoimmune and biliary diseases.³ Increasing evidence indicates that liver fibrosis, even at the cirrhotic stage, is reversible if the major liver diseases and stimulus of liver injury are eliminated.^{4,5} This has been shown in both CHB and CHC populations who underwent long-term antiviral therapy (AVT) with virus suppression or clearance,⁶⁻⁹ and in nonalcoholic steatohepatitis patients after lifestyle changes, predominantly loss of weight.¹⁰ The beneficial effects, particularly of cirrhosis regression, can partly reduce the increased risk of liver-related events, yet, notably, may not eliminate the high risk of hepatocellular carcinoma development.^{9,11} Hence, monitoring of liver fibrosis status after treatment is of clinical significance for establishing prognosis and formulating a follow-up surveillance program.

To date, liver biopsy has been the gold standard for fibrosis assessment. However, routine assessment and surveillance of fibrosis after treatment by liver biopsy are hampered by its invasive nature, sampling error, and observer variability.^{12,13} Therefore, noninvasive alternatives to liver biopsy are being developed, such as serum markers and imaging examinations, among which elastography has emerged as the leading candidate in clinical development. Quantitative elastography modalities include ultrasound (US) elastography and magnetic resonance elastography (MRE); the US elastography can be further divided into vibration controlled transient elastography (VCTE), point shear-wave elastography (pSWE) and two-dimensional shear-wave elastography (2D SWE).^{14,15} Assessment of fibrosis stage prior to treatment by elastography techniques has been a common practice in the clinic setting. More recently, increasing research attention has been put on the role of elastography in longitudinal assessment of liver fibrosis in patients who underwent AVT.

Here, the authors review the current knowledge on US elastography and MRE in terms of their basic principles, acquisition techniques, diagnostic performances, and strengths and weaknesses, highlighting the utility of elastography techniques in monitoring of liver fibrosis among CHB and CHC populations who received AVT and discussing current challenges and future directions to explore the optimization of elastography techniques in practice.

Basic concepts of elastography

Elastography provides a quantitative method to assess liver stiffness, which is a mechanical property of tissue related to the degree of liver fibrosis. In general, liver stiffness values increase with higher fibrosis stages.¹⁶ Hence, liver stiffness is regarded as an "indirect" marker of fibrosis. Notably, despite hepatic fibrosis being the predominant element influencing stiffness of the liver, there are numerous factors that may

Keywords: Liver fibrosis; Elastography; Chronic hepatitis B; Chronic hepatitis C; Antiviral therapy.

Abbreviations: ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; AUCs, area under curves; AVT, antiviral therapy; CHB, chronic hepatitis B; CHC, chronic hepatitis C; FIB-4, fibrosis-4 score; GRE, gradient-recalled echo-based; ICC, intraclass correlation coefficient; LSM, liver stiffness measurement; MR, magnetic resonance; MRE, magnetic resonance elastography; pSWE, point shear-wave elastography; ROI, region of interest; SE-EPI, spin-echo-based echo-planar imaging; SVR, sustained virological response; 2D SWE, two-dimensional shear-wave elastography; US, ultrasound; VCTE, vibration controlled transient elastography.

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exert an impact on liver stiffness, e.g. inflammation, blood flow, and portal pressure.¹⁷ Therefore, interpretation of liver stiffness measurement (LSM) should take into account potential confounding factors. A comparison of quantitative elastography techniques is presented in Table 1.

Ultrasound elastography

VCTE

Principles

One-dimensional VCTE (Fibroscan; Echosens), introduced in France in 2003, is the first Food and Drug Administration-approved elastography technique. For VCTE, three different probes are available, namely, a 3.5-MHz "M" probe (for standard examinations), a 2.5-MHz "XL" probe (for obese patients), and a 5.0-MHz "S" probe (for children). Using a US transducer probe, a low-frequency (50-Hz) mechanical impulse is transmitted to the skin surface, inducing an elastic shear wave that traverses the liver. A pulse echo measures the velocity of shear wave through the liver. Higher shear wave speed indicates greater liver fibrosis. Results are typically recorded as the Young' modulus (E, in kilopascals).^{15,16}

Reliability and failure rate

In general, a valid estimation of VCTE encompasses the following three points: (a) at least 10 valid shots; (b) the success rate (number of valid shots of the total number of shots) greater than 60%; and, (c) the interquartile range-to-median LSM ratio less than 30%.¹⁵ In a study of 13,369 patients with chronic liver diseases, the largest prospective study of VCTE to date, technical failure occurred in 3.1% of cases, whereas unreliable measurements were acquired in 15.8% of cases.¹⁸ Obesity (body mass index >30 kg/m²) and ascites are major factors contributing to failed measurements of VCTE.¹⁴ In obese patients, low-frequency shear waves can be attenuated by the thickened body wall, resulting in a poor signal-to-noise ratio that influences the elasticity measurement algorithm. In these cases, hence, region of interest (ROI) requires being moved deeper below the skin surface so as to avoid fatty tissue. Additionally, in patients with ascites, low-frequency shear waves are unable to propagate through liquids, leading to failed LSM.¹⁶

Diagnostic performance for the staging of liver fibrosis

Previous meta-analyses have confirmed the excellent diagnostic performance of VCTE for the detection of cirrhosis (area under curves [AUCs], 0.92–0.96), superior to that for diagnosing significant liver fibrosis (AUCs, 0.83–0.88).^{19–27} In a study of 916 patients with chronic viral hepatitis (567 CHB and 349 CHC), the accuracy of VCTE to predict significant fibrosis, advanced fibrosis and cirrhosis was 0.79, 0.86 and 0.90, respectively.²⁸ These results indicate that VCTE is more useful for ruling-out instead of ruling-in cirrhosis, with negative predictive value higher than 90%.¹⁴ Considering the low cost and wide availability, VCTE can be used as a cost-effective technique for liver fibrosis screening.

Longitudinal assessment of liver fibrosis after AVT

Screening of advanced fibrosis and cirrhosis. In contrast with the setting of treatment-naïve CHB and CHC populations, in whom the performance of VCTE for the staging of liver fibrosis has been widely validated,^{14,29} data on the use of this method for screening of advanced fibrosis or cirrhosis after AVT are still lacking. According to the data available currently, VCTE has shown approximately good-to-excellent accuracy in diagnosing advanced fibrosis and cirrhosis after AVT, with AUCs of 0.78–0.94 for advanced fibrosis and of 0.86–0.92 for cirrhosis.^{30–33} These findings are of clinical significance given that VCTE can be used as a reliable tool to identify patients who should be monitored for liver-related complications after sustained virological response (SVR). The best cutoff values of LSM, however, varied across published studies, which need to be further determined.

Monitoring of dynamic changes of liver stiffness measurement. It has been demonstrated that liver stiffness values decrease during ongoing AVT (Table 2).^{34–40} However, it remains to be illuminated whether the improvement of liver stiffness after AVT indicates the regression of fibrosis or merely the alleviation of necroinflammation due to virus suppression or clearance.^{31,34} As assumed by some researchers, it might reflect both necroinflammation alleviation and fibrosis regression, as supported by the findings that improvements of liver stiffness values were in concordance with that of biochemical markers and serum fibrosis scores, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase, AST-platelet ratio index score, and fibrosis-4 (commonly known as FIB-4) score.^{34,35} Furthermore, it was considered that the stiffness decline during AVT might be more a result of necroinflammation alleviation than a consequence of fibrosis regression, given that the regression of fibrosis is a relatively slower process as compared with the remission of inflammation.³⁵ To further clarify the clinical implication of the decrease in liver stiffness values, a rapid-to-slow pattern of LSM kinetics during 2-year AVT was proposed by a multicenter, randomized and controlled trial of 534 CHB patients, which may reflect a mixed remission of both necroinflammation and fibrosis during the initial 24 weeks and the regression of fibrosis during long-term AVT, particularly, following ALT normalization.¹¹ To be specific, from baseline to week 24 after the initiation of AVT, liver stiffness manifested as rapid decrease (-2.2 kPa/24 weeks) in parallel with ALT; intriguingly, from week 24 to week 104, liver stiffness displayed slow but persisting declination (-0.3 kPa/24 weeks), whereas ALT levels remained stable within the normal range.¹¹ In other words, significant correlation between the decline in ALT and LSM showed in the first 24 weeks but diminished thereafter. Similar findings were reported in another prospective study of 120 CHB patients, in which a rapid-to-slow pattern of LSM kinetics during 78 weeks of entecavir treatment was noted.³¹

Predicting of fibrosis regression. Correlations between dynamic changes in LSM and histologically-proven fibrosis regression have been assessed in a few studies (Table 3).^{11,30,31} In a cohort of 112 HCV-infected liver transplantation recipients who achieved SVR after long-term AVT, a decrease of 50% in baseline LSM could correctly predict 55% of patients achieving fibrosis regression, with a positive predictive value of 78% and a negative predictive value of 44%. Moreover, baseline LSM seems to be useful to predict the possibilities of fibrosis regression after treatment. A LSM

Table 1. Comparison of quantitative elastography techniques^{14,15,29}

| Modality | Cost | Availability | Evidence | ROI | | Placement | Reported parameter | Major causes for failure of LSM | Accuracy | |
|---------------|------|--------------|-----------|------------------|---------------------------------|-------------------|---|--|-------------------|-------------------|
| | | | | Anatomic imaging | Size | | | | SF | AF |
| VCTE | Low | Widespread | ++++ | None | ~3 cm ³ | No image guidance | Young modulus (kPa) | Obesity; ascites | Good | Good to excellent |
| pSWE | Low | Moderate | +++ ++ | Yes (B-mode US) | ~1 cm ³ | US guidance | Wave speed (m/s) or Young modulus (kPa) | Obesity | Good | Excellent |
| 2D SWE | Low | Moderate | +++ ++ | Yes (B-mode US) | Flexible (≥20 cm ³) | US guidance | Young modulus (kPa) | Obesity | Good to excellent | Excellent |
| MRE | High | Limited | + | Yes (MRI) | ≥250 cm ³ # | MRI guidance | Complex shear modulus (kPa) | Hepatic iron overload; large ascites; obesity*; 3 T (2D GRE) | Good to excellent | Excellent |

* Conflicting results reported regarding magnetic resonance elastography failure in patients with obesity; # Up to 1/3 of the total liver volume.

Abbreviations: 2D GRE, two-dimensional gradient recalled echo; 2D SWE, two-dimensional shear wave elastography; AF, advanced fibrosis; SF, significant fibrosis; US, ultrasound; VCTE, vibration-controlled transient elastography; MRI, magnetic resonance imaging; pSWE, point shear wave elastography; ROI, region of interest; SF, significant fibrosis; US, ultrasound; VCTE, vibration-controlled transient elastography.

cutoff of 21 kPa can be used to accurately predict the probability of cirrhosis regression, with a regression rate of 23% and 57% for patients with baseline LSM ≥21 kPa and <21 kPa, respectively ($p=0.005$).³⁰ Similar findings have been reported by other studies on CHB populations.^{11,31} For instance, a decline of 40% in liver stiffness from baseline to week 78 has been suggested as a significant determinant of fibrosis regression in CHB patients after AVT, with an AUC of 0.69, a sensitivity of 69% and a specificity of 68%.³¹ These promising results indicate that VCTE may be useful for predicting fibrosis regression after AVT. Likewise, further studies are warranted to standardize cutoff values in different etiologies.

Strengths and weaknesses

VCTE is a well validated technique with excellent repeatability and reproducibility, which has been widely used in clinical practice for its portability, cost-effectiveness and patient acceptance.^{14,29} However, the application of VCTE is limited by the following: (a) the lack of gray-scale image guidance to determine the ROI placement; (b) the incapacity to identify and avoid large vessels and masses; (c) the difficulty of application in obese patients and the inability to be performed in patients with ascites; (d) the difficulty in imaging between narrow intercostal spaces; (e) the relatively high technical failure rate and limited precision; and, (f) the requirement for recalibration of the spring in the device every 6~12 months.^{14,15,29}

pSWE

Principles

Unlike VCTE, which adopts A-mode imaging, pSWE is incorporated into a standard B-mode US imaging that enables the operator to visualize the liver tissue and define the best area for reliable measurements. In pSWE, an acoustic radiation force impulse (ARFI) method is used to generate shear waves in a small ROI (~1 cm³) within the liver. Tracking US pulses are then used to measure the velocity of shear waves, which is proportional to the square root of the liver stiffness or elasticity. The "stiffness" values are reported as shear-wave speed (in m/s) or converted into Young's modulus (E, in kilopascals) by using the following mathematical equation: $E = 3\rho c^2$, where c is the shear wave speed and ρ is the density of the tissue in homogeneous.^{14,29}

Reliability and failure rate

pSWE has shown excellent repeatability and reproducibility, with both reported intraobserver and interobserver intraclass correlation coefficients (ICCs) higher than 0.85.^{41,42} The technique failure rate is low (1~2%).⁴³ Obesity is the main cause of failed or unreliable measurements of pSWE.¹⁴ As mentioned previously, the low-frequency elastic waves can be attenuated by the fatty tissue, leading to a poor signal-to-noise ratio that influences the LSM.

Diagnostic performance for the staging of liver fibrosis

pSWE performs well for the diagnosis of advanced fibrosis stages (F3-4).²⁹ A meta-analysis comprising 21 studies with 2691 CHB or CHC patients reported the AUCs of pSWE for

Table 2. Recent studies of elastography for monitoring of dynamic changes of fibrosis after antiviral therapy

| Study | Region | Study design | Method | Examination time | Etiology | No. of patients | Fibrosis markers | Biochemical or other markers | Predictors for improvement in LSM |
|-------------------------------------|-------------|-------------------------------------|-----------|---|----------|-----------------|----------------------------------|------------------------------|--|
| Bachofner et al. 2017 ³⁴ | Switzerland | NA | VCTE | At baseline, within 18 months after therapy | HCV | 392 | LSM values ↓ FIB-4, APRI ↓ | NA | NA |
| Knop et al. 2020 ³⁵ | Germany | Prospective | VCTE | At baseline, EOT, 24 weeks after EOT | HCV | 260 | LSM values ↓ | NA | High PLT at baseline |
| Persico et al. 2018 ³⁶ | Italy | Prospective | VCTE | At baseline, EOT, SVR12 [†] | HCV | 749 | LSM values ↓ | NA | Low ALT, low PLT count, diabetes** |
| Singh et al. 2017 ³⁷ | USA | Systematic review and meta-analysis | VCTE | At baseline, different timepoints after AVT depending on the included studies | HCV | 2934 | LSM values ↓ | NA | NA |
| Stasi et al. 2020 ³⁸ | Italy | Prospective | VCTE | At baseline, EOT, 1 and 2 years after EOT | HCV | 294 | LSM values ↓ | AST, ALT, GGT ↓ | NA |
| Yada et al. 2014 ³⁹ | Japan | NA | VCTE | At baseline, 2 years after treatment | HCV | 26 | LSM values ↓ LFI ↓ | NA | NA |
| Alem et al. 2018 ⁴⁰ | Egypt | Prospective | VCTE pSWE | At baseline, SVR24* | HCV | 58 | LSM values ↓ | AST, ALT, PLT ↓ | Baseline viral load |
| Kohla et al. 2020 ⁴⁵ | Egypt | Prospective | pSWE | At baseline, EOT, week 24 and week 36 | HCV | 165 | LSM values ↓ FIB-4, APRI ↓ | AST, ALT ↓ | NA |
| Osakabe et al. 2015 ⁴⁶ | Japan | NA | pSWE | At baseline, EOT, 1 and 2 years after EOT | HCV | 87 | LSM values ↓ | NA | NA |
| Tachi et al. 2018 ⁴⁷ | Japan | Prospective | pSWE | At baseline, EOT, 24 weeks after EOT | HCV | 176 | LSM values ↓ | NA | Higher inflammatory activity at baseline; † significant fibrosis at baseline** |

(continued)

Table 2. (continued)

| Study | Region | Study design | Method | Examination time | Etiology | No. of patients | Fibrosis markers | Biochemical or other markers | Predictors for improvement in LSM |
|---------------------------------|---------|---------------|--------|--------------------------|----------|-----------------|----------------------------------|------------------------------|-----------------------------------|
| Korda et al. 2019 ⁶⁴ | Hungary | Prospective | 2D SWE | At baseline, EOT | HCV | 23 | LSM values ↓ FIB-4, APRI ↓ | AST, ALT, GGT ↓ INR ↑ | NA |
| Tada et al. 2017 ⁵³ | Japan | Retrospective | 2D SWE | At baseline, EOT, SVR24* | HCV | 210 | LSM values ↓ | ALT ↓ | NA |
| Tada et al. 2018 ⁶⁰ | Japan | Prospective | MRE | At baseline, SVR24* | HCV | 198 | LSM values ↓ | PDFF values ↓ | NA |

* 24 weeks after EOT; [†] 12 weeks after EOT; ** Low ALT, low platelet count, diabetes were inversely associated with the LSM improvement; [‡] Higher inflammatory activity at baseline was associated with an improvement in liver stiffness at the EOT; [§] Significant fibrosis at baseline was associated with an improvement in liver stiffness at 24 weeks after the EOT.
Abbreviations: 2D SWE, two-dimensional shear-wave elastography; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-platelet ratio index; AST, aspartate aminotransferase; EOT, end-of-treatment; FIB-4, fibrosis-4 score; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; LF, liver fibrosis index; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NA, not available; PDFF, proton density fat fraction; PLT, platelet; pSWE, point shear-wave elastography; SVR, sustained virological response.

detecting significant fibrosis, advanced fibrosis and cirrhosis were 0.88, 0.94, and 0.91, respectively.⁴⁴ Therefore, pSWE is recommended for differentiating patients with advanced fibrosis to cirrhosis from those with no to minimal fibrosis.^{29,44}

Longitudinal assessment of liver fibrosis after antiviral treatment

pSWE represents a reliable and reproducible ARFI method for assessing liver fibrosis, however, available data on pSWE for fibrosis surveillance after AVT are still lacking. Similar to VCTE, significant decrease in LSM by pSWE after AVT have been reported, yet, merely in few CHC patients.^{40,45,46} It was considered that reduction of pSWE values indicates not only the improvement of fibrosis but also the resolution of liver inflammation,⁴⁰ as an early decline in liver stiffness after SVR was associated with the grade of histological inflammation at baseline.⁴⁷

Strengths and weaknesses

As compared with VCTE, strengths of pSWE include the following: (a) it is incorporated into a standard B-mode US that can achieve the real-time imaging and guide the ROI placement; (b) large vessels and masses can be detected and avoided; (c) it allows for sampling at different segments of the liver; and, (d) ascites is not a limitation for pSWE, enabling its performance in decompensated liver cirrhosis for fibrosis assessment.²⁹

Limitations of pSWE include the following: (a) difficulty in delineating intermediate fibrosis stages, owing to prominent overlap in shear wave speeds; (b) susceptibility to liver motion (e.g. deep breath or using the Valsalva maneuver) or physiologic motion (e.g. vascular pulsatility), which may influence the LSM; and, (c) measurement dependence upon the operator’s expertise, necessitating operators being properly trained.^{14,29,48}

2D SWE

Principles

2D-SWE, similar to pSWE, induces shear waves by using the ARFI to deform hepatic tissues. Nevertheless, in contrast to pSWE, which emits a single push pulse to a focal point, 2D SWE generates shear waves at multiple points, producing a cone-shaped shear wave front. The shear wave propagation is tracked by conventional compressive US waves and depicted as a color-coded elasticity map – elastogram. Using the B-mode US image, a flexible ROI is delineated within the elastogram. The mean shear wave speed (in m/s) within the ROI is obtained from multiple measurements, which can be converted into the Young modulus and reported in kPa.^{14,29,48}

Reliability and failure rate

2D SWE has demonstrated excellent repeatability and reproducibility, with reported intraobserver ICC greater than 0.90 and interobserver ICC of 0.88.⁴⁹ The failure rate of 2D SWE is low (~5%).⁵⁰ Failed measurement is predominantly attributed to obesity.¹⁴ The mechanism underlying the relationship between high body mass index and failed LSM has been discussed.

Table 3. Recent studies of elastography for the prediction of histologically-proven fibrosis regression after antiviral therapy

| Study | Region | Study design | Method | Examination time | Etiology | No. of patients | Fibrosis regression* | | |
|---------------------------------|--------|--------------|--------|---|----------|-----------------|----------------------|---------------------|--|
| | | | | | | | Rate % (n/N) | Reference standard | Predictors |
| Liang et al. 2018 ¹¹ | China | Prospective | VCTE | At baseline and every 24-28 weeks during follow-up of 104 weeks | HBV | 534 | 60% (98/164) | LB (Ishak score) | Baseline Ishak score; percentage change of LSM values from baseline to week 52 |
| Mauro et al. 2018 ³⁰ | Spain | NA | VCTE | At baseline and 12 months post-SVR | HCV | 112 | 67% (75/112) | LB (METAVIR system) | Baseline HVPg; LSM; decompensations at baseline |
| Wu et al. 2018 ³¹ | China | Prospective | VCTE | At baseline, 26 week, 52 week and 78 week of treatment | HBV | 120 | 45% (54/120) | LB (METAVIR system) | Percentage decline of LSM values from baseline to week 52 and week 78 |

*fibrosis regression was defined as ≥ 1 stage decrease in the METAVIR score or ≥ 1 -point decrease in Ishak at follow-up biopsy score.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HVPg, hepatic venous pressure gradient; LB, liver biopsy; LSM, liver stiffness measurement; NA, not available; SVR, sustained virological response; VCTE, vibration-controlled transient elastography.

Diagnostic performance for the staging of liver fibrosis

2D SWE has shown good-to-excellent performance for the diagnosis of significant fibrosis stages (F2-4). In a previous meta-analysis based on 13 studies with 2303 patients, the reported AUCs of 2D SWE for detecting significant fibrosis, advanced fibrosis, and cirrhosis were 0.87 (95% CI: 0.84–0.90), 0.93 (95% CI: 0.91–0.95), and 0.94 (95% CI: 0.92–0.96), respectively.⁵¹ In addition, our recent meta-analysis involving 1977 CHB patients found AUC of 0.92 (95% CI: 0.89–0.94) for detecting significant fibrosis.⁵² Hence, diagnostic accuracy of 2D SWE for fibrosis assessment might be equivalent or possibly superior to that of VCTE or pSWE. However, further validations regarding the diagnostic performance of 2D SWE are warranted. In addition, thresholds for the staging of liver fibrosis remain to be established.

Longitudinal assessment of liver fibrosis after antiviral treatment

2D SWE is a highly accurate ARFI method for fibrosis estimation in CHB and CHC populations; yet, it is less well investigated than either pSWE or VCTE.¹⁴ In a preliminary study of 210 hepatitis C virus-infected patients undergoing AVT, an early decline of LSM by 2D SWE occurred in those who achieved SVR, and a pronounced decrease in LSM was found particularly in those with progressive liver fibrosis.⁵³ Evidence from this study indicates that the improvement of liver fibrosis may be a gradual process that initiated at the end of AVT. Concretely, it was considered that the significant decline of ALT levels from baseline to end-of-treatment was strongly correlated with improvement of liver stiffness. Intriguingly, despite ALT levels having decreased to low levels at both end-of-treatment and SVR at week 24, suggesting the remission of liver inflammation, hepatic stiffness decreased persistently and significantly from baseline to end-of-treatment and from end-of-treatment to SVR at week 24.⁵³

Strengths and weaknesses

2D SWE, as a new US elastography technique, has the following strengths. First, 2D SWE incorporates conventional B-mode US image with colorized elastogram, which can provide real-time imaging and enables accurate ROI placement for high-quality measurements. In addition, under the guidance of B-mode US, 2D SWE can also be used to depict liver masses, estimate hepatic morphological alterations and monitor changes in blood flow. Similar to pSWE, 2D-SWE is insusceptible to ascites.²⁹

2D SWE also has several limitations. Compared with VCTE and pSWE, the sampling time of 2D SWE may be extended since shear waves are slow-moving and 2D SWE makes more measurements over a larger tissue volume. Moreover, like pSWE, 2D SWE is susceptible to motion and therefore requires breath-holding. Additionally, LSM values of 2D SWE derived from different manufacturers are not directly comparable, which complicates the disease-tracking process if machines from different vendors were used. This is because not only tissue stiffness but the applied frequency of the shear waves would exert an influence on the inferred stiffness. On the assumption that all other parameters are equal, the LSM values are larger when the shear waves are employed at higher frequency. Furthermore, similar to pSWE, 2D SWE should be performed by trained sonographers since the technique is operator-dependent.^{14,29,48}

MRE

Principles

MRE, approved by the Food and Drug Administration in 2009, is currently considered the most accurate noninvasive elastography technique for fibrosis assessment.⁴⁸ In general, during an MRE scan, 60 Hz (ranging from 20–200 Hz) mechanical vibrations generated by an active driver [located outside the MR scanner room] are transmitted via flexible

plastic tubing to a passive driver (placed on the patient's body wall), which then transmits the acoustic pressure into the liver as shear waves. The shear wave propagation is imaged by a MR phase-contrast sequence modified with motion-encoding gradients. The common MRE sequences include the 2D gradient-recalled echo-based (GRE) sequence and 2D spin-echo-based echo-planar imaging (SE-EPI) sequence. Raw data on shear waves acquired from the MRE sequence are postprocessed by an automated inversion algorithm into a color-coded map of liver stiffness, known as an elastogram. Calculating liver stiffness from the elastogram requires delineating ROIs. During this process, anatomical regions that may disrupt the propagation of shear wave, such as lesions, large (>3 mm) vessels, edge artifact and fossae or fissures, need be avoided.^{29,48}

Reliability and failure rate

MRE can provide reliable examinations even in pediatric patients and in those with obesity or hepatic steatosis.¹⁴ MRE has shown high repeatability and excellent reproducibility.^{54,55} The technical failure rate of MRE is low. In a study of 1377 consecutive MRE examinations, technical failure occurred in 5.6% of cases when using a 2D GRE sequence.⁵⁶ The most frequent reason for failed measurement in MRE is hepatic iron deposition, which decreases the liver signal intensity and results in a poor signal-to-noise ratio that influences the elastographic calculation.⁵⁶

Diagnostic performance for the staging of liver fibrosis

MRE has shown good-to-excellent performance for the staging of liver fibrosis in chronic liver diseases. A meta-analysis comprising 12 studies (697 patients) with mixed chronic liver diseases reported AUCs of 2D MRE for detecting any fibrosis, significant fibrosis, advanced fibrosis, and cirrhosis were 0.84 (95% CI: 0.76-0.92), 0.88 (95% CI: 0.84-0.91), 0.93 (95% CI: 0.90-0.95), and 0.92 (95% CI: 0.90-0.94), respectively.⁵⁷ In addition, a recent meta-analysis based on 26 studies (3200 patients) with mixed chronic liver diseases found that there were no significant differences between the GRE sequence and SE-EPI sequence in terms of the pooled sensitivity and specificity for the staging of liver fibrosis; the reported AUCs of GRE-MRE and SE-EPI-MRE for diagnosing any fibrosis, significant fibrosis, advanced fibrosis, and cirrhosis were 0.93 vs. 0.94, 0.95 vs. 0.94, 0.94 vs. 0.95, and 0.92 vs. 0.93, respectively.⁵⁸ Similar diagnostic accuracy as that with 2D MRE and 3D MRE have been reported in a few prospective studies with mixed chronic liver diseases.^{54,59} Based on these observations, MRE is recommended for asymptomatic patients who may have mild fibrosis to accurately define fibrosis stages and guide therapeutic interventions. In addition, for symptomatic patients with advanced fibrosis or cirrhosis, MRE combined with routine magnetic resonance imaging scan can help to establish the fibrosis stages, assess morphologic alterations of the liver, and detect intra- or extra-hepatic complications.

Longitudinal assessment of liver fibrosis after antiviral treatment

Given its limited availability and recent clinical introduction, data on MRE for longitudinal assessment of fibrosis after AVT are scarce. In a prospective cohort of 198 CHC patients, liver

stiffness values assessed by MRE significantly decreased from baseline to SVR at week 24.⁶⁰ Likewise, it was considered that the reduction of liver stiffness after SVR was associated with both fibrosis regression and inflammation remission, given that elevated ALT levels, corresponding to the presence of necroinflammation, also declined significantly from baseline to SVR at week 24.⁶⁰ MRE holds promise to illuminate the underlying mechanisms of liver stiffness improvement following AVT, as the use of MR T1 mapping of diffusion and perfusion may be able to differentiate a real fibrosis regression from a mere reduction of interstitial edema.³⁴

Strengths and weaknesses

Unlike US elastography with localized spot measurements at limited depth in the liver, MRE provides a quantitative map of tissue stiffness over a large area of coverage of the liver, which can produce a more reliable LSM and higher accuracy for fibrosis assessment. In addition, MRE is much less operator-dependent and has a lower technical failure rate than US elastography. More importantly, MRE can be incorporated into a routine abdominal magnetic resonance imaging scan protocol, providing a comprehensive estimation of the liver, such as evaluation of liver fat content, diagnosis of focal liver diseases, and detection of complications of cirrhosis, like hepatocellular carcinoma, splenomegaly, varices, and ascites.⁶¹

Despite these advantages, MRE also has several limitations. First, the presence of hepatic iron overload and motion artifacts result in failed examinations. In addition, a minority of patients cannot tolerate MR examinations, owing to claustrophobia. Moreover, MRE might be contraindicated in patients with incompatible implantable devices, or those who cannot fit into the MR scanner bore.^{14,29} Finally, MRE is costlier and less available compared with US elastography,¹⁴ which may limit its clinical use to a certain extent.

Current challenges and future directions

To date, available data on the use of elastography-based methods, particularly of MRE or AFRI methods, for longitudinal assessment of liver fibrosis after AVT are limited. However, it is apparent that only when sufficient evidence has been obtained to validate these novel techniques will they be recommended for monitoring strategies. Moreover, prospective studies comparing the performance of MRE and US elastography for fibrosis evaluation in patients with AVT, particularly for detecting those with advanced fibrosis after SVR, are warranted.

It is still controversial whether a decline in LSM after AVT reflects a real regression of fibrosis, or merely a resolution of hepatic necroinflammation due to virus eradication, or mixed remission of both fibrosis and inflammation. Therefore, robust evidence remains to be provided that will elucidate the correlation of a decline in liver stiffness values with histological changes after SVR.

Despite emerging lines of evidences showing the potential of changes in LSM for the prediction of histological fibrosis regression after long-term AVT,^{11,30,31} further validations in different populations are required. More importantly, standardization of cutoff values for these promising biomarkers is urgently needed.

It is clear that liver stiffness is an "indirect" marker of fibrosis; thus, LSM may not be sensitive enough to monitor

subtle changes in fibrosis after AVT or antifibrotic treatment. Recently, molecular imaging probes targeting fibrosis-specific cells or molecules (e.g. hepatic stellate cells, collagen and elastin) might become novel, noninvasive, promising biomarkers for fibrosis.^{62,63} These “direct” markers hold promise for a reliable assessment of fibrosis and monitoring of its dynamics during a long-term follow-up period, which can be used to predict the antifibrotic potential of new drugs and to select responders to antifibrotic therapies. These molecular markers could serve as a complementary method to elastography in the future. The combination of these techniques may produce increased accuracy for fibrosis evaluation.

Conclusions

Liver fibrosis is a dynamic process with potential for regression if the underlying causes of chronic liver injury are removed. Fibrosis regression can be achieved after long-term AVT. Monitoring of dynamic changes in liver fibrosis after AVT is of strategic importance for the prediction of prognosis and the surveillance of liver-related events. Routine surveillance of liver fibrosis after AVT by liver biopsy, the gold standard for fibrosis assessment, is hindered by its invasive nature, sampling error, and observer variability. Elastography represents a noninvasive alternative that has been widely used and validated for fibrosis assessment prior to treatment. Emerging evidence indicates that quantitative elastography methods can be used to monitor fibrosis status after long-term AVT, with great potential for screening advanced fibrosis and cirrhosis, monitoring dynamic changes in LSM and predicting histologically-proven fibrosis regression. Future research on elastography is required to elucidate the correlations between liver stiffness improvement and histological changes after AVT, to standardize the cutoffs for both screening and predicting strategies, and to develop noninvasive molecular markers as complementary tools to LSM.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (BS), literature research (HW), drafting of the manuscript (HW), critical revision of the manuscript for important intellectual content (BS, HW), and approval of final version of submitted manuscript (BS, HW).

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