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ShearWave™ Elastography: a reliable and outperforming diagnostic tool for liver fibrosis assessment in chronic hepatitis. A literature review

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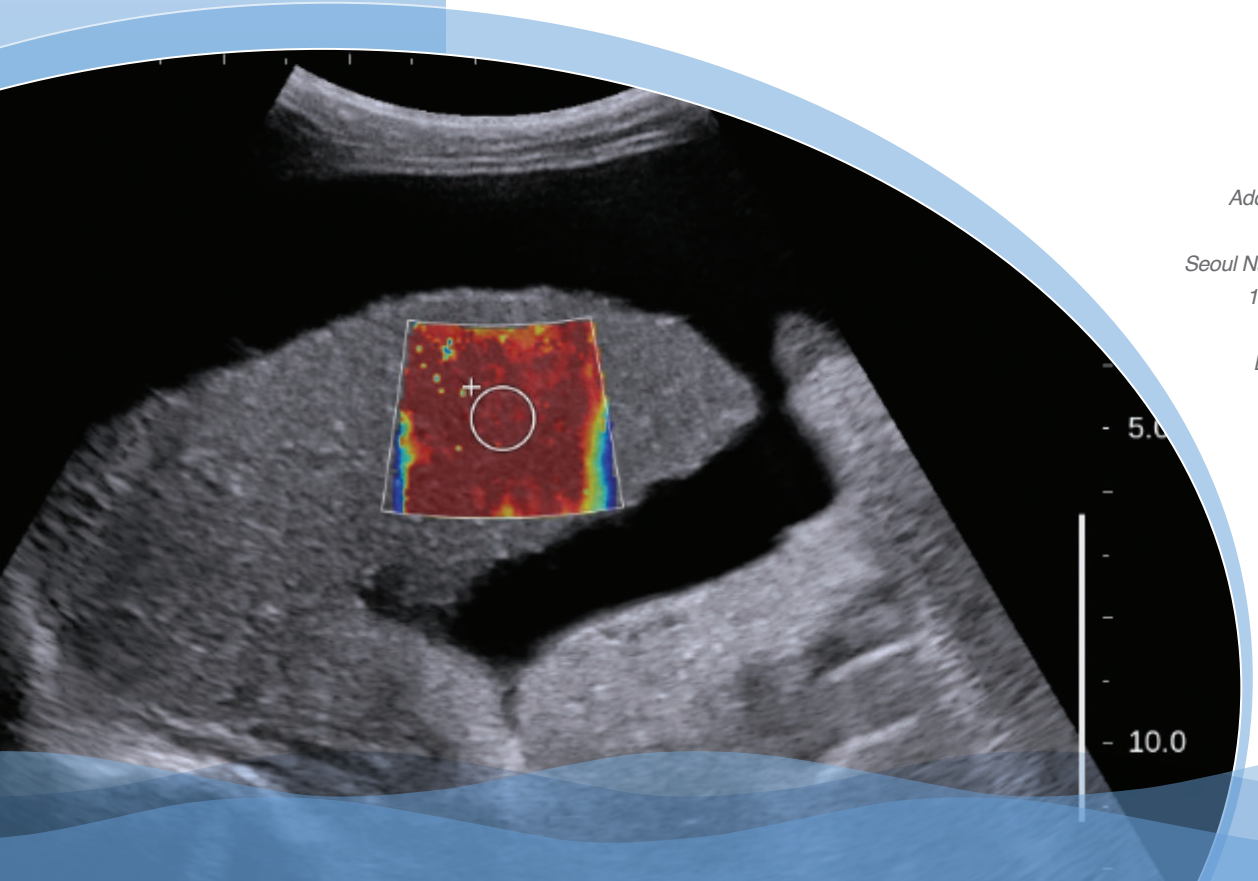

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Introduction

Ultrasound (US) imaging plays a major role in the diagnosis, the regular follow-up, and the therapeutic management of chronic liver disease. Its use covers a wide spectrum of clinical applications, such as:

- Analyzing liver parenchyma echotexture and assessing risk of chronic liver disease (such as changes in the size of individual segments or liver dysmorphia and signs of portal hypertension),
- Detecting and characterizing nodules in the cirrhotic liver (and in particular identifying any suspicious lesion such as hepatocellular carcinoma (HCC)),
- Guiding while performing the percutaneous focal treatment (such as radiofrequency-ablation, cryotherapy, etc…) of lesions such as HCC,
- Evaluating therapeutic response.

Conventional US imaging is limited by the subjective nature and the variability in assessing the hepatic parenchyma echotexture alteration and liver dysmorphia, and thus is unable to accurately differentiate hepatic fibrosis stages. However, quantification of hepatic fibrosis is of critical importance in chronic hepatitis not only for diagnosis, but also for antiviral treatment decision-making. Two end-points are clinically relevant: detection of significant fibrosis, which is an indication for antiviral treatment, and detection of cirrhosis, which is an indication for specific monitoring of complications related to portal hypertension and of an increased risk of developing HCC[1].

ShearWave™ Elastography (SWE™) is an ultrasound-based elastography technique that has the ability to map and measure liver stiffness[2]. It has been implemented on a complete ultrasound imaging system, the Aixplorer®, and therefore might address the limitations of conventional US imaging to characterize liver fibrosis. This modality could also become part of the routine examination of liver nodules (e.g. HCC) in cirrhotic contexts.

SWE has three advantages over other methods that perform liver stiffness measurements. Because it is integrated into a diagnostic ultrasound system, the use of grayscale images to guide SWE acquisitions (for example, to avoid large arteries) might increase the repeatability of stiffness measurements[3]. Also, it should benefit from improved separation of stiffness levels, i.e. fibrosis stages, thanks to the use of shear waves with greater bandwidths[4]. Finally, it provides a real-time, two-dimensional, quantitative, color-coded map of liver tissue stiffness. The spatial heterogeneity of liver stiffness can be visualized and the Q-Box™ (region of interest) size used for a measurement can be selectively placed and/or adjusted to target a homogenous part of the liver parenchyma. As a result, physiological variations of liver fibrosis can be averaged out. Its real time aspect also ensures that excessive liver motion is avoided.

We have reviewed the clinical results that have been reported in the literature up to September 2013 and we are providing an interpretation of these reports, taking into account our own experience of SWE in the assessment of liver fibrosis.

ShearWave™ Elastography has a low technical failure rate

Hudson et al recently investigated the reproducibility of SWE in healthy volunteers and demonstrated that 98% of SWE images were quantifiable in liver segments 6 and 8, whereas this percentage decreased to 83% in segment 2/3 [5].

When performed on the right liver lobe through the intercostal space on liver segments 6 and 8, SWE demonstrated a failure rate ranging from 2% to 3%. This low rate can be positively compared to the failure rate of Transient Elastography (TE), usually reported as ranging between 2.4-9.4% [6]. The difference between the 2 techniques may be due to the fact that SWE measurements are not impacted by the presence of ascites. Shared limiting factors for both techniques include narrow intercostal spaces and obesity [3,7-8]. Ferraioli et al excluded patients with ascites from their study population and therefore could observe that the technical failure rate (2.5%) for both techniques was due to the same patients conditions, i.e. narrow intercostal spaces in 2 patients and a BMI>32 kg/m² in 1 patient[3]. However, SWE may be less impacted by obesity as extra pressure on the probe reduces the thickness of the fatty layer between the probe and the rib cage, and the depth of SWE measurements can be adapted to go down to 10-12 cm.

The experience of Leung showed different conclusions: SWE was successful in 449/454 (98.9%) subjects including patients and healthy volunteers, while TE was successful in 407/454 (89.6%). Similarly to Ferraioli's experience, common reasons for technical failures between SWE and TE were obesity and narrow intercostal spaces. In addition, the inability of patients to perform an optimal breath suspension was also a factor for technical failure[9].

Reproducibility of ShearWave™ Elastography

Intra-observer Reproducibility

In a prospective study to investigate the reproducibility of SWE™ measurements in normal livers, Ferraioli et al demonstrated that the intraclass correlation coefficients (ICC) for the intraobserver agreement were close to perfect for measurements performed on the same day by both an expert and a novice operator[10] . Similarly, Hudson reported that the reproducibility of SWE measurements was almost perfect on liver segments 6 and 8, with the maximum reproducibility obtained for measurements performed on the same scanning session by the most experienced operator[5]. Intra-operator reproducibility of SWE measurements on liver segment 2/3 was also very good (>0.60), although lower than that on segments 6 and 8.

The fact that the lowest agreement (although showing a good ICC > 0.60) was obtained for measurements performed by operators with less experience in ultrasound imaging and between 2 different scanning sessions, suggests that SWE operators must ensure sound imaging technique, in order to reproduce a given scanning imaging plane over time.

Using the Bland-Altman statistical analysis, Ferraioli demonstrated that the mean differences between measurements within a scanning session or between scanning sessions were 0.01 kPa for the expert and -0.01 kPa for the novice, and 0.06 kPa for the expert and 0.26 kPa for the novice, respectively[10].

Leung et al also reported intra-observer reproducibility data with ICCs ranging from 0.86 to 0.98 for 3 different operators [9].

	Expert		Novice	
	Same day	Different days	Same day	Different days
Ferraioli[10]	0.95	0.84	0.93	0.65
Hudson[5]	0.91	0.63	0.92	0.84

Table 1.
Within-session and between-session intra-operator ICCs of SWE measurements performed on right liver lobe segments.

Inter-observer Reproducibility

Ferraioli reported an inter-observer ICC of 0.88, indicating almost perfect agreement between 2 operators on liver segments 6 and 8, with a mean difference between measurements reported to be -0.12 kPa by the Bland-Altman analysis[10]. Similarly, Leung's experience showed an ICC of 0.85 (95% CI: 0.70-0.94) for the inter-observer reproducibility.

In Hudson's study, the inter-operator ICCs were 0.78 and 0.76 for segments 6 and 8, respectively. As in previous experience, the inter-operator agreement was poorer for measurements performed on liver segment 2/3 (ICC=0.65)[5]. Liver measurements performed by 2 operators were found to be not statistically different in segments 6 and 8 (p=0.16 and p=0.20, respectively), whereas they led to significantly different measurements in segment 2/3 (p=0.02). However, the analysis showed that only 1% to 8% of the variance was due to the operator.

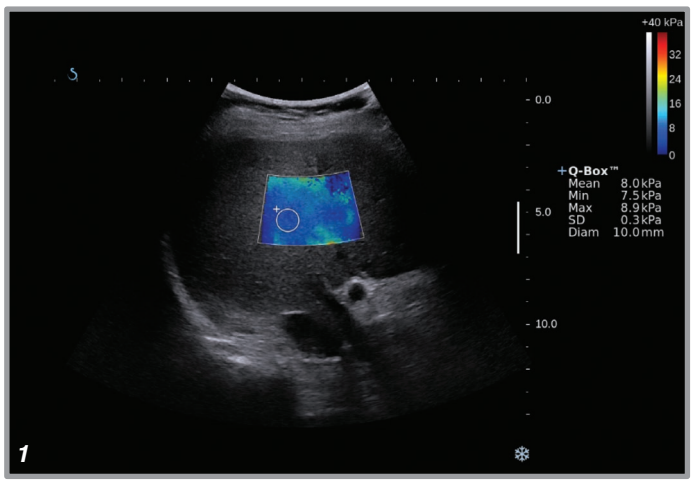

Fig. 1. *A 62 year-old man with chronic hepatitis. Mean elasticity was 8.0 kPa with ShearWave Elastography. Biopsy confirmed a METAVIR F2 liver fibrosis.*

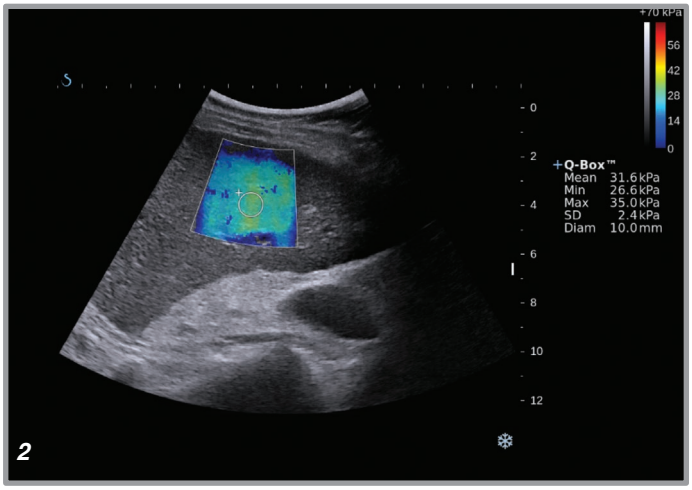

Fig. 2. *A 68 year-old woman with liver cirrhosis. Mean elasticity was 31.6 kPa with ShearWave Elastography. Surface nodularity was seen, representative of cirrhosis. Biopsy confirmed liver cirrhosis.*

Diagnostic Performance of ShearWave™ Elastography in Chronic Hepatitis Patients

In the first study reporting the diagnostic performance of the supersonic shear imaging (SSI) technique (on which SWE™ is based) to evaluate liver fibrosis in patients with Hepatitis C, good correlation was found (r=0.8296) between the elasticity measured with SWE and TE, although a mean offset of 2.40 kPa was observed between the 2 techniques[7]. In addition to the measurement of liver stiffness, SWE also provides information on the heterogeneity of liver stiffness, which cannot be assessed with TE. As shown in Table 2, the Receiver Operating Characteristic (ROC) analysis of liver stiffness measurements performed with SWE showed areas under the ROC curve (AUROC) all greater than 0.95 for the diagnosis of significant fibrosis (METAVIR F≥2), severe fibrosis (METAVIR F≥3), and liver cirrhosis (METAVIR F4). The authors also assessed a better accuracy of SWE over TE, on the basis of several criteria such as misclassification rates, Youden's index, specificity at 95% of sensitivity, and sensitivity at 95% of specificity.

As was further demonstrated by Ferraioli et al in patients with hepatitis C (Table 2), the use of different cut-off values for SWE and TE favored SWE in the assessment of early fibrosis stages[3]. The use of different cut-off values for both techniques is supported by the fact that the Young's modulus (corresponding to the liver stiffness) is derived from the shear group velocity, which is measured from the broadband mechanical excitation (60 Hz–600 Hz) generated using the acoustic radiation force for SWE, whereas TE elasticity values are assessed using an external vibrator acting at a single frequency of 50 Hz[2-4]. Therefore, the stiffness assessed by SWE is based on higher frequency vibrations and integrates both elasticity and viscosity properties[7].

AUROC[1]	CLD[2]	F≥2		F≥3		F=4	
		SWE	**TE**	**SWE**	**TE**	**SWE**	**TE**
Bavu[7]	Hep C	0.95	0.85 P=0.005	0.96	0.86 P=0.001	0.97	0.94 P=0.15
Ferraioli[3]	Hep C	0.92	0.84 P=0.002	0.98	0.96 P=0.14	0.98	0.96 P=0.48
Leung[9]	Hep B	0.88	0.78 P=0.01	0.933	0.83 P=0.01	0.98	0.92 P=0.04

Table 2.
Summarized performances of SWE and TE in published studies.[1] Area under the ROC curve; [2] Chronic liver disease.

In results published by the Liver Fibrosis Study Group in Pavia, Italy, the optimal cutoff values for the diagnosis of METAVIR F≥2, F≥3 and F4 were 7.1 kPa (1.5 m/s), 8.7 kPa (1.7 m/s), and 10.4 kPa (1.9 m/s), respectively, with sensitivities of 87.5 to 97.3 % and specificities of 87.5 to 96.8 %[3]. Leung et al reported their experience on 226 chronic hepatitis B carriers, and demonstrated a better correlation to fibrosis METAVIR scores for stiffness measurements performed with SWE (r=0.81) as compared to TE (r=0.58)[9]. The values for AUROCs on this population of chronic hepatitis B infected patients are reported in Table 2. The calculated cut-off values were consistent with those found in other studies on chronic hepatitis C patients: 6.5 kPa (METAVIR F≥1), 7.1 kPa (METAVIR F≥2), 7.9 kPa (METAVIR F≥3), and 10.1 kPa (METAVIR F4)[9]. Interestingly, this group also studied the diagnostic value of spleen stiffness in staging liver fibrosis. AUROCs and the optimal cut-offs elasticity values (in kPa) for spleen stiffness for METAVIR F≥1, F≥2, F≥3, and F4 were found to be 0.81 and 19.4, 0.82 and 19.8, 0.83 and 20.6, and 0.84 and 22.0, respectively. The authors could not demonstrate any improvement of the AUROCs by combining the stiffness information from the liver and the spleen. However, the authors concluded that spleen stiffness measured with SWE may serve as an ancillary parameter to detect advanced fibrosis.

Another recent paper reported the results of a study performed without using biopsy as the gold standard[11]. This study used the cut-off values defined for TE for both the TE and the SWE techniques. Therefore, it showed

decreased performances of SWE™ as compared to TE. However, when analyzed separately, these results showed that the AUROC of SWE in differentiating F1 from F2, and F2 from F3, were higher than those of TE: 0.590 versus 0.574, and 0.600 versus 0.509, respectively.

SWE demonstrated a good correlation with other elastography techniques such as acoustic radiation force impulse imaging (ARFI) in patients with Hepatitis C, although diagnostic performances were not assessed due to the limited number of patients[8].

Conclusion

This review of the results of ShearWave™ Elastography in assessing liver fibrosis and cirrhosis shows that SWE, only available on the Aixplorer®, has better performances in identifying early stages of liver fibrosis (especially METAVIR F≥2) and similar performances in assessing liver cirrhosis, as compared to other elastography techniques currently available. However, specific stiffness cut-off values should be used, due to the inherent technical differences. SWE provides a 2D quantitative map of liver stiffness, thus the spatial heterogeneity of liver stiffness can be visualized in real time and easily averaged to better analyze the overall fibrosis state. In our experience, as well as in the literature review, this map has proven to be very useful to avoid artifacts arising from pulsating vessels, reverberation, or motion. As a consequence, SWE has demonstrated almost perfect intra-observer reproducibility and a very good inter-observer reproducibility. As it is available on a premium ultrasound imaging system, which encompasses other imaging modes such as gray scale imaging, Doppler modes and contrast-enhanced ultrasound imaging, Aixplorer and SWE offer a complete diagnostic tool to assess chronic liver diseases.

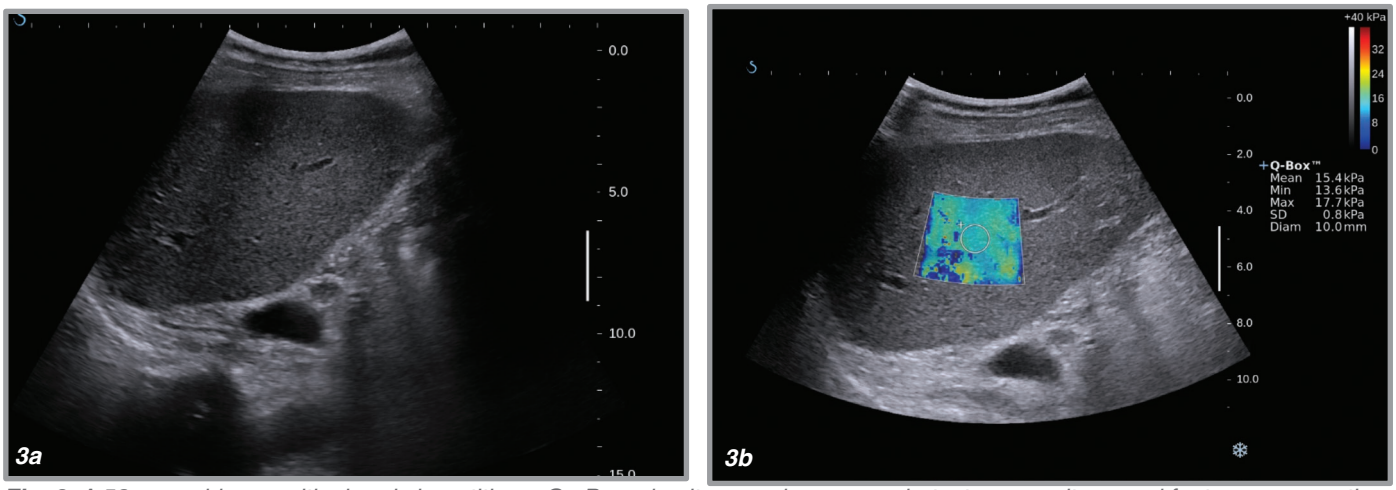

Fig. 3. *A 52 year-old man with chronic hepatitis.* ***a.*** *On B-mode ultrasound, coarse echotexture, an ultrasound feature representing chronic hepatitis.* ***b.*** *Mean elasticity was 15.4 kPa on ShearWave Elastography. Biopsy confirmed a METAVIR F3 liver fibrosis.*

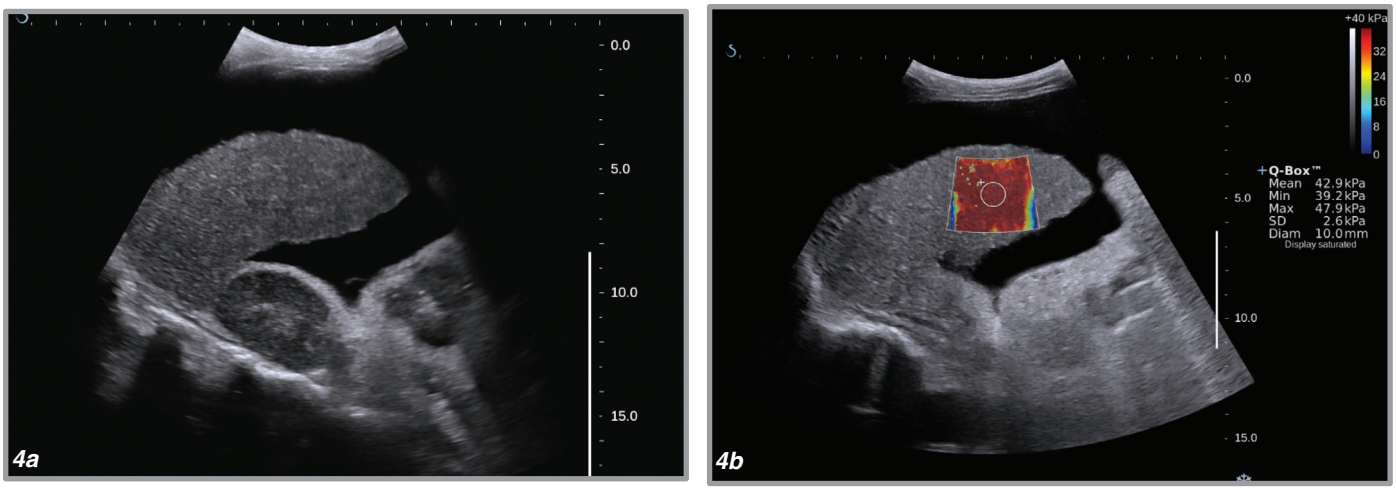

Fig. 4. *A 61 year-old man with liver cirrhosis.* ***a.*** *Shrunken liver with surface nodularity and a large amount of ascites was clearly seen on B-mode ultrasound.* ***b.*** *On ShearWave Elastography, mean elasticity was 42.9 kPa. No correlation to biopsy was available for this patient.*

Appendix. Staging Methods for Liver Fibrosis

Chronic liver diseases are known to be diffuse, heterogeneous[12-13], and usually combine hepatocyte and/or cholangiocyte necrosis or apoptosis with inflammation and interstitial fibrosis. The extension of the latter may result in alterations of the hepatic architecture and the appearance of regeneration nodules, which define cirrhosis.

Liver Biopsy

The outcome of liver biopsy has traditionally been considered as the standard of reference for assessing liver fibrosis severity in patients with chronic liver diseases, and especially those with chronic hepatitis. Liver biopsy can be performed percutaneously, or by a transvenous route in case of hemostasis disorder. One of the main advantages of biopsy is that it provides additional information about the inflammatory reaction, the level of steatosis. Nevertheless, it has several drawbacks:

- It is an invasive technique, which is associated with morbidity (3%, including 0.6% severe complications) and mortality (approximately 1‰).
- It is expensive, requiring a day of hospitalization[14],
- It can lead to false outcomes:
- The biopsy core sample is not very large (<25 mm in length and 1 mm in diameter) and may not be representative of the liver fibrosis heterogeneity. Therefore, the diagnosis of fibrosis seems to be underestimated in 10 to 30% of cases[15]
    - Although the histo-pathological outcome of liver biopsy has been standardized by the use of scoring systems such as the METAVIR or the Ishak scores, these semi-quantitative methods show an inter-observer variability[16]. Indeed, the percentage of fibrotic areas that can be measured for successive intermediate METAVIR scores are very similar to each other: 2.0±0.1% for F0, 3.4±0.3% for F1, 5.8±0.7% for F2, 14.7±0.8 for F3, 25.1±1.4% for F4)[17].
    - As a consequence, for biopsy cores under 20 mm in length, there is an increased risk (>30%) of misclassification of intermediate METAVIR stages[17]. Also the assessment of liver fibrosis by several pathologists can show a very high discordance rate (>60%) for intermediate METAVIR stages[18].
- Liver biopsy is not ideal for repeated assessment of disease progression[16].

Both the progression and the regression of hepatic fibrosis over time could be of clinical significance. Recent research has demonstrated a reduction in liver fibrosis with treatment, even in advanced stages[19-20].

Therefore new, non-invasive techniques to assess hepatic fibrosis have been an important focus of research in hepatology for the last 10 years. Currently available methods rely on two different approaches: a "biological" approach based on the dosage of serum biomarkers of fibrosis[21-23], and a "physical" approach based on the measurement of liver stiffness[24-25].

Non-invasive Staging

Although the large number of publications over the past decade confirms the growing interest regarding these new non-invasive methods, specific limitations must be considered. As an example, in most studies the fibrosis level was derived from the liver biopsy METAVIR score, which suffers from its own limitations described above for intermediate stages. Other examples preventing an accurate assessment of intermediate stages are the variability of the measurements and the limited sampling used for the measurement[26].

Serum Biomarkers

Serum markers are used to calculate a fibrosis score from the measurements of biological parameters. Several tests are available to the clinicians depending on the etiology of the underlying chronic liver disease. The FibroMeter®[22], the Hepascore[23] and the FibroTest® are amongst the most used blood tests. The latter combines the dosage of 5 serum markers (α2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, γ-glutamyltranspeptidase) with an adjustment for sex, age and body mass index (BMI). It has been extensively studied and has demonstrated a diagnostic accuracy ranging from 70% to 85%[21]. However, it has limitations in cases of hyperbilirubinemia, hemolysis, inflammation or concomitant illness. All serum markers and blood tests share similar strengths and limits. They are not routinely available in most hospital settings, therefore limiting their clinical use.

Elastography Techniques

Conventional imaging techniques provide anatomical, hemodynamic and perfusion information, which are valuable in the context of focal diseases, but are of limited benefit in diffuse chronic liver diseases. The elasticity (or, equivalently, stiffness) of body tissues varies greatly and is a parameter that can be coded to differentiate tissues and also lesions in surrounding tissues[27]. Many disease processes produce changes in tissue elasticity. Tumors (especially malignant) are generally harder than surrounding normal tissue. Interstitial fibrosis, which appears in some diffuse diseases (liver cirrhosis, renal failure...), also causes a change of elasticity[28-29]. As a result, additional information on the viscoelastic properties of the organs or tumors is of great interest to the clinicians.

Elasticity imaging of the human body is a fairly new modality currently being evaluated. It proposes replacement of subjective palpation with imaging the elastic properties of tissue. Static elastography is currently available on many ultrasound diagnostic imaging devices. However, it does not provide quantitative values of the elastic properties of tissues. Elastography imaging is also being developed in MRI (Magnetic Resonance Elastography, MRE, or elasto-MR)[28-30].

Three other techniques, based on the properties of shear waves, have been developed in the last decade to quantitatively measure the elastic properties of tissues. Indeed, the speed of a shear wave propagating in a medium is directly related to the longitudinal modulus of elasticity of the biological tissue; the tissue elasticity modulus can then be derived from this measurement. Accordingly, the shear wave speed in stiff or "hard" tissue will be greater than in a softer region.

One-Dimensional Transient Elastography

The first technique, called Transient Elastography (TE) is a one-dimensional non-invasive, non-imaging, bedside method to evaluate liver fibrosis by measuring liver stiffness[24]. This technique is dedicated to liver fibrosis assessment and allows/permits the diagnosis of cirrhosis and significant fibrosis.

The shear wave is generated by an external low frequency vibrator (50 Hz), which strikes the patient's skin. This external pitch is sufficient to produce a shear wave whose propagation is measured by a one-dimensional ultrasound system (approximately 5 MHz) and provides an average elasticity measurement. This technique is currently commercially available (FibroScan®, Echosens™, Paris, France).

It has been widely studied and validated in clinical practice to measure the elasticity of the liver parenchyma in a cylindrical volume sample[24]. The measurement is typically performed intercostally on the right liver lobe and covers a small (30 - 40 mm) region of interest (from a given depth). The outcome is a value that corresponds to the average elasticity in the single explored cylinder. The measurement is typically repeated 10 times and the median is considered to be the representative elasticity value.

When hepatic elasticity (liver stiffness) measured with TE produces values greater than 12.5-14.5 kPa, cirrhosis could be diagnosed with a high positive predictive value[32-35]. Significant fibrosis could be suggested by TE when elasticity values would be greater than 7.1-8.7 kPa[32-34]. Among all the non-invasive approaches that have been developed and evaluated to stage liver fibrosis in the last decade, TE is the only tool that has successfully entered clinical practice, particularly in Europe, and is now reimbursed in some countries.

However, there is considerable variation in the performances reported for TE to predict significant fibrosis in the literature (AUROCs of 0.75 to 0.91), most probably due to the known limitations of the technique[36]. In fact, the majority of failed TE exams (between 2.4% and 20%) were reported to originate from variability within the acquisitions[36-37]. These limitations are:

- Low volume of parenchyma explored,
- Absence of ultrasound imaging to guide the measurement,
- Spatial distribution of liver elasticity is not provided.
- Measurement/technical difficulties in obese patients and those with ascites,
- Lack of specificity for the distinction of significant fibrosis level,
- Learning curve required to acquire correctly, without imaging guidance.

ARFI-Based Techniques

The second technique, Acoustic Radiation Force Impulse (ARFI) quantification is also a one-dimensional technique but has been integrated onto a conventional ultrasound imaging system[25]. Unlike TE, it relies on the mechanical excitation of tissue by providing localized, bursting, acoustic radiation force. This results in the propagation of a shear wave away from the region of excitation. Using conventional beamforming architecture, beams are continuously transmitted until the passing shear wave front is detected. Like TE, ARFI-based systems are commercially available to measure tissue stiffness. Limitations include:

- No elasticity map of tissue,
- The elasticity measurement is not real time,
- The elasticity measurement cannot be performed retrospectively,
- Only one acquisition can be acquired at a time,
- The evaluated area of parenchyma is a small pre-determined size and cannot be modified,
- Only the average elasticity in the ROI is calculated, without any information on standard deviation,
- The depth of the ROI is restricted due to transducer limitations; limiting the frequency and magnitude of push pulses prevents excessive heating.

ShearWave™ Elastography

The third quantitative imaging technique is ShearWave™ Elastography (SWE™) and has been implemented on the Aixplorer® ultrasound imaging system[2]. SWE allows two-dimensional, real time, quantitative imaging of tissue elasticity in combination with conventional ultrasound grayscale imaging. This technique has been validated for the characterization of breast lesions[38-40] and thyroid nodules[41-45], for the staging of liver fibrosis[3,7,9], for the diagnosis of liver nodules[46] and for the detection and characterization of prostate cancer[47-48].

SWE relies on the measurement of the shear wave propagation speed in soft tissue. Like ARFI-based techniques, it does not require an external vibrator to generate the shear wave and it is based on the generation of a radiation force in the tissue to create the shear wave. However, in SWE, several focal points are generated almost simultaneously, in a line perpendicular to the surface of the patient's skin. This creates a conical shear wave front around the focal point, which sweeps the image plane on both sides[49].

The progression of the shear wave is then captured by UltraFast™ imaging: the very rapid acquisition of ultrasound images (up to 20,000 images per second). The process takes only a few milliseconds. The high-speed acquisition is necessary to capture the shear wave as its propagation velocity ranges from 1 to 10 m/s. A comparison of two consecutive ultrasound images allows the measurement of displacements induced by the shear wave and creates a "movie" showing the propagation of the shear wave whose local speed is linked to local tissue elasticity. The propagation speed of the shear wave is then estimated from the movie that is created and a real-time, two-dimensional color map is displayed. The color codes either the elasticity of the medium in kilopascals (kPa) or the shear wave speed in meters per second (m/s). This color map is displayed on top of the anatomic grayscale (or B-mode) image[49].

Using a region-of-interest quantification tool (ROI) called the Q-Box™, local tissue elasticity or shear wave velocity can be measured retrospectively over an area of interest ranging from 1 to 700 mm². Since each pixel in the color-coded map corresponds to a tissue elasticity measurement, the stiffness of the tissue is locally assessed. Additionally, the automatic standard deviation calculation provides relevant information on the stiffness value distribution within the region of interest.

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