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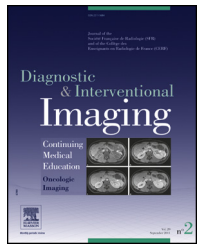

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Ultrasound elastography in liver

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KEYWORDS
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Liver fibrosis;
Liver tumors;
Ultrasound elastography

Abstract Conventional imaging techniques cannot provide information about tissue mechanical properties. Many injuries can cause changes in tissue stiffness, especially tumors and fibrosis. In recent years, various non-invasive ultrasound methods have been developed to study tissue elasticity for a large number of applications (breast, thyroid, prostate, kidneys, blood vessels, liver...). For non-invasive assessment of liver diseases, several ultrasound elastography techniques have been investigated: Transient elastography (the most extensively used), Real Time Elastography (RTE), Acoustic Radiation Force Impulse Imaging (ARFI) and more recently Shear Wave Elastography (SWE). Even if evaluation of liver fibrosis in chronic liver disease remains the principal application, there are many others applications for liver: predicting cirrhosis-related complications; monitoring antiviral treatments in chronic viral liver disease; characterizing liver tumors; monitoring local treatments, etc. The aim of this article is to report on the different hepatic ultrasound elastography techniques, their advantages and disadvantages, their diagnostic accuracy, their applications in clinical practice.

Introduction

Ultrasound imaging plays a major role in the diagnosis, monitoring and therapeutic decisions of chronic liver diseases. It has many clinical indications: morphological examination of the liver parenchyma and assessment of the risk of chronic liver disease by investigating

Abbreviations: A2M, Alpha-2 macroglobulin; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; APRI:, Aspartate to platelet ratio index [ratio of ALT (expressed as ''number of times the upper limit of normal'') × 100/platelets (10^9/L)]; ARFI, Acoustic Radiation Force Impulse Imaging; AST, Aspartate aminotransferase; AUROC, Area under the ROC curve (*receiver operating characteristic curve*); CPAM, French National Health Insurance system; FNH, Focal nodular hyperplasia; FS, FibroScan®; GGT, Gamma glutamyltranspeptidase; HA, Hyaluronic acid; HAS, French National Health Authority; HCC, Hepatocellular carcinoma; LB, Liver biopsy; NAFLD, non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NPV, Negative predictive value; OV, Oesophageal varices; PH, Portal hypertension; PPV, Positive predictive value; PT, Prothrombin time; ROI, Region of interest; RTE, Real Time Elastography; Se, Sensitivity; Sp:, Specificity; SWE, Shear Wave Elastography; US, Ultrasound.

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for signs of dysmorphism and/or portal hypertension; detecting and characterizing liver lesions; monitoring local treatments (such as percutaneous radiofrequency) and assessment of treatment response.

Conventional imaging techniques do not provide information on tissue mechanical properties although its stiffness may vary considerably. In addition, many diseases can lead to changes in tissue stiffness: tumors (particularly malignant) are generally stiffer than the normal surrounding tissue; fibrosis also causes a change in the organ stiffness (liver-kidney).

Liver fibrosis is a common pathway for several liver injuries. Viral (hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV)-HCV co-infection), autoimmune, hereditary, metabolic and toxin-mediated liver disease can result in hepatocellular dysfunction, expansion of extracellular matrix with distortion of hepatic architecture, portal hypertension and finally liver cirrhosis. Approximately 20 to 30% of patients with chronic liver disease develop cirrhosis. The incidence of cirrhosis is increasing due to the development of chronic hepatitis C, non-alcoholic fatty liver disease (NAFLD) and more specifically non-alcoholic steato-hepatitis (NASH); the latter one affecting almost 3% of the population in western countries. Liver fibrosis is therefore a major public health problem.

Different levels of fibrosis exist which in practice are assessed using a histological score. The most widely used is the METAVIR score, which incorporates five stages of fibrosis: F0 (no fibrosis), F1 (portal fibrosis without septa: minimal fibrosis), F2 (portal fibrosis with a few septa: moderate fibrosis or clinically significant fibrosis), F3 (septal fibrosis with many septa but no cirrhosis: severe fibrosis) and F4 (cirrhosis).

Staging liver fibrosis in patients with chronic liver disease is essential for patient management as it allows:

- firstly to identify the severity of the liver damage in order to decide whether or not to start treatment (chronic viral liver disease) to avoid progression to cirrhosis when the fibrosis becomes significant ($\geq$ F2);
- secondly to assess the progression or regression of liver fibrosis during treatment;
- lastly to institute specific monitoring to screen for and treat complications (HCC, oesophageal varices) in patients suffering from cirrhosis and even severe fibrosis ($\geq$ F3).

Conventional ultrasound cannot differentiate accurately the different liver fibrosis stages. Existing tools to assess liver fibrosis include liver biopsy (LB), which is invasive, and other non-invasive methods.

Up to recently, LB has been considered as the gold standard to assess activity and fibrosis in patients with chronic liver disease, and is still the reference method for assessing fibrosis. It can also be used to investigate the cause of liver disease and/or to assess other possible causes of concomitant liver disease. Despite its diagnostic utility, LB has several limitations, including patient reluctance, adverse events, accessibility, effective cost, sampling error, and intra- and inter-observer variability. Moreover, considering the fact that fibrosis is heterogeneously distributed in the liver, liver biopsy has been criticized because it evaluates only 1/50,000 of the total volume of the liver, due to the small volume of the tissue. For these reasons this technique is becoming increasingly challenged. As a result, non-invasive techniques for liver fibrosis assessment have been widely developed in clinical practice.

To assess liver fibrosis, two types of non-invasive methods exist [1]:

- the first one is based on blood serum markers. Single blood marker (such as hyaluronic acid) or an indirect ''score'' derived from a combination of blood markers can be used. While single markers exhibit insufficient sensitivity and specificity for fibrosis staging, indirect scores benefit from added diagnostic values of each marker and have sufficient diagnostic performance to avoid a number of biopsies. The three most widely used tests approved by the HAS in specific indications are the Fibrotest® [2], Hépascore® [3] and Fibromètre® [4], which use different combinations of blood serum markers indices. These different markers and their diagnostic performance are listed in Table 1 [1—6];
- the second one is based on a physical parameter that measures the tissue elasticity and is called elastography. Elastography techniques include transient elastography (FibroScan®), ARFI, Real Time Elastography, Shear Wave mode elastography and elasto-MR. Elastography can replace subjective palpation and is intended to image the mechanical properties of tissues and more particularly their stiffness. Tissue stiffness is described by the Young modulus expressed in kilopascals ($E = 3\gamma C^2$). The elastography methods are based on a common approach: measurement of deformation induced in a tissue by a force.

Elastography is therefore an application, which produces the force coupled with a measurement system for the deformities caused by the force. There are several types of forces or applications:

- static compression induced externally by manual compression or internally by organ motion (heart, vessel, breathing);
- dynamic compression induced with a continuous vibration at a given frequency;
- impulse compression (transient vibration): induced externally by a transient mechanical impulse (FibroScan®) or internally by an ultrasound impulse (ARFI, SWE), both compression types producing shear waves.

The aim of this article is to review the different ultrasound elastography techniques, their advantages and limitations, their diagnostic accuracy, and their applications in clinical practice for liver applications.

The different ultrasound elastography techniques

Impulse elastography

This technique uses an external mechanical device (FibroScan®) or an internal acoustic radiation force (ARFI and SWE) to induce shear waves in the tissue to be explored (Table 2). Shear wave propagation velocity (Vs) is then

Table 1 Characteristics and diagnostic performance of the main indirect blood serum markers to assess liver fibrosis, which can be used in clinical practice.

Tests	Variables	Disease	Diagnostic objective	Performance (AUROC)
APRI [5]	AST, platelets	HCV	F2 F4	0.76/0.80 0.82/0.89
Fib4 [6]	Age, AST, ALT, platelets	HIV-HCV	F2	0.76—0.85
Fibrotest [2]	A2M, GGT, haptoglobin, apoA1, total bilirubin	HCV	F2 F4	0.78/0.85 0.89—0.92
Hépascore [3]	Age, sex, HA, A2M, GGT, bilirubin	HCV	F2 F4	0.82/0.85 0.89/0.94
Fibromètre V virus [4]	Age, HA, A2M, PT, platelets, urea, AST	HCV, HBV	F2 F4	0.89 0.9
Fibromètre A alcohol	Age, HA, A2M, PT	Alcohol	F2	0.96
Fibromètre S fatty liver disease	AST, ALT, platelets, ferritine, blood glucose, weight, age	Fatty liver disease	F2	0.96

A2M: alpha-2 macroglobulin; PT: prothrombin time; HA: hyaluronic acid; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

Table 2 The principle techniques of elastography.

The different elastography techniques			
Real time	Dynamic	Impulse	
		Mechanical	Ultrasound
HI-RTE® (Hitachi)	MR Touch® (GE)	Fibroscan® (Echosens)	ARFI® (Siemens) Shear Wave® elastography (Supersonic Imaging)

measured in m/s using ultrasound imaging in the tissue being studied in order to assess its stiffness.

Uni-dimensional transient elastography: FibroScan®

Principle

The FibroScan® (Echosens, Paris, France) has been developed around 10 years ago and is based on shear wave, which is generated by an external mechanical impulse and whose speed is measured by an ultrasound one-dimensional probe. The one-dimensional probe (3.5 MHz) is mounted along the axis of an electro-dynamic transducer (vibrator). The FibroScan® estimates liver stiffness by measuring the velocity of elastic shear waves in the liver parenchyma generated by the mechanical push. The propagation velocity is directly related to the stiffness of the medium, defined by the Young modulus. Stiff tissues exhibit higher shear wave velocities than soft tissues. The elasticity is expressed in kPa (kilopascals) and is measured at depth ranging from 25 to 65 mm in a 1×4 cm area: the assessed liver volume is therefore two hundred times greater than the volume examined in a LB. The obtained values range from 2.5 kPa to 75 kPa. Mean liver elasticity in ''normal'' subject is 5.81 ± 1.54 and 5.23 ± 1.59 kPa respectively for men and women [7]. The measurement is painless and does not take more than 5 to 10 minutes (Fig. 1).

Patient examination

Patients are placed in the supine position, with the right arm in maximum abduction to make the right hypochondrium accessible and to increase intercostal space. Measurements are taken in the right lobe of the liver through an intercostal space at the intersection of the mid-axillary line and a transverse line at the level of the xiphoid process. The investigation involves ten measurements. The result produced by the instrument is expressed in kPa and is the median of ten measurements. The result is interpreted as a METAVIR equivalent score (F0 to F4) by the expert physician, which is based on elasticity cut-off values for fibrosis stages published in the literature for each chronic liver disease. The apparatus also displays the interquartile range (IQR) and success rate (number of measurements obtained as a function of the number of impulses applied).

Advantages

- It is a rapid, painless technique;
- the result is available immediately;
- it can be carried out by trained paramedical staff;

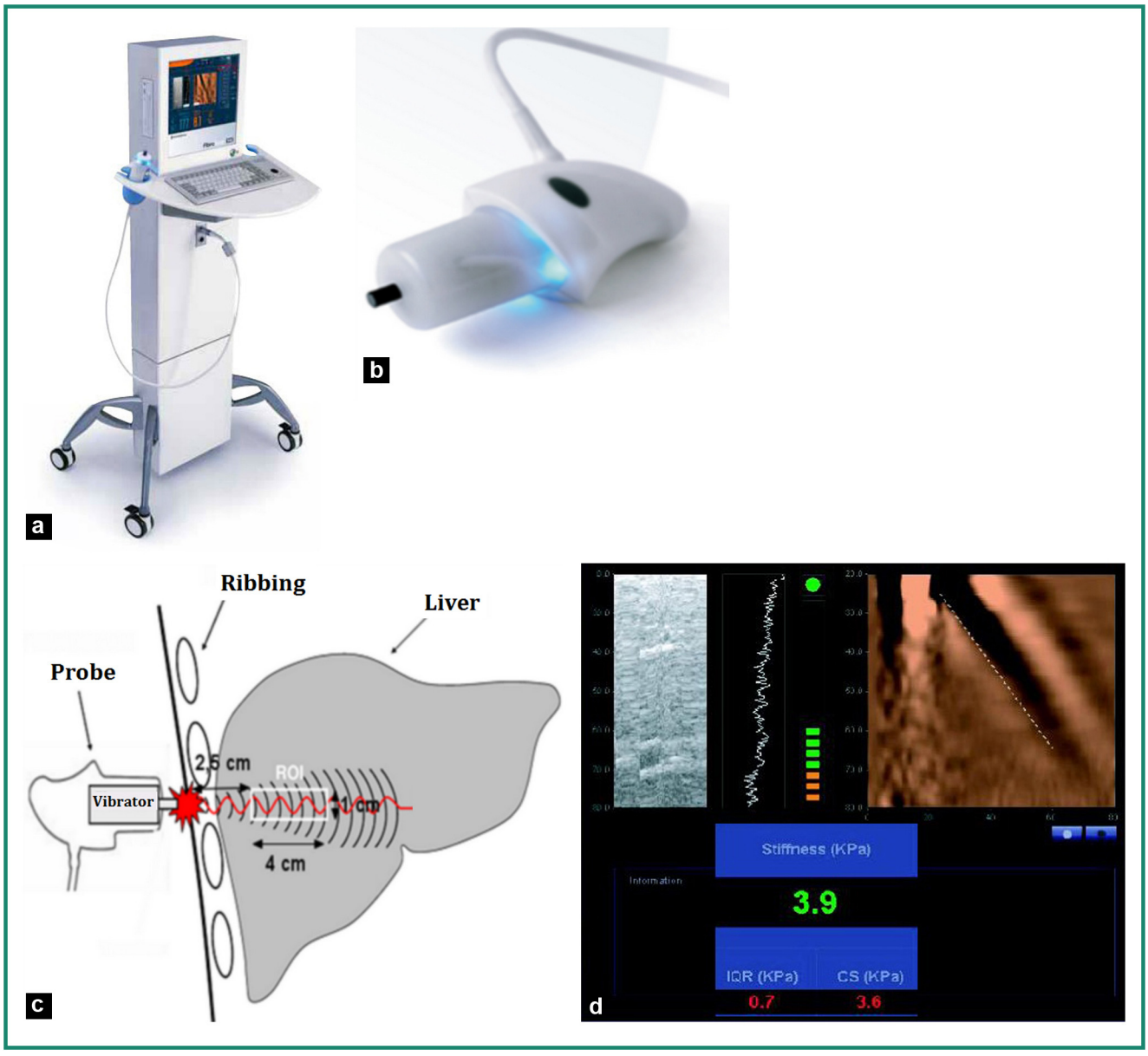

Figure 1. Fibroscan®: a: Fibroscan® instrument; b: Fibroscan® probe; c: diagram summarising the principle of a measurement; d: example of result produced by the device.

- intra- and inter-operator reproducibility is excellent with an intra-class correlation coefficient of 0.98 [8];
- it offers good diagnostic accuracy and has been described in many publications;
- it has been approved by the HAS to ''assess untreated chronic hepatitis C without comorbidities in adults who do not have a clear diagnosis of cirrhosis'' and in ''assessment of untreated chronic viral hepatitis C with HIV co-infection in adults without a clear diagnosis of cirrhosis'';
- it is recommended by the European Association for the Study of the Liver (EASL) in the management of patients with chronic viral hepatitis C [9].

Limitations

- Measurements are difficult when intercostal spaces are narrow, the chest wall is thick, in case of obesity, and are impossible in the presence of ascites. The average failure rate is 3.1% and highly depends on body mass index. Measurements are unreliable in 15.8% of cases [10]. The problem of overweight is being resolved with the development of an ''XL probe'', which has a reduced failure rate in obese patients (decreased from 59% for the M probe to 4.9% for the XL probe for patients with BMI over 40 kg/m^2) [11];
- the studied hepatic parenchyma is not visualized and therefore no precise knowledge is obtained about the studied segment. Lack of visualization of the studied area is a major limitation as the liver can be heterogeneous, with areas of steatosis and more or less fibrotic;
- the left side of the liver cannot be examined;
- the apparatus is expensive;
- there is a learning curve in order to obtain reliable acquisitions without ultrasound guidance;

- the system has not been coupled with ''standard clinical ultrasound'' and cannot provide liver morphological examination.

Applications and diagnostic performance

The FibroScan® is used mostly to assess liver fibrosis in chronic liver disease.

Diagnostic performance in assessing liver fibrosis. In recent years, many prospective studies have examined the diagnostic performance of the FibroScan® for liver fibrosis staging in chronic liver disease: viral hepatitis C [12], viral hepatitis B [13], HIV-HCV co-infection [14,15], alcoholic liver disease [16] and NAFLD [17].

In most of the world, LB is still considered the reference test to determine liver fibrosis stages. As a result, all diagnostic technique performance studies for liver fibrosis staging have compared the non-invasive test results to LB histological score (METAVIR). A diagnostic tool is defined as being perfect if the area under the ROC curve (AUROC) is 100%, excellent if the AUROC is over 90%, and good if the AUROC is over 80% [18]. However, the diagnostic performance of LB in significant fibrosis is only moderate (AUROC approximately 0.8). It is therefore difficult to precisely determine the performance of non-invasive markers to diagnose significant fibrosis, as the reference test itself is less than perfect.

In chronic hepatitis C fibrosis staging studies, AUROC of TE ranged from 0.77 to 0.90 for the assessment of significant fibrosis ($F \geq 2$), and from 0.90 to 0.97 for assessment of cirrhosis respectively [12,19—21].

Similar results have been found in other diseases such as chronic hepatitis B and HIV-HCV co-infection. It appears, however, that the performance of the FibroScan® is slightly poorer in the diagnosis of alcoholic cirrhosis (AUROC = 0.88) than for viral cirrhosis (AUROC = 0.94).

AUROC values in chronic viral hepatitis B ranged from 0.81 to 0.95 for METAVIR fibrosis scores of $F \geq 2$ and from 0.80 to 0.98 for the diagnosis of cirrhosis [13,22—24].

AUROC values ranged from 0.72 to 0.87 for METAVIR fibrosis scores of $F \geq 2$ and from 0.87 to 0.99 for the diagnosis of cirrhosis [14,15] in HIV-HCV co-infection. Finally and more recently, studies have shown the utility of the FibroScan® in assessing fibrosis in non-viral liver disease such as primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease and even in some patients on methotrexate [25—28].

The diagnostic performance of the FibroScan® has been examined in four meta-analyses [29—32]. Mean AUROC for diagnosis of significant fibrosis and cirrhosis in the meta-analysis which included the largest number of studies ($n = 50$) were 0.84 and 0.94, respectively [30].

Basis of interpretation: what cut-off values should be used for liver fibrosis? While FibroScan® result is not operator-dependent, interpretation of the result is part of the overall diagnosis process and must take into account all the disease clinical, biological, and morphological findings. Interpretation of the FibroScan® depends on the reliability of the measurement, the pathology and the clinical endpoint and goal (sensitivity, specificity, positive predictive value and negative predictive value).

In terms of the result quality, the measurement is deemed to be ''reliable'' if the success rate is over 60%, the interquartile range (IQR) is less than 30% of the median value even below 21% for certain authors [8,33]. Elasticity values should also be interpreted with caution in thin subjects, as a body mass index of under 19 k/m^2 is associated with greater discordance between fibrosis and hepatic elasticity.

In terms of pathology, it is important to distinguish acute hepatitis in which ''elasticity'' values are raised and correlate with transaminase levels, from chronic liver disease. It is essential in chronic liver disease to interpret liver elasticity values according to the etiology. Cut-off values offering maximum sensitivity, specificity and positive and negative predictive values vary depending on etiologies and for different studies. In chronic viral hepatitis C, cut-off values range from 6.2 to 8.7 kPa to predict a METAVIR fibrosis score of $F \geq 2$ and from 9.6 to 14.8 kPa for the diagnosis of cirrhosis [12,19—21]. In chronic viral hepatitis B, the cut-off values range from 6.3 to 7.9 kPa to predict a METAVIR fibrosis score of F ≥$2 and from 9 to 13.8 kPa for the diagnosis of cirrhosis [13,22—24]. In HIV-HCV co-infection, the cut-off values range from 4.5 to 9.3 kPa for a METAVIR fibrosis score of $F \geq 2$ and from 11.8 to 14 kPa for the diagnosis of cirrhosis [14,15].

Table 3 summarizes the diagnostic performance and optimal cut-off values to diagnose fibrosis stages $F \geq 2$, $F \geq 3$ and $F = 4$ [8,12—15,19—21,23,24,26,29,30,34—38].

Optimal cut-off values in Friedrich's meta-analysis were 7.6 and 13.01 kPa [30], for the diagnosis of significant fibrosis (≥ F2) and cirrhosis (= F4) respectively. Most of the studies included in this meta-analysis were based on western populations with isolated HCV infection and consequently, it would be unwise to apply these cut-off values from previous meta-analysis to patients with diverse chronic liver disease etiologies. Finally, some authors do not consider it reasonable to interpret a FibroScan® value against a cut-off, but rather according to a likely ''range'' of correlation between liver fibrosis and the FibroScan® value in which these ''ranges'' vary depending on etiology [39].

Acoustic Radiation Force Impulse Imaging mode elastography

Principle

Acoustic Radiation Force Impulse (ARFI) imaging is a new method for quantifying mechanical properties of tissue, without manual compression, by measuring the shear wave velocity induced by acoiustic radiation and propagating in the tissue. This technique has been developed by Siemens and is available on Acuson S2000 and S3000 ultrasound diagnostic imaging devices (Issaquah, WA, USA), and on the iU22 diagnostic imaging device developed by Philips (Bothell, WA, USA). This quantitative technique provides a single uni-dimensional measurement of tissue elasticity like the FibroScan®, although the measurement area can be positioned on a two-dimensional Bmode image. The region is a 1×0.5 cm rectangular, which can be freely moved in the two-dimensional Bmode image to a maximum depth of 8 cm from the skin plane. The measurement is expressed in m/s, expressing shear wave speed, travelling perpendicular to the shear wave source. The technique has been implemented on the ultrasound probe designed for abdominal imaging (Fig. 2).

Patient examination

Elastrography measurements can be performed just after morphological and Doppler vascularization examination of

Table 3 Performance of the Fibroscan® and cut-off values to diagnose significant fibrosis (F ≥ F2), severe fibrosis (F ≥ F3) and cirrhosis (F = F4).

Authors	Patients(*n*)	Diseases	AUROC FS			Cut-off values FS (kPa)		
			≥ F2	≥ F3	= F4	≥ F2	≥ F3	= F4
Ziol et al. [12]	251	HCV	0.79	0.91	0.97	8.8	9.6	14.6
Castera et al. [19]	183	HCV	0.83	0.9	0.95	7.1	9.5	12.5
Rigamonti et al. [34]	90	HCV	0.93	0.97	–	7.8	12	–
Carrion et al. [35]	124	HCV	0.9	0.93	0.98	8.5	–	12.5
Arena et al. [20]	150	HCV	0.91	–	0.98	7.8	–	14.8
Nitta et al. [36]	165	HCV	0.88	–	0.9	7.1	9.6	11.6
Sirli et al. [37]	150	HCV	0.77	–	0.97	6.8	–	13.3
Kim et al. [21]	91	HCV	0.9	–	0.97	6.2	–	11
Marsellin et al. [13]	173	HBV	0.81	0.93	0.93	7.2	–	11
Zhu et al. [23]	175	HBV	0.95	–	0.98	7.9	–	13.8
Ogawa et al. [24]	44	HBV	0.86	–	0.89	6.3	–	12
Corpechot et al. [26]	95	Cholestatic diseases	0.92	0.95	0.96	7.3	9.8	17.3
Fraquelli et al. [8]	200	All liver diseases	0.84	0.87	0.90	7.9	10.3	11.93
Gomez-Dominguez [38]	103	All liver diseases	0.74	0.72	0.94	5	11	16
De ledinghen et al. [14]	72	HIV-HCV	0.72	0.91	0.97	4.5	–	11.8
Vergara et al. [15]	169	HIV-HCV	0.88	–	0.95	7.2	–	14.6
Friedrich-Rust et al. [30]	[a]	All liver diseases	0.84	0.89	0.94	7.6	–	13.01
Talwalkar et al. [29]	[a]	All liver diseases	0.87	–	0.96			

AUROC: area under the ROC curve; FS: FibroScan®; HCV: hepatitis C virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus.
[a] Meta-analysis.

the liver. Patients are placed in the supine position, with the right arm in maximum abduction to make the right hypochondrium accessible and to increase intercostal space (to improve the acoustic window). The probe is placed parallel to the intercostal space within the space with sufficient gel in order to minimize rib shadowing. The region of interest is positioned within the liver parenchyma under visual control in two-dimensional B-mode, distant from vessels and 2 cm beneath the Glisson's capsule [40]. When ARFI is activated, the measurement (m/s) is displayed on the screen after a few seconds. The manufacturer has not given any recommendations/guidelines about the practical process for an examination. In practice, ten measurements are taken in the right lobe of the liver, in the intercostal space with the patient holding his/her breath gently. Measurement should be avoided after deep inspiration, which increases ARFI values significantly by an average of 13% [41]. The median, mean and standard deviation of the ten measurements are calculated (for the Philips device only).

Advantages

- It is an easy, rapid, painless technique;
- results are available after a few seconds;
- intra-operator (intra-class correlation coefficient ICC = 0.9) and inter-operator (ICC = 0.81) producer ability is good [42];
- visual control of measurement location unlike FibroScan®, with the ability to:
  - avoid vascular structures when taking measurements,
  - study regions of interest (area of steatosis, liver with tumor),
  - correlate elasticity to the tissue architecture seen (necrosis, steatosis),
  - study the right and left lobes of the liver;
- the ability to select the measurement depth, unlike the FibroScan®;
- good diagnostic performance: although still undergoing assessment this technique has already appeared in many publications;
- ARFI is incorporated onto a conventional ultrasound diagnostic imaging device, which allows the combination, in one exam, of quantitative elastography after a complete morphological ultrasound examination of the liver (to investigate for signs of cirrhosis, portal hypertension and to identify focal lesions).

Limitations

- The elasticity measurement is not given in real time;
- the elasticity measurement cannot be performed retrospectively;
- only one acquisition can be taken at a time;
- the measurement region is a small, predetermined area, the size of which cannot be changed;
- only the mean shear wave speed of the measurement region is calculated, with no information about the standard deviation;
- there are no quality criteria to accept or exclude the measurement;
- the technique has not been validated as extensively as transient elastography (FibroScan®).

Application and diagnostic performance

The main indications of ARFI in the liver are assessment of fibrosis and characterization of hepatic tumors.

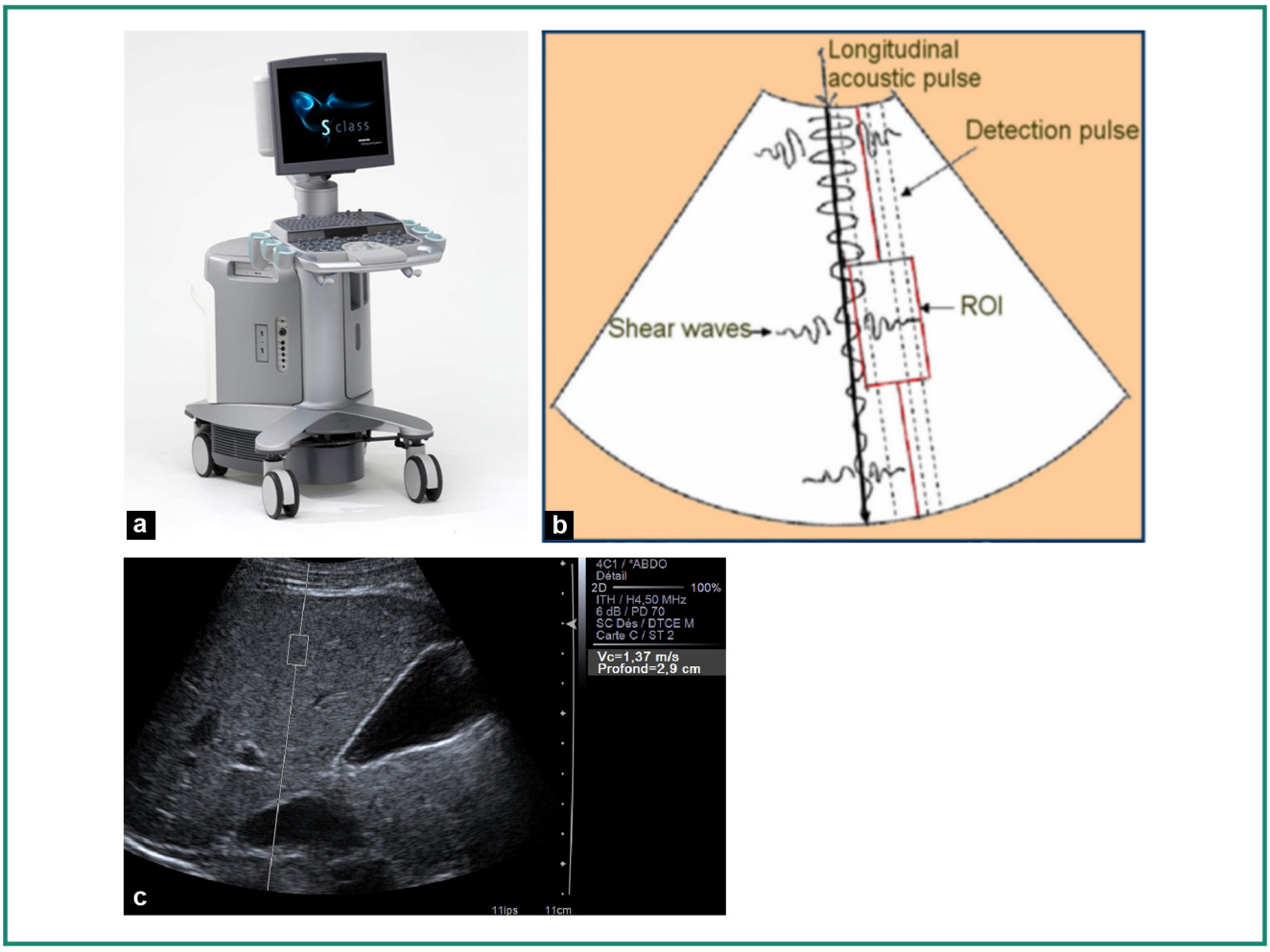

Figure 2. ARFI: a: ultrasound diagnostic imaging device onto which the ARFI® software has been implemented; b: diagram summarizing the principle of a measurement with the ''Virtual Touch Tissue Quantification Imaging'' system; c: example of result produced by the device.

Diagnostic performance in the assessment of liver fibrosis. Although it has been less investigated than transient elastography, diagnostic performance of ARFI is showing promises. AUROC values in a study conducted by Sporea et al. on 274 patients with isolated HCV infection were calculated retrospectively to be 0.893, 0.908 and 0.937 to predict fibrosis stages $F \geq F2$, $F \geq F3$ and $F = F4$ [43] respectively. AUROC values in a meta-analysis performed by Friedrich-Rust, which included 518 patients with combined chronic liver diseases, were calculated retrospectively to be 0.87 to diagnose significant fibrosis ($F \geq 2$), 0.91 to diagnose severe fibrosis ($F \geq 3$), and 0.93 to diagnose cirrhosis [44]. Overall, ARFI can be considered to be an adequate diagnostic technique for the assessment of fibrosis, particularly in chronic viral hepatitis C (where the AUROC is > 0.8 regardless of the stage of fibrosis). A comparative meta-analysis of the diagnostic performance of ARFI and the FibroScan®, however, showed that results varied depending on the study. The diagnostic performance results for ARFI in the different studies are summarized in Table 4 [40,45—54]. The diagnostic performance of ARFI and FibroScan® was identical to predict severe fibrosis, regardless of the study author [40,45,46] whilst for some authors, the diagnostic performance of the FibroScan® appeared to be better than the ARFI [40,46] to predict $F \geq 1$ or $F \geq 2$ and was the same according to other authors [45]. More recently, Rizzo et al. have shown ARFI to perform better than FibroScan® regardless of fibrosis stage [52]. The comparison of ARFI with FibroScan® in 312 patients from four different studies in the meta-analysis by Friedrich-Rust showed results to be similar for the two techniques to predict severe fibrosis and slightly superior performance for the FibroScan® to diagnose significant fibrosis and cirrhosis [44]. The number of patients involved, however, was not large enough to draw definitive conclusions.

Bases for interpretation — what cut-off values should be used for liver fibrosis? The interpretation of an ARFI examination depends amongst other things on the reliability of the measurements and the etiology. Although the manufacturer has not produced any recommendations about the reliability of the measurements, some authors recommended that the same criteria are used as for the FibroScan® (success rate $\geq$ 60% and IQR < 30%) [55].

The cut-off values used to define the different stages of fibrosis as METAVIR equivalents vary with etiologies and publication. The diagnostic performance and cut-off values for the different stages of fibrosis are shown in Table 4. In Friedrich's meta-analysis these cut-off values were 1.34 m/s, 1.55 m/s and 1.80 m/s to predict fibrosis

Table 4 Performance of the Fibroscan® and Acoustic Radiation Force Impulse Imaging (ARFI) and optimal cut-off values for ARFI to diagnose significant fibrosis ($F \geq F2$), severe fibrosis ($F \geq F3$) and cirrhosis ($F = F4$).

Authors	Patients(*n*)	Diseases	AUROC Fibroscan®			AUROC ARFI			ARFI cut-off values (m/s)		
			$\geq F2$	$\geq F3$	$= F4$	$\geq F2$	$\geq F3$	$= F4$	$\geq F2$	$\geq F3$	$= F4$
Friedrich-Rust et al. [45]	70	HCV	0.84	0.9	0.91	0.82	0.91	0.91	1.35	1.55	1.77
Lupsor et al. [46]	112	HCV	0.941[a]	0.926	0.945	0.851[a]	0.869	0.911	1.34	1.61	2
Takahashi et al. [47]	55	Chronic liver disease	—	—	—	0.94	0.94	0.96	1.34	1.44	1.8
Fierbinteanu-Braticevici et al. [48]	74	HCV	—	—	—	0.972	0.993	0.99	1.21	1.54	1.94
Goertz et al. [49]	57	HCV—HBV	—	—	—	0.85	0.92	0.87	—	—	—
Yoneda et al. [50]	54	NAFLD	—	0.99	0.998	—	0.973	0.976	—	1.77	1.9
Sporea et al. [40]	114	Chronic liver disease	0.908[a]	—	0.99	0.767[a]	—	0.95		—	1.78
Sporea et al. [53]	223	Chronic liver disease	0.953[a]	—	0.985	0.89[a]	—	0.931	1.27	—	1.7
Rizzo et al. [52]	139	HCV	0.78[a]	0.83[a]	0.8[a]	0.86[a]	0.94[a]	0.89[a]	1.3	1.7	2
Sporea et al. [51]	197	HCV	0.87	—	0.97	0.84	—	0.91	1.2	—	1.8
Friedrich-Rust et al. [44]	518 (ARFI)	Chronic liver disease	—	—	—	0.87	0.91	0.93	1.34	1.55	1.8
Sporea et al. [54]	911 (ARFI)	HCV	—	—	—	0.792	0.829	0.842	1.33	1.43	1.55
	400 (FS)		0.818	0.866	0.932	0.813	0.862	0.885	1.36	1.47	1.69

FS: FibroScan®; HCV: hepatitis C virus; HBV: hepatitis B virus; NAFLD: non-alcoholic fatty liver disease; AUROC: area under the ROC curve.
[a] Statistically different significance between the diagnostic performance of the two techniques.

stages $F \geq 2$, $F \geq 3$ and $F = 4$, in combined chronic liver diseases, [44]. The cut-off values in Sporea's multicentre study were 1.33 m/s (AUROC = 0.792), 1.43 m/s (AUROC = 0.829) and 1.55 m/s (AUROC = 0.842) to predict fibrosis of $F \geq 2$, $F \geq 3$ and $F = 4$ respectively in patients with chronic hepatitis C [54].

Shear Wave Elastography® (SWE)

Principle

Shear wave elatography (SWE) was introduced in 2005 on the diagnostic Imaging device, called Aixplorer™ (SuperSonic Imagine, Aix-en-Provence, France). It relies on the measurement of the shear wave propagation speed in soft tissue; Like ARFI, it does not require an external vibrator to generate the shear wave. It is based on the generation of a radiation force in the tissue to create the shear wave. The ultrasound probe of the device produces a very localized radiation force deep in the tissue of interest. This acoustic radiation force/push induces a shear wave, which then propagates from this focal point. Several focal points are then generated almost simultaneously, in a line perpendicular to the surface of the patient's skin. This creates a conical shear wave front, which sweeps the image plane, on both sides of the focal point. The progression of the shear wave is captured by the very rapid acquisition of ultrasound images (up to 20,000 images per second), called UltraFast™ Imaging. The acquisition takes only a few milliseconds, thus the patient or operator movement does not impact the result. A high-speed acquisition is necessary to capture the shear wave as it moves at a speed in the order of 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 intrinsically linked to elasticity. The propagation speed of the shear wave is then estimated from the movie that is created and a two-dimensional color map is displayed, for which each color codes either the shear wave speed in meters per second (m/s), or the elasticity of the medium in kilopascals (kPa). This color map is accompanied by an anatomic reference gray scale (or B-mode) image. This quantitative imaging technique is a real-time imaging mode. Quantitative measurements can be performed in the color window by positioning one or more ROI (regions of interest) called Q-Box. The Q-Boxes are variable in size (from 3 mm^2 to 700 mm^2). Measurements can be performed retrospectively from the saved image or cineloop. The measurements provided by Q-Box are the mean, standard deviation, and minimum and maximum elastography values. Results are given in m/s or kPa (Figs. 3 and 4).

Process of the investigation

As for ARFI, SWE acquisition can be performed just after a complete morphological and Doppler vascularization examination of the liver. Patients are placed in the supine position, with the right arm in maximum abduction to make the right hypochondrium accessible and to increase intercostal space (to improve the acoustic window). The probe is placed parallel to the intercostal space within the space with sufficient gel in order to minimize rib shadowing. To insure reliable SWE acquisition and contrary to what has been recommended as a rule for most of the organs, a pressure must be applied to the probe when scanning the liver. It allows a better acoustic coupling by opening the rib space and decreasing tissue thickness between the probe and the ribs (The ribs will absorb the pressure and the elasticity of the liver will not be impacted). When SWE is activated, a real time two-dimensional box appears overlaid on the B-mode with an elastography map. The window is positioned within the liver parenchyma, avoiding artifact from vessels and 2 cm beneath the Glisson's capsule. It is essential that the operator waits for 2 to 3 seconds in order for the signal to stabilize before freezing. The 2D acquisition window offers a qualitative approach to the stiffness of the tissue using color mapping. Measurements are taken with patients holding their breath gently, without deep inspiration. The manufacturer recommends that three acquisitions be taken in the same area of liver parenchyma and that the average of the values provided by the Q-Box be calculated (Fig. 3). The

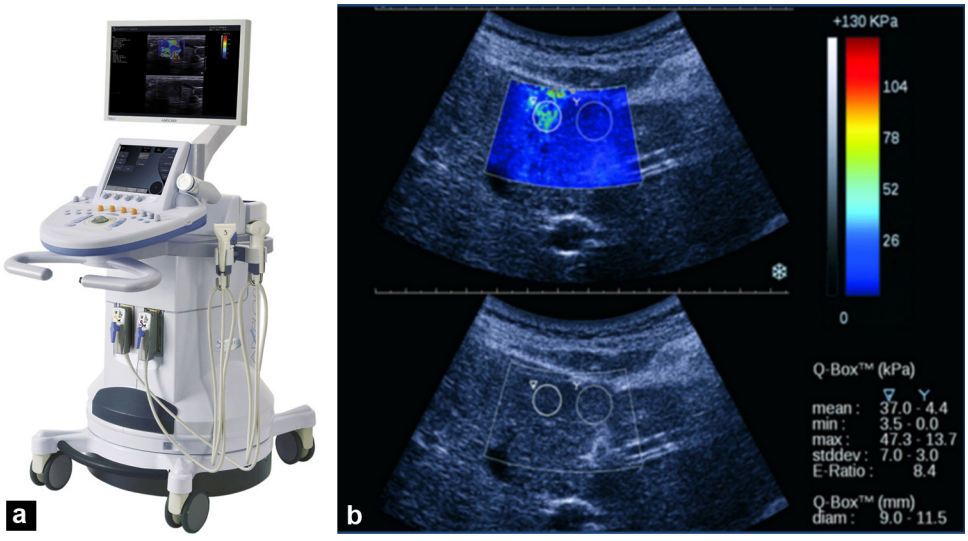

Figure 3. Shear Wave elastography: a: ultrasound diagnostic imaging device onto which Shear Wave elastography software has been implemented; b: example of result provided by the instrument: color mapping and Qbox.

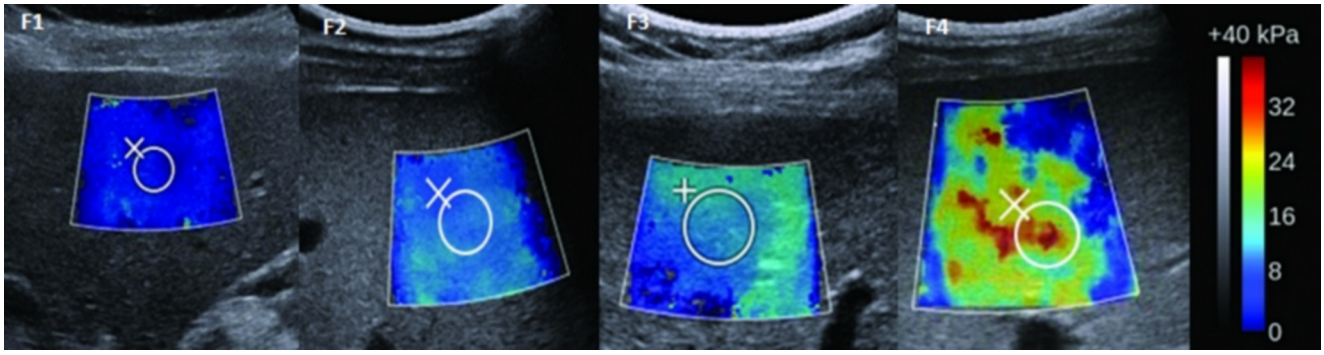

Figure 4. Shear Wave elastography: the different stages of fibrosis in color mapping.

temporal stability is also a good criteria to insure reliable SWE acqusitions.

Advantages
- It is an easy, painless, rapid technique;
- good intra-operator reproducibility with an intra-class correlation coefficient of 0.95 when measurements are taken the same day and 0.84 when they are taken at different days by the same operator [56];
- good inter-operator reproducibility (ICC = 0.88) [56];
- the result is immediately available;
- SWE is incorporated onto a conventional ultrasound diagnostic imaging device, which allows the combination, in one exam, of quantitative elastography assessment of the liver fibrosis and/or tumor after the morphological ultrasound examination of the liver (to investigate for signs of cirrhosis, portal hypertension and to identify focal lesions);
- quantitative assessment of soft tissue elasticities in kPa or in m/s;
- real time two-dimensional map of tissue elasticities;
- visual control of measurement location unlike FibroScan®, with the ability to:
  - avoid vascular structures when performing acquisition,
  - study regions of interest (area of steatosis, liver with tumor) and visualize the spatial distribution of fibrosis,
  - correlate elasticity to the tissue architecture seen (necrosis, steatosis),
  - study the right and left lobes of the liver;
- the ability to select the measurement depth, and an area free of SWE artifact (due to vessels, Glisson's capsule, or other lesions);
- the ability to perform several measurements retrospectively on saved images on the device;
- the ability to choose the size of the ''Q-Box'';
- results expressed and displayed in kPa or m/s.

Limitations
It is a recent technique, which needs to be evaluated, although initial results are promising.

Applications and diagnostic performance
As for ARFI, the main indications are assessment of liver fibrosis and examination of liver tumors.

Diagnostic performance in the assessment of liver fibrosis. As this is a more recent technique, there are few published studies at present. The calculated AUROC values in the study performed by Ferraioli et al. were 0.92 and 0.84 for Shear Wave elastography and FibroScan® respectively to differentiate F0-F1 compared to F2-F4, 0.98 and 0.96 to distinguish F0-F2 compared to F3-F4, and 0.98 and 0.96 to distinguish F0-F3 compared to F4. According to this study, Shear Wave elastography performs better than the FibroScan® to diagnose significant fibrosis ($\geq$ F2) [57]. Other studies, however, are needed to draw definitive conclusions.

Bases for interpretation — what cut-off values should be used for liver fibrosis?. The optimal cut-off values for SWE are for the different fibrosis stages 7.1 kPa for F $\geq$ 2; 8.7 kPa for F $\geq$ 3 and 10.4 kPa for F = 4 respectively [57].

Static elastography

Static elastography

Principle
The initial systems were developed by Hitachi (EUB-8500, EUB 900). The operator manually applies gentle pressure with the ultrasound probe in order to induce in the underlying tissues a deformation. In this situation, only the deformed tissue subject to the manual compression is measured, rather than a direct measurement of elasticity. The deformation is considered to be inversely proportional to elasticity. A color map of tissue elasticity is obtained: this is a qualitative approach (Fig. 5). In more recent systems, the deformation of the liver parenchyma as a result of vascular beating or respiration alone has also been used (Philips, Hitachi...).

Advantages
- It is a fast, painless, reproducible technique;
- ascites is not a limiting factor;
- visual control of measurements;
- the results are immediately available;
- real time elastography is incorporated onto a conventional ultrasound diagnostic imaging device, which allows the combination, in one exam, of elastography assessment of the liver fibrosis and/or tumor after the morphological ultrasound examination of the liver (to investigate for signs of cirrhosis, portal hypertension and to identify focal lesions).

Limitations
- It is a non-quantitative technique;
- it is operator-dependent (for manual compression systems);

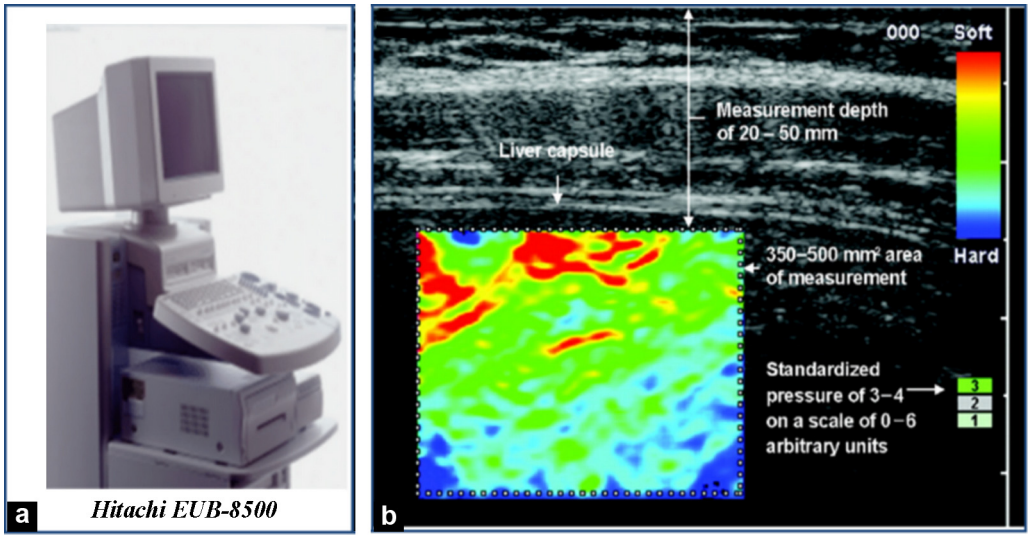

Figure 5. Standard elastography: Hi-RTE: a: ultrasound; b: example of measurement [58].

- lack of information in the literature;
- lack of standardization for the technique.

Process of an investigation

Patients are positioned on their back with their right arm raised behind their head. The depth of elastography measurement ranges from 20 to 50 mm with a region of interest of 350 to 500 mm^2. The results are deemed to be reliable if the manual pressure exercised is 3—4 on an arbitrary scale ranging from 0 to 6 (Fig. 5). Ten acquisitions are taken from the right lobe of the liver in the intercostal space with free respiration. The ''relative elasticity'' of the tissue is determined and represented on a color map on conventional B mode imaging. Hard tissues appear in blue and soft tissues in red. Different elasticity scores have been described [58—60].

Application and diagnostic performance

The main applications are measurement of liver fibrosis and an investigation of liver tumours.

Diagnostic performance for the assessment of liver fibrosis and basis for interpretation. Different elasticity scores have been published up to now in the literature:

- the ''German elasticity'' score (between 65 and 122), with calculated AUROC values of 0.75 for a diagnosis of significant fibrosis ($F \geq 2$), 0.73 for a diagnosis of severe fibrosis ($F \geq 3$), and 0.69 for a diagnosis of cirrhosis [58];
- the ''Japanese elasticity'' score (between 0 (blue) and 255 (red)) [59];
- the liver fibrosis index, with AUROC values of 0.784 to differentiate F0-F1 from F3-F4, and 0.803 to differentiate F0-F3 from F4 [60].

Whilst the initial publications showed that the RTE technique did not perform better than the other non-invasive methods, the technology has been improved since then and more recent studies have shown more encouraging results [61,62].

Colombo et al. compared the diagnostic performance of three ultrasound elastography techniques: ARFI, FibroScan® and a new real-time elastography technique (RTE). There was no significant difference between the three techniques in the diagnosis of cirrhosis (calculated AUROC values of 0.922, 0.934 and 0.852 for the FibroScan®, ARFI and RTE respectively). The FibroScan®, however, performed as well as ARFI but significantly better than RTE to predict significant fibrosis (calculated AUROC values of 0.897, 0.815 and 0.751 respectively) [63]. Finally, although the latest results obtained with the new RTE technique appears to open new future prospects for this type of liver elastography, this approach is still too limited in terms of diagnostic performance to be recommended in clinical practice.

Application of US elastography techniques

Apart from fibrosis assessment indication, the applications of US elastography to the liver are prediction of cirrhosis-related complications, characterization of focal lesions, and monitoring interventional radiology treatments.

Assessment of fibrosis

Which method(s) should be chosen to assess liver fibrosis?

HAS recommendations for assessment of liver fibrosis in chronic liver disease

To diagnose cirrhosis [64].

- In isolated chronic hepatitis C without co-morbidities and not previously treated: a non-invasive test is recommended such as shear wave based elastography (Fibroscan®, ARFI or SWE) or blood serum marker test (Fibrotest®, FibroMètre® or Hépascore®), as first intention test. At the second intention test, a non-invasive test and/or needle liver biopsy are recommended;
- in HIV-HCV co-infection: a non-invasive test such as shear wave based elastography (Fibroscan®, ARFI or SWE) or blood serum marker test (Fibrotest®, FibroMètre® or Hépascore®), is recommended as a first intention test, with LB as second intention test;

- a needle liver biopsy must be performed for all other etiologies and treatment cases.

To diagnose fibrosis, regardless of stage [65]. In chronic hepatitis C infection in an untreated adult and in the absence of a concomitant cause or co-morbidity, hepatic fibrosis may be assessed first line from a non-invasive test (impulse elastography or Fibrotest®). The limitations of the use of these two techniques must be understood. Their results must be interpreted taking account the clinical context and by a trained clinician. If the result of the non-invasive test is not consistent with the clinical situation, or if the test fails technically (impulse elastography) or if an abnormality is present hindering interpretation (Fibrotest®), another diagnostic method is required. Use of the second validated non-invasive method would appear to be logical if it can be performed and can be interpreted. Another possible option is a LB either initially or if the results of two non-invasive tests are inconsistent.

In other situations, such as chronic hepatitis C in a treated patient, or if a concomitant cause or co-morbidity is present, and in chronic liver disease due to other causes (particularly alcohol or HBV) and in childhood liver disease, the only currently validated assessment method for liver fibrosis remains LB.

Similarly, to monitor patients suffering from chronic liver disease or to assess the results of antiviral treatments:

- performing the shear wave based elastography in combination with blood serum marker test has not been validated today to assess progression of liver lesions because of insufficient data;
- finally, the combination of shear wave based elastography in combination with blood serum marker test has not yet been validated to assess the results of antiviral treatments.

In practice

It appears obvious that in the near future there will not be a single method used in preference but a combination of several non-invasive methods, leading to patient management algorithms. New approaches involving combining the non-invasive methods have recently been established in order to improve diagnostic performance. The Castera algorithm, which combines the FibroScan® and Fibrotest®, can be used to avoid liver biopsy in approximately 75% of cases [19,66] (Fig. 6). The algorithm by Boursier et al., which combines the Fibromètre® and FibroScan®, can avoid biopsy in 80% of cases [67]. Sporea et al. have also shown that the combination of FibroScan® and ARFI can increase the specificity for the diagnosis of significant of fibrosis with a PPV 96.8% when the two techniques are combined to predict $F \geq 2$, and an NPV of 94.4% to predict F4 [51].

Reimbursement of non-invasive methods by the French National Health Insurance system

Tests for measurement of liver elasticity using impulse elastography and serum marker tests for the assessment of liver fibrosis (Fibrotest®, Fibromètre® or Hépascore®) are reimbursed by the French National Health Insurance funds since May 2011, only within the indications recommended by the HAS and to a limit of once a year except if risk factors of rapid progression to cirrhosis are present. The reimbursement for the shear wave based elastography procedure is 31.29 euros in France.

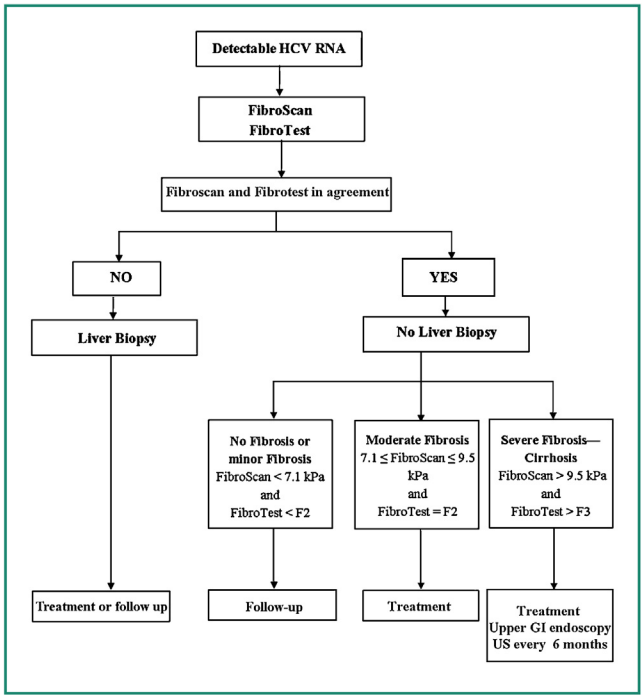

Figure 6. Algorithm from Castera et al. [19].

Caution in the interpretation of non-invasive methods

While elastography techniques have good diagnosis performance, the interpretation of their results is part of the overall diagnosis process and must take into account all the disease clinical, biological, and morphological findings. Interpretation of the elastography results depends on the reliability of the measurement, the pathology and the clinical endpoint and goal (sensitivity, specificity, positive predictive value and negative predictive value). Cut-off values have been validated for each elastography technique in order to determine the different stages of fibrosis as METAVIR equivalents. Stiffness is not ''synonymous to fibrosis'' and other confounding factors may influence elastography results: extra hepatic cholestasis [68], liver congestion [69], acute hepatitis and cytolytic changes, and necrotic and inflammatory lesions [70,71]. Results must be interpreted by a doctor who is an expert in ''hepatic elasticity''.

Prediction of cirrhosis-linked complications

Prediction of development of oesophageal varices (OV)

Various publications have assessed the utility of the FibroScan® and ARFI in predicting development of portal hypertension and oesophageal varices [72—76]. Several studies have demonstrated a significant correlation between FibroScan® values and the presence of oesophageal varices [72—74]. Although results are encouraging, diagnostic performance varies according to the studies (AUROC values

range from 0.76 to 0.85 for the FibroScan® and from 0.58 to 0.9 for ARFI) and considerable variations exist in the cut-off values. For these reasons, impulse elastography cannot at present be used to select patients who need to undergo endoscopy. Other studies are therefore necessary, probably in the future using a combination of several factors to increase diagnostic accuracy.

Prediction of development of hepatocellular carcinoma

Several studies have shown that the risk of developing HCC increases in parallel with hepatic elasticity values: patients with higher FibroScan® values are at greater risk of developing HCC. In addition, elasticity values are considered to be an independent risk factor for developing HCC [77]. Vermehren et al. compared the diagnostic performance of ARFI in the liver and spleen to that of the FibroScan® and the Fibrotest® in predicting the development of HCC in patients with cirrhosis. The diagnostic performance results (AUROC) for predicting development of HCC were 0.54, 0.58, 0.56 and 0.72 for ARFI in the liver, ARFI in the spleen, the FibroScan® and the Fibrotest® [76] respectively.

Assessment of the efficacy of antiviral treatments

Several publications have studied the utility of elastography techniques to assess the effectiveness of antiviral and/or anti-fibrosing treatment by monitoring changes in liver ''elasticity'' in populations of patients with isolated HCV and HBV infection [24,78,79]. Liver elasticity falls after antiviral treatment in parallel to virological response, although interpretation of these reduced values is difficult and must not lead to the patient's usual treatment being changed.

Characterization of liver tumors

Only a few authors have studied the utility of elastography for the characterization of liver tumors and the differentiation between benign and malignant tumors [80—86]. Table 5 summarizes the results, conclusions and limitations of each of these publications. Results vary according to the publication, some authors reporting that it is possible to differentiate benign from malignant tumors [80,82,83,85], whereas others do not have equivalent results [84,86]. The differences depend on a large number of factors: the proportions and type of tumor included in each of the two benign and malignant groups, whether or not the tumor is homogeneous, the composition of the tumor, the regions where measurements were performed, particularly with the ARFI technique whose region of interest is small. Our group has correlated quantitative ARFI values found in each tumor type with histological findings and shown that large variations in ARFI measurements can be seen between each type of tumor and also within the same tumor type because of tissue heterogeneity [86]. These variations are increasingly pronounced with larger heterogeneous tumors. Elastography measurements are very dependent on the composition of the tissue (necrosis, hemorrhagic change, the presence of a colloid component, congestion, sinus distension, peliosis, fibrosis, etc.), which is often seen, in variable proportions in benign and malignant tumors (Figs. 7 and 8). Treatments (chemotherapy, anti-angiogenesis etc.) can also change the stiffness of tumor and of the adjacent liver.

Future prospects

Ultrasound elastography and assessment of liver fibrosis

The answer to the question of whether ultrasound elastography techniques are sufficiently effective to assess liver fibrosis in clinical practice in patients suffering from chronic liver disease is likely to be positive for the quantitative techniques. It is clear that in the years to come, the use of algorithms combining different non-invasive techniques will be used in everyday practice, greatly reducing the number of indications for LB. The elastography techniques, however, also have a major role to play in screening for chronic liver disease in ''all-comers''. In a study conducted by Roulot et al. on 1190 people over 45-years-old, 89 (7.5%) had a FibroScan® liver elasticity value of over 8 kPa, despite normal blood serum markers, and a cause for liver disease was found in 43% of these cases [87].

In terms of assessing the effectiveness of antiviral treatments and predicting the risk of complications of cirrhosis, ultrasound elastography techniques appear to be promising, although further studies are required to validate them.

Alongside these ultrasound elastography techniques, a new technique, elasto-MR, is also being developed. This MRI technique has the advantage of performing a precise morphological analysis of the liver at the same time as a measurement of fibrosis, and therefore contributes to the investigations into the cause of the liver disease and screening for HCC. Promising results have been reported from several studies in chronic viral hepatitis B and C and NASH. Huwart et al. ($n = 141$) showed that calculated AUROC values for elasto-MR (of 0.994 for $F \geq F2$, 0.985 for $F \geq F3$ and 0.998 for $F = 4$ respectively) were significantly better than ultrasound elastography (0.837 for $F \geq F2$; 0.906 for $F \geq F3$ and for $F = 0.93$) and the blood serum marker, APRI [88]. In view of the small number of patients studied, the length of the examination and its cost, this technique cannot at present be used routinely in clinical practice.

Other applications

Ultrasound elastography techniques can also be used to characterize tumors and monitor local treatments, such as monitoring thermal ablation treatments.

Elastography techniques can be of assistance in guiding the diagnosis to characterize liver tumors when they are combined with the results of contrast imaging investigations. In view of the heterogeneity of both benign and malignant tumors, it is not currently conceivable to envisage a cut-off value to characterize all types of liver tumor. Similarly, it appears to be difficult to establish a cut-off to differentiate benign from malignant because of the overlap of elastography values between benign and malignant lesions. These techniques, however, allow us to better

Table 5 Summaries of the results, conclusions and limitations of publications on elastography to characterize liver tumors.

References	Type of elastography	No. of tumours Type of tumours	Results	Conclusions	Limitations
Kato et al. [81]	Real time elastography *Qualitative Elastography*	$n = 55$	21/22 HCC are classified as intermediary hard tumours	Real time elastography differentiates tumours and the surrounding tissue	No quantitative measurement
		Malignant T	24/28 metastases are classified as hard tumours	HCC and metastases can be differentiated from the TES score	Only angiomas were included in the group of benign tumours
		HCC ($n = 22$) Metastases ($n = 28$) CholangioK ($n = 4$) Benign T Angiomas ($n = 1$)	1 angioma is classified as soft tumour	HCC appear as soft or intermediary T and metastases as hard T	No correlation with histology
Cho et al. [82]	ARFI *Qualitative elastography* ($n = 60$)	$n = 60$ Malignant T ($n = 43$)	Mean Velocity (m/s)	There is a significant difference between a benign T (angiomas) group and the malignant T (metastases—CholangioK + HCC)	Only angiomas were included in the group of benign tumours
	Quantitative elastography ($n = 36$)	HCC ($n = 25$) Metastases ($n = 15$) CholangioK ($n = 3$) Benign T ($n = 17$) Angiomas ($n = 17$)	Metastases + CholangioK ($n = 8$): 2.18 ± 0.96 HCC ($n = 17$): 2.5 ± 0.81 Angiomas ($n = 11$): 1.51 ± 0.7	The cut-off value to differentiate benign from malignant is 2 m/s	No correlation with histology
Heide et al. [84]	ARFI *Quantitative elastography*	$n = 62$ Malignant T ($n = 24$) HCC ($n = 5$) Metastases ($n = 17$)	Mean velocity (m/s) Benign tumours group: 2.6 ± 0.97 Angiomas: 2.36 ± 0.77 FNH: 3.11 ± 0.93	No significant difference between benign and malignant T groups	No correlation with histology Small number of adenomas

Table 5 (*Continued*)

References	Type of elastography	No. of tumours Type of tumours	Results	Conclusions	Limitations
		CholangioK ($n = 2$)	Adenomas: 2.23 ± 0.96		
		Benign T ($n = 38$)	Malignant tumours group: 2.9 ± 1.16		
		Angiomas ($n = 13$)	HCC: 2.63 ± 1.09		
		FNH ($n = 17$)	Metastases: 2.88 ± 1.16		
		Adenomas ($n = 2$)	CholangioK: 3.78 ± 1.73		
Davies and Koenen [83]	ARFI *Quantitative elastography*	$n = 45$	Mean velocity (m/s)	Significant difference between angiomas and metastases	Small number of malignant tumours
		Malignant T ($n = 10$) Metastases ($n = 10$) Benign T ($n = 35$) Angiomas ($n = 35$)	Angiomas: 1.35 ± 0.48 Metastases: 4.18 ± 0.71	The cut-off value to differentiate benign (Angiomas) from malignant (Metastases) was 2.5 m/s	Only angiomas were included in the benign T group No correlation with histology
Shuang ming et al. [80]	ARFI *Quantitative elastography*	$n = 128$	Mean velocity (m/s)	Significant difference between angiomas and metastases	Small number of FNH and adenomas
		Malignant T ($n = 68$) HCC ($n = 31$) Metastases ($n = 30$) CholangioK ($n = 7$) Benign T ($n = 60$) Angioma ($n = 28$) FNH ($n = 7$) Adenoma ($n = 1$) Others ($n = 25$)	Benign tumours group: 1.47 ± 0.53 Malignant tumours group: 3.16 ± 0.80	The cut-off value to differentiate between benign and malignant was 2.22 m/s	No correlation with histology

Table 5 (*Continued*)

References	Type of elastography	No. of tumours Type of tumours	Results	Conclusions	Limitations
Guibal et al. [85]	Shear Wave elastography	$n = 139$	Mean elasticity (kPa)	Significant difference between the benign and malignant T groups	Limited number of some lesions
	Qualitative elastography	Malignant T	Benign tumours group: 18.53 ± 13.5	SWE can differentiate adenomas from FNH	No details about number of different sub-types of adenomas
	Quantitative elastography	HCC ($n = 26$)	Angiomas: 13.8 ± 5.5	SWE can differentiate HCC and cholangioK	
		CholangioK: ($n = 7$)	FNH: 33 ± 14.7	The most discriminating cut-off values to differentiate HCC from cholangioK was > 27.5 kPa	
		Metastases: ($n = 53$)	Adenomas: 9.4 ± 4.3		
		Benign T	Malignant tumours group: 26.9 ± 18.8		
		Angiomas: ($n = 22$)	HCC: 14.86 ± 10		
		FNH: ($n = 16$)	Metastases: 28.8 ± 16		
		Adenomas: ($n = 10$)	CholangioK: 56.9 ± 25.6		
		Others			
Frulio et al. [86]	ARFI *Quantitative elastography*	$n = 79$ Malignant T	Mean velocity (m/s)	No significant difference between benign and malignant T groups	Small number of some lesions
		HCC ($n = 24$)	Benign tumours group	Large tissue heterogeneity for the same type of tumour and between tumour types	No cholangiocarcinomas
		Metastases ($n = 12$)	Angiomas: 2.14 ± 0.49		
		Benign T	FNH: 3.14 ± 0.63		
		Angiomas ($n = 15$)	Adenomas: 1.9 ± 0.86		
		FNH ($n = 19$)	Malignant tumours group		
		Adenomas ($n = 9$)	CHC: 2.4 ± 1.01		
			Metastases: 3.0 ± 1.36		

T: tumour; cholangioK: cholangicarcinoma; HCC: hepatocellular carcinoma; ARFI: Acoustic Radiation Force Impulse Imaging.

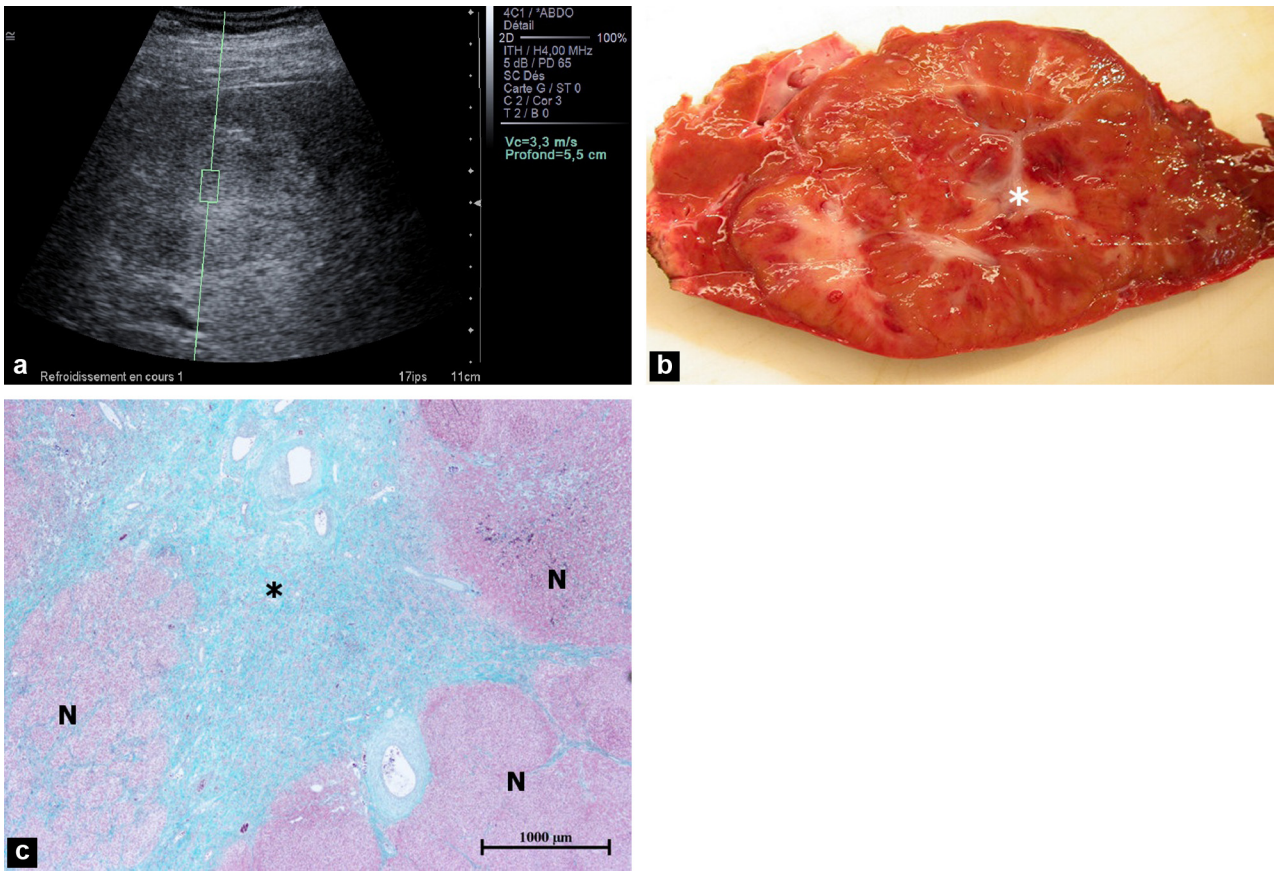

Figure 7. Correlation between ARFI measurements, macroscopic and microscopic appearance: example of FNH: a: ultrasound investigation: the tumor (60 mm) is heterogeneous and hyperechogenic centrally and isogenic peripherally. The median ARFI value is 3.6 m/s; b: macroscopic: non-encapsulated, multi-modular tumor with a central fibrous scar (asterisk); c: microscopy (Masson trichrome): the hepatocyte nodules (N) are separated by dense fibrous tissue (asterisk).

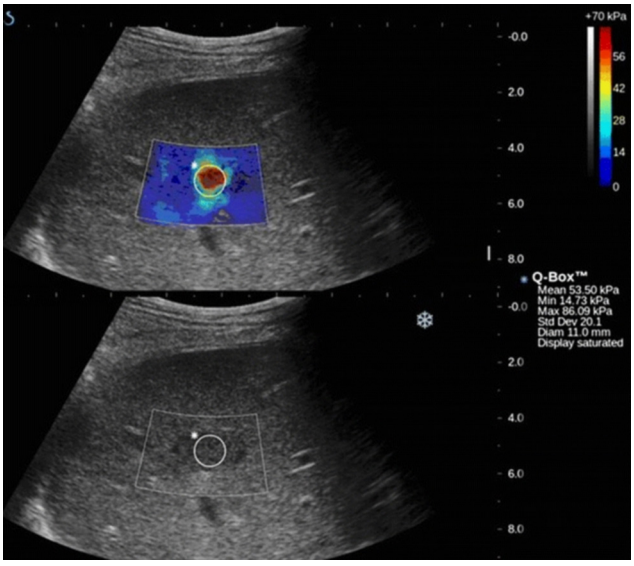

Figure 8. Shear wave elastography: example of a cholangiocarcinoma [85]. SWE mode color mapping shows a hard (red) lesion in a ''soft'' (blue) liver. Mean elasticity obtained by the Q-box is 53.5 kPa (±20 kPa). The lesion is hypoechogenic in B mode.

understand the relationships between tissue composition and ''tissue elasticity''.

In terms of monitoring thermal ablation therapy treatments, Kolokythas et al. have shown in vivo that the ablation therapy region was associated with a rise in stiffness, which could be clearly differentiated from the untreated surrounding tissue [89]. Similarly, Van Vledder et al. have shown both in animals and in human beings that the boundaries of the ablation therapy sites could be identified better by elastography mapping than with B mode imaging. They also showed that elastography was straightforward to perform per procedure and that the volume treated identified by elastography correlated well with the volume found on the hepatectomy specimen [90]. Elastography techniques seem to be a promising tool in the control and real time follow up of liver tumor thermal ablation as their elasticity increases with the increasing treated volume.

Conclusion

To conclude, elastography imaging in a novel imaging technique for assessing human soft tissue mechanical properties, which is currently under clinical evaluation for several organs, such as breast, thyroid, prostate, kidney, vessels, parotids, liver and other organs.

For liver applications, fibrosis staging is the main diagnostic indication and shear wave based techniques have been validated clinically in a first and second intention to diagnosis for fibrosis staging in chronic viral hepatitis C, replacing the invasive conventional liver biopsy, which was up to now the gold standard. However there are many other promising indications for elastography that are currently under clinical evaluation, such as hepatic tumor characterization, predicting cirrhosis-related complications, monitoring antiviral treatments in chronic viral liver disease, and monitoring local treatments etc.... that might play a major role in the management of hepatic diseases.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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