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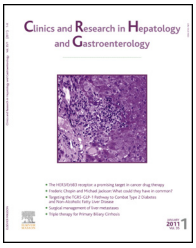

MINI REVIEW

Imaging modalities for the diagnosis of hepatic fibrosis and cirrhosis

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Summary Non-invasive methods for liver fibrosis diagnosis are now commonly used as first-intention tests for liver fibrosis diagnosis in chronic liver diseases. Even morphological parameters provided by ultrasound is now challenged by blood fibrosis tests and transient elastography, in experienced hands, it performed well and in certain situations, imaging can still be useful to detect patients with fibrosis. In parallel, to ultrasound and Doppler imaging, various methodologies have been explored. Some of them remain confined to clinical research for the moment, as perfusion, MR diffusion-weighted imaging, intravoxel incoherent motion or acoustic structure quantification; others have already taken a place in clinical practice. Regarding fast growing of new technology some methods may become available for daily practice in the near future. Ultrasound tools or automated quantification of different physical parameters of imaging data could provide an opportunity for early diagnosis of liver diseases; MRI techniques could lead to the development of a ''global'' liver examination.

Introduction

The diagnosis of liver fibrosis lesions remains an important issue in patients with chronic liver diseases. The early detection of fibrosis is important for determining disease progression and postponing the evolution of chronic hepatitis into cirrhosis via the implementation of prompt and specific treatment [1]. Moreover, after diagnosis, the evolution of fibrosis could be a prognostic factor of complications.

Currently, histopathological examination of a liver biopsy is still the reference for liver fibrosis diagnosis and staging [2]. However, due to sampling errors, liver biopsy is hindered by an approximately 24% false negative rate for the diagnosis of cirrhosis [3,4]. Moreover, it is an invasive procedure that causes patient anxiety and carries with it a risk of complications, with 3% morbidity and 0.03% mortality rates [5]. Thus, liver biopsy cannot be widely performed in clinical practice.

Non-invasive methods for liver fibrosis diagnosis have been developed over the last decade. In this setting, blood fibrosis tests (FibroMeter, Fibrotest, Hepascore) and transient elastography (Fibroscan) have been shown to be accurate [6—10] and are now commonly used as

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Table 1 Changes seen in imaging methods used for the diagnosis of liver fibrosis.

Morphological changes	Coarse echogenicity Irregular surface Left hypertrophy/Right hypotrophy Segment I hypertrophy Segment IV hypotrophy Enlargement of Hilar Periportal Space Right posterior hepatic notch sign
Portal hypertension	↗ portal vein diameter ↘ of portal flow velocity ↗ spleen size Porto-systemic collaterals
Other morphological and Doppler signs	Demodulation of hepatic venous flow ↗ hepatic arterial flow velocity and RI Ascites Gallbladder wall thickness
Elastography	↗ of the stiffness
Perfusion	↘ mean transit time with ultrasound contrast agents ↗ mean transit time, arterial fraction,↘ in overall perfusion with CT or MRI contrast agents
Diffusion WI	↘ of apparent coefficient of diffusion (ADW) ↘ of perfusion-related diffusion (D*, f)
ASQ	↗ of the scatter

first-intention tests for liver fibrosis diagnosis in chronic liver diseases.

Before these tests, imaging, with morphological or functional parameters, was the best non-invasive tool for the diagnosis of severe fibrosis. In experienced hands, it performed well with accuracy ranging from 82 to 88% [11]. Today, in certain situations, imaging can still be useful to detect patients with fibrosis.

In parallel, various methodologies have been explored to increase the performance of non-invasive tests and to increase the availability of diagnostic tests in different situations (screening, quantification, global diagnosis). Thus, various methods within different techniques have been and continue to be evaluated (Table 1). The aim of this short revue is to present the imaging tools presently available for fibrosis diagnosis and those that may become available in the future.

Morphological and Doppler ultrasound

For a long time, the best non-invasive approach to diagnosing severe fibrosis and cirrhosis was to study the morphological changes induced by liver fibrosis. In daily practice, ultrasound, which allows for morphological and functional study by combining B mode and Doppler, has been the tool of choice for this.

Its performance varies as a function of the signs or combination of signs studied, but can be as high as 85% in experienced hands [12]. The diagnosis of fibrosis is based on two principal signs: dysmorphic liver and portal hypertension [11,13]. Signs of dysmorphic liver may include (but may not be limited to): a nodular aspect of the liver surface; a coarse aspect of parenchyma; right hepatic length, plane ratio of the right lobe/left lobe lengths; a different ratio of measurement of segments I and IV. Signs of portal hypertension may include (but may not be limited to) morphological and Doppler signs: spleen length; portal vein diameter, collateral circulation; maximum and mean velocity in the portal vein.

Additionally, other hemodynamic signs may be used, such as the demodulation of the Doppler hepatic vein spectrum [14] or an increase in the resistance index (RI) of the hepatic artery [15,16]. This latter sign is described in the literature but not used in clinical practice because it is difficult to obtain and associated with significant variability. Indeed, variability remains a major concern in ultrasound examinations. More so than the variability of the measurement, the real concerns are the unpredictable limitations to ultrasound examinations due to patients, and the impossibility of keeping, and thus reanalyzing, objective data.

Among the above-listed signs, the nodular aspect of the liver surfaces, increased spleen length and the demodulation of the hepatic vein appear to be the most efficient for severe fibrosis diagnosis. However, it is important to keep in mind that there is no specific sign permitting the diagnosis of severe fibrosis; its diagnosis is usually based on an association of signs [13].

Others signs may be encountered in severe fibrosis or cirrhosis, but are less frequently used as diagnosis elements. These include thickening of the gallbladder wall, irregularity of hepatic vein edges, or a decrease of the normal respiratory variation of the splenic vein. Ascites could of course be a sign of cirrhosis but it is more particularly a sign of decompensation. At this time, there are numerous other clinical and biological signs to diagnose cirrhosis.

In the literature, the accuracy of sonographic and Doppler measurements for the detection of cirrhosis falls between 82% and 88% [17,18].

CT and MRI have not been widely used to assess fibrosis in clinical practice, despite the fact that they can provide interesting morphological signs of cirrhosis. Enlargement of the hilum [19], decrease of the transversal size of segment IV [20], and posterior liver plication [21] have been reported to provide good accuracy for cirrhosis. Additionally some signs of portal hypertension, like mesenteric infiltration or thickening of the colon wall, are not visible on ultrasound but easily visualized on CT or MRI. Although not possible in CT, portal flow can be studied in MRI with a simple phase-contrast sequence [22]. It is probably possible to diagnose severe fibrosis or cirrhosis via CT scan or MRI using morphological and portal changes induced by the fibrosis, as with ultrasound, but such an approach would be more difficult and expensive in daily practice.

Although ultrasound is time consuming and limited by the variability of its measurements, it is nonetheless frequently used in the clinical workup of patients with diffuse liver disease. With the advent of new tools for non-invasive diagnosis, i.e., elastometry and blood tests, the place of

ultrasound examination has changed. Today, ultrasound is an easy way to confirm an initial clinical suspicion, or to discover liver abnormalities in patients referred to ultrasound for other symptomatologies, which may permit the discovery of unknown liver fibrosis in 0.5 to 2% of the general population of patients [23]. More recent studies appear to be trending toward the association of elastometry with morphological or functional ultrasound signs to unite the benefits of the different methods.

Ultrasound elastometry

In just a few years, transient elastography (Fibroscan, developed by echosens) has become the leading non-invasive tool for the diagnosis of liver fibrosis [24].

Elastography assesses the viscoelastic properties of tissues. For this, a wave is created that passes through the tissue to be examined. The speed of the propagation of the wave is then measured using ultrasound: briefly, the stiffer the tissue the faster the wave travels.

The principle has been adapted so as to function as a supplementary module of an ultrasound imaging system. To date, two other elastography systems, ARFI from Siemens and SSI from Aixplorer, have been evaluated in the literature, but it is probable that other manufacturers will develop comparable systems in the near future.

The main difference between Fibroscan and ARFI and SSI is that Fibroscan used mechanical stimulation to produce an excitation along the acoustic wave propagation path, whereas ARFI and SSI create a shear wave by high energy ultrasound pulses. In addition, as ARFI and SSI are guided by ultrasound image they are not ''blind'' in contrast to Fibroscan. Moreover, SSI uses a very high speed acquisition technology that provides tissue elastography mapping, which allows the practitioner to choose the area of measurement of stiffness.

The accuracy of ARFI and SSI for fibrosis and cirrhosis are reported in Table 2. Their results are close to those obtained by Fibroscan [24—26].

However, these two new techniques are affected by the same drawback as the original: elastography is not a direct measurement of fibrosis. Indeed, there are numerous causes of increased liver stiffness such as congestion, cholestasis, inflammation or tumoral tissue among others. Another drawback, often forgotten, is that most of the evaluations of all three of the elastography techniques were done in populations of patients with viral causes of liver disease. The characteristics of those patients are probably different from those of patients with alcoholic or metabolic causes of fibrosis. Also, the shear wave frequencies created by the systems differ, which may explain why fibrosis diagnosis thresholds vary from one system to another.

Finally, the main advantage of elastometry as a module of an ultrasound imaging system is its availability. Currently, patients are referred to a hepatologist for a Fibroscan examination, which means that there is already a suspicion of liver disease. The diagnosis of asymptomatic fibrosis is therefore missed. There is thus an opportunity for improvement: by generalizing elastometry to any patient referred for abdominal ultrasound, the number of patients benefiting from early diagnosis could be increased.

Magnetic resonance elastometry (MRE)

Liver stiffness may be measured alternatively using MRE. In this still experimental technique, the fundamentals are similar to those of ultrasound elastometry in that an initial wave is produced by a transducer placed, in MRE, against the lowermost ribs of the patient. The speed of the propagation of the wave is then measured by specific, motion-sensitized MRE sequences. MRE may offer the considerable advantage of analyzing a substantially larger liver volume compared to ultrasound, and thereby decreasing the problem of sample variability. Also it may make possible a precise analysis of the viscoelastic properties of the liver via a full three-dimensional assessment of the displacement of the wave. The technique would allow stiffness to be broken down into two, more precise parameters, i.e., elasticity and viscosity, which may provide greater accuracy for the diagnosis of liver fibrosis [27].

MRE accuracy has been estimated in several studies with good results. For example, with the following cut-off values for elasticity: 2.4 kPa for $F \geq 1$, 2.5 kPa for $F \geq 2$, 3.1 kPa for $F \geq 3$ and 4.3 kPa for $F = 4$, the sensitivity and specificity obtained were >0.85 and ≥0.91, respectively [28].

Despite real potential advantages, this technique is still in the clinical research phase because of several important weaknesses: it will not be readily available until commercial sets are marketed and it is also a time consuming process that needs standardization and automation for both the acquisition and post-processing protocols.

MR diffusion-weighted imaging (DWI) and intravoxel incoherent motion (IVIM)

Diffusion-weighted imaging (DWI) enables the visualization of Brownian molecular motion: it is based on the motion of water molecules in the extracellular space. This motion can be quantified through the apparent diffusion coefficient (ADC) of protons. This parameter is dependent on the tissue structure, and therefore was largely evaluated for the diagnosis and quantification of liver fibrosis in the 2000s. The hypothesis was that low ADC would reflect a restriction of water diffusion in fibrotic tissue [29]. This hypothesis was confirmed by several published studies [30,31], with sensitivity and specificity ranging from 80 to 90% for the diagnosis of significant fibrosis (stages F3—F4).

However, DWI was significantly influenced by technical parameters, especially the b-value on the result. Thus results of ADC were poorly reproducible and the lack of a strong cut-off value limited its use in clinical practice. For example in the literature, cut-off values of ADC for the diagnosis of severe fibrosis ranged from 1.1 to 1.9 $10^3 mm^2/s$ depending on the b-value used.

Another finding led to abandoning this technique: the signal obtained in DWI was composed of 2 different parts, the second of which was really due to diffusion in relation with tissue architecture. However, the first part of the signal was related to microvascularization. This observation led to the rise of a new MR technique: the measurement of numerous points of ADC at different b-values. This technique is called intravoxel incoherent motion MR imaging (IVIM). It provides a biexponential signal curve where the second part

Table 2 Performances of the different methods of elastography.

	Significant fibrosis (≥ F2)		Severe fibrosis (≥ F3)		Cirrhosis (≥ F4)	
	AUROC	Threshold	AUROC	Threshold	AUROC	Threshold
Fibroscan [24]	0.83	7 KPa	0.90	9.5 KPa	0.95	12.5 KPa
ARFI SWE [25]	0.87	1.34 m/s	0.91	1.55 m/s	0.93	1.80 m/s
SSI SWE [26]	0.92	7.1 KPa	0.98	8.7 KPa	0.98	10.4 KPa

of the curve is related to pure molecular-based (D) diffusion parameters and the first to perfusion-related (D*, f) diffusion parameters. Regarding the initial results of this new technique, restricted diffusion observed in patients with cirrhosis may be related mainly to D* and f variations, which reflect decreased perfusion, rather than to alterations in pure molecular water diffusion in cirrhotic livers. [32,33]. As it stands today, the complexity of this technique limits its use to clinical research.

Perfusion

Cirrhosis induces regional hepatic and systemic hemodynamic changes: arterialization of capillaries, reduction in portal perfusion, temporarily compensated by an increase in arterial vascularization, then finally a fall in global perfusion.

There are 2 mains approaches to quantifying liver perfusion. The first is a semi-quantitative method involving a signal/time curve. It provides parameters like time to peak, area under the curve, and a gradient of enhancement. The second approach uses pharmacokinetic models that assume different vascular compartments in the liver with non-homogeneous repartition of the contrast agent. The second approach can provide parameters like arterial and portal fractions, distribution volume, and mean transit time [34] but the data obtained in this approach will depend on the model used [35].

Ultrasound, CT and MRI all use contrast agents to quantify perfusion parameters, but more studies are needed to improve knowledge of the specificity of the different techniques.

Ultrasound

Currently ultrasound contrast agents contain microbubbles. They are purely intravascular agents, with no interstitial or cellular phases. Thus the most relevant perfusion parameter is liver transit time, which is shortened in cirrhotic patients.

This shorter liver transit time is reported as being secondary to arteriovenous shunting and arterialization of capillary beds in the liver. Furthermore, a relationship between severity of the Child-Pugh score and the shortening of the transit time has been shown [36,37]. Using Sonovue, the transit time cut-off value for severe fibrosis is 24 seconds.

There are two main drawbacks regarding ultrasound contrast agents. First, these agents differ in their design and kinetics; they may yield different results and cannot be used interchangeably. Second, quantification requires manual post-treatment using specific computer programs that are commercially available but poorly distributed.

CT

Iodine contrast is not a purely intravascular agent and thus extravascular leakage needs to be taken into account. In computed tomography, the tracer concentration curve over time is proportional to changes in attenuation measured in Hounsfield units. The different parameters of perfusion are quantified using a dual-input one-compartment model [38], Bloomley et al. demonstrated an increased arterial fraction, mean transit time and fall in overall perfusion in cirrhotic patients. The increase in mean transit time is reportedly due to a reduction of motility of low molecular weight contrast agents (iodine contrast) in the space of Disse in fibrotic liver. More recently, it was shown that perfusion CT was capable of differentiating early stages of fibrosis [39].

Technically, exposure to radiation and the injection of iodinated contrast are disadvantages of perfusion CT. However, the additional radiation is low (10—15 μSv) and can be reduced further by optimizing acquisition settings, improving detectors and using reconstruction algorithms. Similarly, the volume of iodine contrast needed is quite low (40 mL) also.

MRI

Like iodine contrast, the interstitial leakage of gadolinium has to be taken into account in MRI studies. A non-linear relationship between signal intensity and tracer concentration is another concern in MRI. The concentration is related to the relaxivity of the medium and requires measurement of T1, which can be performed using samples of increasing gadolinium concentration. This leads to a more complicated process and possibly imperfect reproducibility.

Findings similar to those in CT have been reported, that is, a reduction in portal perfusion and an increase in arterial perfusion and mean transit time in established cirrhosis, but only a few studies have been done [40,41].

Acoustic structure quantification (ASQ) software

ASQ is a computer program capable of quantifying the distribution of the amplitude of echoes, and especially as concerns scatter, i.e., the deflection of ultrasound waves,

produced by different interfaces. In the case of fibrosis, scatter will increase proportionally with parenchyma distortion. Measurements are easy to obtain and reported as reproducible. The software is available on a classic ultrasound imaging device made by Toshiba. Very few studies have assessed this technique in hepatic fibrosis quantification, and initial results remain lower than those obtained with other techniques, with AUROCs of 0.77 and 0.72 for the diagnosis of cirrhosis (≥F4) and fibrosis (≥F1) respectively [42].

The future

Automated image analysis

The methods discussed here (ultrasound, CT, MRI) produce digital images, which may be analyzed by computer programs to quantify and automate the parameters commonly used for fibrosis diagnosis e.g., liver surfaces, space enlargement, segmental surface or volume, etc. For example, image structures could also be analyzed and specific fractal constructions or histograms could be researched.

As CPU performance increases, these analyses are becoming increasingly possible and promising initial results have been obtained [43,44].

The interest of such technologies is that they are post-processed and thus do not require particular acquisitions. Therefore, specific tests may be performed for any patient with an imaging examination.

Photoacoustic imaging

Photoacoustic imaging is a new technology that permits the visualization of tissue microarchitecture. It can create images of living biological structures ranging from organelles to organs. This emerging technology uses the photoacoustic effect to overcome the high degree of optical photon scattering in biological tissue. Different implementations of photoacoustic tomography allow spatial resolution to be scaled with the desired imaging depth in tissue, while a high depth/resolution ratio is maintained. At present, the spatial resolution is on the order of 1/200 of the desired imaging depth, which can reach up to 7 centimeters. Photoacoustic imaging can provide anatomical, functional, metabolic, molecular, and genetic contrasts of vasculature, hemodynamics, oxygen metabolism, biomarkers, and gene expression.

This is a particularly promising technology but many technical challenges need to be met to maximize its impact in biomedicine. Nonetheless, in 10 or 20 years, photoacoustic imaging may become the new gold standard modality [45,46].

Discussion

Regarding the different methods detailed in this short review, we can make your point that performances for the diagnosis of cirrhosis are obviously higher than those for the quantification of fibrosis. Another point to raise is that evaluations are mainly done on HCV hepatopathies. Alcoholic causes, largely present in many countries, are poorly represented in study populations. Metabolic syndrome, a new and growing etiology, adds to the questioning on the validity of these results. In the future, threshold values and test significations should be given as a function of the etiology of the hepatic disease. It is likely that techniques will perform differently within different etiologies.

Although there are numerous ways of diagnosing and quantifying liver fibrosis with imaging tools, ultrasound methods remain the mainstay of current clinical practices. This is not without interest for screening. Indeed the gold standard non-invasive methods for liver fibrosis detection (blood fibrosis tests and transient elastography) are usually performed by hepatologists to whom patients are referred following the appearance of symptoms suggestive of chronic liver disease. Thus, the number of patients benefiting from early diagnosis with these new tools remains quite low in relation to the prevalence of the disease, estimated at 2.8% of the general population [23]. Since abdominal ultrasound is widely used for various symptoms, it could be an excellent way to detect patients with signs evoking liver fibrosis or cirrhosis, who could then be referred to liver specialists for confirmation of the diagnosis by blood fibrosis tests and/or transient elastography.

Other imaging techniques remain currently confined to clinical research or expert centers, mainly because of their complexity or because necessary software is not commercially available. Nevertheless they hold great promise: MRI techniques could lead to the development of a ''global'' liver examination permitting the quantification of steatosis, iron, and fibrosis and the characterization of nodules in a single exam. More widely used ultrasound or CT-based techniques could be effective screening tools, particularly if the search for different parameters identified as potential signs of liver fibrosis can be automated.

Conclusion

Imaging techniques allow for the diagnosis of chronic liver diseases in many ways. Some of them are easy to perform and repeat, thus providing an opportunity for early diagnosis of liver diseases. Others remain confined to clinical research for the moment, but may become available for daily practice in the near future, as the automated quantification of different physical parameters of imaging data improves rapidly.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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