Review

JOURNAL OF HEPATOLOGY

New imaging techniques for liver diseases

Bernard E. Van Beers*, Jean-Luc Daire, Philippe Garteiser

Laboratory of Imaging Biomarkers, UMR1149 INSERM-University Paris Diderot, Sorbonne Paris Cité, Department of Radiology, Beaujon University Hospital Paris Nord, Clichy, France

Summary

Newly developed or advanced methods of ultrasonography and MR imaging provide combined anatomical and quantitative functional information about diffuse and focal liver diseases. Ultrasound elastography has a central role for staging liver fibrosis and an increasing role in grading portal hypertension; dynamic contrast-enhanced ultrasonography may improve tumor characterization. In clinical practice, MR imaging examinations currently include diffusion-weighted and dynamic MR imaging, enhanced with extracellular or hepatobiliary contrast agents. Moreover, quantitative parameters obtained with diffusion-weighted MR imaging, dynamic contrast-enhanced MR imaging and MR elastography have the potential to characterize further diffuse and focal liver diseases, by adding information about tissue cellularity, perfusion, hepatocyte transport function and visco-elasticity. The multiparametric capability of ultrasonography and more markedly of MR imaging gives the opportunity for high diagnostic performance by combining imaging biomarkers. However, image acquisition and post-processing methods should be further standardized and validated in multicenter trials.

Introduction

Liver ultrasonography and magnetic resonance (MR) imaging is increasingly used for detecting, characterizing and assessing the response to treatment of focal and diffuse liver diseases [1–3]. Ultrasonography remains a first-line examination, but it has recently gained increasing capabilities due to the implementation of dynamic contrast-enhanced (DCE) studies and elastography.

The quality and speed of MR imaging examinations have been substantially improved by the development of higher clinical field strengths, larger gradients, improved surface coils, and parallel imaging techniques [2]. Hepatobiliary contrast agents, such as gadoxetate, have been introduced for DCE MR imaging [4]. Relative to computed tomography (CT), MR imaging has several advantages, including lack of radiation, higher contrast-to-noise ratios, and multiparametric capabilities [1]. Indeed, the pulse sequences at MR imaging can be adjusted to produce images that assess different tissue characteristics such as diffusion, perfusion, and visco-elasticity [2,3]. These functional characteristics can be assessed not only qualitatively, but also as quantitative parameters that provide useful imaging biomarkers [3].

Keywords: Ultrasonography; Magnetic resonance imaging; Perfusion and diffusion imaging; Dynamic gadoxetate-enhanced MR imaging; Elastography; Imaging biomarkers; Liver diseases; Liver tumors.
Received 18 June 2014; received in revised form 8 October 2014; accepted 11 October 2014

* Corresponding author. Address: Laboratory of Imaging Biomarkers and Department of Radiology, Beaujon University Hospital, 100 Boulevard du General Leclerc, 92110 Clichy, France. Tel.: +33 1 40 87 56 54; fax: +33 1 40 87 44 77.
E-mail address: bernard.van-beers@bjn.aphp.fr (B.E. Van Beers).

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ADC, apparent diffusion coefficient; APRI, aspartate aminotransferase to platelets ratio index; ARFI, acoustic radiation force imaging; AUROC, area under the receiver operating curve; CT, computed tomography; D, pure diffusion coefficient; D^*, perfusion-related diffusion coefficient; DCE, dynamic contrast-enhanced; DW, diffusion-weighted; EASL, European Association for the Study of the Liver; EFSUMB, European Federation of Societies for Ultrasound in Medicine and Biology; f, fraction of diffusion related to microcirculation; F, plasma flow; G^*, shear wave modulus; Gd, storage modulus; Gl, loss modulus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IVIM, intravoxel incoherent motion; K^{trans}, transfer constant; K_{1a}, arterial transfer constant; K_{1p}, portal venous transfer constant; K_{1t}, total liver plasma transfer constant; MR, magnetic resonance; MRP, multidrug resistance protein; MTT, mean transit time; NASH, non-alcoholic steatohepatitis; OATP, organic anion transporting polypeptide; mRECIST, modified response evaluation criteria in solid tumors; RECIST, response evaluation criteria in solid tumors; STARD, standards for reporting diagnostic accuracy; v_d, distribution volume; v_e, volume of extravascular extracellular space; v_p, plasma volume; WFUMB, World Federation for Ultrasound in Medicine and Biology.

ELSEVIER

Key Points

- Dynamic contrast-enhanced ultrasonography has the potential to give similar diagnostic performance for single liver tumour assessment as dynamic contrast-enhanced MR imaging and can provide quantitative perfusion information
- Dynamic ultrasound elastography has a central role in liver fibrosis staging and is increasingly used to grade portal hypertension
- Acoustic radiation force ultrasound elastography measurements are fully integrated into comprehensive ultrasound examinations of the liver
- In patients with hepatocellular carcinoma, the quantitative MR diffusion and perfusion parameters, determined one month after intra-arterial or anti-angiogenic treatments, have been shown to be better predictors of patient outcome than the RECIST, mRECIST or EASL criteria
- Dynamic gadoxetate-enhanced MR imaging improves the assessment of focal and diffuse liver diseases relative to dynamic contrast-enhanced imaging with extracellular contrast agents by adding information about hepatocyte transport function during the hepatobiliary phase
- Several visco-elastic parameters including the stiffness, elasticity, viscosity and wave scattering coefficients can be obtained in whole liver and spleen with multifrequency MR elastography, potentially improving the characterization of multiple liver diseases, including fibrosis, inflammation, NASH, portal hypertension, and liver tumours
- Biomarkers obtained with diffusion imaging, perfusion - hepatocyte transport imaging and with elastography have to be further validated in multicentre studies and the methods of image acquisition and post-processing have to be standardized
- Given the multiparametric capabilities of MR imaging and ultrasonography, imaging biomarkers can be combined to further improve the detection and characterization of diffuse liver diseases and liver tumours and to assess their response to treatment

Ultrasonography

Dynamic contrast-enhanced ultrasonography

Method

Dynamic contrast-enhanced ultrasonography is performed after intravenous injection of ultrasound contrast agents. Ultrasound contrast agents are blood agents that are composed of gas-filled microbubbles stabilized by a shell made of lipids, proteins or polymers. Because of the non-linear oscillation of the microbubbles at low to mid-high mechanical index, harmonic or non-linear imaging is used to increase the contrast-to-tissue-ratio relative to fundamental B-mode imaging [5].

Liver tumors

Dynamic contrast-enhanced ultrasonography improves the detection and characterization of focal liver lesions [5]. Technical and diagnostic guidelines for the detection, characterization, and treatment monitoring of liver lesions at contrast-enhanced ultrasonography have been published under the auspice of the World Federation for Ultrasound in Medicine and Biology (WFUMB) and the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [6].

However, the diagnostic role of DCE ultrasonography relative to DCE-CT and MR imaging remains debated [7]. Besides DCE-CT and MR imaging, DCE ultrasonography was included in the diagnostic algorithm for suspected hepatocellular carcinoma (HCC) in liver cirrhosis in the 2005 recommendations of the American Association for the Study of Liver Diseases (AASLD) [8] and in the recommendations of the Japan society of hepatology [9]; however, it was not included in the recent updated versions of either AASLD or European Association for the Study of the Liver (EASL) guidelines [10,11]. Reasons for this change have been based on the fact that the typical hypervascularity and washout pattern of HCC may be observed in some intrahepatic cholangiocellular carcinomas at DCE ultrasonography without being observed at DCE MR imaging [12]. The different pattern observed at ultrasonography and MR imaging or CT may be explained by differences in the distribution volumes between the ultrasound microbubbles, which remain intravascular, and the small-molecular-weight CT and MR contrast materials, which instead distribute into the vascular and extravascular-extracellular spaces.

Other reasons for the variable use of DCE ultrasonography are defect in standardization, dependence on the operator, variability of results related to the physical characteristics of any individual patient, and the lack in three-dimensional dynamic imaging [7]. In contrast, the real-time capability of DCE ultrasonography may be a benefit relative to CT and MR imaging for observing the transient signal intensity enhancement of hypervascular liver tumors such as HCCs [13].

A meta-analysis of sulphur hexafluoride microbubble enhanced ultrasonography reported that it could provide improved cost-effectiveness and similar diagnostic performance to DCE-CT and MR imaging for the assessment of focal liver lesions [14]. However, the authors highlighted limitations in the reporting of many studies of the review, and stressed the need for further high-quality studies, based on the standards for reporting diagnostic accuracy (STARD) criteria, which compare the performance of all three imaging modalities (DCE ultrasonography, CT, and MR imaging) in the same patients and provide standardized definitions of a positive imaging test for each target condition. Moreover, the effectiveness of DCE ultrasonography in the assessment of multiple lesions of the liver should also be considered [14].

Future perspectives in DCE ultrasonography include quantitative perfusion imaging and molecular imaging [5,15]. The *in vivo* feasibility of determining absolute tumor perfusion parameters at DCE ultrasonography with deconvolution of the tumor enhancement curve by the arterial input function has been shown [16].

In animal models, molecular imaging of angiogenesis and inflammation has been performed with targeted ultrasound contrast agents directed to surface receptor molecules expressed on the luminal side of activated endothelium, in response to either inflammatory or angiogenic stimuli [5]. However, the unspecific