

# Real-time Contrast-enhanced and Real-time Virtual Sonography in the Assessment of Benign Liver Lesions

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## Abstract

Imaging techniques, in particular ultrasonography, have led to great advances in clinical hepatology in the past few decades. The introduction of second-generation contrast agents and the development of contrast specific techniques have opened new prospects in the detection and characterization of liver lesions. New hybrid imaging techniques that combine in real-time transabdominal ultrasound with other cross-sectional imaging techniques (CT or MR) might add even more valuable information in the cases with focal lesions. The aim of this review is to describe the role of real-time contrast-enhanced and real-time virtual sonography in the assessment of benign liver lesions.

## Keywords

Real-time contrast-enhanced ultrasonography – focal liver lesions – hybrid imaging – real-time virtual sonography.

## Introduction

B mode sonography represents a useful screening technique for the detection of focal liver masses, but a specific diagnosis can rarely be established based only on the gray scale characteristics. Recently, the introduction of contrast agents has opened new prospects in the characterization of focal liver lesions. Newer microbubbles based on high molecular weight gases such as sulphur hexafluoride (used in Sonovue) can persist for much longer in the blood. Contrast-enhanced ultrasound (CEUS) has improved to the point at which it equals the sensitivity and specificity of contrast computer tomography (CT) and magnetic resonance imaging (MRI) [1, 2].

## Contrast agents for ultrasound imaging

Four ultrasound contrast agents are currently approved and marketed within European countries: Levovist, Optison, SonoVue and Luminity. SonoVue (Bracco, Milan) is a second-generation contrast agent that contains a hydrophobic gas (sulphur hexa-fluoride), an extremely stable and inert molecule [3]. The usual way of administering SonoVue is an intravenous bolus injection followed by a flush with 5 ml sodium chloride 0.9 % [4]. The recommended dose for a single injection is 2.4 mL, but the optimal dose for a particular clinical situation depends on the individual patient and on the scanner technology. During a single examination, a second injection of the recommended dose can be made when deemed necessary by the physician [4]. The contrast agents should not be administered to patients with known hypersensitivity to the components, patients with severe cardiac or pulmonary disease or during pregnancy and lactation. Because of their inert constituents, ultrasound contrast agents are very safe and do not have nephrotoxic effects [4]. The overall reporting rate of serious adverse effects was 0.0086%, lower than or similar to that reported for radiologic and MR contrast agents [5].

## Clinical application in liver diseases

Contrast-enhanced ultrasound applied to the diagnosis of liver diseases has many advantages. Thus, contrast-enhanced digital technologies allow the differentiation of signals produced by the contrast agent in the liver from the time of microbubble arrival in the hepatic artery, portal vein and liver parenchyma, until their disappearance. All vascular phases can be examined and focal liver lesions can be characterized according to the temporal and spatial pattern of contrast perfusion. The method is easy to perform, in real-time, with a very low incidence of severe allergic reactions.

Due to the dual blood supply of the liver provided by the hepatic artery (25-30%) and portal vein (70-75%), three vascular phases can be visualized in CEUS. Arterial phase starts when hepatic artery shows enhancement (10-20 seconds post- injection into a peripheral vein) and lasts

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for approximately 10-15 seconds. Portal venous phase begins when portal vein shows enhancement and lasts for approximately 2 minutes after contrast agent injection. Delayed phase corresponds to the washout period up to approximately 4-6 minutes postinjection of SonoVue. The arterial phase provides information on the degree and pattern of vascularity, while the portal and late phase can provide important information in the differentiation of the benign or malignant liver lesion [4].

The guidelines published in 2008 by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) clearly defined the indication and recommendations for the use of contrast agents in liver ultrasound [4]: characterization of focal liver lesions (benign versus malignant), guidance and monitoring of local ablative treatment and measuring the hepatic transit time and studying the hepatic vessels.

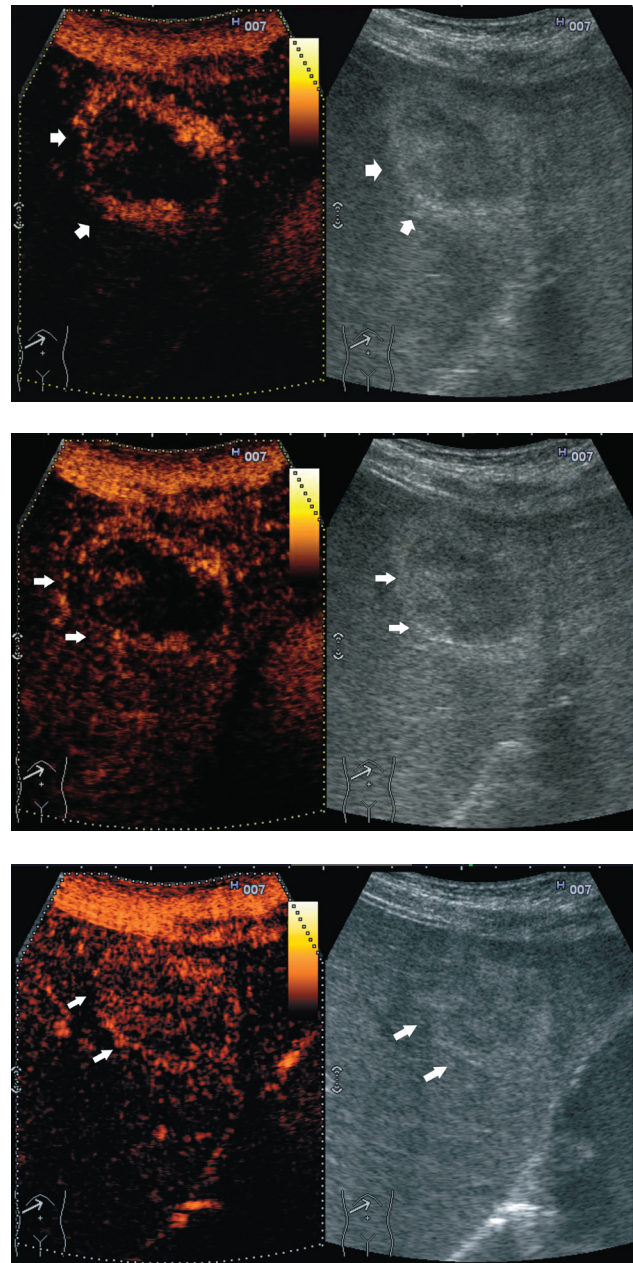
### Characterization of benign liver lesions

Sustained contrast-enhancement in the portal-late phase characterizes most benign solid lesions [4].

**Haemangiomas** typically show a globular peripheral enhancement in the arterial phase (Fig. 1a) and a centripetal filling in the portal venous phase (Fig. 1b). In a study published by Quaia et al, centripetal fill-in preceded or not preceded by peripheral nodular/rim-like enhancement was the pattern prevalently observed (more than 80% of patients), equivalent to the typical enhancement pattern of liver hemangiomas on contrast-enhanced CT or MRI [6]. In the late phase, the lesion is iso- or hyperenhanced as compared to the surrounding parenchyma as a result of sluggish flow (Fig. 1c). In two recent series, these characteristic features have been shown in 78-93% of hemangiomas [7, 8]. This typical pattern makes a definitive diagnosis of haemangioma and no further investigation is required in patients with low risk for hepatic malignancy [9]. The authors followed-up 213 patients with typical aspect of hemangiomas and a low risk of malignancy for more than two years. CEUS may therefore improve noninvasive functional characterization and differentiation of hemangiomas [10]. However, in a small percentage, atypical features may be present. In these circumstances correlative imaging modality or even biopsy must be considered [11].

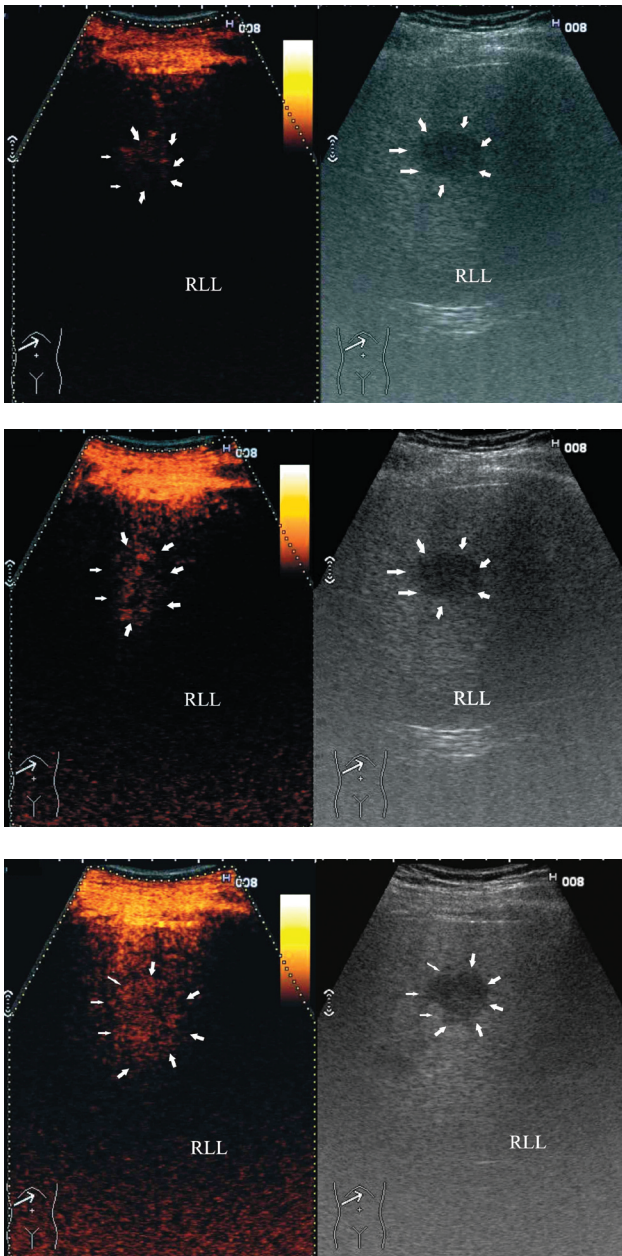
**Focal nodular hyperplasia (FNH)** is usually composed of multiple nodules separated by fibrous bands radiating from a central scar. It is a highly vascular lesion, with central and radial arteries at Doppler exam. At real-time CEUS, FNH shows a typical centrifugal spoke wheel pattern, followed by complete enhancement during the arterial phase (Fig. 2a). The persistent homogeneous enhancement is present in the portal and late phase (Figs. 2b,c). A central scar could be found in about 50% of cases [12]. The typical patterns have been observed in 74-100% of FNH [7, 8, 13, 14].

**Adenomas** are rare benign lesions, more frequent in women who take oral contraceptives. Differentiation from FNH is essential because of different therapeutic approaches:



**Fig 1.** Haemangioma. Contrast enhanced US images: the lesion shows peripheral nodular enhancement in the arterial phase (a), with progressive centripetal filling in portal venous (b) and delayed phases (c).

surgery is often recommended for adenomas, while it is not needed for FNH. In contrast with FNH, adenomas do not have portal vessels, branches of hepatic artery are numerous with a peripheral distribution, and the lesions are well defined with a capsule. Typical features of adenomas are complete centripetal hyper-enhancing involving the capsule as well as the internal portion during arterial phase. In the late phase the lesions maintain persistent enhancement. The capsule remains generally hyper-enhanced. In CEUS, the differentiation with FNH is made by the absence of a central feeding artery, the presence of a capsule and of areas of necrosis. Therefore, CEUS might improve the functional



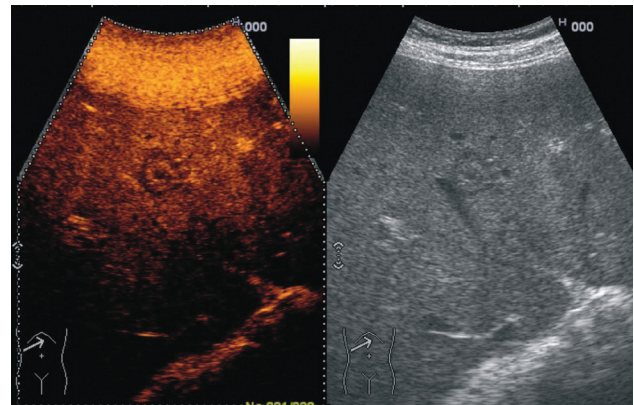
**Fig 2.** Focal nodular hyperplasia (FNH). During the arterial phase an intense enhancement of the FNH and its feeding vessel, as well as the central scar were clearly depicted (a). The persistent homogeneous enhancement is present in the portal and late phase (b, c). Delineation is clearly improved.

characterization of benign hypervascular focal liver lesions [15].

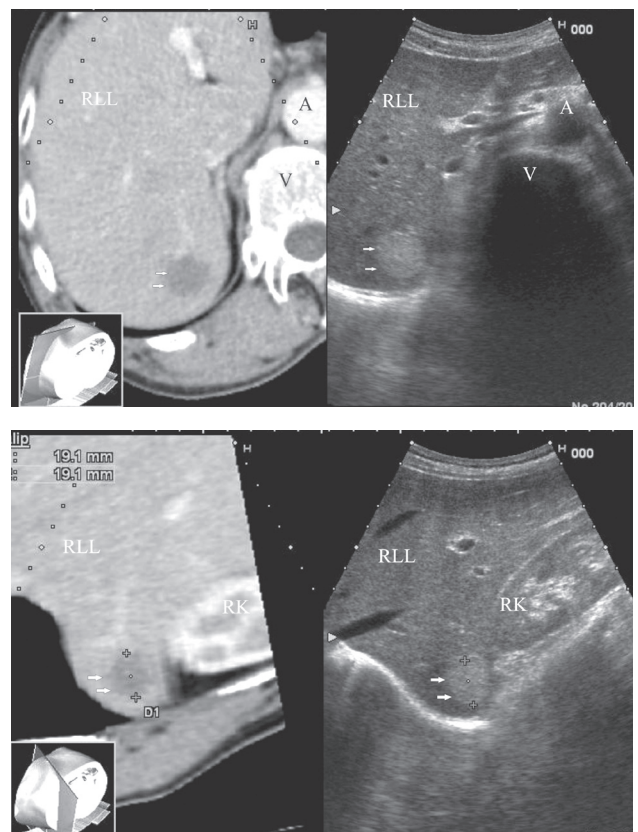
**Regenerative nodules** are iso-enhancing during all three phases (Fig. 3).

### Real-time virtual sonography

The real-time virtual sonography (RVS) module displays the real-time ultrasound image simultaneously with the corresponding CT or MR virtual multi-planar view reconstructed from a stored volume data set. The module offers a simultaneous display of the CT or MR section which



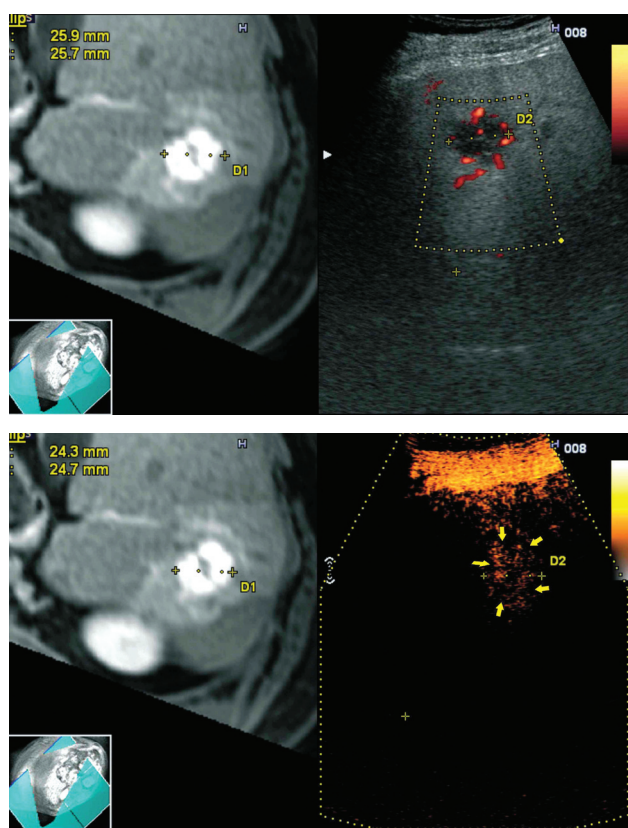
**Fig 3.** After injection of contrast agent, a 1.5 cm regenerating nodule is iso-enhancing during all three phases.



**Fig 4.** Real-time virtual sonography with simultaneous display of the contrast-enhanced CT section and real-time B-mode US image. The image shows concomitant view of the right liver lobe (RLL), vertebra (V), aorta (A), right kidney (RK) and a focal liver lesion - haemangioma (arrows).

corresponds to the real-time ultrasound image. Consequently, RVS offers better image guidance for all interventional procedures, especially for radiofrequency ablation. It can provide a better understanding of the ultrasound anatomy, enabling a more accurate needle placement and a more precise monitoring of the treatment area during ablative therapies. By using ultrasound throughout the procedure, rather than CT guidance, the patient's exposure to radiation is also reduced.

The RVS module is compatible with B-mode (Fig.



**Fig 5.** Focal nodular hyperplasia (FNH) in the right liver lobe in a 31-years old patient. Real-time virtual sonography shows concomitant view of the contrast-enhanced MR and power Doppler ultrasound image (a). After SonoVue injection a rapid and persistent enhancement was noted in the arterial phase (b).

4a, b), colour Doppler and dynamic Contrast Harmonic Imaging modes. Thus the module allows the simultaneous visualization of contrast-enhanced CT or MR, with real-time CEUS, allowing a better delineation of the morphology and vascularization of focal lesions (Fig. 5a, b). The cost-effectiveness of this approach is debatable, but future studies are necessary because the usage of the module certainly prolongs the examination time.

In conclusion, benefits of the RVS module include an increased diagnostic confidence, direct comparison of the lesions using different imaging modalities, more precise monitoring of interventional procedures, reduced radiation exposure and compatibility with several US modes, including power Doppler and CEUS.

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### Conflicts of interest

Nothing to declare

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