Contrast-enhanced Sonography — New Diagnostic Method for Hepatic Tumors

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This editorial reffers to "Value of Liver Contrast-enhanced Sonography to Diagnose Malignant or Benign Tumors" by Pascarenco Ofelia et al.

Ultrasound is an imaging technique that can provide anatomical and functional images with good resolution and great flexibility at low cost. Worldwide, ultrasound is the first imaging modality for screening focal liver lesions and the main advantages are speed, simplicity, availability and non-invasiveness. Because of either patient or technical limitations, the sensitivity of conventional sonography remains poor (between 55% and 75%) and generally lower than other modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)[1].

This method has serious limitation in detecting and characterising focal lesions, even with the addition of Doppler. The most common problem is the low or absent contrast between the lesion and the surrounding liver, so-called iso-echoic lesions. In addition, lesions smaller than 1 cm in diameter may be difficult to detect. A further problem is the inaccessibility of some portion of the liver, especially segment eight, which is difficult to reach because it lies high under the diaphragm. Characterising focal liver lesions is also difficult, because the wide range of grayscale appearances causes overlap in the patterns. B-mode ultrasound can specifically characterise some focal lesions — cysts, hyperreflexive hemangiomas in a nonsteatotic liver or typically localized focal fat accumulations — without needing further diagnostic procedures. In hypervascular hepatic tumors such as focal nodular hyperplasia or hepatocellular carcinoma, power or color Doppler imaging has revealed characteristic vascular patterns suggesting a tumor diagnosis, but without providing an accurate diagnosis. For this reason, the detection of a solid focal lesion in conventional ultrasound frequently necessitates further investigation — computed tomography(CT) and magnetic resonance imaging(MRI) with intravascular administered contrast agents or biopsy.

Contrast-enhanced ultrasound has improved on both detection and charactersation of focal liver lesions, because it highlights malignant lesions against the enhanced background of the normal liver in the sinusoidal phase and because it allows both the macrocirculation of larger vessels and the microcirculation at capillary and sinusoidal level to be imaged.

The development of ultrasound contrast agents (UCAs), which perform as blood pool tracers, have overcome the limitations of conventional B-mode and color or power Doppler ultrasonography. Depending on the contrast agent and the US-mode, the dynamic lesion enhancement pattern is visualized during intermittent or continuous imaging. Enhancement patterns are described in real time during subsequent vascular phases (arterial, portalvenous and late phase for liver lesions) similar to contrast enhanced computed tomography and contrast enhanced magnetic resonance imaging [2].

The ultrasound contrast agents (UCAs) which are currently used for ultrasound are microbubbles. The gas (air or a perfluoro compound) is constrained by a thin shell of either a phospholipid mix or denatured human albumin, which are chosen for their biocompatibility and acoustic properties. They are made to be smaller than red blood cells (typical mean diameters are two to five microns) so that they cross capillary beds freely; thus, following intravenous injection they flood the entire blood pool. Since they are too large to cross intact endothelial membranes, they act as pure blood pool markers, and do not have the interstitial phase that characterises the common CT and MRI contrast agents, which are molecular solutions. Because of their inert constituents, ultrasound contrast agents are very safe and do not have nephro- or cardiotoxic effects. The UCAs should be avoided in pacients with severe cardiopulmonary disease. There are essentially no contraindications to their use, beyond the routine cautions for pregnant and lactating women and in paediatrics due to the lack of testing in these populations. Rare anaphylactoid reactions have been reported, which manifest as acute hypotension occurring within a few seconds of injection

Contrast specific US modes are generally based on the cancellation and separation of linear US signals from tissue and utilisation of non-linear response from the bubbles and provide high resolution images of tissue vascularization.

Focal liver diseases have evolved into the single most important application of contrast-enhanced ultrasound (CEUS) because of marked improvement over conventional ultrasound in both their detection and characterisation; it also provides important dates on lesions vascular patterns. Persistance of microbubbles in the late phase provides a marker for the sinusoidal space, thus the late phase is mainly used for detection of malignancies.[2]

The liver have a dual blood supply: the hepatic artery(25–30%) and the portal vein (70–75%) and because of this reason imaging post-injection of microbubbles con-

trast is performed in arterial (starts 10–15s, ends 25–35s), portal venous(starts 30–45s, ends at 120s) and sinusoidal late(>120s) phase. In differentiating between types of focal liver lesion, it is important to take into account the haemodynamics by both the late phase and the arterial phase soon after contrast injection [3]. Portal and late phase enhancement can provide important information regarding the character of the lesion: most malignant lesions are hypoenhancing while the majority of benign lesions are iso- or hyper-enhancing.

CEUS is indicated in the following situations: incidental findings of focal liver lesions on routine US; lesions or suspected lesions in chronic hepatitis or liver cirrhosis; lesions or suspected lesions in patient with a known history of malignancy; patient with inconclusive MRI/CT or cytology/histology results; characterization of portal vein thrombosis [2].

Hemangioma: an initial solitary circular vascularity pattern in the arterial phase followed by a nodular fill-in pattern during the venous phase. Necrotic or thrombosed regions, which are more common in larger hemangiomas, do not fill. Eventually, in the late phase, when its enhancement matches that of the surrounding liver, the lesion disappears or at least appears smaller.

Focal nodular hyperplasia fills from a central artery, often supplied by a prominent tortuous feeding artery, and enhances rapidly, usually before liver parenchymal enhancement begins, so that it forms an intensely enhancing region in the arterial phase. In the portal-venous and late phase the lesion appear iso- or hyperenhanced. At this stage, a stellate central defect corresponding to the central scar is seen in about 25% of these lesions.

Liver adenomas have a variety of patterns, but commonly appear as hypervascular lesions with a peripheral supply, and often disappear in the late phase[4].

Lesions consisting of essentially normal liver tissue, such as regenerating nodules and regions of focal fatty sparing or change, behave exactly as the normal liver in all phases. Tipically post-contrast, focal fatty sparing and the regenerative nodules are iso-enhancing with the surrouding parenchyma.

Hypoenhancement of solid lesions (darker than the surrouding liver) in the late phase characterize malignancies. Scanning in the late phase is most important in the detection of liver malignancies, as defects appear as the contrast washes out of them before it washes out of the liver tissue. Once the liver parenchyma has reached maximum enhancement, usually at one or two minutes postinjection, the entire liver volume is scanned with slow subcostal and intercostal sweeps, looking for filling defects. All metastases show an irregular chaotic intratumoral vascularity in the arterial phase, followed by wash-out(hypoenhancement of the tumor) in the late phase. A typical HCC is characterized by arterial phase hypervascularity and wash-out in the late phase. Tumour trombus in the portal or hepatic vein contains malignant neovascularity which can be demonstrated by CEUS. Several prospective studies have shown the comparability of this technique to contrast CT and MRI for metastases [5,6] and, in some cases, lesions that are too small to detect with CT or MRI are clearly shown on CEUS [7]. In a study comparing unenhanced ultrasound with CEUS in the detection of liver metastases, the average number of confirmed metastases increased from 3.06 to 5.42 following contrast administration, with the sensitivity for detecting individual metastases improving from 63 to 91%. More importantly, sub-centimetre lesions were identified in over 92% of confirmed cases following contrast compared with 54% at baseline[8]. Other study compared with contrast-enhanced helical CT scanning, CEUS was shown to detect more metastases in 12%, an equal number in 74% and fewer in 14% of the 83 patients presenting with fewer than five lesions [9].

In cirrhotic patients an ultrasound is used for surveillance every 6 to 12 months in order to detect focal lesions. Further investigation to characterise such lesions depends on their size – lesions smaller than 2 cm in diameter require two dynamic studies showing suspicious features, while one is considered sufficient for larger lesions. Contrast CT or MRI were previously stipulated, but the new guidelines recommend CEUS as an alternative. The main limitations of the method are the difficult evaluation of deep-sited lesions and the attenuating livers.

A particularly useful application of contrast agents is in evaluating the completeness of ultrasound guided ablation therapy: when all tumor appears to have been destroyed, microbubbles often reveal residual portions of perfused tumor that can be ablated immediately. The recommended uses and indication in the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines are: as a complement to Contrast-Enhanced Computed Tomography (CECT) and/or Contrast-Enhanced Magnetic Resonance Imaging (CEMRI) for pretreatment staging and assessemnet of target lesion vascularity; facilitation of needle positioning in case of incomplete or poor lesion delineation on unenhanced US; evaluation of immediate treatment effect after ablation and guidance for immediate re-treatment of residual unablated tumoral areas; assesment of tumor recurrence, when follow-up CECT or CEMRI are contraindicated or not conclusive [2]. Although CECT and/or CEMRI are considered to be the standard techniques for assessment of treatment outcome, CEUS may be used in the follow-up protocols.

CEUS using modern agents and equipment is recommended as a valuable diagnostic tool both in detection and characterisation of a variety of focal liver lesions, allowing the differentiation between benign and malign disease. CEUS has similar sensitivity to contrast-enhanced CT for liver metastases and for hepatocellular carcinomas, but without exposing the patient to radiation. It is recommended for evaluating lesions discovered during the surveillance of cirrhotic patients and for the immediate monitoring of interstitial ablation therapy.

References

1. Tranquart F, et al. – Role of contrast-enhanced ultrasound in the blinded assessement of focal liver lesions in comparison with MDCT and CEMRI. EJC 2008, 6: 9–19.
2. Claudon M, Cosgrove D, Albrecht T, et al. – Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)-Update 2008, Ultraschall in Med 2008, 28–44.
3. Wilson SR, Burns PN – An algorithm for the diagnosis of focal liver masses using microbubble contrast-enhanced pulseinversion sonography. Am J Roentgenol 2006, 186: 1401–12.
4. Dietrich CF, Schuessler G, Trojan J, et al. – Differentiation of focal nodular hyperplasia and hepatocellular adenoma by contrast-enhanced ultrasound. Br J Radiol 2005, 78: 704–7.
5. Dietrich CF, Kratzer W, Strobe D, et al. – Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT and MRI. World J Gastroenterol 2006, 12: 1699–1705.
6. Albrecht T, Hoffmann C, Schmitz S, et al. – Detection of liver metastases: comparison of contrast-enhanced phase inversion ultrasound and dual phase spiral CT with intraoperative sonographic correlation. Radiology 2000, 207(P): 459.
7. Konopke R, Kersting S, Bergert H, et al. – Contrast-enhanced ultrasonography to detect liver metastases: A prospective trial to compare transcutaneous unenhanced and contrast-enhanced ultrasonography in patients undergoing laparotomy. Int J Colorectal Dis 2007, 22: 201–7.
8. Albrecht T, Hoffmann CW, Schmitz SA, et al. – Phase-inversion sonography during the liver-specific late phase of contrast enhancement: improved detection of liver metastases. Am J Roentgenol 2001, 176: 1191–8.
9. Quaia E, Bertolotto M, Forgacs B, et al. – Detection of liver metastases by pulse inversion harmonic imaging during Levovist late phase: comparison with conventional ultrasound and helical CT in 160 patients. Eur Radiol 2003, 13: 475–83.