CLINICAL IMAGING

The Role of Real-time Contrast-Enhanced and Real-time Virtual Sonography in the Assessment of Malignant Liver Lesions

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Abstract

Contrast enhanced ultrasound has recently been introduced and is recommended in daily practice in many circumstances, mainly for the detection and characterization of focal liver lesions. Also, contrast enhanced ultrasound has the potential of becoming the primary liver-imaging modality, preceding CT or MR, for the diagnosis of hepatocellular carcinoma in patients with cirrhosis, detection of liver metastases in oncology patients and guidance and assessment of the outcome of percutaneous tumor ablation procedure. Recently, a new imaging technique that combines in real-time, transabdominal ultrasound with CT or MR, has been introduced in clinical practice. Real-time virtual sonography uses a magnetic positioning system attached to the ultrasound probe in order to calculate the spatial position and to display both imaging methods in real-time. Benefits include an increased diagnostic confidence, direct comparison of the lesions using different imaging modalities, more precise monitoring of interventional procedures and reduced radiation exposure. We describe the role of real-time contrast-enhanced and real-time virtual sonography in the assessment of malignant liver lesions.

Keywords


Contrast enhanced ultrasound (CEUS)

The development of microbubble contrast agents has had a major impact on the role of ultrasound in the liver, particularly for focal lesions. As a result of their double blood supply provided by the hepatic artery and portal vein, focal liver lesions present a complex temporal and spatial picture of increased and reduced contrast [1].

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 investigation [2]:

1. characterization of focal liver lesions (benign versus malignant);
2. guidance and monitoring local ablative treatment, and
3. measuring the hepatic transit time and studying the hepatic vessels.

1. Characterization of malignant liver lesions

Hypo-enhancement of solid lesions (darker than the surrounding liver) in the late phase characterizes malignancies [2].

Recognition of hepatocellular carcinomas (HCC) in liver cirrhosis is difficult if the echo texture is very inhomogeneous due to the presence of regenerative nodules and architectural changes caused by extensive fibrosis. The progression from a regenerative nodule to a frank HCC is characterized by loss of visualization of portal tracts and development of new arterial vessels, which become the dominant blood supply in HCC lesions [3-5]. This arterial neoangiogenesis is the landmark of HCC and is the key for imaging diagnosis [6-8]. Several reports have shown that CEUS is the perfect tool to detect arterial neoangiogenesis in HCC [9, 10-12]. Typical features of hepatocellular carcinoma in cirrhotic liver show strong, early, complete enhancement in the arterial phase [Fig. 1a], while macrogeneric nodules are iso-enhancing with liver parenchyma. In other cases, basket pattern, chaotic vessels or rim-like enhancement can be detected in HCC lesions. Selective arterial enhancement on CEUS has been observed in 91-96% of HCC lesions [13, 14]. In subsequent phases, most hepatocellular carcinomas have a wash-out pattern and become hypo-enhanced in the parenchimal phase (Fig. 1b,c). Both the 2005 EASL conference on HCC and the AASLD practice guidelines have recommended the further
investigation of nodules detected during US surveillance with dynamic imaging techniques (including CEUS, multidetector CT or dynamic MR imaging) to highlight the different vascular supply of HCC versus non-malignant entities [15, 16]. The diagnosis of hepatic nodules depends on the lesion size. For lesions larger than 2 cm a single imaging technique showing the characteristic vascular profile of HCC (arterial hypervascularization with washout in the portal venous or the late phase) may confidently establish the diagnosis. In lesions ranging from 1 to 2 cm, AASLD guidelines have recommended that typical imaging findings should be confirmed by two coincident dynamic imaging modalities for HCC diagnosis [15]. Currently, liver biopsy is recommended only if the lesion does not show typical features of HCC [15]. CEUS has been proven to be an effective noninvasive tool in the screening and diagnosis of HCC.

Metastases may be hypo- or hypervascular in the arterial phase or may have a peripheral rim enhancement (Fig. 2). All metastases have washout of the contrast and become hypo-enhanced in the portal and late phase (Fig. 3). Metastases of carcinomas are the most common malignant infiltration of the liver. In addition, the liver is the parenchymatous organ in which metastases are encountered most often. The introduction of CEUS in clinical practice has markedly improved the detection rate of liver metastases versus conventional ultrasound, especially for small size or isoechoic lesions, and also for metastases in difficult anatomical areas (e.g. in the superficial subdiaphragmatic areas and around the ligamentum teres) [17-19]. Some studies have shown that the accuracy in the detection of liver metastases is comparable to CT [20, 21]. It has also been demonstrated that CEUS can detect metastases not visible on CT [20, 22, 23], but can also miss lesions shown on CT. Current recommendations

Fig 1. HCC nodule that shows progressive and intense enhancement, with stelate pattern and central necrosis, in the arterial phase [a]. In subsequent portal and parenchymal phases, due to perfusion of surrounding liver parenchyma together with wash-out of the contrast agent from the nodule, it appears hypo-enhanced and less evident [b,c].

Fig 2. A 65-year-old male patient with a history of gastric cancer under chemotherapy and regular imaging follow-up. The non-enhanced B-mode US of the right liver lobe shows a liver metastasis with a strong peripheral rim enhancement in the arterial phase.

Fig 3. Contrast-enhanced US scan of the right lobe shows multiple metastases. The metastatic lesions are clearly delineated in the portal-venous and late phase as ‘black spots’, due to the lack of portal-venous blood supply.
for the use of CEUS in liver imaging include the exclusion of liver metastases in oncology patients, even if the baseline scans do not show any abnormality [2]. In addition, CEUS is useful to assess the number and location of liver metastases, if it is important for treatment planning [2]. CEUS is also a promising modality to monitor chemotherapy for liver metastases [24], especially when antiangiogenic or targeted therapies are used [25].

2. Guiding and monitoring local ablative treatment

Percutaneous ablation (radiofrequency ablation and percutaneous ethanol injection) is currently the most used technique for both HCC and liver metastases [26-28]. The objective of this technique is to achieve complete necrosis of the tumoral tissue, including a sufficient safety margin. The use of contrast agents can provide many advantages [2, 29, 30]: evaluation of the number of lesions with the exclusion of patients initially enrolled for percutaneous treatment with unexpectedly large number of metastases detected; better delineation of lesions poorly visualized on baseline US scans; evaluation of ablation result with immediate detection of residual viable tumour area in the interventional room, not at a distance as CT or MRI, and with the same operator and the same US equipment used for the ablative procedure; additional percutaneous treatment application in the same session until no further residual enhancement is detectable; post-ablation follow-up (Figs. 4, 5). Recent studies have shown an accuracy of CEUS in the assessment of percutaneous treatment from 91 to 100% [31-33]. Also, CEUS has almost the same sensitivity in the detection of residual HCC as CT [31-36]. Following these excellent results, some authors have suggested that CEUS should be used as the first imaging technique to evaluate the initial response to percutaneous treatment, thus avoiding the use of more expensive and time-consuming facilities [35].

3. Measuring the hepatic transit time and studying the hepatic vessels

Despite the major advances in imaging techniques, the detection of smaller (less than 1 cm) metastases is still very difficult. Several studies have revealed a significant shortening of the hepatic transit time (from hepatic artery to hepatic vein) in patients with liver metastases [37-39]. It was also demonstrated that a transit time of more than 10 seconds rules out metastases with a sensitivity of 100% and specificity of 91% [38].

CEUS is also useful for differential diagnosis between benign and malignant portal vein thrombosis. The malignant portal thrombus has arterial hypervascularity and marked late hypovascularity (Fig. 6) in contrast to benign thrombus which shows no arterial enhancement [40].

New prospect in contrast enhanced ultrasound

The use of microbubbles for treatment may eventually be even more important than their diagnostic uses. Microbubbles can aid drug delivery by themselves with application in the emerging area of gene therapy or in other specific treatments as a minimally invasive means for treating pathologies via a targeted drug-delivery strategy [41]. Further research is required to develop this technique into a clinically useful tool. CEUS can be used, also, for the quantification of tumoral perfusion in the early assessment and monitoring of the efficacy of antiangiogenic agents in quantitative terms based on changes in vascularity, before morphological changes become apparent [42, 43].
Real-time virtual sonography (RVS)

Real-time virtual sonography is a new imaging technique that combines in real-time transabdominal ultrasound with CT or MR. This technique includes magnetic positioning sensors on the probe of the ultrasound scanner, for the creation of images with identical cross-sections in real time according to the position and angle of the probe in relation to the CT and MR volume data that has been acquired.

The actual procedure is: 1) first, the CT and MR volume data is transferred into the ultrasound machine; 2) the magnetic position sensor unit is prepared with attention to the positions of the orientation marks; 3) the transmitter (the instrument that produces magnetic waves) for the magnetic position sensor unit is installed on the left flank of a patient; 4) the xyphoid process is selected as the reference point; 5) the first ultrasound section is sagittal, with the left hepatic lobe. The virtual image (CT or MR and ultrasound) shows on the workstation monitor. Corrections are possible when the positions of virtual images and ultrasound images do not align.

Several studies have proved already the feasibility of the RVS module, especially for the percutaneous radiofrequency ablation of poorly visible or unidentifiable focal liver lesions during B-mode sonography [44-47] (Fig. 7). Improvement of the CT technique also allows the identification of the relationship between the intrahepatic vessels and the HCC nodule during RVS (Fig. 8), consequently contributing to an accurate and safe performance of radio frequency ablation [48].

The real-time virtual sonography has some limitations. First, in patients in whom CT or MR is contraindicated (patients with known contrast medium allergies, renal insufficiency or metallic implant). Second, RVS does not show always the best synchronization of ultrasound and CT or MR image, but the discrepancy can be adjusted with neighboring portal and hepatic veins in most cases.

In conclusion, the 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. Benefits include an increased diagnostic confidence, direct comparison of the lesions using different imaging modalities, more precise monitoring of interventional procedures and reduced radiation exposure.

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Fig 8. Real-time virtual sonography of the HCC nodule with simultaneous display of the contrast-enhanced MR section and real-time ultrasound image: power Doppler [a] and dynamic Contrast Harmonic image [b, c]. The HCC nodule had rapid enhancement in the arterial phase [b], followed by wash-out in subsequent phases [c].

Conflicts of interest
Nothing to declare.

References


