Eur. Radiol. 13 (Suppl. 3) N79-N86 (2003)

Imaging of liver metastases with contrast-specific low-MI real-time ultrasound and SonoVue

T. Albrecht, A. Oldenburg, J. Hohmann, J. Skrok, C.W. Hoffmann, S. Schettler, K.-J. Wolf

Klinik und Poliklinik für Radiologie und Nuklearmedizin, Charité - Campus Benjamin Franklin, Universitätsmedizin Berlin, Freie Universität Berlin und Humboldt-Universität zu Berlin, Germany

Introduction

The liver has several features that make it a common site for metastases from malignancies of other organs. These are the dual blood supply via the portal vein and the hepatic artery, the high volume of blood flow (about a quarter of the cardiac output), the microscopic vascular anatomy which favours tumour cell trapping, and the major role that the liver plays in metabolism that provides an ideal environment for rapid growth [1]. Therefore, in 25–50% patients with a known malignancy, liver metastases are found at the time of diagnosis with decreasing frequency in colon, gastric, pancreatic, breast and lung cancer [2].

Accurate and timely detection of hepatic metastases is very important because of the far-reaching therapeutic and prognostic implications. Especially after the recent improvements in liver resection and thermoablation of metastases from colorectal carcinoma, liver imaging has become more demanding. Accurate assessment of the number, size and segmental location of liver metastases is required for treatment planning and so as to identify patients that are suitable for surgical or interventional therapy.

Besides metastases, there are a number of other, mainly benign, types of focal liver lesions which have to be differentiated from metastases. Benign liver lesions are very common: their prevalence has been reported to be more than 20% in non-selected autopsy series [3, 4]. As a consequence of this, in patients with extrahepatic malignancy, about 50% of solid lesions smaller than 2 cm are benign [5, 6]. The most common benign liver lesions are simple cysts, but they are usually easily recognised as such by imaging. More challenging is the characterisation of common solid lesions such as haemangiomas, focal nodular hyperplasia (FNH) and focal fatty change/sparing. Adenomas are much rarer and occur almost exclusively in patients on sex hormone medication. Other rare but relevant benign lesions include focal hepatic infections: pyogenic, parasitic or fungal abscesses. Furthermore, there is a worldwide increase in primary malignant liver lesions, namely hepatocellular carcinomas (HCC), of which 80% are associated with cirrhosis and/or chronic viral hepatitis [3], and this is an important differential diagnostic clue. Other primary malignant liver lesions such as cholangiocarcinoma are much rarer.

The cross-sectional imaging methods used for liver imaging (computed tomography) (CT), magnetic resonance imaging (MRI) and grey-scale ultrasound (US) are based on assessment of lesion morphology. The use of contrast agents increases both sensitivity and specificity of lesion detection considerably and provides crucial additional information about the dynamic contrast behaviour for lesion characterisation. In contrast to CT and MRI, US is inexpensive and widely available with no radiation exposure and good patient acceptance. US is therefore often the first-line investigation for hepatic screening of cancer patients. However, mainly due to a lack of contrast agents, US used to be less sensitive and less specific compared with CT and MRI [7], even when recent sonographic techniques such as tissue harmonic imaging were used [8–11]. These limitations have been overcome with the advent of US contrast agents and new contrast-specific imaging techniques such as pulse or phase inversion imaging, and in some cases contrast-enhanced sonography now has the edge over other imaging modalities.

Microbubble contrast agents for liver imaging

The most important recent developments for US of the liver have been in the field of contrast agents, including both the different kinds of contrast agents with their individual properties and contrast-specific imaging techniques. The advent of the first microbubble US contrast agents was in the mid-1990s, which was relatively late compared to CT and MRI.

In the late 1990s, high-mechanical-index (MI) US techniques were used for contrast-enhanced US (CEUS) of the liver, mainly using the air-based agent Levovist (Schering AG, Berlin, Germany). This led to a considerable improvement of lesion detection and characterisation compared with unenhanced US. Sensitivity in detecting liver metastases with high-MI CEUS has been shown to be similar to dual-phase spiral CT [12]. High-MI techniques rely on microbubble destruction, which is necessary for clinically useful enhancement when air-based agents are used. The technique is limited by the extreme transience of the contrast enhancement. It does not permit continuous imaging during contrast enhancement and instead requires special scanning techniques such as rapid sweeping and cine loop review or intermittent imaging for maximum exploitation of the contrast effect. These techniques are somewhat cumbersome and they counteract the real-time nature of US.

More recent microbubble agents use other gases than air, mainly perfluor chemicals. Their major advantage is a much lower water solubility and thus a much higher stability in the blood pool. They are strong harmonic reflectors even at low MI, when only minimal microbubble destruction occurs. This means that they provide strong and continuous signal enhancement on low-MI contrast-specific US, permitting continuous imaging of the liver for several minutes after their injection.

SonoVue (Bracco, Italy) was the first of these agents and so far the only one to be licensed for liver imaging in Europe. It consists of sulphorhexafloride microbubbles surrounded by a thin layer of phospholipid and palmitic acid, which allows the bubbles to withstand several passes through the pulmonary capillaries. Like all microbubbles and unlike contrast material for CT and MRI, SonoVue is a blood pool agent that remains in the intravascular fluid compartment and does not leak into the interstitium. The size of the microbubbles is less than 8 μm, which ensures that there is no embolisation of capillaries.

In the liver, SonoVue is used for dynamic real-time imaging during the arterial, portal venous and delayed phase. The delayed phase is a particular property of several US contrast agents, during which the microbubbles pool in the liver sinusoids (the precise reason for this phenomenon remains unclear). It begins approximately 2 min after injection and persists for about 3 min. It is particularly useful for detection of metastases, since the delayed phase enhancement invariably spares metastases and thus increases liver-to-lesion contrast and improves their detection. The delayed phase of SonoVue is fundamentally different from the "equilibrium phase" of non-specific contrast agents for CT and MRI. Instead, it is comparable to delayed imaging with liver-specific agents for MRI.

Clinical use of SonoVue for imaging of liver metastases

Examination technique

Prior to contrast injection, a detailed unenhanced baseline examination of the liver is performed. This includes the use of tissue harmonic imaging and power Doppler to assess lesion vascularity. The baseline images are used to assess the hepatic anatomy and any masses, including cysts, typical haemangiomas and any solid masses that might be metastases. Baseline images are the basis for planning the contrast-enhanced scan, and the findings of both parts of the examination are interpreted together.

SonoVue is injected intravenously followed by a 10-ml normal saline flush. The typical dose is 2.4 ml; if necessary two further injections and/or a dose of 4.8 ml can be administered. It is mandatory to use contrast-specific imaging modes for post-contrast scanning. The acoustic output of the US system has to be controlled carefully by the operator: Best results are usually obtained at an MI of 0.1–0.2 and it should not exceed 0.3**,** as this would result in considerable bubble destruction and reduction of the contrast effect.

If solid lesions are already present on the baseline scan, one or several of these will be selected for arterial phase imaging. The imaging plane should be selected in such a way that as many lesions as possible are covered during the arterial phase. Sweeping through the liver during the arterial phase may be required to cover several lesions. This can be technically demanding, since the arterial phase lasts only until approximately 30 s after injection. In most cases it is, however, sufficient to study one solitary or representative lesion in the arterial phase.

The portal venous phase (30 s to 2 min) and the delayed phase (2–5 min) are much longer. During these phases, the entire liver is continuously surveyed in multiple planes in a similar way to routine unenhanced scanning.

For image documentation, representative digital movie clips of the relevant parts of the liver are recorded during all three phases. Alternatively, still images can be obtained. Review of the recorded clips or of the cine loop after completion of the examination is often very helpful for comprehensive assessment of the liver without time constraints.

Dynamic imaging features of metastases

Metastases show characteristic features in all three phases after contrast injection (Figs. 1–3). In the arterial phase the appearances are twofold: hypovascular metastases appear as hyporeflective lesions usually with a typical rim enhancement of varying size, while hypervascular deposits appear as brightly enhancing hyper-reflec-

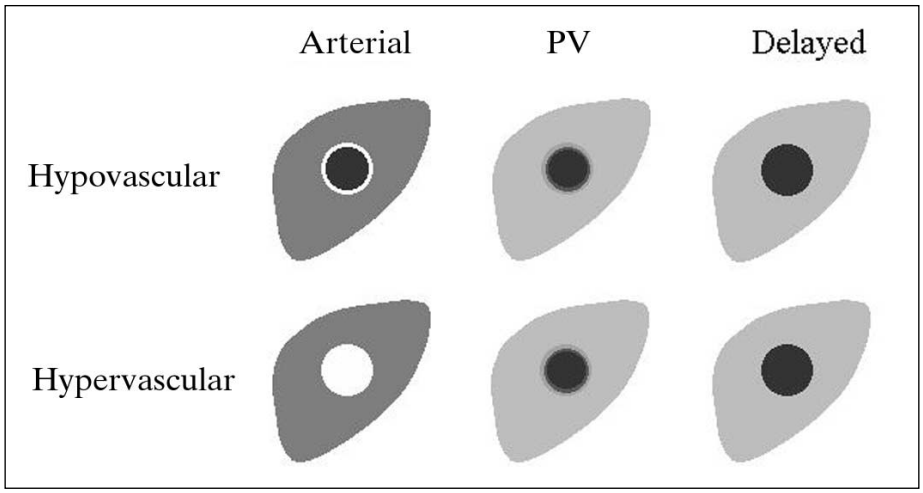
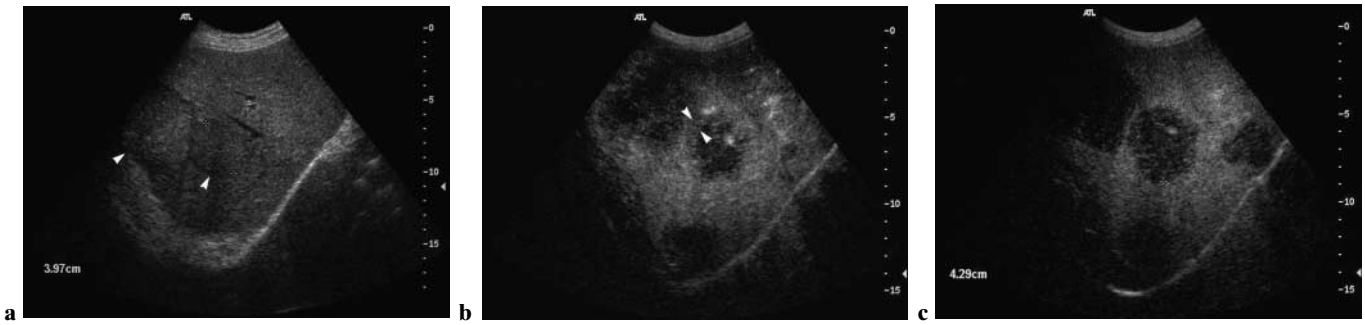
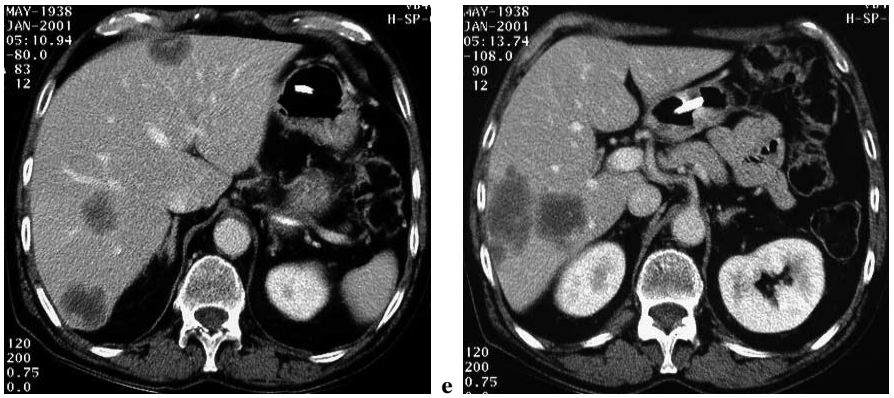


Fig. 1. Schematic display of the dynamic enhancement of hypo- and hypervascular metastases after SonoVue during the arterial, portal venous and delayed phase

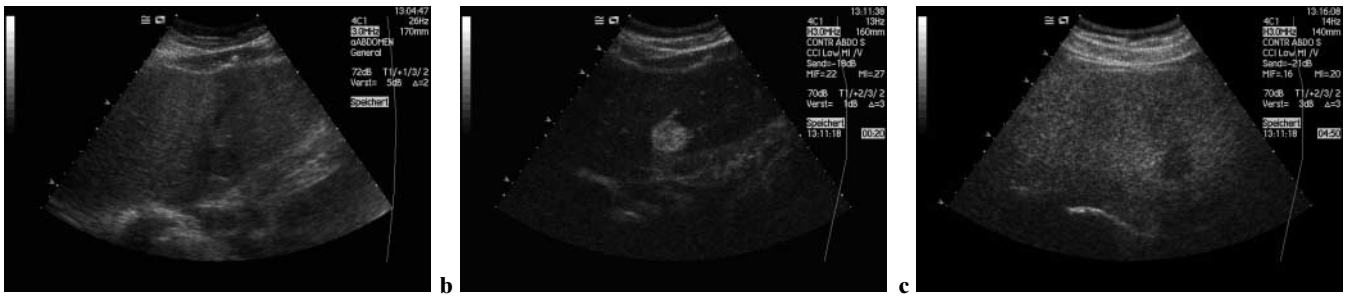


a b c



d e

Fig. 2a-e. Hepatic metastases from nasopharyngeal carcinoma. **a** Baseline US using tissue harmonic imaging shows two nearly isoechoic lesions measuring 4 and 5 cm respectively (*arrowheads*). **b** In the arterial phase after SonoVue, the lesions become hypoechoic with peripheral rim enhancement (*arrowheads*). At least two additional such lesions are revealed in the mid and far field. **c** In the delayed phase, the lesions are homogeneously hypoechoic against the enhancing normal liver tissue. The lesion margins are now very sharp. A total of five metastases are seen in the delayed phase. **d**, **e** CT confirms the presence of five metastases



a b c

Fig. 3a-c. Hypervascular metastasis of thyroid carcinoma. **a** Baseline grey-scale image with a hypoechoic lesion. **b** During the arterial phase, 20 s p.i. of SonoVue, the lesion shows a homogeneous enhancement while the liver parenchyma remains almost not visible. **c** Delayed phase image (4:50 min p.i.) with enhancement of liver parenchyma and a contrast defect caused by the metastasis

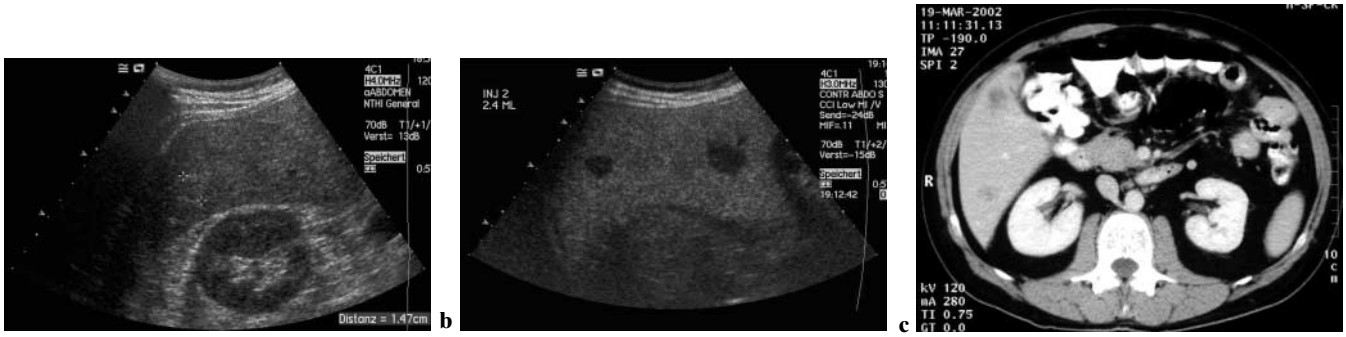


Fig. 4a-c. Patient with colorectal carcinoma. **a** Baseline US shows an almost isoechoic lesion in segment VI measuring 1.5 cm. **b** In the delayed phase after SonoVue (2.5 min) the metastasis appears as a typical enhancement defect and is much more visible. A second metastasis of 2 cm is now detected in segment V**. c** Spiral CT examination in portal venous phase (150 ml Iohexol 300) confirms the presence of the two metastases

tive and homogeneous lesions. At the beginning of the portal venous phase, the (rim) enhancement fades and the entire lesion becomes increasingly hyporeflective. In the delayed phase both hypo- and hypervascular metastases invariably appear as dark enhancement defects while the enhancement persists in normal liver parenchyma. During this phase the lesions are usually particularly well defined often with sharp, "punched out" borders. Both portal venous and delayed phase imaging markedly increase the contrast between the enhancing normal liver and the non-enhancing metastases and thus improve detection, especially of small lesions or lesions that are isoechoic on baseline US (Figs. 2, 4).

Dynamic features of benign lesions

As discussed in the previous section, solid benign liver lesions are very common. It is therefore of utmost importance to differentiate these from metastases in cancer patients. Fortunately, all common solid benign liver lesions have characteristic dynamic imaging features on contrast-enhanced CT and their diagnosis is thus usually unproblematic. Most of these features are analogous to those of dynamic CT and MRI.

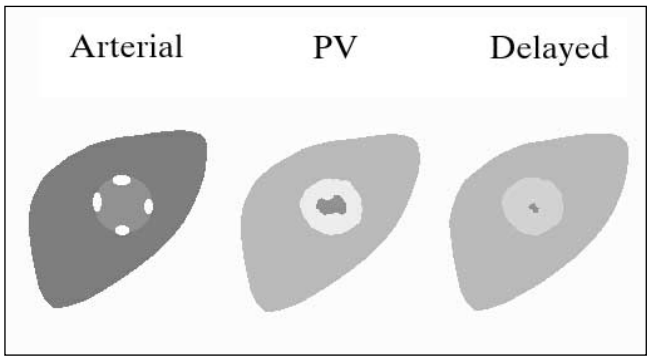


Fig. 5. Schematic display of the dynamic enhancement of haemangiomas after SonoVue during the arterial, portal venous and delayed phase

Haemangiomas show a characteristic peripheral nodular arterial phase enhancement followed by gradual centripetal in-filling during the later phases (Figs. 5, 6). The filling may be partial or complete. The speed of filling is size dependent: while small haemangiomas often fill within less than 1 min, large lesions may take 10 min or more. Many large haemangiomas will not fill completely, but this can also occur in smaller lesions and can sometimes lead to confusion with metastases.

FNHs appear as lesions with homogeneous enhancement in the arterial phase. In about 50% of FNHs this is preceded by a typical spoke-wheel arterial pattern with centrifugal filling early in the arterial phase, lasting for a few seconds (Figs. 7, 8). In some cases the feeding artery is also seen. In the subsequent phases the lesions show a similar degree of enhancement as the normal liver, due to the liver-like tissue that the lesion consists of. Delayed phase imaging is particularly useful for FNHs as they invariable appear as isoechoic or hyperechoic lesions, often with a central scar that was previously invisible (Figs. 7, 8). They can thus not be confused with metastases. Not unusually, especially small FNHs may become completely occult in the delayed phase because of their liver-like contrast behaviour.

Focal fatty change and focal fatty sparing show the same contrast behaviour as normal liver parenchyma on all phases, since they contain no abnormal vessels and essentially consist of normal parenchyma. Again, these lesions usually "disappear" after contrast injection (Fig. 9).

Liver abscesses are rare; they may, however, be confused with metastases since they also show a rim enhancement in the arterial phase and produce enhancement defects in the later phases. An important differential diagnostic clue is the complete absence of vessels and enhancement in the central liquid portion of an abscess, whereas even hypovascular metastases will display some weak but visible central enhancement owing to small vessels, provided they are not necrotic.

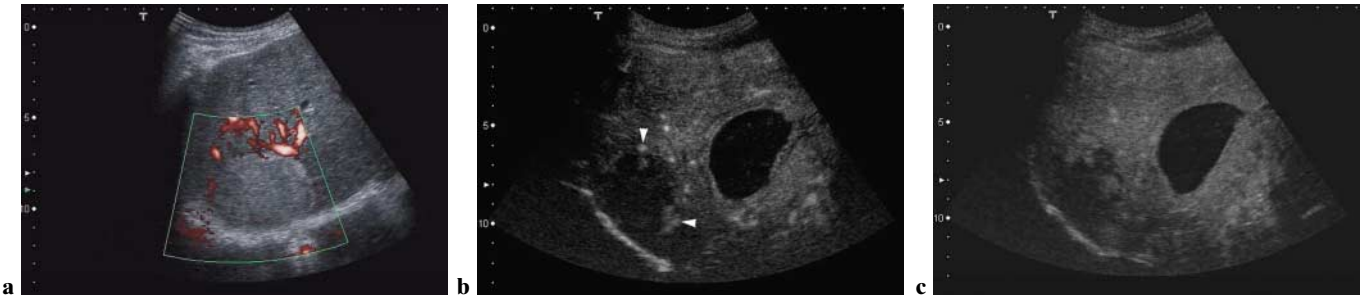


Fig. 6a-d. Typical haemangioma. **a** Baseline US shows a 5-cm homogeneously hyperechoic lesion posteriorly in the liver in segment VIII with no flow signals on power Doppler. **b** In the arterial phase, 15 s p.i. of SonoVue, peripheral nodular enhancement is seen (*arrowheads*). **c**, **d** Progressive centripetal filling of the lesion with microbubbles later in the arterial and in the portal venous phase

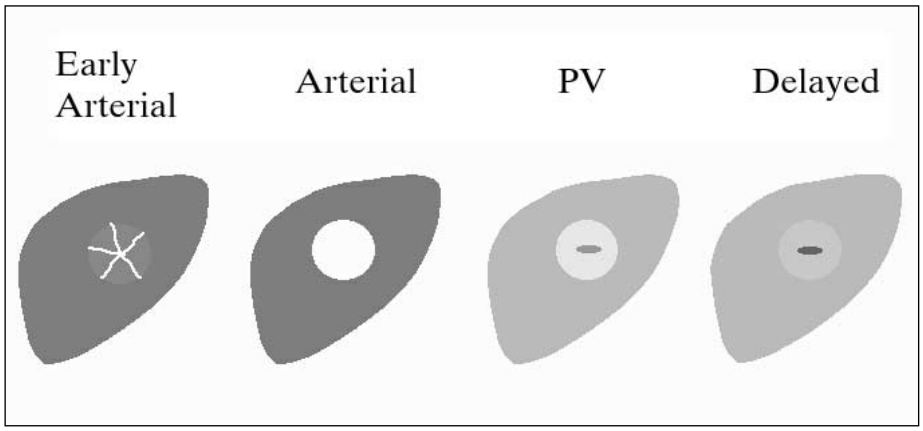


Fig. 7. Schematic display of the dynamic enhancement of FNH after SonoVue during the arterial, portal venous and delayed phase

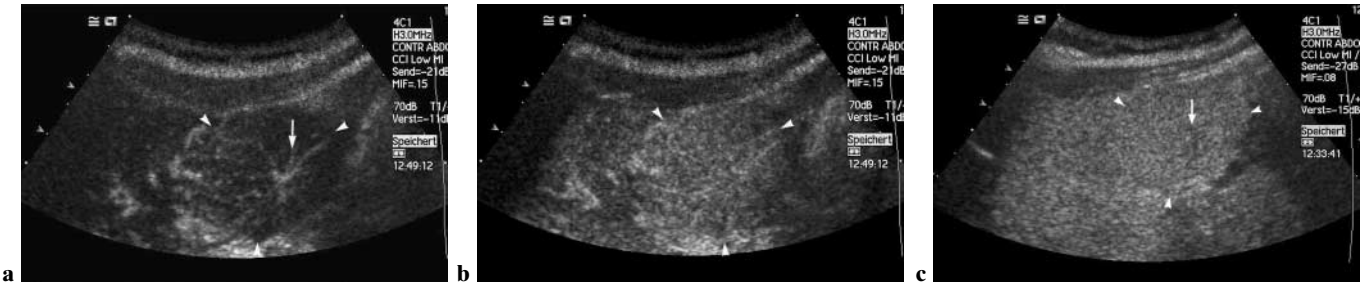
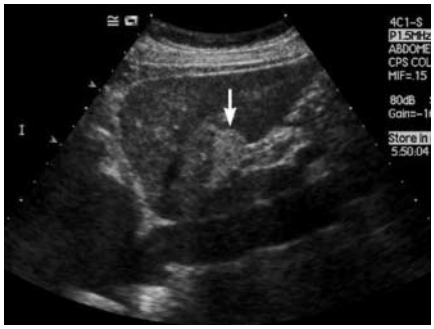


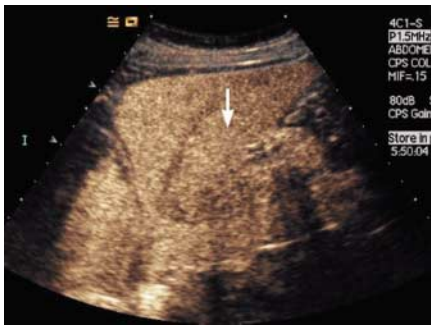
Fig. 8a-c. Focal nodular hyperplasia (*arrowheads*). **a** Typical spoke-wheel vascular pattern in the early arterial phase 13 s after SonoVue (*arrows*). **b** Three seconds later, the lesion is completely filled with contrast and appears hyperechoic to normal liver. **c** In the delayed phase the lesion is isoechoic to normal liver with the exception of a small hypoechoic central scar (*arrow*)

Limitations

The same limitations that apply to conventional US also apply to CEUS. Any patient with difficult sonographic access to the liver due to obesity or otherwise unfavourable anatomy will also be difficult to image with contrast agents. Particularly problematic are patients with severe steatosis and limited penetration of sound



a



b

Fig. 9a,b. Focal fatty infiltration (*arrow*) in a patient on chemotherapy for breast cancer. **a** Baseline US shows a triangular hyperechoic lesion in segment III. **b** Delayed phase imaging after SonoVue shows normal enhancement of the lesion; the lesion has disappeared. The CPS technique (Acuson Siemens) used here displays the contrast information as a colour overlay and allows switching between the conventional B-mode and the contrast image (**a** and **b** are an identical image pair without and with the contrast information)

into the liver. In such cases it is often not possible to see contrast enhancement beyond a few centimetres in depth, which is usually not sufficient.

Clinical results

We present the results of two clinical studies on imaging of liver metastases with SonoVue. Both studies were performed by the authors at the Benjamin Franklin University Hospital in Berlin, Germany.

The purpose of the first study was to assess whether SonoVue-enhanced low-MI real-time contrast-specific US improves the detection of liver metastases in comparison to conventional unenhanced US. Thirty-eight patients with extrahepatic malignancy and at least one focal liver lesion were included. Comparison of unenhanced baseline US and SonoVue-enhanced contrast-specific US was made. Contrast-enhanced dual-phase spiral CT (n=27) or dynamic MRI (n=11) was performed within a maximum of 4 weeks (mean 5 days) of the US examination and served as the standard of reference. The sonographic technique, the contrast administration procedure and the criteria for evaluating the contrast-enhanced sonograms were as described in the previous sections. The following contrast-specific imaging modes were used: Coherent Contrast Imaging, Contrast Pulse Sequencing (both Siemens Acuson, Mountain View, USA), Pulse Inversion (Philips Ultrasound, Bothell, USA), Ensemble Contrast Imaging (Siemens US Group, Issaquah, USA), and Pulse Subtraction Imaging (Toshiba Medical systems, Zoetermeer, NL). Both the US and reference examinations were interpreted by separate and independent blinded readers.

Of the 38 patients, 35 had hepatic metastases as judged by reference imaging and confirmed after histology (n=14) or follow-up imaging (n=5), while 3 patients showed only haemangiomas and no metastases. Baseline US showed metastases in 32 of the 35 positive patients, while CEUS showed metastases in all 35 cases. On a patient level, sensitivity thus increased from 94% on baseline US to 100% after contrast (not significant).

A total of 121 individual metastases were present on reference imaging. Baseline US detected 71 (59%) and CEUS 103 (85%) of these. CEUS showed more individual metastases than baseline US in 12 (34%) of the 35 patients with metastases. The mean number of reference-confirmed metastases per patient increased from 1.84±1.82 on conventional US to 2.7±2.57 after SonoVue (p<0.05). Using CT or MRI as the reference, the mean weighted sensitivity to individual metastases increased from 70% (95% confidence interval: 57–82%) on baseline US to 91% (95% confidence interval: 83–99%) after contrast (p<0.0005).

Subjective lesion conspicuity increased after contrast in 29 patients (83%; Figs. 1–4) and it remained unchanged in the other 6 (17%). Metastases smaller than 10 mm were seen in 5 patients on baseline US, in 12 after contrast and in 14 on reference imaging.

Lesions suggestive of metastases that were not confirmed by reference imaging were present on baseline US in three patients (5 lesions) and on CEUS in eight patients (13 lesions).

In summary, this study shows that SonoVue-enhanced US is considerably more sensitive than baseline US in the detection of liver metastases. Lesion conspicuity is improved and smaller metastases can be detected. A limitation of the study is the lack of a reliable gold standard, since neither CT nor MRI are perfect modalities for detection of metastases. The results have to be viewed bearing this point in mind. In particular, we do not know if the lesions seen on (CE)US but not on reference imaging represent false-positive cases or if they were true lesions that CT or MRI missed.

In a second study [13], we addressed the question of whether or not characterisation of focal liver lesions can be improved by dynamic SonoVue-enhanced low-MI real-time contrast-specific US in comparison to baseline US (including unenhanced grey-scale and power Doppler US). The results of this study will be presented with a focus on metastases.

Sixty-three patients were included, and one lesion per patient was evaluated. The US methodology used and the criteria for image interpretation were identical to the previous study. The final lesion diagnosis was based on histology in 25 cases and on unequivocal imaging

findings on MRI (n=19), CT (n=18) or intraoperative US (n=1) in the remaining 38 patients. In 11 patients with lesion characterisation based on imaging, confirmatory follow-up imaging data were available. The lesions studied were 27 metastases, 6 HCC, 2 cholangiocarcinomas, 11 haemangiomas, 11 FNHs, 3 areas of focal fatty change/sparing, 2 regenerating nodules and 1 abscess.

Ten of the 27 metastases were "hypervascular" on arterial phase imaging with homogeneous enhancement; the primaries in these patients were malignant melanoma (n=6), small cell lung cancer, thyroid carcinoma, neuroendocrine carcinoma and breast cancer (one each). The remaining 18 metastases were "hypovascular" and showed either a rim enhancement (n=10) or no enhancement at all (n=7) in the arterial phase; the most common primaries in this group were colorectal (n=9) and bronchogenic carcinoma (n=3). In the portal venous and delayed phase all 27 metastases were hypoechoic compared with normal liver.

On baseline US, 25 (93%) metastases were correctly diagnosed, whereas after contrast all 27 (100%) metastases were identified.

Twenty-eight of the lesions were benign; correct diagnosis of benignity was made in 12 (43%) of these on baseline US and in 25 (89%) after contrast. Two benign lesions were misinterpreted as malignant after contrast: one abscess (as above) and one atypical haemangioma which did not fill with contrast after the arterial phase. One regenerating nodule remained unclear.

In summary, the study shows marked improvement in characterisation of focal liver lesions by the use of SonoVue. Overall, the number of correctly diagnosed lesions improved from 41 of 63 (65%) on baseline US to 58 of 63 (92%) after contrast (p<0.001). Comparison with the literature suggests that CEUS is superior to CT and equivalent to MRI in this application [14–16]. The most important aspect of these results with regards to imaging cancer patients is the increase in specificity, i.e. the improved ability to recognise benign lesions and to rule out metastases.

Conclusion

Until recently, US was the preferred screening method for focal liver lesion disease because of the inherent advantages; however, it suffered a relatively poor sensitivity and specificity rate compared with other imaging techniques, such as CT and MRI, and further imaging was often required for a definitive diagnosis.

Since the advent of US contrast agents and new contrast-specific US techniques, US of the liver has improved dramatically. Detection of metastases is markedly improved as is lesion characterisation. The detection of liver metastases using CEUS is similar to spiral CT. The ability of contrast US to characterise focal liver lesions is superior to that of CT and at least equivalent to that of MRI. On the other hand, some limitations of US remain, such as its operator dependence or the limited access to certain parts of the liver especially in obese patients and/or fatty livers.

CEUS is a young field in which unexpected progress has been made in the last few years and is now at a stage where it is ready for routine clinical use. It adds a new dimension to liver US. We would like to encourage all radiologists and sonographers to start using it, since it provides crucial diagnostic information that is completely occult in conventional sonography, allowing it to rival CT and MRI.

References

1. Robinson PJ (2000) Imaging liver metastases: current limitations and future prospects. Br J Radiol 73:234-241
2. Cosgrove DO (2001) Malignant liver disease. In: Meire HB, et al (eds) Clinical ultrasound: a comprehensive text. Churchill Livingstone, London pp 211-231
3. Karhunen PJ (1986), Benign hepatic tumours and tumour like conditions in men. J Clin Pathol 39(2):183-188
4. Edmunson HJ Craig (1987) Neoplasms of the liver. In: Schiff L (ed) Diseases of the liver. Lippincott, Philadelphia pp 1109
5. Jones EC, Chezmar JL, Nelson RC, Bernardino ME (1992) The frequency and significance of small (less than or equal to 15 mm) hepatic lesions detected by CT. AJR Am J Roentgenol 158(3):535-539
6. Kreft B, Pauleit D, Bachmann R, Conrad R, Kramer A, Schild HH (2001) Häufigkeit und Bedeutung von kleinen fokalen Leberläsionen. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 173(5):424-429
7. Helmberger T, Rau H, Linke R, Reiser M (1999) Diagnostik und Stadieneinteilung der Lebermetastasen mit bildgebenden Verfahren. Chirurg 70(2):114-122
8. Wernecke K, Rummeny E, Bongartz G, Vassallo P, Kivelitz D, Wiesmann W, Peters PE, Reers B, Reiser M, Pircher W (1991) Detection of hepatic masses in patients with carcinoma: comparative sensitivities of sonography, CT, and MR imaging. AJR 157(4):731-739
9. Clarke MP, Kane RA, Steele DG, Hamilton ES, Ravikumar TS, Onik G, Clouse ME (1989) Prospective comparison of preoperative imaging and intraoperative ultrasonography in the detection of liver tumors. Surgery 106:849-855
10. Ohlsson B, Tranberg KG, Lundstedt C, Ekberg H, Hederstrom E (1993) Detection of hepatic metastases in colorectal cancer: a prospective study of laboratory and imaging methods. Eur J Surg 159:275-281
11. Albrecht T, Hoffmann CW, Schmitz SA, Schettler S, Bolze X, Wolf KJ (2000) Detection of liver metastases: comparison of contrast-enhanced phase inversion ultrasound and dual phase spiral CT with intraoperative sonographic correlation. Radiology 207(P):459
12. Albrecht T, Blomley MJ, Burns PN, Wilson S, Harvey CJ, Leen E, Claudon M, Calliada F, Correas JM, LaFortune M, Campani R, Hoffmann CW, Cosgrove DO, LeFevre F (2003) Improved detection of hepatic metastases with pulse-inversion US during the liver-specific phase of SHU 508A: multicenter study. Radiology 227(2):361-70
13. Hohmann J, Skrok J, Puls R, Albrecht T (2003) Characterization of Focal Liver Lesions with Contrast-Enhanced Low MI Real Time Ultrasound and SonoVue. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 175(6):835-43
14. Oudkerk M, van Beek EJ, Wielopolski P, van Ooijen PM, Brouwers-Kuyper EM, Bongaerts AH, Berghout A (2002) Comparison of contrast-enhanced magnetic resonance an-

giography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: a prospective study. Lancet 359(9318):1643-1647
15. Pirovano G, Vanzulli A, Marti-Bonmati L, Grazioli L, Manfredi R, Greco A, Holzknecht N, Daldrup-Link HE, Rummeny E, Hamm B, Arneson V, Imperatori L, Kirchin MA, Spinazzi A (2000) Evaluation of the accuracy of gadobenate dimeglumine-enhanced MR imaging in the detection and characterization of focal liver lesions. AJR Am J Roentgenol 175(4):1111-1120
16. Semelka RC, Martin DR, Balci C, Lance T (2001) Focal liver lesions: comparison of dual-phase CT and multisequence multiplanar MR imaging including dynamic gadolinium enhancement. J Magn Reson Imaging 13(3):397-401