Contrast-Enhanced Ultrasound in Clinical Practice
Liver, Prostate, Pancreas, Kidney and Lymph Nodes

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The value of ultrasound contrast agents (USCA) in clinical practice depends on the pharmacokinetics, the signal processing, and the contrast-specific imaging modalities.

USCA are exogenous non-toxic substances smaller than red blood cells, which after intravenous administration must be stable enough to pass through the pulmonary capillary bed and enter the blood pool producing the necessary contrast enhancement for the duration of the examination. Recently, second-generation agents, such as SonoVue (Bracco Imaging SpA, Milan, Italy), have been introduced into the market. These agents, taking advantage of the stability of their microbubbles, withstand the acoustic pressure of insonation much better than previous USCA, resulting in an increased half-life of the agent and thus in a prolonged diagnostic window. These agents are blood pool agents that remain in the intravascular compartment and do not leak into the organ tissue. Therefore, they are used to increase the Doppler signal amplitude during their dynamic vascular phase. Concomitant with the improvement of contrast agents, different contrast-specific imaging modalities have been developed which, used in combination with USCA and a low mechanical index (MI), allow continuous real-time grey-scale imaging. These recent technical improvements have opened new possibilities in the use of USCA in a variety of indications, as shown in the contributions contained in this book. In the following chapters, some of the most distinguished users of second-generation USCA will share their knowledge and experience.

The first contributor is Dr. Thomas Albrecht, Department of Radiology, University Hospital of Berlin, Germany. Dr Albrecht dis-
cusses how to distinguish between benign and malignant focal liver lesions by evaluating various dynamic vascular patterns of the second-generation USCA.

Dr. Lars Thorelius of the Department of Radiology, University Hospital of Linköping, Sweden, explains the use of USCA in indications beyond the liver and shares his experience in diseases of the kidneys and pancreas.

The third contribution is from Dr. Luigi Solbiati, Department of Radiology, General Hospital of Busto Arsizio, Varese, Italy. Dr. Solbiati presents the preliminary results of the use of USCA in the characterization of reactive and malignant lymph nodes, with emphasis on the technical improvement of transducers.

Finally, Dr. Ferdinand Frauscher, Department of Radiology II, University Hospital Innsbruck, Austria, describes how the application of USCA is a promising and useful tool for the detection and clinical staging of prostate cancer.

In conclusion, this publication represents an overview of current and possible future new applications of USCA in routine and clinical practice by some very experienced experts.

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FERDINAND FRAUSCHER
Modern liver imaging of cancer patients requires an imaging modality that is not only highly sensitive in detecting lesions but also provides reliable characterisation of lesions and thus allows differentiation of metastases from frequently found benign lesions.

Conventional ultrasound (US) has a relatively poor sensitivity and specificity for imaging focal liver lesions, and US used to be inferior to CT and MRI mainly due to a lack of contrast agents. This has changed with the advent of microbubble contrast agents for US. The use of recent contrast agents such as SonoVue (Bracco Imaging SpA, Milan, Italy) combined with low-mechanical index contrast-specific imaging techniques such as Contrast Pulse Sequencing provides high-quality, dynamic, real-time imaging of focal liver lesions in the arterial, portal venous and delayed phase.

This improves lesion detection and characterisation. The typical dynamic features of all common focal liver lesions are discussed in this chapter and clinical results are presented.
Introduction

Both benign and malignant focal liver lesions are extremely common, and imaging the liver for focal lesions especially in cancer patients is one of the most frequent tasks in everyday radiological practice.

The most common malignancy of the liver are metastases from other organs: 25-50% patients with a known non-haematological malignancy have liver metastases at the time of diagnosis [1] with decreasing frequency in colon, gastric, pancreatic, breast and lung cancer [2]. The second most common malignant liver tumour is hepatocellular carcinoma (HCC). It is strongly associated with chronic viral hepatitis and cirrhosis and this is an important differential diagnostic clue. Other primary malignant liver tumours such as cholangiocarcinoma are much rarer.

The prevalence of solid benign liver tumours has been reported to be more than 20% in autopsy series [1, 3], and in patients with malignancy 25-50% of lesions under 2 cm in size are benign [4, 5]. The most frequent benign lesion is haemangioma with a prevalence of 7-21% [3, 6], followed by focal nodular hyperplasia (FNH), which has a prevalence of up to 3% [3, 7]. Adenomas are much rarer than FNH (by a factor of approximately 50) and they occur almost exclusively in female patients with a history of oestrogen medication. Other rare benign lesions are pyogenic, parasitic or fungal abscesses. Areas of focal fatty change or focal fatty sparing are very common; they do not represent true lesions but may appear as pseudo-tumours on ultrasound (US) and are thus easily confused with real tumours such as metastases. From the above it is obvious that imaging of focal liver lesions requires an imaging modality that is not only highly sensitive in detection but also provides reliable characterisation of lesions and thus allows differentiation of malignant from benign tumours. Characterisation of focal liver lesions by imaging is based on the assessment of the dynamic enhancement patterns of a focal liver lesion.

Contrast-enhanced US (CEUS) is a relatively new imaging technique that combines excellent contrast and spatial resolu-
tion with unrivalled temporal resolution of more than ten frames per second. CEUS is ideally suited for comprehensive dynamic real-time imaging of the contrast behaviour of focal liver lesions, especially if recent perfluor gas-based contrast agents such as SonoVue (Bracco SpA, Italy) combined with low-mechanical index (MI) contrast-specific imaging are used.

General Principles of Contrast-Enhanced Liver Sonography with SonoVue

CEUS of the liver and other abdominal organs requires contrast-specific imaging techniques. These techniques selectively display the non-linear response from contrast microbubbles with a high sensitivity. The most widespread contrast-specific mode is phase or pulse inversion harmonic imaging. It exploits mainly the second harmonic microbubble response.

SonoVue microbubbles consist of sulphur hexafluoride, which has a much lower water solubility than air and thus a higher bubble stability in the blood pool. SonoVue microbubbles are strong non-linear reflectors even at low MI, when only minimal microbubble destruction occurs. This means that they provide strong and continuous signal enhancement on low-MI CEUS, permitting continuous imaging of the liver for several minutes after injection.

In the liver, SonoVue is used for dynamic real-time imaging during the arterial (up to 30 s p.i.), portal venous (40 s–2 min p.i.) and delayed phases (>2 min p.i.). 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 in case of SonoVue it persists for about 3 min. The delayed phase is particularly useful for characterisation of focal liver lesions since almost all malignant lesions (with the exception of some HCCs) are hypoenhancing in this phase, while the large majority of solid benign lesions show considerable delayed contrast uptake. Furthermore,
the detection rate of malignant lesions and especially of metastases is highest on delayed-phase imaging. The delayed phase of SonoVue is fundamentally different from the “equilibrium phase” of non-specific contrast agents for CT and MRI. Instead, it is more comparable to delayed imaging with liver-specific agents for MRI.

Low-MI Real-Time Imaging with SonoVue: Examination Technique

Prior to contrast medium 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 which 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 must 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 detected 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 manner 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 for only 10-15 s and more than one injection may be required. In most cases, however, it is sufficient to study one or two representative lesions in the arterial phase.
The portal venous phase (40 s to 2 min) and the delayed phase (2-5 min) last much longer, and the entire liver is continuously surveyed in multiple planes during these phases in a similar way as routine unenhanced scanning is performed. This will include lesions studied in the arterial phase, so that the enhancement patterns of these lesions can be assessed during all three phases.

For image documentation, representative digital movie clips of the relevant parts of the liver are recorded during all three phases. Alternatively, or in addition, 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 agent injection (Fig. 1). In the arterial phase the appearances are twofold: hypovascular metastases appear as hyporeflective lesions usually with a typical rim enhancement of varying size (Fig. 2A), while hypervascular metastatic deposits appear as brightly enhancing hyper-reflective and homogeneous lesions,
Fig. 2. “Hypovascular” hepatic metastasis from breast carcinoma. A In the arterial phase after SonoVue administration, the lesion displays strong peripheral rim enhancement (arrow). B Portal venous phase imaging shows fading of the rim. C In the delayed phase, the lesion presents as a hypoechoic enhancement defect with sharp margins.
Fig. 3. Hypervascular metastasis. A Baseline grey-scale image with a slightly hyperechoic lesion. B During the arterial phase the lesion shows homogeneous enhancement while most of the liver parenchyma is only partially filled with contrast material. C Partial washout of contrast material from the lesion, which is now hypo-enhancing compared to homogeneously enhancing normal liver. D Complete washout of contrast material from the lesion in the delayed phase results in a sharply circumscribed “punched out” enhancement defect.

sometimes with non-enhancing necrotic areas. At the beginning of the portal venous phase, the (rim) enhancement fades and the entire lesion becomes increasingly hyporeflective (Fig. 2B).

In the delayed phase, both hypo- and hypervascular metastases invariably appear as dark defects while the enhancement persists in normal liver parenchyma (Fig. 2C). 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 less than 1 cm in diameter (Figs. 4, 5) and of lesions that are isoechoic on baseline.
Fig. 4. Patient with multiple metastatic deposits. A Baseline US shows three ill-defined hypoechoic lesions in a slightly heterogeneous liver. B, C In the portal venous and delayed phase after Sonovue (Bracco Imaging, Italy) administration, multiple lesions are revealed throughout the liver, some of them only a few millimetres in diameter. D, E Multi-detector CT in the portal venous phase (150 ml iohexol 300 Schering AG, Berlin, Germany) confirms the presence of multiple lesions.
Fig. 5. Patient with bronchogenic carcinoma. A Baseline scan shows a single hypoechoic metastasis (arrow) in segment IV close to the left hepatic vein. B After administration of SonoVue (late phase), this lesion appears as a typical enhancement defect. C A second metastases of 6 mm is revealed after contrast administration (portal venous phase) in segment IV/VIII.
Dynamic Features of Common Benign Lesions

As discussed above, 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 CEUS and their diagnosis is thus usually unproblematic. Most of these features are analogous to those of dynamic CT and MRI.

Haemangiomas show a characteristic peripheral nodular arterial phase enhancement followed by gradual centripetal in-filling during the later phases (Figs. 6-8). The filling may be partial (Fig. 8) or complete. The speed of filling is size dependant: while small haemangiomas often fill within less than 1 min (Fig. 7), large lesions may take 5 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.

Fig. 6. Schematic display of the dynamic enhancement of haemangiomas after SonoVue administration during the arterial, portal venous (PV) and delayed phase
Fig. 7. Atypical haemangioma on conventional US with typical dynamic enhancement pattern after SonoVue administration. A Baseline US shows a 2-cm hypoechoic lesion in segment II, suggestive of a metastasis. B In the arterial phase, peripheral nodular enhancement is seen (arrow). C, D Complete filling of the lesion with microbubbles in the portal venous and delayed phase.
Fig. 8. Haemangioma (arrows). A Peripheral nodular enhancement (arrowhead) in the arterial phase. B In the portal venous phase the lesion shows some centripetal filling. C Most of the lesion has filled in the delayed phase with the exception of a small central area (arrowhead). Note: with this imaging technique (Vascular Recognition Imaging, VRI, Toshiba, Zoetermeer, The Netherlands), stationary microbubbles are displayed in green, flowing bubbles in red or blue