Contrast-enhanced Ultrasound in Focal Liver Lesions – Guidelines for Clinicians

a report by
David Cosgrove

Imperial College School of Medicine and Hammersmith Hospital, London

While ultrasound is generally the first-choice imaging technique for the liver, mainly because of its cost-effectiveness and ready availability, it has serious limitations in detecting and characterising focal lesions, even with the addition of Doppler. Its sensitivity is poor, with a false-negative rate of more than 50%, the most common problem being the low or absent contrast between the lesion and the surrounding liver – so-called iso-echoic lesions. In addition, lesions smaller than 1cm in diameter may be difficult to detect, even when the contrast is high. A further problem is the inaccessibility of portions of the liver, notably segment eight, which is difficult to reach because it lies high under the diaphragm. Characterising focal liver lesions is also often difficult because the wide range of grey-scale appearances causes overlap in the patterns. Here, Doppler has been of some help by delineating the arterial patterns that may be characteristic, for example the radiating spoke-wheel pattern of vessels in focal nodular hyperplasia (FNH).

Contrast-enhanced ultrasound (CEUS) has improved on both of these limitations, because it highlights malignant lesions against the enhanced background of the normal liver in the late (sinusoidal) phase, and because it allows both the macrocirculation of larger vessels and the microcirculation at capillary and sinusoidal level to be imaged. This greatly improves its ability to characterise focal liver lesions. In both of these applications, CEUS has improved to the point at which it equals (and in some cases even exceeds) the sensitivity and specificity of contrast computed tomography (CT) and magnetic resonance imaging (MRI).

Contrast Agents for Ultrasound

The contrast agents used for ultrasound are microbubbles. Modern agents contain high-molecular-weight gases, such as perfluoro compounds, which are chosen for their biological inertness and because their molecular weight slows diffusion and thus prolongs their life after injection. The gas 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. Once injected, they dissolve slowly, giving an effective life of two to five minutes, following which repeat injections may be given. However, as well as the blood pool distribution, most microbubble contrast agents have a prolonged phase in the liver and spleen, where they persist for several minutes after clearance from the bloodstream. For some agents, this late phase has been shown to be caused by phagocytosis, while for others it seems simply to reflect the large sinusoidal volume of the liver, in which the microbubbles barely move.

The arterial phase, which begins some 15–30 seconds after injection, is invaluable in revealing the haemodynamics of a tissue or lesion – in much the same way as Doppler, but with far greater sensitivity and detail. The late phase is important in detecting malignancies because they lack the sinusoidal spaces of liver and so do not retain contrast, appearing as filling defects. While this statement is true of all metastases and of cholangiocarcinomas, some well-differentiated hepatocellular carcinomas (HCCs) do possess a sinusoidal structure and show partial or even complete retention of contrast. This is an uncommon but important limitation of CEUS, though such lesions usually do show the hypervascularity typical of HCCs in the arterial phase. Fluid-filled lesions such as cysts and abscesses also do not retain microbubbles in the late phase, but most have characteristic features on conventional ultrasound and so do not pose a clinical problem.

Detection of microbubbles relies on their response to the pressure changes of the ultrasound field, which contrasts starkly with the response of tissue. Tissue is virtually incompressible, but microbubbles contract and expand in the compression and rarefaction phases of the ultrasound field. In doing so, they return signals at double and half the frequency emitted by the ultrasound transducer. This so-called nonlinear behaviour arises because microbubbles offer more resistance to compression than they do to expansion. The special pulse sequences and reception software that constitute the ‘contrast mode’ of modified scanners are used to image the distribution of the microbubbles in realtime, while the conventional grey-scale realtime image is displayed simultaneously, usually as a registered side-by-side pair. One of the strengths of CEUS is the high frame-rate that is available – this allows the arrival of the agent in a lesion to be examined continuously, while with CT and MRI it can be sampled only intermittently.

Because of their inert constituents, ultrasound contrast agents are very safe and do not have nephro- or cardiotoxic effects.
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. Users must be familiar with resuscitation techniques.

Contrast-enhanced Ultrasound in the Liver
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 post-injection, the entire liver volume is scanned with slow subcostal and intercostal sweeps, looking for filling defects. Blood vessels may also appear as defects, depending on how much contrast is still in the vascular system, but they can be distinguished by their linear shapes. While the left of the liver and the inferior parts of the right are easily covered, reaching segment eight usually necessitates turning the patient into the left decubitus position and having them hold a deep breath so that this portion can be accessed with subcostal sweeps.

Several prospective studies have shown the comparability of this technique to contrast CT and MRI for metastases and, in some cases, lesions that are too small to detect with CT or MRI are clearly shown on CEUS. 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. More recently, 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. Thus, CEUS is emerging as the standard technique for staging the liver. However, there remain some technical limitations – the difficult access to segment eight has already been referred to, while contrast-specific modes do not penetrate beyond about 10cm, so that deeper parts of the liver may be difficult to study; this problem is exacerbated when the liver is highly attenuating, for example in cirrhosis.

The value of CEUS for cholangiocarcinoma is also clear. This tumour, with its infiltrating margin, is usually difficult to delineate accurately with conventional imaging, but CEUS reveals the lesion as non-enhancing regions in the late phase. In one study of 18 lesions, all (100%) showed hypo-enhancement in the late phases.

The situation for HCCs is similar in that here also CEUS is more sensitive than conventional ultrasound (see Figure 1). In a study of 107 lesions, late-phase defects were seen in 95.3%. The majority (94%) were also hypervascular in the arterial phase.

Contrasting between types of focal liver lesion, it is important to take into account the haemodynamics as revealed by both the late phase and the arterial phase soon after contrast injection.
benign lesions have typical arterial supply patterns, both anatomically and temporally, and these are similar to those seen on dynamic CT and MRI. For example, haemangiomas fill from their margins, where the supply artery discharges into vascular lakes that are seen as peripheral nodules of enhancement. From these the contrast gradually percolates in a centripetal pattern so that the lesion fills more or less completely. Necrotic or thrombosed regions, which are more common in larger haemangiomas, obviously 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. FNH 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, the so-called ‘light-bulb sign’. As the liver takes up contrast, it comes to match the enhancement in the FNH, which consequently disappears as it blends into the background. 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 hypervacular lesions with a peripheral supply, and often disappear in the late phase. 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.

The European Federation Guidelines

A set of guidelines on the indications and practice of contrast ultrasound, focusing on the liver, was published by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) in 2004,14 and a revised set is to be published in late 2007. The guidelines embody the recommendations of a panel of 18 experts, based on the published literature and on a consensus of their own experiences. Important conclusions were that contrast ultrasound using modern agents and equipment was equivalent to contrast CT in staging for metastases, in detection of HCC and in characterising focal liver lesions. Because ultrasound is often the first imaging technique used for the liver, the guidelines recommend the use of contrast for these problems unless the conventional ultrasound scan is unequivocal (for example, in a patient with a known primary tumour where multiple focal lesions typical of metastases are found). Used in this way as a replacement for contrast-enhanced CT, CEUS results in savings of €75–90 per subject,15,16 as well as expediting the diagnosis. Importantly, for incidentally discovered lesions that turn out to be benign (typically haemangiomas and FNH), the immediate use of contrast can establish the diagnosis straight away, thus saving the patient an anxious wait as well as the additional cost and, in the case of CT, exposure to ionising radiation.

The new guidelines also incorporate the Barcelona 2000 European Association for the Study of the Liver (EASL) Conference on the imaging surveillance of patients with cirrhosis.17 Discovery of a focal lesion in such a patient must raise the suspicion of HCC. Usually, ultrasound is used for surveillance every six to 12 months, but HCCs have a wide range of appearances, so the demonstration of a nodule lacks specificity. Further investigation to characterise such lesions depends on their size – lesions smaller than 2cm in diameter require two dynamic studies showing auspicious 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 use of CEUS in thermal ablation of the liver will also be included in the EFSUMB guidelines. Since ultrasound is preferred for guidance of all types of interstitial therapy because of its realtime and interactive nature, estimation of the extent of ablation using ultrasound is obviously desirable. Unfortunately, conventional ultrasound performs poorly as it cannot usually discriminate between viable and ablated tumour. This means that the patient must be moved to CT for a contrast study, and may have to return to ultrasound for further ablation, usually in another session, which is cumbersome and costly. The superior capability of CEUS to define tumour margins allows the ablation to be better planned and enables immediate post-ablation monitoring to ensure that the lesion and a 0.5–1cm margin has been coagulated.18 Prospective studies have demonstrated better ablation and cost savings in terms of avoiding CT scans – the improvement in patient wellbeing is harder to quantify, but is certainly considerable.

Conclusions

The development of microbubble contrast agents has had a major impact on the role of ultrasound in the liver, especially for focal lesions. CEUS has similar sensitivity to contrast-enhanced CT for liver metastases, and for HCC, and the same applies in the differential diagnosis of benign focal lesions. It is recommended for evaluating lesions discovered during the surveillance of cirrhotic patients and for the immediate monitoring of interstitial ablation therapy.

Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) – Update 2008

EFSUMB study group


Affiliations

Affiliation addresses are listed at the end of the article.

Key words
- contrast agent
- liver
- urinary
- v. ureteric reflux
- pancreas
- trauma
- transcranial US

Thematic groups composition

<table>
<thead>
<tr>
<th>Chairpersons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
</tr>
<tr>
<td>1 General considerations</td>
</tr>
<tr>
<td>2 Liver</td>
</tr>
<tr>
<td>2.1 Characterisation of focal liver lesion</td>
</tr>
<tr>
<td>2.2 Detection of focal liver lesion</td>
</tr>
<tr>
<td>2.3 Monitoring of ablative treatment</td>
</tr>
<tr>
<td>3 Kidney</td>
</tr>
<tr>
<td>4 Reflux</td>
</tr>
<tr>
<td>5 Pancreas</td>
</tr>
<tr>
<td>6 Blunt abdominal trauma</td>
</tr>
<tr>
<td>7 Transcranial US</td>
</tr>
<tr>
<td>8 Technical appendices</td>
</tr>
</tbody>
</table>

Ultrasound (US) contrast agents (UCAs), in conjunction with contrast specific imaging techniques, are increasingly accepted in clinical use for diagnostic imaging and post-interventional workup in several organs. To those not intimately involved in the field, the rapid advances in technology and techniques can be difficult to follow. In March of 2003, at the EUROSON Congress in Copenhagen, it was agreed that it would be useful to produce a document providing a description of essential technical requirements, proposed investigator qualifications, suggested study procedures and steps, guidance on image interpretation, recommended and established clinical indications and safety considerations. Initially a set of guidelines for the use of ultrasound contrast agents in the liver alone were developed. These were presented and discussed in detail at an EFSUMB special consensus meeting held in Rotterdam in January 2004. The resulting consensus document was published in the August 2004 edition of Ultraschall in der Medizin/European Journal of Ultrasound, and has also been published in French [1] and Chinese [2]. Time has however moved on, and EFSUMB and the group of experts who developed these first guidelines took the view in 2006 that they should be revisited and expanded to include recommendations for applications in the kidney, in vesico-ureteric reflux, in the pancreas, in trauma and in the cerebral circulation. In order to facilitate the production of these new guidelines and recommendations a further two meetings of experts were held, the first in Bologna in September 2006 in conjunction with the EUROSON/SIUMB meeting, the second immediately following the European Symposium on Ultrasonic Contrast Agent Imaging in Rotterdam in January 2007. As previously these guidelines are based on comprehensive literature surveys including results from prospective clinical trials. On issues where no significant study data were available, evidence was obtained from expert committee reports or was based on the actual consensus of experts in the field of US and contrast enhanced Ultrasound (CEUS) during the consensus conferences. During the meeting of experts in Rotterdam many additional new and exciting developments were discussed, and whilst some are quickly entering clinical practice, it was felt too early to include them in the current recommendations.

These guidelines and recommendations provide general advice for the use of UCAs. They are intended to create standard protocols for the use and administration of UCAs and improve the management of patients. Individual cases must be managed on the basis of all clinical data available for that specific case. This second version will be subject to change to reflect future advances in scientific knowledge and the rapidly evolving field of US technology.

Correspondence
Prof. Michel CLAUDON
Department of Radiology, CHU de Nancy Brabois
Allée du Morvan
54511 Vandœuvre les
Tel.: ++ 33/3/83 15 41 83
Fax: ++ 33/3/83 15 35 23
m.claudon@chu-nancy.fr

Published online 2008
Ultraschall in Med 2008; 29: 28 – 44
1 General Considerations

1.1 Introduction

The development of ultrasound contrast agents (UCAs), which perform as blood pool tracers, have overcome the limitations of conventional B-Mode and colour or power Doppler US and enable the display of parenchymal microvasculature [3–5]. 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 during subsequent vascular phases (e.g. arterial, portal-venous and late phase for liver lesions) similar to contrast enhanced computer tomography (CECT) and/or contrast enhanced magnetic resonance imaging (CEMRI). Contrast enhanced ultrasound (CEUS) and CECT or CEMRI are not equivalent as UCAs have different pharmacokinetics and are confined to the intravascular space, whereas the majority of currently approved contrast agents for CT and MRI are rapidly cleared from the blood pool into the extracellular space.

An inherent advantage of CEUS is the possibility to assess the contrast enhancement patterns in real time with a substantially higher temporal resolution than other imaging modalities, without the need to predefine scan-timepoints or to perform bolus-tracking. Furthermore, administration can be repeated due to the excellent patient tolerance of UCAs.

In addition to intravenous (IV) use, UCA intracavity applications such as intravasal administration can be performed. UCA studies are subject to the same limitations as other types of ultrasound: as a general rule, if the baseline ultrasound is very suboptimal, CEUS may be disappointing.

1.2 Commercially Available Ultrasound Contrast Agents in Europe

Four transpulmonary UCAs are currently approved and marketed within European Countries:

- Levovist® (air with a galactose and palmitic acid as a surfactant) (Schering, introduced in 1996). Main indications include heart, abdomen, vesico-ureteric reflux and transcranial.
- Optison® (octafluoropropane (perflutren) with an albumin shell) (GE Healthcare, introduced in 1998). Solie indication is to date cardiac.
- SonoVue® (sulfur hexafluoride with a phospholipid shell) (Bracco, introduced in 2001). Approved indications are cardiac (endocardial border delineation), macrovascular (cerebral and peripheral arteries, portal vein) and microvascular (characterisation of focal lesions in liver and breast).
- Lumiray® (octafluoropropane perflutren with a lipid shell) (Bristol-Myers Squibb, introduced in 2006). Solie indication is to date cardiac.

The composition, packaging, storage, indications and contraindications of these agents are detailed in appendix 1. There are other UCAs approved outside Europe or under investigation.

1.3 Imaging Techniques using Ultrasound Contrast Agents

1.3.1 Background on UCAs and contrast specific modes

The UCAs which are currently used in diagnostic US are characterized by a microbubble structure consisting of gas bubbles stabilized by a shell [3, 4, 6–8]. UCAs act as blood pool agents. They strongly increase the US backscatter and therefore are useful in the enhancement of echogenicity for the assessment of blood flow. While conventional ultrasound can detect high concentrations of microbubbles, in practice their assessment usually requires contrast-specific imaging modes.

Contrast specific US modes are generally based on the cancellation and/or separation of linear US signals from tissues and utilization of the nonlinear response from microbubbles [9–12]. Non-linear response from microbubbles is based on two different mechanisms:

- non-linear response from microbubble oscillations at low acoustic pressure, chosen to minimize disruption of the microbubbles,
- high energy broadband non-linear response arising from microbubble disruption.

Non-linear harmonic US signals may arise also in tissues themselves due to a distortion of the sound wave during its propagation through the tissue. The extent of this harmonic response from tissue at a given frequency increases with the acoustic pressure, which is proportional to the mechanical index (MI).

Low solubility gas UCAs (e.g. SonoVue®, Optison®, Lumiray®) are characterized by the combination of improved stability with favorable resonance behavior at low acoustic pressure. This allows minimally disruptive contrast specific imaging at low MI and enables effective investigations over several minutes with the visualization of the dynamic enhancement pattern in real time.

Low MI techniques furthermore lead to effective tissue signal suppression, as the non-linear response from the tissue is minimal when low acoustic pressures are used [9, 12, 13]. US imaging with air filled microbubbles (e.g. Levovist®) at high pressure is dependent on microbubble disruption which is a significant limitation for real time imaging.

1.3.2 Intracavitary administration of UCAs

In addition to intravenous use, UCAs are suitable for intracavitary administration, particularly for performing contrast-enhanced voiding urosonography (VUS) [14–16]. After intravesical administration UCAs markedly enhance the US backscatter of bladder content. Consequently, refluxing microbubbles in the ureter and pelvicalyceal system and flow in the urethra are easily visualized. Levovist® has been approved for this indication in children in a number of countries. A few clinical studies using SonoVue® for sonographic reflux examination have been published recently [17–20].

1.3.3 Assessment of Anti-angiogenic Treatment

Since anti-angiogenic treatment very frequently induce lesion necrosis with no change in the volume of the initial tumor, new functional imaging technologies are particularly suitable for the early assessment of the response to treatment [21], a task for which the RECIST and WHO size criteria [22, 23] appear inappropriate. Studies of various types of tumor treated with targeted therapies have recently confirmed that the use of microbubble contrast agents enable early prediction of the response to treatment, demonstrating changes in tumor parenchymal perfusion and emergence of necrosis with no change in tumor volume [24, 25]. Early detection of the emergence of secondary resistance could also be demonstrated 6 to 9 months prior to the increase in lesion bulk, thus providing an opportunity for rapid adjustment of the therapeutic strategy [26].

1.3.4 Equipment and Technical Requirements

See systems specification in appendix 2.
1.4 Investigator Training

The EFSUMB minimal training requirements for the practice of medical ultrasound in Europe define three levels of training requirements [27]. It is likely that most CEUS examinations would be performed by level 2 or 3 investigators. Specific minimum training recommendations will be developed for the use of UCAs.

It is recommended that investigators wishing to undertake CEUS examinations should gain experience by observing contrast studies being performed by experts in this field. They should also ensure that their equipment is optimised for contrast examination by discussion with their equipment manufacturers. It is also important that in their own department there are sufficient numbers of examinations being performed and different types of pathological processes being observed to acquire and maintain their skills.

Practitioners need to be competent in the administration of contrast agents, familiar with any contra-indications and be able to deal with any possible adverse effects within the medical and legal framework of their country.

1.5 Safety Considerations

In general, UCAs are very safe with a low incidence of side effects. They are not nephrotoxic and do not interact with the thyroid and therefore it is not necessary to perform laboratory tests of renal function before administrating them. UCAs are not licensed in pregnancy and breastfeeding is a contra-indication in some countries.

The incidence of severe hypersensitivity or allergic events is lower than current X-ray and comparable to MR contrast agents. Life threatening anaphylactoid reactions in abdominal applications have been reported with a rate of 0.001% [28]. Investigators, therefore, should take the necessary precautions. A few fatal events in critically ill patients who have undergone also contrast enhanced echocardiographic examinations have been reported. Contraindications for the use of Sonovue® were defined with the EMEA in 2004. In October 2007, the Food and Drug Administration issued a warning which cautions the use of Definity® and Optison® in patients with severe cardiopulmonary disease (FDA Alert 10/2007): the basis of this alert is currently under evaluation by the scientific and clinical communities, as well as other regulatory agencies, as of December 2007.

In echocardiographic applications, premature ventricular contractions have been described when high MI ultrasound and end-systolic triggering have been used together [29, 30], and the release of subclinical myocardial bio-markers has been reported in high MI clinical studies [31].

There is a theoretical possibility that the interaction of diagnostic ultrasound and UCAs could produce bioeffects. In vitro cellular effects that have been observed include sonoporation, haemolysis and cell death. Although observed in vitro, such bioeffects may have relevance for the in vivo situation as they result from interactions between single gas bodies and single cells. Data from small animal models suggest that microvascular rupture could occur when microbubbles are insonated. This might be a potential safety issue in special situations where such vascular damage would be clinically important such as ocular and brain US.

The MI provides a useful, albeit very rough, on-screen indicator of the potential for non-thermal effects. The potential for non-thermal bioeffects exists in all modes, including conventional 2D imaging and 3D methods.

Users should balance the potential clinical benefit from the use of UCAs against the theoretical possibility of associated adverse bioeffects in humans.

Some general recommendations are:

- Caution should be considered for offshore use of UCAs in tissues where damage to microvasculature could have serious clinical implications, such as in the eye, the brain and the neonate.
- As in all diagnostic ultrasound procedures, the operator should be mindful of the desirability of keeping the displayed MI and Thermal index (TI) low, and of avoiding unduly long exposure times.
- Caution should be exercised when using UCAs in patients with severe coronary artery disease.
- The use of contrast agents should be avoided 24 hrs prior to extra-corporeal shock wave therapy.

2 Liver

Focal liver diseases have evolved into the single most important application of CEUS setting aside the applications in echocardiography because of the marked improvement over conventional ultrasound in both their detection and characterisation. Subject to some limitations that are detailed in the following sections, CEUS now equals CECT and in some instances exceeds it in accuracy. Partly this is because of the real-time nature of modern contrast ultrasound which reveals important rapid flow phenomena; CT, with its intermittent imaging, sometimes misses these. Partly also the persistence of microbubbles beyond the large vessel enhancement period the late phase provides a marker for the sinusoidal space, lesions that lack this vascular space, notably metastases, appear as late phase defects.

Thus the late phase is mainly used for detection of malignancies and the arterial phase mainly for characterising focal liver lesions. In this section, characterisation is covered first, followed by detection. While this may seem illogical, it reflects the order of usage dictated by the liver’s haemodynamics.

2.1 Characterisation of focal liver lesions (FLL)

2.1.1 Background

Due to the dual blood supply of liver tissue by the hepatic artery (25–30%) and the portal vein (70–75%), three overlapping vascular phases can be defined and visualized using contrast enhanced sonography. Depending on individual circulatory status, enhancement resulting exclusively from the hepatic artery supply usually starts from 10–20 seconds post-injection into a peripheral vein and lasts for approximately 10–15 seconds. This is followed by the portal venous phase, which usually lasts until 2 minutes after UCA injection. The late phase lasts until the clearance of the US contrast agent from the hepatic parenchyma, up to approximately 4–6 minutes post injection for Sonovue®. This late phase differs from the equilibrium phase of extracellular CT and MRI agents. The origin of this late phase is subject of ongoing scientific discussion; suggested mechanisms include sinusoid pooling and RES/Kupffer cells uptake [32, 33] (Table 1).

The arterial phase provides information on the degree and pattern of vascularity. The portal and late phases provide information about the wash out of UCA from the lesion compared to normal liver tissue.
Portal and late phase enhancement can provide important information regarding the character of the lesion: most malignant lesions are hypo-enhancing while the majority of solid benign lesions are iso- or hyper-enhancing [34–59].

### 2.1.2 Study Procedure

#### 2.1.2.1 Low Mechanical Index (MI) Techniques

Low MI contrast specific techniques allow dynamic imaging with subsequent evaluation of the three different vascular phases using a low solubility gas UCA.

The steps recommended in the study procedure are as follows:

- **Baseline investigation in B-Mode, potentially including Doppler techniques.**
- **After identification of the target lesion(s) the transducer is kept in a stable position while the imaging mode is changed to low MI contrast specific imaging.**
- **Using low MI contrast specific imaging modes, it is crucial to provide sufficient tissue cancellation with maintenance of adequate depth penetration (a function of MI and gain, both of which must be adjusted). Adequate cancellation of tissue signals is characterized by disappearance of the B-Mode parenchymal liver structures. Major vascular structures and some anatomical landmarks such as the diaphragm remain barely visible.**
- **UCA is administered as a bolus injection followed by a 5–10 ml saline flush. It is advised to use a needle diameter of at least 20 Gauge whenever possible to avoid loss of bubbles due to mechanical impact during injection. The needle diameter should not be smaller than 20 Gauge to avoid loss of bubbles due to mechanical impact during injection. A stop clock should be started at time of UCA injection.**
- **Because of the dynamic nature of real time CEUS, it is recommended to document the investigation on video or digital media (essential clips for each vascular phase should be stored).**
- **Note: In some contrast specific US modes a simultaneous display of tissue and contrast signals has been implemented. This modality is particularly useful for small lesions to ensure that the target lesion is kept within the scanning field during CEUS.**
- **A single bolus is usually adequate, but further injections can be used if the examination after the first bolus was inconclusive.**
- **Continuous scanning for 60–90 seconds is recommended to continuously assess the arterial and portal-venous phase. For assessment of the late phase scanning may be used intermittently until the disappearance of the UCA from the liver microvasculature has been observed.**

#### 2.1.2.2 High Mechanical Index (MI) Techniques

High MI techniques in which microbubbles are deliberately destroyed, have been initially used for characterisation of FLLs. When required, intermittent scanning of the lesion is performed during all 3 phases. Such high MI techniques are no longer recommended.

### 2.1.3 Image Interpretation and Evaluation (Enhancement Patterns of FLL)

#### 2.1.3.1 Benign Lesions

Sustained enhancement in the portal-late phase characterizes most benign solid liver lesions. They can be further characterized by enhancement patterns during the arterial phase: e.g., enhancement of the whole lesion (typical of focal nodular hyperplasia [FNH]) or initial peripheral globular-nodular enhancement (haemangioma).

The typical enhancement patterns are summarized in Table 2 for the following lesions: haemangioma, FNH, focal fatty sparing, focal fatty change, regenerative nodule, simple cyst, adenoma, abscess.

#### 2.1.3.2 Malignant Lesions

**Hypoenhancement of solid lesions (darker than the surrounding liver) in the late phase characterizes malignancies:** all metastases show this feature and no exception has been reported to date. A typical HCC is characterized by arterial phase hypervascularity and wash-out in the late phase. Atypical variations occur, especially in well-differentiated tumours, as are described in the table. The arterial phase is important for demonstrating hypervascularity of HCC and of hypervascular metastases. Bland (blood) thrombus is usually avascular, though when well organised, venous recanalisation channels may form. Since they are formed of at least partly viable tumour tissue, tumour thrombus in the portal or hepatic veins contains malignant neovascularity which can be demonstrated with CEUS. The enhancement patterns are different (a tumour blush rather than discrete vessels) and the arterial signals in tumour can be confirmed on contrast enhanced spectral Doppler [60]. A marked wash out in the portal and late phases may occur in metastatic portal vein thrombosis, up to anechoic appearance, resembling bland thrombus in this vascular phase [61].

The enhancement patterns used for the characterization of malignant lesions (HCC, hypovascular Mets, hypervascular Mets, cholangiocarcinomas) are summarized in Table 3.

#### 2.1.4 Recommended Uses and Indications

CEUS should be performed and interpreted with knowledge of clinical and laboratory data. With typical enhancement patterns on CEUS and in an appropriate clinical setting, characterization of haemangiomata, focal nodular hyperplasia, metastasis and HCCs can be obtained at a high level of probability and confidence. Focal liver lesions with atypical enhancement patterns or technical suboptimal studies require further investigation.

#### 2.1.4.1 Recommended Indications

CEUS is indicated in the following clinical situations (Fig. 1a, b):

- Incidental findings on routine US
- Lesions or suspected lesion in chronic hepatitis or liver cirrhosis

Table 1: Vascular Phases in Contrast Enhanced Ultrasound of the Liver. The individual global haemodynamic situation in a given patient will influence the time of onset of the three vascular phase times

<table>
<thead>
<tr>
<th>phase</th>
<th>post-injection time (seconds)</th>
<th>start</th>
<th>end</th>
</tr>
</thead>
<tbody>
<tr>
<td>arterial</td>
<td>10 – 20</td>
<td>25 – 35</td>
<td></td>
</tr>
<tr>
<td>portal-venous</td>
<td>30 – 45</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>late</td>
<td>&gt; 120</td>
<td>bubble disappearance (approx. 240 – 360)</td>
<td></td>
</tr>
</tbody>
</table>
Lesions or suspected lesion in patient with a known history of malignancy.

Patient with inconclusive MRI/CT or cytology/histology results.

Characterization of portal vein thrombosis.

2.1.4.2 Limitations

Specificity and sensitivity are markedly reduced in attenuating livers and for deep-sited lesions.

2.2 Detection of focal liver lesions

2.2.1 Background

Conventional US is the most frequently used imaging procedure for the primary diagnosis of abdominal organs and the liver, but is less accurate in detection and staging of liver lesions than contrast-enhanced CT and MRI or intraoperative US. The main reasons for this are problems in the detection of small sized and/or isoechoic lesions, especially for deep lesions or in difficult anatomical areas (e.g. in the subdiaphragmatic areas).

### Table 2  Enhancement (E) patterns of benign focal liver lesions

<table>
<thead>
<tr>
<th>Tumor Entity</th>
<th>Arterial Phase</th>
<th>PV Phase</th>
<th>Late Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemangioma</td>
<td>Peripheral-nodular E, no central E</td>
<td>Partial/completely centripetal filling</td>
<td>Complete E.</td>
</tr>
<tr>
<td>FNH</td>
<td>Hyper-enhancing, complete, early</td>
<td>Hyper-enhancing</td>
<td>Iso/hyper-enhancing</td>
</tr>
<tr>
<td>Simple Cyst</td>
<td>Non-enhancing</td>
<td>Non-enhancing</td>
<td>Non-enhancing</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Hyper-enhancing, complete</td>
<td>Iso-enhancing</td>
<td>Iso/hypo</td>
</tr>
<tr>
<td>Regenerating Nodule</td>
<td>Non-enhancing areas</td>
<td>Hyper-enhancing</td>
<td></td>
</tr>
<tr>
<td>Other Features</td>
<td>Non-enhancing</td>
<td>Non-enhancing</td>
<td>Non-enhancing</td>
</tr>
<tr>
<td>Abscess</td>
<td>Rim E, no central E</td>
<td>Hyper/iso-enhancing rim, no central E</td>
<td>Hypo-enhancing rim, no central E</td>
</tr>
</tbody>
</table>

### Table 3  Enhancement patterns of malignant focal liver lesions

<table>
<thead>
<tr>
<th>Tumor Entity</th>
<th>Arterial Phase</th>
<th>PV Phase</th>
<th>Delayed Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Hyper-enhancing, complete</td>
<td>Iso-enhancing</td>
<td>Hypo/iso-enhancing</td>
</tr>
<tr>
<td>Hypovascular Mets</td>
<td>Hyper-enhancing E</td>
<td>Hypo/non enhancing</td>
<td>Hypo/non enhancing</td>
</tr>
<tr>
<td>Hypervascular Mets</td>
<td>Hyper-enhancing, complete</td>
<td>Hypo-enhancing</td>
<td>Hypo/non enhancing</td>
</tr>
<tr>
<td>Cystic Metastasis</td>
<td>Hyper-enhancing nodular/rim component</td>
<td>Hypo-enhancing</td>
<td>Hypo-enhancing</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Rim E</td>
<td>Hypo/non enhancing</td>
<td>Hypo/non enhancing</td>
</tr>
</tbody>
</table>
2.3.2 Study Procedures

2.3.2.1 Pre-treatment Contrast-Enhanced Ultrasound
- For procedure, refer to 2.2.
- Accurate pre-treatment size assessment (measurement of the three largest diameters in two orthogonal scan planes) of every mass to be treated is mandatory. Either real-time volumetric (4 D) studies or post-processing volume reconstructions for volume calculation of every target are highly recommended. This enables accurate treatment planning: number of needle/probe insertions needed to thoroughly treat each tumor mass, path of every insertion and in case of large tumors, modality of overlapping contiguous ablation volumes [86, 87]. This procedure is to be performed under CEUS imaging only when CEUS and conventional US provide significantly different identifications of the mass borders. Field depth, selected scan plane, acoustic gain and mechanical Index (MI) (or acoustic power) used for the pre-treatment CEUS study of each lesion must be pre-defined.
- Images and/or movie clips are to be video- or digitally stored for precise comparison with immediate post-ablation studies.

2.3.2.2 Positioning of probe/needle (only when the lesion is not visible on unenhanced US).
- For procedure, refer to 2.2.
- Probe/needle is inserted during the vascular phase in which the target is optimally depicted.
- Periprocedural Assessment of Treatment Response (for thermal ablation).
- Unenhanced US is used to monitor the reduction of the hyperechoic “cloud” due to gas formation caused by ablation. This usually requires 5 - 15 minutes.
- For procedure, refer to 2.2.
- For each treated lesion, the same system settings and scan planes must be used as for the pre-ablation assessment.
- Images and/or movie clips are to be digitally stored for comparison with previously stored pre-ablation images.
- If additional probe/needle insertions are performed, repeated doses of UCA can be given.

2.3.2.3 Follow-up Investigation to Assess Tumor recurrence
- See procedure described at 2.2.

2.3.3 Image Interpretation – Definition of Complete Treatment Response

The most important imaging finding that indicates complete ablation is the disappearance of any previously visualized intraluminal enhancement on contrast-enhanced images. This must be assessed throughout the whole volume of each tumor which has undergone ablation. The size of the post-treatment avascular volume of the necrosis achieved should be compared with the size of pre-treatment volume of tumor(s). The simultaneous display of tissue and contrast signals, available on some equipment, is of particular value for short and long term follow up of treated lesions, to ascertain whether persistent enhancing portions of tissue are inside or outside the ablated lesion. In hypoenhancing lesions (e.g. most liver metastases), completeness of treatment can be assessed by comparing the pre-treatment lesion volume and location with the volume and location of the post-treatment coagulated or necrotic region. This also determines whether a sufficient perilesional “safety” margin has been achieved. Due to the reported high incidence of satellite nodules around small HCCs (5 – 10 mm range of distance from the main tumor [88]), it is strongly recommended to assess the presence and thickness of the “safety margin” following ablation not only for liver metastases but also for HCCs.

In the early (e.g., within the first 30 days) post-ablative evaluation using CEUS, a thin and uniform enhancing rim can be visible along the periphery of the necrotic area, similar to findings on CECT. Misinterpretation of this perilesional hyperemic halo as residual viable tumour can be avoided by comparing post-ablation images with pre-ablation scans.

2.3.4 Recommended Uses and Indications
- As a complement to CECT and/or CEMRI for pretreatment staging and assessment of target lesion vascularity. Pretreatment optimized CECT and/or CEMRI are recommended.
- Facilitation of needle positioning in cases 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.
- Assessment of tumour recurrence, when follow-up CECT or CEMRI are contraindicated or not conclusive. 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.

3 Kidney

In most centres, ultrasound is the preferred first imaging modality in patients with known or suspected renal disease. Main objectives are to measure renal size, to prove or rule out focal lesions, to detect obstruction of the collecting system and to look for vascular disorders by means of Doppler techniques [89]. Often unexpected findings like anatomic variations or focal lesions are detected and need further clarification.

The differentiation between simple cyst and solid or complex tumour can often be made by greyscale US. However, acoustic properties do not contribute in distinguishing between different types of tissue and therefore benign and malignant lesions may be difficult to distinguish. Pulse wave and color Doppler techniques help to characterize renal blood flow, with limitation because of attenuation, lack of sensitivity, blooming, and angle dependency. A benefit from using CEUS can therefore be expected [90].

The following recommendations deal with the uses of ultrasound contrast agents for the evaluation of the micro- and macrovasculature of the kidneys, including the characterization of focal renal lesions, the detection of lesions and the monitoring of local treatment. The use of CEUS in this indication has not yet obtained regulatory approval and thus represents an off-label use, which should be justified by an individual risk/benefit assessment for the respective patient, based on the available scientific data.

3.1 Characterization of Focal Renal Lesions

3.1.1 Background

The kidneys receive 20 – 25% of the cardiac output. The renal cortex tissue receives 90% and the medulla the remaining 10%. Medullary blood flow is slower than cortical flow. Unlike CECT or CEMRI, CEUS may be performed in patients with impaired renal function or ureteric obstruction that may
R. Lencioni
D. Cioni · C. Bartolozzi (Eds.)

Focal Liver Lesions
Detection, Characterization, Ablation

With Contributions by
A. Adam · T. Albrecht · V. Apell · R. S. Arellano · C. Bartolozzi · R. Basilico · E. Batini
M. Bazzocchi · C. D. Becker · L. Bolondi · M. P. Bondioni · G. Brancatelli · L. Bonomo
F. Caseiro-Alves · M. Celestre · D. Cioni · M. Colombo · A. Conti · D. O. Cosgrove
L. Crocetti · C. Del Frate · C. Della Pina · A. D'Errico · F. Di Fabio · K. Eichler · J. Fasel
M. P. Federle · A. Ferreira · A. Filippone · D. A. Gervais · A. R. Gillams · J. A. Goode
L. Graziani · R. M. Hammerstingl · T. K. Helmerger · M. Holtappels · K. M. Josten
C. Kulinna · R. Lagalla · A. Laghi · T. Lehnert · R. Lencioni · S. Leoni · J. Lera · K. H. Link
P. Loubeyle · M. Mack · P. Majno · D. Mathieu · G. Mentha · M. Midiri · M. Mörschel
S. Montagnani · P. Morel · K. Mortelè · P. R. Mueller · P. Paolantonio · R. Passariello
F. Piscaglia · R. Pozzi-Mucelli · E. Rocchi · G. Ronchi · T. Sabharwal · T. A. Sagban
I. Sansoni · W. Schima · W. V. Schwarz · L. Staib · R. Straub · S. Terraz · R. Thimm
K. Tischbirek · A. Venturi · V. Vlgrain · T. J. Vogl · T. F. Weigel · K. Zayed · C. Zuiani

Foreword by
A. L. Baert

With 268 Figures in 727 Separate Illustrations, 83 in Color and 39 Tables
1 Ultrasound and Contrast Ultrasound

David O. Cosgrove

CONTENTS

1.1 Introduction 3
1.2 Technology 5
1.3 Microbubble Contrast Agents 7
1.3.1 Principles 7
1.3.2 Interactions of Microbubbles with Ultrasound Waves 7
1.3.3 Safety of Microbubbles 8
1.4 Normal Appearance 9
1.5 Focal Lesions 9
1.5.1 Contrast Enhanced Ultrasound 13
1.6 Conclusions 15
References 15

1.1 Introduction

Ultrasound is a tomographic imaging technique that can provide anatomical and functional images with high resolution and great flexibility at low cost (Kremkau 1997; McDicken 1991). Structural detail down to around a millimetre is available without the need for contrast agents (Fig. 1.1). The high intrinsic contrast is produced by the tissues’ structure at a submillimetre level and is chiefly attributable to the differences in rigidity and density between fluids, watery tissue, connective tissue and fat. The tomograms are formed very rapidly, allowing real time imaging so that studies are quick and interactive. Immediate viewing of tissue motion is intrinsic to ultrasound imaging; examples include the effects of respiration or palpation and the direct visualisation of the position of a biopsy needle (Pederson et al. 1993). The tomograms can be taken in any plane, allowing optimal display of critical anatomy and pathology. Small, self-contained scanners can be made and these can be taken to the patient’s bedside (Machi and Sigel 1996). No or minimal preparation is required so that the procedure is well tolerated, the only practical problem for the liver being abdominal tenderness that may make probe contact painful. The hazards of ionising radiation do not exist and the acoustic powers used in diagnosis appear to be completely safe, though there are emerging concerns over the possibility that its interaction with the microbubbles used as contrast agents may produce free radicals that could be injurious.

The flexibility of ultrasound technique has led to several specialised applications. Small transducers can be mounted on an endoscope with the advantage that higher quality images are obtained because higher frequency ultrasound can be used (Bezzi et al. 1998). Endoscopic ultrasound is, of course, somewhat invasive and only tissues with a few centimetres of the gut wall are accessible. The same is true of intravascular ultrasound. Small transducers suitable for use in the operating theatre offer the benefit of higher resolution as well as of guiding needle placement for biopsies or cannulation of small portal vein branches while the development of transducers small enough to fit into standard laparoscopic instruments extends these advantages to minimally invasive surgery (Herman 1996; Barbot et al. 1997; Klotter et al. 1986).

Doppler has extended the role of ultrasound in the diagnosis and management of vascular pathology of the liver and is now an indispensable component of hepatic imaging (Grant 1992). It is particularly helpful in liver transplants, both pre-operatively [to establish portal vein (PV) and caval patency] and post-operatively (for the PV and hepatic artery) and in the Budd Chiari syndrome. In cirrhosis Doppler can establish the patency of the PV and of many types of shunts. For spectral (pulsed) Doppler, a sensitive gate is positioned over a vessel and the temporal pattern of flow analysed to display its velocity spectrum; volume flow can also be estimated, though with less precision (Fig. 1.2). In colour Doppler, a vascular map is presented as an overlay on the grey scale scan to provide a form of angiogram that gives a non-invasive picture of vascular anatomy (Fig. 1.3)
Metastases may be unimpressive in the arterial phase but sometimes have a peripheral artery that forms a halo; this must be distinguished from the nodular peripheral contrast around a haemangioma (Wilson and Burns 2001). Metastases that are hypervascular fill rapidly and often heterogeneously from their supply artery. The contrast washes out more rapidly than from the normal liver (a manifestation of their small vascular volume) so that metastases become prominent as enhancement defects in the sinusoidal (late) phase (Fig. 1.9).

Hepatocellular carcinomas have complex patterns that do not always allow a diagnosis on a contrast study (Kim et al. 2002). They are usually hypervascular and show rapid and sometimes spectacular increase in signal a few seconds after the injection, though some are hypovascular. Their late phase appearance is variable, presumably because of the spectrum of differentiation they show on histology. Many behave in the same way as metastases and become prominent as defects from around 45 s after injection and this finding is clinically useful. Unfortunately some (perhaps 25%) retain contrast to a greater or lesser extent in this phase and thus simulate benign lesions. This obviously limits the value of contrast studies in evaluating cirrhotic patients for HCC.

A particularly useful application of contrast agents is in evaluating the completeness of ultrasound-guided interstitial therapy; when all tumour appears to have been destroyed, microbubbles often reveal residual portions of perfused tumour that can be ablated immediately so that the patient does not have to be moved to CT (Lencioni et al. 1997; Solbiati et al. 1999).

1.6 Conclusions

Ultrasound technology has continued its rapid progress and many of the innovations have quickly become accepted as routine tools. Examples include tissue harmonic imaging and extended field of view scans. An important invention is the development of microbubble contrast agents that allow a contrast-enabled scanner to depict both the macro and microcirculation. In the liver they have proved to be especially valuable for detecting and characterising focal lesions and their use as tracers can reveal the arteriovenous shunting that is part of the metastatic process, even when the deposits are undetectable on conventional staging.

References

Role of contrast-enhanced ultrasound in the blinded assessment of focal liver lesions in comparison with MDCT and CEMRI: Results from a multicentre clinical trial


aCIC-IT Ultrasound-Radio Pharmacuetiques, INSERM U930-CNRS 2448, Université François Rabelais, Hôpital Bretonneau, CHRU Tours, 37044 Tours Cedex 9, France
bCIC INSERM 202, Hôpital Bretonneau, CHRU Tours, 37044 Tours Cedex 9, France
cService de Radiologie Adultes, Hôpital Necker, AP-HP, 75743 Paris Cedex 15, France
dService de Radiologie et Image Medicale, Hôpital Robert Debré, CHU Reims, 51092 Reims Cedex, France
eService de Radiologie C, Hôpital St Jacques, CHU Besançon, 25000 Besançon, France
fService de Radiologie et d’Echographie, Hôpital Beaujon, AP-HP, 92118 Clichy Cedex, France
gService de Radiologie A, CHU Angers, 49033 Angers Cedex 01, France
hService de Radiologie, Hôpital Paul Brousse, AP-HP, 94804 Villejuif, France
iService d’Echographie, Institut Gustave Roussy, 94805 Villejuif, France
jService de Radiologie, Hôpital d’Enfants, CHU Nancy, 54511 Vandoeuvre Les Nancy, France
kService de Radiologie, Hôpital Nord, CHU Saint Etienne, 42055 St Etienne Cedex, France
lService d’Imagerie Medicale, Hôpital Haut-Lévêque, USN, CHU Bordeaux, 33604 Pessac Cedex, France
mService d’Imagerie Medicale, Hôpital St Eloi, CHRU Montpellier,34295 Montpellier Cedex 5, France
nService de Radiologie, Hôpital La Pitié Salpêtrière, AP-HP, 75651 Paris Cedex 13, France
oService de Radiologie, Hôpital Hôtel Dieu, HCL, 69002 Lyon, France
pService de Radiologie, Hôpital de La Croix Rousse, HCL, 69317 Lyon Cedex 04, France
qService d’Imagerie Médicale, Hôpital de la Milétrie, CHU Poitiers, 86000 Poitiers, France
rService de Radiologie, Hôpital St André, CHU Bordeaux, 33075 Bordeaux, France
sService Information Médicale, Epidémiologie et Economie de la Santé, CHRU Tours, 37044 Tours Cedex 9, France

Sponsored by unrestricted educational grant from Bracco International BV.
* Corresponding author: Tel.: +33 2 47 47 38 48; fax: +33 2 47 47 38 76.
E-mail address: tranquart@med.univ-tours.fr (F. Tranquart).
1359-6349/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejcsup.2008.06.003
1. Introduction

Worldwide, ultrasound is the first imaging modality for screening focal liver lesions in various situations such as abdominal pain, dyspeptic syndrome or cancer staging. Because of either patient or technical limitations, the sensitivity of conventional sonography remains poor (between 55% and 70%) and generally lower than with other modalities such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Moreover, once a lesion has been detected, the foremost question is always the differentiation of benign or malignant lesions. These limitations are reinforced by the non-specific ultrasound pattern of focal liver lesions even when using modern methods including harmonic, compounding or Doppler imaging. The higher accuracy reported with CT and MRI is partly related to the use of contrast agents which allows the description of specific vascular patterns whatever the tissue specificity is. The use of contrast agents is therefore pivotal in the detection and the characterisation processes, whatever the imaging modality is.

The characterisation of focal liver lesions using the imaging faces many challenges due to the high incidence of lesions incidentally discovered during abdominal examinations, limited access to some imaging techniques, cost, patient compliance and its efficiency.

Another frequent limitation reported for conventional sonography is reliability and reproducibility described as operator-dependant. On the contrary, CT and MR techniques are known for their high reliability and their easy review for further comparison. The US limitation is related to many factors, including inappropriate delineation in terms of limits or contrast, poor lesion identification on still images, absence of standard cineloops for review of complete examination, differences between machine performances and display as well as its dependence on operator experience. Sonography is often limited to the detection of abnormalities in the general population whilst CT or MRI is used at a second stage to confirm the diagnosis and thus guides the treatment.4

The combined development of ultrasound contrast agents and non-linear imaging at low acoustic power has improved diagnostic imaging accuracy.5 Real-time imaging has greatly simplified the scanning technique making it comparable to conventional US. Moreover, the improved contrast to tissue ratio between the lesion itself and the surrounding tissue, and the possibility of studying the contrast kinetics have allowed the detection and characterisation of lesions not visible or poorly visible on either conventional sonography or other modalities. In the recent years, an increasing interest6–15 on the use of CEUS has been reinforced by the publication of the European EFSUMB guidelines for contrast agents in ultrasound.16 However, the number of multicentre studies is limited, and the lack of pharmaco-economical studies remains a problem.

The main aim of this multicentre prospective study was to determine the clinical value of Sonovue® administration for the characterisation of focal liver lesions incidentally detected in oncological or cirrhotic patients. Eight hundred and seventy four consecutive patients with 1034 nodules (diameter between 5 and 100 mm) not fully characterised by conventional US or previous single-phase CT-scan were imaged using real-time contrast-enhanced scanning after intravenous injection of 2.4 ml of Sonovue®. Blinded off-site assessment was conducted to evaluate the diagnostic performance of contrast-enhanced ultrasound (CEUS) in comparison with gold standard, i.e. triphasic CT-scan or contrast-enhanced MRI or histology.

In the differentiation between benign and malignant lesions, CEUS yielded a sensitivity of 79.4% and a specificity of 88.1%. In the subgroup of patients with cirrhosis, the kappa value for off-site diagnosis between CEUS and reference modality was slightly lower compared to the non-cirrhotic group: 0.42 and 0.66 (p = 0.0002), respectively. The concordance rate and kappa value of CEUS for benign to malignant differentiation between on-site and blinded review were 90.2% and 0.80%, respectively, compared to 83.4% and 0.66%, respectively, for the reference imaging technique.

These results indicate that CEUS using Sonovue® is a competitive and effective diagnostic tool for the characterisation of focal liver lesions compared to other modalities such as CT and MR imaging.

2. Subjects and methods

A total of 874 consecutive patients, involving 1034 nodules with adequate imaging, were included in this multicentre prospective study between May 2005 and December 2007. Fifteen radiology centres with expertise in liver imaging participated in the trial (Table 1). The patient population characteristics were as follows: 438 females and 436 males mean age 55.7 +/- 17.9 years and mean body weight 71.2 +/-