

Advantages and Limitations of Focal Liver Lesion Assessment with Ultrasound Contrast Agents: Comments on the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines

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Key Words

Guidelines · Focal liver lesions · Contrast-enhanced ultrasound · Computed tomography · Magnetic resonance imaging

Abstract

Contrast-enhanced ultrasound (CEUS) represents a significant breakthrough in sonography. Due to US contrast agents (UCAs) and contrast-specific techniques, sonography offers the potential to show enhancement of liver lesions in a similar way as contrast-enhanced cross-sectional imaging techniques. The real-time assessment of liver perfusion throughout the vascular phases, without any risk of nephrotoxicity, represents one of the major advantages that this technique offers. CEUS has led to a dramatic improvement in the diagnostic accuracy of US and subsequently has been included in current guidelines as an im-

portant step in the diagnostic workup of focal liver lesions (FLLs), resulting in a better patient management and cost-effective therapy. The purpose of this review was to provide a detailed description of contrast agents used in different cross-sectional imaging procedures for the study of FLLs, focusing on characteristics, indications and advantages of UCAs in clinical practice.

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Introduction

Contrast-enhanced ultrasound (CEUS) is a relatively innovative contrast diagnostic procedure. Used for over 10 years, CEUS has been largely implemented in clinical practice being a rapid, noninvasive, cost-effective and simple diagnostic procedure which can be performed at the patient's bedside [1–5].

Table 1. Commercially available UCAs

Name	Company	Gas	Shell	Main characteristics
SonoVue®	Bracco	sulfur hexafluoride	phospholipids	pure blood pool CA
Optison®	GE Healthcare	octafluoropropane	human albumin	pure blood pool CA
Definity®	Lantheus	octafluoropropane	phospholipids	pure blood pool CA
Sonazoid®	GE Healthcare	perfluorobutane	hydrogenated egg phosphatidyl serine	uptake by macrophages and Kupffer cells
Levovist®	Schering AG	air	galactose/palmitic acid	uptake by macrophages and Kupffer cells

In this review, we have illustrated the advantages and limitations of using US contrast agents (UCAs) in comparison to contrast agents (CAs) used in computed tomography (CT) and magnetic resonance imaging (MRI).

The Basics of UCAs

UCAs are gas-filled microbubbles stabilized by a shell and administered intravenously in a bolus in small volumes (0.1–4.8 ml). The region of interest is visualized using tissue harmonic imaging and a low mechanical index. UCAs perform as blood pool tracers and enhance the visualization of the parenchymal microvasculature with the best temporal resolution [6]. Even though technological advancements have led to time resolution values of 83 ms for dual-source CT [7] and of about 35 ms for MRI [8, 9], the advantages of CEUS are due to the practically real-time examination and real-time assessment [10], allowing for a better visualization of enhancement patterns during all phases, without the need of specifically planned time acquisitions. The size of the microbubbles is fairly uniform between 1 and 4 μm . This means that they are smaller than erythrocytes and flow easily through small capillaries.

Even if the vascular pattern of enhancement is described with the same criteria as in contrast-enhanced CT (CECT) and contrast-enhanced MRI (CEMRI), the examinations are not equivalent due to the different pharmacokinetics of UCAs. In contrast to cross-sectional CAs, which are rapidly cleared from the blood pool into the extracellular space, UCAs are strictly intravascular and do not diffuse into the tumor interstitium [1, 6, 11–16], allowing for a better characterization of focal liver lesions (FLLs) [17]. Several enhancement patterns can be identified for FLLs after UCA administration. The most commonly observed patterns of enhancement for benign and malignant FLLs are shown in table 1 as previ-

ously published [2, 3]. Issues such as enhancement during the arterial phase, including onset, peripheral or central initial enhancement, homogeneity/heterogeneity of FLL enhancement, as well as presence or absence of portal-venous or late-phase washout should all be assessed, as these parameters are important for the differentiation between malignant and benign FLLs and for a further differential diagnosis [10]. Some examples are shown in figures 1–3.

Characteristics of CT CAs

Nowadays, nonionic low-osmolality CAs are used for intravenous administration in CECT examinations. As reported in several studies, the overall acute adverse reaction rate ranges from 0.2 to 3.1% of the patients. The majority of side effects are mild and non-life-threatening [18–22]. Approximately 0.04% of the patients develop serious acute reactions [22], with a fatality rate of 0.9 per 100,000 injections as reported in a meta-analysis [23].

The use of CT and also of MRI CAs is limited in patients with renal insufficiency. Contrast-induced nephropathy (CIN) develops within 48–72 h after CA injection and is defined as an increase of at least 25% in the serum creatinine level. CIN is one of the main causes of hospital-acquired renal failure and leads to a significant increase in morbidity and mortality [24–26]. A retrospective study by Davenport et al. [27] showed that the use of intravenous low-osmolality CAs has a significant effect on the development of acute kidney injury in patients with a pre-examination serum creatinine level of ≥ 1.6 mg/dl. Patients with creatinine levels of < 1.5 mg/dl are not at risk of developing CIN. Despite the widespread application during the last decade, there are no studies or reports showing that UCAs can cause damage to the kidneys [28]; therefore, they are considered safe in patients with renal insufficiency.

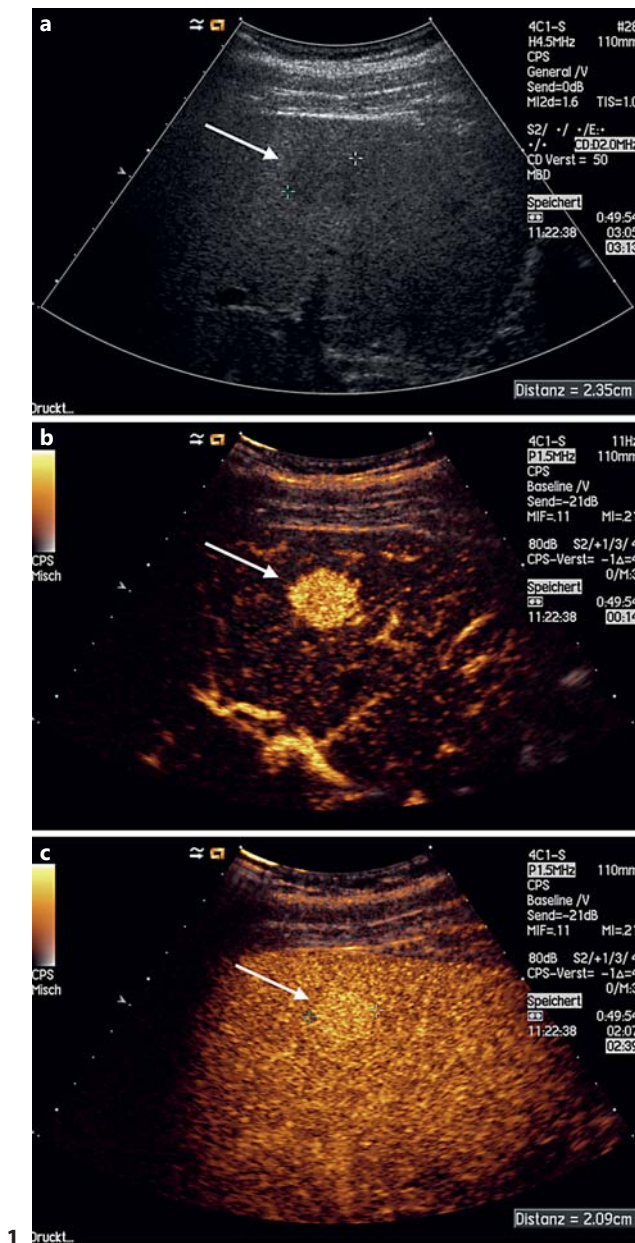
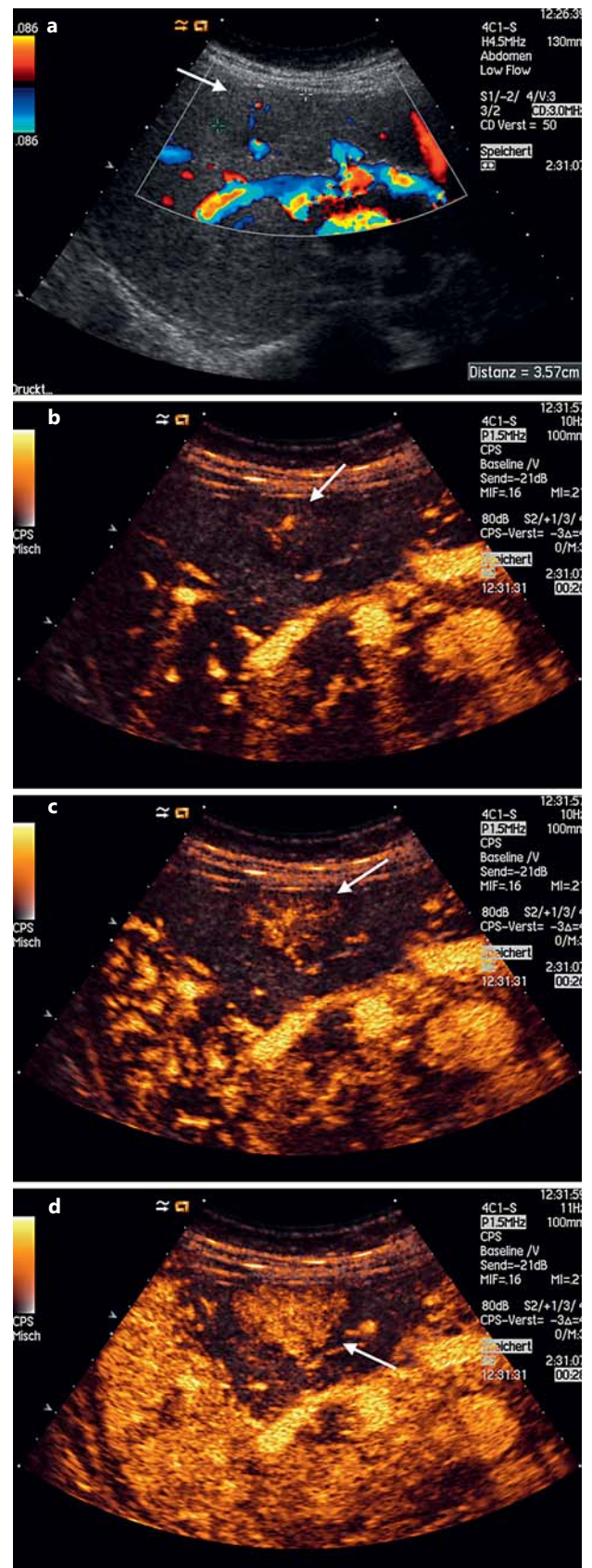


Fig. 1. Shunt hemangioma. **a** Hypoechoic lesion seen on gray-scale US. **b** Hyperenhancement during the arterial phase (14 s after intravenous CA administration). **c** The lesion is still enhanced during the late venous phase (160 s after intravenous CA administration), proving that it is benign.

Fig. 2. Focal nodular hyperplasia. **a** Discrete hypoechoic FLLs with central arterial vessel seen on color Doppler US. **b, c** ‘Spoke-wheel’ pattern of arterial centrifugal enhancement (26 s after intravenous CA administration), characteristic of a focal nodular hyperplasia. **d** Homogeneous enhancement (28 s after intravenous CA administration) rapidly seen after the first CA uptake within the lesion, also in favor of a focal nodular hyperplasia.



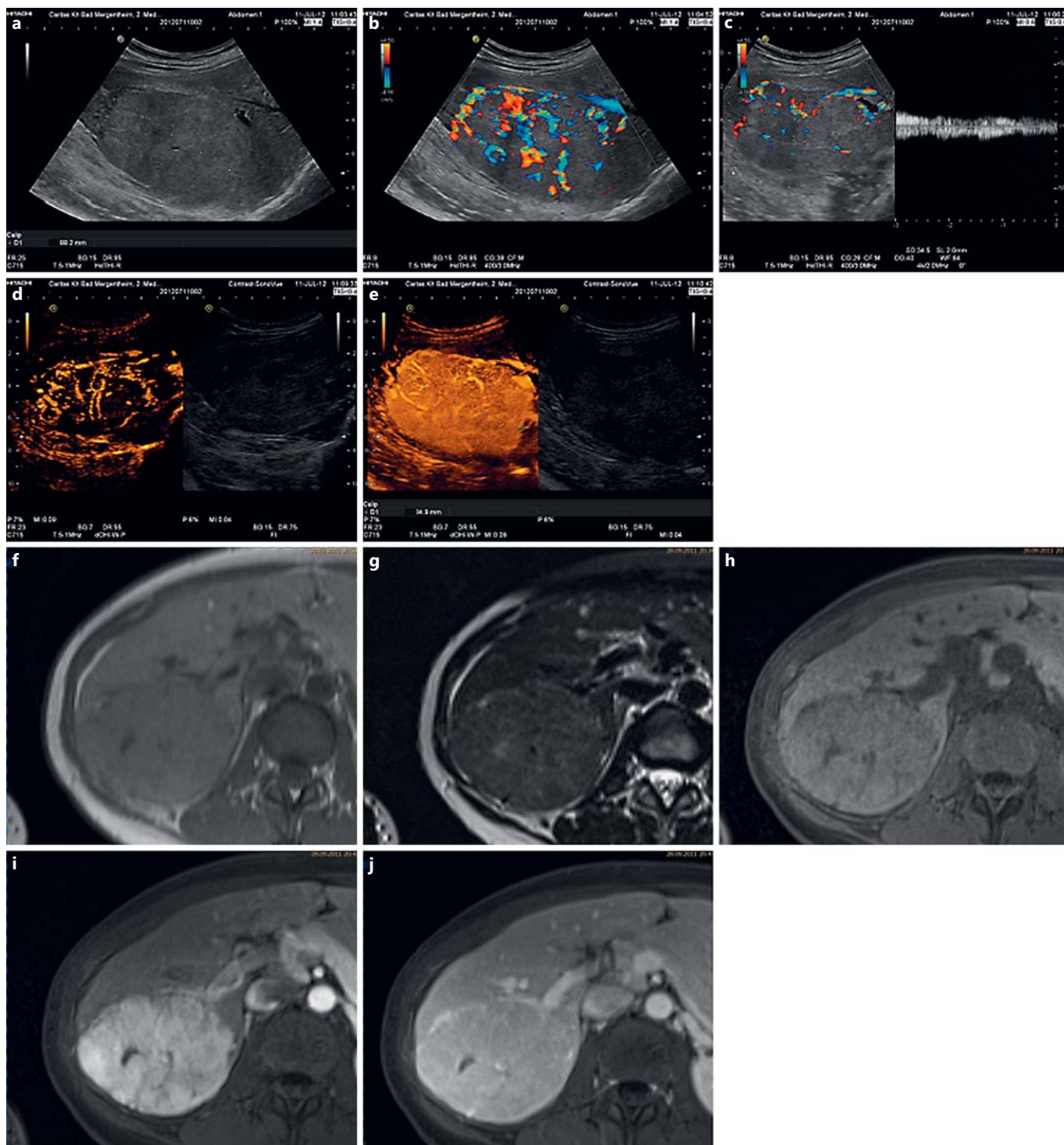


Fig. 3. Focal nodular hyperplasia. **a** Almost isoechoic FLL, well delineated and relatively homogeneous. **b, c** Highly vascularized lesion with central arterial blood supply seen on color Doppler US. **d, e** CEUS showing early arterial star-like centrifugal enhancement with rapid and persistent homogeneous filling. **f** T1-weighted MR image showing a slightly hypointense homogeneous FLL. **g** FLL

with a slightly hyperintense appearance on the T2-weighted MRI sequence and a more hyperintense central scar. **h** There is no fat suppression. **i** Homogeneous arterial enhancement (except for the central scar which remains unenhanced). **j** There is no washout during the portal venous phase.

Characteristics of MRI CAs

Intravenous MRI CAs include chelates of paramagnetic ions, both ionic and nonionic. Gadolinium chelates are the most commonly used MRI contrast media and show an extracellular hepatic distribution. Another MRI CA used especially for the differential diagnosis of liver lesions is ferumoxide (Endorem®) which contains superparamagnetic iron oxide nanoparticles that allow an imaging time of 30 min up to 6 h after administration [29]. It is a reticuloendothelial system-specific agent which improves the detection of hepatic lesions with negligible reticuloendothelial cells such as liver metastases [30, 31]. Recently, the use of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA; Primovist® in Europe and Eovist® in the USA) further improved the detection and characterization of FLLs by CEMRI due to its progressive distribution within the hepatocytes during the so-called hepatobiliary phase [10, 32, 33].

The Safety of MRI CAs

The CAs containing gadolinium are generally safe in healthy subjects and usually have no effect on laboratory tests, but adverse effects have been reported in some cases [34, 35]. Out of 65,009 adults and 13,344 pediatric patients examined with gadolinium-enhanced MRI, Dillman et al. [36] reported acute allergic-like reactions in 0.07 and 0.04% of the adult and pediatric patients, respectively. The majority of acute allergic-like reactions were mild (74%), and 50% of them occurred in patients with one or more presumed risk factors for contrast material reactions, such as a history of previous allergic-like reactions to either gadolinium or iodine-containing contrast media, a prior allergic reaction to a substance different from contrast media, or documented asthma. When exposed to gadolinium CAs, patients with severe renal failure can manifest a condition called nephrogenic systemic fibrosis which is primarily characterized by fibrosis of the skin, but it can also evolve with involvement of the skeletal muscles, heart, and lungs secondary to circulating fibrocytes which are believed to be inappropriately stimulated by gadolinium [37–41]. This condition is extremely rare but is associated with increased mortality [42].

Advantages of UCAs

The Safety of UCAs

While iodinated CAs may be associated with renal or systemic toxicity, UCAs are generally safe, with a very low

incidence of side effects and without significant cardio-, hepato- or nephrotoxic effects [28, 43, 44]. In a retrospective study [28] of 23,188 investigations with second-generation UCAs (SonoVue®), the rate of serious adverse events was only 0.0086% (29 cases), including one pseudo-anaphylactic shock and one bronchospasm, but no fatal event occurred. Death had been reported during contrast echocardiography with the UCAs Definity® and Optison®, but the 4 patients concerned were critically ill, and no evidence suggested that the deaths were related to the UCAs [45]. In addition, SonoVue® is currently the most widely used UCA, while Definity® and Optison® are seldom used in hepatic US. Bio effects may be produced by the interaction of US and UCAs; however, no studies have shown that this may cause adverse effects in human organs [2, 3].

One advantage of UCAs is that CEUS allows an immediate evaluation of any detected or suspected FLL on B-mode US, without the need of prior laboratory testing for renal or hepatic function [5]. The risk of allergic and hypersensitivity reactions is comparable to the risk encountered with MRI CAs, and it is generally lower than that associated with X-ray CAs [28]. The excellent safety profile of UCAs allows a rapid and repeated evaluation also in the same US session when needed [1, 2, 28, 44, 46].

UCAs Are Strictly Intravascular

Contrast enhancement characteristics of CEUS, CECT and CEMRI are not equivalent due to the different biochemistry and pharmacokinetics of the respective CAs. Due to their physical size, UCAs are true blood pool agents and do not diffuse outside the capillaries or other vessels, unless there is an ongoing hemorrhage. Being strictly intravascular, UCAs allow a better characterization of FLLs, especially during portal and late venous phases, and a more confident evaluation of washout phenomena compared to CT or MRI CAs, which are rapidly cleared from the blood pool into the extracellular space and may conceal washout [1–3, 6, 11–17, 47, 48].

Two UCAs (Levovist® and Sonazoid®) are taken up by Kupffer cells approximately 15 min after intravenous injection. This phase is called postvascular phase or Kupffer imaging phase [49]. UCAs like Sonazoid®, which contain perflubutane microbubbles, have a more prolonged resonance period without collapsing. Thus, Kupffer imaging is stable for more than several hours, facilitating whole-liver scanning. CEUS with Sonazoid® is helpful in differentiating malignant from benign FLLs [50] and may detect hepatocellular carcinoma nodules not visible at conventional US [51].

The diffusion of cross-sectional CAs into the interstitium is seen in malignant but not in benign lesions, leading to the conclusion that CAs diffuse from leaky vessels of malignant lesions, differently from UCAs [52, 53]. As discussed above, due to the strictly intravascular distribution of UCAs, CEUS allows a more prolonged enhancement than CT and MRI and also a quantitative assessment of the microcirculation [5]. This characteristic can be really helpful in the differential diagnosis of FLLs. By a time-intensity curve analysis, for example, a differentiation between focal nodular hyperplasia and liver adenoma may be possible using SonoVue® [54], which can otherwise be challenging even for histologists.

No Radiation Exposure

The estimated effective dose for adults ranges from 1 to 10 mSv for an abdominal CT examination with CA, and from 10 to 30 mSv for an abdominal CT examination with and without CA [55, 56]. Since the primary risk associated with exposure to ionizing radiation is cancer, it is important to select the appropriate imaging procedure [56]. One important criterion for recommending an imaging procedure should be to reduce the radiation exposure. However, there is a large consensus that the radiation risk can be justified by obtaining useful diagnostic clues that otherwise could not be evident with other imaging procedures [57–59]. Ideally, the selection of an appropriate imaging procedure that avoids any radiation exposure should be seriously considered, and CEUS is devoid of any radiation exposure to the patient [56, 60, 61].

The availability of an imaging method such as CEUS has improved the risk/benefit ratio in patients undergoing diagnostic contrast examinations. In the clinical setting of a patient with an FLL needing a final diagnosis and follow-up, CEUS represents an excellent alternative to CECT or CEMRI as it is better tolerated and not inferior to these techniques [62, 63]. Therefore, CEUS examination should always be considered as a first diagnostic procedure when appropriate [52].

Availability

CEUS is a widespread technique [64]; it is portable and can be performed at the patient's bedside, in the operating room and CT suite. Moreover, it is less stressful and less invasive for the patient than CT or MRI because it does not provoke anxiety or claustrophobia [65]. Even young children often tolerate the investigation without sedation. Furthermore, it can be performed immediately after detection of FLL by baseline US. The results are better when the patients are cooperative and comply with the exami-

nation, which is usually accomplished due to the non-stressful examining conditions and also due to the availability of a discussion between examiner and patient with explanatory information given to the patient during the diagnostic procedure [44].

Low Cost

The CEUS is a cost-efficient examination which is relatively inexpensive compared to conventional cross-sectional contrast-enhanced imaging techniques for the first-line diagnosis of FLLs [66]. For these reasons, it is used in many radiology departments [67–69]. If the initial identification of an FLL has been done by conventional B-mode US, the addition of CEUS in the same session is cost-effective [70]. The costs for the diagnostic workup of FLLs of unknown etiology found on conventional US may be reduced by more than 50% by using CEUS as a second imaging modality when compared to CT or MRI used for the same purpose [71, 72]. The costs may even further be reduced if we consider that the use of 1.2 ml of UCA is comparable, in terms of diagnostic efficacy, to a dose of 2.4–5 ml of the same agent [73].

Other CEUS Applications

CEUS can provide excellent guidance for different invasive intraoperative procedures. CEUS has been proven to be useful in the assessment of liver tumor response to chemotherapy. Also, it can be used to differentiate tumor recurrence from the normal scarring process after surgical and ablative procedures, which normally takes place at the periphery of the ablated tissue [74, 75]. CEUS is also useful in the differentiation of tumor recurrence from benign periablational enhancement and fibrosis [76–78]. The imaging aspect of recurrence is a focal and asymmetrical area of enhancement on the edge of the treated area. Symmetrical rim enhancement is considered to be a benign process – the imaging expression of scarring and inflammation [79]. On the other hand, immediate imaging after tumor ablation is essential in order to evaluate the success of the procedure by excluding residual tumor tissue. This can be proven by means of CEUS which has the advantage of immediate imaging if the ablation procedure has been carried out under US guidance. CEUS can identify vital tissue which can be further ablated during the same session [80]. Because of the strict intravascular characteristics of UCAs, a better delineation of the remaining foci can be obtained by CEUS than by CECT, which further influences the success of the procedure [44].

Other CEUS applications in the liver include evaluation of trauma [2, 3], diagnosis of vascular disorders such as portal vein thrombosis, aneurysms and their complications [81], as well as detection of arteriovenous or arterioportal fistulas [82].

Limitations of CEUS

CEUS can be efficiently applied only in patients who can be optimally scanned by gray-scale US, a good quality of the two-dimensional US image being a requested condition [2, 43]. In patients with extreme meteorism, obesity or in cases of an awkward position of the lesion that renders the CEUS image suboptimal, cross-sectional imaging techniques are mandatory [67, 83].

A correct diagnosis by CEUS is dependent on the operator skills and requires an extensive training for effective use [4]. The recommended way to gain experience is by observing contrast studies performed by experts in this field [2].

The use of a high mechanical index or continuous insonation must be avoided in order not to destroy the microbubbles, which can lead to false hypoenhancement and subsequently to a false diagnosis [44].

Another main limitation of CEUS compared to cross-sectional imaging is that only one FLL can be evaluated at a time and repeated bolus administration of UCA is required in order to assess other FLLs. While cross-sectional imaging allows the simultaneous characterization of multiple FLLs, this is only rarely possible with CEUS because image planes and technical parameters need to be optimized for each FLL examined and the transducer has to be kept still during the examination [43, 84, 85]. However, in clinical practice, only 2 and maximally 3 FLLs

located in the same segment or lobe may be simultaneously and easily examined with CEUS.

CEUS, like any other imaging modality, is subject to specific artifacts. Their knowledge is of utter importance for operators in order to avoid misinterpretation with subsequent misdiagnosis and mismanagement [86]. Problems arising from documentation, not least concerning legal issues, have long been debated and regarded as a limitation of US examinations in general.

Summarizing the limitations of CEUS, the operator dependency needs to be mentioned first [44]. Secondly, the quality of the baseline US determines the quality of CEUS and may be disappointing if the conventional US was suboptimal [2]. Furthermore, CEUS does not allow an evaluation of multiple FLLs at the same time [43]. The smallest detectable lesions range from 3 to 5 mm in diameter [87]; deep-seated and subdiaphragmatic lesions may not be accessible, and very small FLLs may be overlooked [2]. CEUS has a reduced sensitivity and specificity in fatty liver [2], and artifacts need to be excluded [86].

Conclusions

CEUS is an innovative and important imaging technique that can be an alternative to modalities such as CECT and CEMRI in the appropriate clinical context. The examinations should be performed by skilled operators in order to obtain excellent images and reliable results. With increasing evidence regarding the usefulness of CEUS in applications other than FLLs, CEUS is becoming largely integrated into clinical practice, thus avoiding any radiation exposure and biologic risk in patients undergoing diagnostic procedures.

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