

The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): Update 2011 on non-hepatic applications

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List of Abbreviations

AAA = Abdominal Aortic Aneurysm
 AUC = Area Under the Curve
 CE = Contrast Enhanced
 CECT = Contrast Enhanced Computed Tomography
 CEMRI = Contrast Enhanced Magnetic Resonance Imaging
 CEUS = Contrast Enhanced Ultrasound
 CE-TCCS = Contrast Enhanced Transcranial Colour-Coded duplex Sonography
 CE-EUS = Contrast Enhanced Endoscopic Ultrasound
 CT = Computed Tomography
 DCE-US = Dynamic Contrast Enhanced Ultrasound
 EFSUMB = European Federation of Societies for Ultrasound in Medicine and Biology
 EUS = Endoscopic Ultrasound
 HCC = Hepatocellular Carcinoma
 NFS = Nephrogenic systemic fibrosis
 GIST = Gastrointestinal Stromal Tumour
 MI = Mechanical Index
 RECIST = Response Evaluation Criteria in Solid Tumours
 PET = Positron Emission Tomography
 RI = Resistance Index
 ROI = Region of Interest
 TIC = Time Intensity Curve
 UCA = Ultrasound Contrast Agent
 US = Ultrasound
 VUR = Vesico-ureteral Reflux
 WFUMB = World Federation of Societies for Ultrasound in Medicine and Biology

1. Introduction

The first studies on the clinical use of ultrasound contrast agents (UCAs) with contrast specific imaging techniques were published at the beginning of this century using Levovist® as UCA [1, 2]. A couple of years later sulphur hexafluoride (SonoVue®, Bracco, Milan) was marketed in Europe, opening the era of real time low mechanical index (MI) contrast enhanced ultrasound (CEUS). The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) released the first Guidelines on the use of CEUS in 2004 [3]. This document, which focused mainly on liver applications, contributed to the rapid expansion of CEUS and sanctioned the acronym "CEUS". CEUS was felt to be a revolutionary technique and many new applications, besides those in the liver, were developed in the following years. Therefore, in the update of the Clinical Recommendations on the use of CEUS by the EFSUMB, published in 2008 [4], applications in some other organs were described. Since then, there has been exponentially increasing interest in the clinical applications of CEUS and new fields have been investigated, so that nearly all organ systems have now been subjected to some kind of CEUS study. More than half of the approximately 900 original investigative articles (editorials and letters excluded) found in PubMed® under the search term "Contrast Enhanced Ultrasound" by the end of 2010 were published after 2008, after the last update of the EFSUMB guidelines [4]. Therefore, in 2010 EFSUMB felt it was the right time to start preparing a new update of the Guidelines. In the light of the expansion in CEUS usage, it was felt that a new update on CEUS for liver applications would be more beneficial to the clinical community if endorsed on a worldwide basis. Therefore, an agreement was reached with the World Federation of Societies for Ultrasound in Medicine and Biology (WFUMB) to prepare joint guidelines with EFSUMB exclusively for liver applications, taking advantage of its previous experience and of the previously published document [4]. These are expected to be issued as double simultaneous publications in *Ultraschall in der Medizin*/European Journal of Ultrasound and in *Ultrasound in Medicine and Biology*. At the same time the EFSUMB Executive Bureau decided that non-liver applications would be covered by a dedicated EFSUMB document under the guidance of a steering committee. The steering committee chose a panel of authors on the basis of their publication records in the various fields of interest and their reputation as international experts in research and teaching CEUS. By necessity, this list of co-authors could include only a limited number of persons and we acknowledge that many other highly qualified CEUS operators are active throughout Europe and have published valuable scientific articles on different CEUS topics. EFSUMB regrets not being able to include all of them in this process.

These Clinical Recommendations on the use of CEUS are based on comprehensive literature surveys including results from prospective clinical trials. In the case of topics for which no or little significant study data were available, evidence was obtained from expert committee reports or was based on the views of experts in the field during a consensus conference held in Frankfurt in April 2011.

As with the previous editions, these 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 patient management. Individual cases must be

managed on the basis of all clinical data available for that specific patient.

A few points are worth special mention. Many applications included in this article continue to be off-label. UCAs registered in Europe are licensed only for cardiac or, in the case of SonoVue®, for liver, breast and vascular applications. Levovist® is also registered for vesico-ureteric studies, but is practically no longer marketed, and is expected ultimately no longer be available. The current legal requirements for registration of pharmaceutical products in Europe are strict. In order for a new indication to be registered, the manufacturer must provide data on safety and efficacy, with a dedicated phase III trial specifically designed to obtain that registration approval. Diagnostic agents, including contrast microbubbles, are not exempt from this rule, which is designed to protect patients from misuse of drugs or diagnostic agents but, on some occasions, may limit the potential benefit to patients. In fact, applications for indications not only follow clinical or scientific needs, but also the financial expectations of the producer. Similarly, for some products, the marketing forecast for income from additional indications is lower than the cost of a registration trial, so that new indications, especially for some organs, are highly unlikely to appear. However, lack of registration does not mean lack of efficacy of a marketed compound. Having said that, we must not forget that UCAs continue to be off-label for many non-liver indications detailed in the present recommendations. This means that patients should be informed and must consent to the investigation, and this is the responsibility of the operator. Indeed, non-liver CEUS is frequently performed on demand, to address specific questions raised in the individual patient. This explains (and justifies!) why it is not simple to write definitive guidelines and recommendations for the extrahepatic applications of CEUS.

CEUS has a number of distinct advantages over CT and MRI. It can be performed immediately, without any preliminary laboratory testing, and it can be carried out in a variety of scenarios (bedside, operating room, CT suite, etc.). Importantly also, it operates in real time so that rapid changes can be captured.

What then is the role of the current document? Firstly, it explains rationale for proceeding with the investigation, both to patients and clinicians, since for most situations the benefits are clearly outlined in this article. Secondly, it reports on the extremely rare and limited risks to which patients are exposed when they undergo a CEUS examination. These two points together facilitate and expedite the explanation of the risk/benefit ratio for the specific investigation to which a patient may be asked to consent. One example of this is in paediatric applications, for which the EFSUMB officers have already expressed a similar point of view [5].

Finally, based on the literature and the experts' consensus, an attempt was made to provide a recommendation level for each indication. The British guidelines for reporting on this topic have been used, as found at http://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=guidelines, accessed in March 2011, in which the more detailed criteria of the Centre for Evidence Based Medicine in Oxford have been incorporated after slight adaptation (• **Table 1**).

A: There is good research-based evidence to support the recommendation.

B: There is fair research-based evidence to support the recommendation.

Grade level	Type of evidence (adapted from the modality of the Centre for Evidence Based Medicine, Oxford)	
1a:	Systematic review of level 1b studies	
1b	Prospective independent blind comparison (separate readers) of an <i>appropriate</i> spectrum/number of <i>consecutive</i> patients, all of whom have undergone both the diagnostic test and the reference standard	
2a	Systematic review of level 2b or level 4 studies	
2b	Study performed in a set of <i>non-consecutive</i> patients or confined to a <i>narrow</i> spectrum/number of patients all of whom have undergone both the diagnostic test and the reference standard	
3	Systematic review of case-control studies (no intra-individual comparison)	
4	Reference standard was not valid (unobjective, unblinded or not independent) or study was performed in an <i>inappropriate</i> spectrum /number of patients	
5	Expert opinion	
This scale will be also translated into a synthetic judgement of strength of recommendation using the following scale:		
A	Recommendation based on good evidence	At least one multicentre level 1 or 2 study or ≥ 3 monocentric level 1 or 2 studies
B	Recommendation based on moderate evidence	One of the following: < 3 monocentric level 1 or 2 studies 1 level 3 study (systematic review) 1 multicentre level 4 study ≥ 3 monocentric level 4 studies
C	Recommendation based on experts opinions	Consensus of experts not supported by sufficient data of evidence level A or B.
0	No indication	
X	Contraindication	

Table 1 Criteria for the assessment of the level of evidence for the EFSUMB non-liver CEUS guidelines. Adapted from: Centre for Evidence Based Medicine, Oxford (http://www.essential-evidenceplus.com/product/ebm_loe.cfm?show=oxford).

C: The recommendation is based on expert opinion and panel consensus.

X: There is evidence that the intervention is harmful

0: We added level 0 for situations in which not enough information was available to provide a recommendation.

In addition to the level of the recommendation (A, B, C, X or 0), we reported the strength of the recommendation based on the study with the highest quality supporting the recommendations, according to the classification detailed in **Table 1**.

2. General Considerations

Any CEUS examination should be preceded by careful assessment of the target with conventional B-mode US and, when appropriate, with Doppler (spectral and/or colour/power). Before starting any CEUS examination, all relevant clinical information, including laboratory tests and previous imaging investigations, useful for reaching the expected final diagnosis, should be reviewed. This also helps to explain the expected benefit of the proposed CEUS study to the patient, an important step in obtaining consent.

Four transpulmonary UCAs are currently approved by the European Medicines Agency for use in European countries. The products and indications may vary on other continents.

- ▶ Levovist® (air with a galactose shell and palmitic acid as a surfactant) (Bayer-Shering Pharma AG, introduced in 1996). Production of Levovist has been discontinued and its use is not considered in these Recommendations.
- ▶ Luminity® (perflutren) (octafluoropropane with a phospholipid shell) (Lantheus Medical Imaging, inc., introduced in 2006). Sole European indication to date is cardiac which is outside the scope of these recommendations.
- ▶ Optison® (octafluoropropane – perflutren with an albumin shell) (GE Healthcare Inc., introduced in 1998). Sole European indication to date is cardiac which is outside the scope of these recommendations.

- ▶ SonoVue® (sulfur hexafluoride with a phospholipid shell) (Bracco Spa, introduced in 2001). Registered indications in Europe are cardiac, macrovascular, liver and breast lesions. This is the main agent in general use.

The composition, packaging, storage, indications and contraindications of these agents are detailed in the respective webpages of the manufacturers, whose addresses can be reached following the informations reported in Appendix 1.

Other UCAs are approved outside Europe and several more are under investigation.

Dose of contrast agent and data storage. For SonoVue®, which is the focus of the current document and which is the UCA used in almost all of the referenced articles, the recommended dose is 2.4 mL. This can be increased to 4.8 mL or decreased to 1.0 mL or less depending on the sensitivity of the equipment used, the type of transducer and the organ under investigation. When using higher frequency transducers, a dose of 4.8 mL performs better. A real-time videoclip should be recorded, preferably digitally, for review and documentation. The clip should include at best the whole examination or at least the most relevant parts, usually corresponding to the initial 10–40 seconds starting at the onset of enhancement with additional shorter clips taken at 2–3 minutes. Finally, either the entire clip (preferred choice) or at least various selected most relevant frames should be stored permanently [6–9].

3. Equipment

Contrast-specific US modes are required and are generally based on the cancellation and/or separation of linear US signals from tissue and the utilisation of the non-linear response from microbubbles.

The non-linear response from microbubbles arises from two different mechanisms:

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

Non-linear harmonic US signals also arise in tissues themselves from distortion of the sound wave during its propagation through the tissue. The extent of this tissue harmonic response increases with the acoustic pressure, which is proportional to the MI. The precise unit of measurement for acoustic pressure is the Pascal, but the most common reference unit is the MI. Minimisation of bubble disruption is the main reason for using low MIs for real time imaging but it also reduces tissue harmonics and artefacts, thus facilitating the separation of signals from UCAs from those of tissue. Low MI is typically below 0.3, but most equipments work well at MIs much below this (for details see manufacturers' recommendations or contact the manufacturers' representatives). For the purpose of this document, CEUS is defined as low MI real time contrast specific imaging, unless otherwise specified. This is in agreement with the terminology of the vast majority of the literature.

Technical information on US equipment capable of CEUS imaging can be accessed via the respective webpages reachable through the web address reported in Appendix 1. Updating this information is the responsibility of the companies.

EFSUMB is unable to express any judgement on the quality of particular scanners or transducers. However, the following features should be kept in mind, as they characterise the quality of the equipment used for CEUS examinations:

Sensitivity reflects the ability of a system to detect extremely small amounts of microbubbles. Good sensitivity extends the duration of useful enhancement.

When using high frequency probes, higher doses of UCA may be needed to achieve a sufficient enhancement level, as these frequencies are higher than those at which current UCAs resonate most strongly.

The ability to image small differences in local contrast concentration is a component of sensitivity. It reflects the dynamic range of contrast performance.

Tissue suppression is mandatory to differentiate contrast enhancement from tissue echoes. Strongly reflective structures such as vessel walls, the abdominal wall and gas-filled structures can break through and appear on the CEUS part of the screen.

Resolution. As in B-mode, temporal and spatial resolution are important for CEUS imaging. Temporal resolution is defined by the frame rate at a given line density, depth and width. A high frame rate allows visualisation of the flow direction in arteries. It may also produce more rapid destruction of bubbles within the acoustic field. Spatial resolution mainly refers to the ability to display bubble echoes with optimal detail. Additionally, the image should be homogeneous throughout.

Like all imaging techniques, CEUS has artefacts, mainly caused by incorrect machine settings or UCA dosages [10]. The MI is the most important setting for CEUS and gain is the second one. Adequate training allows knowledge, recognition and prevention of artefacts.

4. Investigator Training

Competence ensured by adequate training is a prerequisite to achieve correct diagnoses when using ultrasonography and

especially CEUS. EFSUMB has defined three levels of training in its minimal training requirements [11] (EFSUMB Appendix 14) [12] and recommends that CEUS should be performed by operators at a competence level higher than Level 1. To ensure adequate training, EFSUMB started a new initiative to organise dedicated Euroson Schools on CEUS in 2009 [13].

EFSUMB advises that investigators intending to start using CEUS spend some time under the supervision of an expert, who is preferably at Level 3. It is important that there is a sufficient number and variety of examinations in their own department. Investigators should also consult the manufacturers to ensure that their scanner is optimised for CEUS examinations. The practice of CEUS also requires knowledge of UCA administration and contraindications and the skill to handle possible side effects within the medico-legal framework of their country.

5. Terminology

UCAs were initially developed to enhance Doppler US and any scanner with Doppler facilities can be utilised for this. Conventional Doppler US operates at a higher acoustic power than real-time contrast-specific modes. Consequently microbubble disruption occurs at a high rate and the enhancement does not last long (a few minutes) after bolus injection. Moreover, the injection of contrast as a bolus often produces an initial "blooming" effect (proportional to the amount of contrast utilised), so that either smaller amounts or a continuous infusion (1–2 ml per minute) may be preferable. This technique has few applications nowadays since CEUS can provide information either more accurately or in an easier way in most organs.

During CEUS, the screen should show only a few signals from intensely reflective structures, such as signals generated by the large difference in acoustic impedance between the lung and the diaphragm (overload of the tissue suppression software). This applies both to single-screen contrast-only displays and to the split-screen display, where the CEUS image is shown alongside a low MI version of conventional B-mode image. In some equipment a single panel mixed mode is used. In these cases, the underlying conventional B-mode image is seen, with the CEUS overlay displayed in a different colour, potentially with the addition of colour Doppler information.

The description of the behaviour of tissue or lesion under examination should be in terms of its enhancement, taking into consideration its temporal behaviour, degree of enhancement, and contrast distribution.

1. As regards the **timing** of enhancement, two phases are apparent for most organs:
 - a) the arterial phase, starting from the first arrival of contrast (usually in 10–20 seconds) until around 30–45 seconds, during which the degree of enhancement increases progressively.
 - b) the venous phase which starts from approximately 30–45 seconds after contrast injection, during which the degree of enhancement shows a plateau and then decreases progressively until microbubble signals have disappeared completely or fallen to the noise level. Most organs have a single blood supply with a single inflow (namely arterial) phase, the exceptions being the liver, which is supplied by its artery and the portal vein, leading to two distinct inflow phases (arterial and portal venous) and the lungs, which are supplied by pulmonary and bronchial arteries with different arrival times.

The liver and spleen are also exceptions in that they tend to retain microbubbles longer than other organs, probably due to the trapping of microbubbles in their unique microcirculations after clearance from the remainder of the macrovasculature. Consequently, the wash-out phase in most organs is shorter than in the liver and spleen, whose prolonged retention is termed the late phase. There is no precisely definable event that allows an exact distinction between the arterial and venous and late phases.

The time of contrast arrival is usually 10 to 20 seconds after i.v. injection, but factors such as a slow injection of microbubbles in very peripheral small veins or cardiac diseases may prolong it, whereas intracardiac or pulmonary shunting or a hyperdynamic circulation may shorten it.

2. The **degree** of enhancement is difficult to assess, unless measurements are made using in-built or off-line software, for example, in the assessment of tumour response to antiangiogenesis treatment [14]. Generally, when the target of the study is a focal region in a parenchymal organ, the degree of enhancement should be compared to the surrounding parenchyma or to the paired organ when available. The lesion might be relatively hyperenhancing, isoenhancing, hypoenhancing or non-enhancing and the pattern should be described separately for the arterial and venous phases. The transition from hyper- or iso-enhancement to hypoenhancement is commonly referred to as “wash-out”. The use of this term for other enhancement patterns creates confusion and should be avoided. EFSUMB recommends that reports on CEUS are made in terms of the degree of enhancement. For targets that have no background tissue to describe the relative enhancement (studies of large vessels, endocavitary administration, or when a mass occupies an entire organ, etc), it is important to describe the presence or absence of enhancement and its distribution (e.g. in septa within a complex cystic mass or a fluid-containing structure, or blood flow where this is not expected to be present, for instance outside an organ) whereas the degree of enhancement is more difficult to assess.
3. Contrast **distribution**. When enhancement is seen, its distribution should be described. The relevant terms have not been predetermined and should be chosen with the aim of characterising the tissue and reaching a diagnosis. The description of whether the enhancement is homogeneous or heterogeneous and, in the latter case, if non-perfused regions exist, should be included. Any further description of the enhancement pattern is left to the operator inspired by the recommendations for each organ. In general terms, the CEUS depiction of non-perfused (potentially necrotic or liquid) areas might be relevant prior to any US-guided biopsy in order to better identify the target.

6. Safety

In general, UCAs are very safe with a low incidence of side effects. They are not nephrotoxic and do not interact with the thyroid gland and it is therefore not necessary to perform laboratory tests before their administration. The incidence of severe hypersensitivity or anaphylactoid reactions is lower than with current X-ray agents and is comparable to that of MR contrast agents. UCAs are not licensed in pregnancy. Breastfeeding is a contraindication in some countries.

Life threatening anaphylactoid reactions have been reported with a rate of less than 0.002% [15, 16]. Previous allergic/anaphylactoid reaction to X-ray iodinated contrast agents does not necessitate the prophylactic use of steroids or antihistamines prior to UCA injection since the two types of agent are completely different.

There is a theoretical possibility that the interaction of diagnostic US and UCA 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 gas bodies and cells. Data from small animal models suggest that glomerular capillary haemorrhage and other microvascular rupture could occur when microbubbles are insonated at high MI [16]. This could be injurious in specific situations in which such vascular damage would be clinically important such as in the eye and brain. This potential for non-thermal bioeffects exists with all modes, including conventional 2D imaging and 3D methods. The MI provides a useful, albeit very rough, on-screen indicator of the potential for non-thermal effects. Changes have been observed *in vivo* in mammalian tissue models for diagnostic US exposures with an MI greater than ~0.4 in the presence of UCAs. In addition, premature ventricular contractions have been described when high MI end systolic triggering is used in echocardiography [17, 18].

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

Some general recommendations are:

- ▶ Resuscitation facilities should be available.
- ▶ Caution should be exercised for off-label use of UCA in tissues in which damage to the microvasculature may have serious clinical implications, such as in the eye, the brain and in the neonate.
- ▶ As in all diagnostic US procedures, the operator should be mindful of the desirability of keeping the displayed MI low and of avoiding unduly long exposure times. Caution should be exercised when using UCAs in patients with severe coronary artery disease and pulmonary hypertension. Unstable ischaemic heart disease in the 7 days prior to administration is a relative contraindication. Caution with respect to the use of UCAs in these cardiac instances derives from an anecdotal temporal, but unproven causal, association between contrast injection and death in severely compromised cardiac patients. However, in very large patient cohorts, the use of UCAs for acute cardiac patients has been shown to be associated with a decreased, not increased risk of death, thanks to the efficacy of the modality [19, 20].

7. Paediatrics

The current use of CEUS in paediatric work-up in Europe is peculiar. Two UCAs are registered for clinical non-cardiac use, Levovist® and SonoVue®. However only Levovist® is approved for use in children and adolescents and only for the indication of vesico-ureteral reflux study. At the same time production of Levovist® has ceased and it is no longer available. SonoVue®, performs equally well for this particular indication, but has to be used off-label, as previously mentioned.

CEUS in paediatric applications remains of critical importance, because of its obvious benefits compared to alternative imaging modalities, which in most cases necessitate exposure to ionizing radiation and the use of potentially harmful contrast agents. The benefit of avoiding ionizing radiation is clearly far more important in children and adolescents than in adult patients. This important question was addressed recently in a Letter to the Editor of *Ultraschall in der Medizin/European Journal of Ultrasound*, with a reply from the EFSUMB Executive Board [5]. There is no easy solution to this problem as strict rules and regulations apply to the official registration of medical drugs, which is of course for the safety of patients and thus to the benefit of all, including the medical community and pharmaceutical producers. In some situations, however, strict regulations may inhibit use of the most beneficial and simple techniques or drugs, and CEUS is one such example.

8. Pancreas



8.1 Background

CEUS is not indicated for the detection of focal solid or liquid pancreatic lesions, but can be utilised for the characterisation of sonographically detected lesions [21–23]. The use of CEUS improves the diagnostic accuracy of US in the study of pancreatic pathologies.

8.2 Study Procedure

CEUS is an accurate imaging method, superior to Doppler techniques, for the visualisation of intrapancreatic vessels and microvessels [24]. Enhancement of the pancreas begins immediately after aortic enhancement. After this early arterial phase (10 to 30 sec), there is a transient venous phase (30 to approximately 120 sec), as with other dynamic imaging modalities [4].

The CEUS study of a pancreatic mass should aim at its characterisation and the evaluation of its relationship with the peripancreatic arteries and veins [21, 22, 25, 26]. After completion of the pancreatic study, the liver should be assessed in the late phase, exploiting the same contrast injection, searching for metastases [22].

8.3 Pancreatic Masses

8.3.1 Image interpretation for lesion characterisation

The enhancement pattern of focal pancreatic lesions is usually compared with the adjacent pancreatic tissue. Therefore, the field of view should include the mass under investigation together with a portion of surrounding pancreatic parenchyma.

8.3.2 Adenocarcinoma

Ductal adenocarcinoma, the most common primary malignancy of the pancreas, is typically hypoenhancing in all phases, presumably because of the desmoplastic reaction and low mean vascular density [27–29]. This pattern is reported in about 90% of cases [23, 27, 30]. Lesion size and margins as well as the relationship with peripancreatic vessels are better visualised with CEUS than with conventional US [25, 26].

CEUS can demonstrate changes in pancreatic tumour vascularisation during chemotherapy [31, 32] raising a hope for future use in clinical practice.

8.3.3 Neuroendocrine tumours

Neuroendocrine tumours typically present as hyperenhanced masses in the arterial phase, owing to their abundant arterial vascularisation, even when the Doppler study is negative [21, 33, 34]. In larger tumours necrotic avascular areas result in inhomogeneous enhancement [33, 34].

8.3.4 Mucin-producing cystic tumours

CEUS improves the ultrasonographic differential diagnosis between pseudocysts and cystic tumours of the pancreas by accurately revealing vascularisation of intralésional septa or nodules [22].

Mucinous cystadenoma is a potentially malignant lesion that may transform into cystadenocarcinoma. Usually unilocular, it appears as a round macrocystic lesion, with particulate content, irregular thick walls and internal inclusions which enhance on CEUS [30, 35]. In general, mucinous cystic pancreatic tumours have vascularised septa and parietal nodules [22, 35]. Intraductal papillary mucinous neoplasms (IPMN) are divided into main-duct and side branch-duct types. CEUS is helpful for differentiating between perfused (nodules) and non-perfused (clot) regions [36]. Magnetic resonance imaging (MRI) and endoscopic US (EUS) are the imaging methods of choice for the study of this tumour to demonstrate the communication of the cystic lesion with the pancreatic ducts [37, 38]. CEUS can be employed in the follow-up of borderline cystic lesions of the pancreas, if well visualised on US, in order to reduce the use of MRI.

8.3.5 Serous cystadenoma

Serous cystadenoma is a benign cystic lesion, typically with a lobulated microcystic appearance with thin and centrally oriented septa, which are vascularized on CEUS [22]. When the cysts are minute, microcystic serous cystadenoma may mimic a solid lesion, both on conventional US and CEUS. They are hyperenhanced on CEUS [38].

8.3.6 Pseudocysts

Pseudocysts typically contain non-vascularised material (debris), with the exception of transversing vessels, which are typically found in the early stages. Pseudocysts do not show any signal on CEUS and remain completely non-enhancing in all phases, even when they are heterogeneous on US [30, 35]. The reported sensitivity and specificity of CEUS in characterising pseudocysts is up to 100% [35].

8.4 Pancreatitis

In severe acute pancreatitis, CEUS may help identify and delineate necrotic areas, which do not enhance [39]. If the pancreatic region is clearly visible on US, CEUS can be used in the follow-up of acute pancreatitis after CT staging, in order to reduce the number of CT examinations [39].

Focal mass-forming pancreatitis and autoimmune pancreatitis have been reported to have similar enhancement to that of the normal pancreatic parenchyma [27].

8.5 Recommended uses and indications

Focal pancreatic lesions identified with US can be studied with CEUS in order to improve:

1. Characterisation of ductal adenocarcinoma. (Recommendation Level: A;1b)

2. Differential diagnosis between pseudocysts and cystic tumours. (Recommendation Level: A;1b)
3. Differentiation of vascular (solid) from avascular (liquid/necrotic) components of a lesion. (Recommendation Level: A;1b)
4. Defining the dimensions and margins of a lesion, including its relationship with adjacent vessels. (Recommendation Level: B;2b)
5. Management of the lesion with a better distinction between solid and cystic lesions, thus providing information for the choice of the next imaging modality (i.e. MRI and/or Endoscopic US for cystic lesions). (Recommendation Level: C;5)
6. Diagnosis in cases that are indeterminate on CT (vascularisation of solid pancreatic lesions; differential diagnosis between pseudocysts and pancreatic cystic tumours, especially mucinous cystic tumour). (Recommendation Level: C;5).

9. Contrast Enhanced Endoscopic US (CE-EUS)



9.1. Background

Contrast enhanced endoscopic ultrasound (CE-EUS) is a newly established method which combines the advantage of high resolution US of internal organs with the administration of UCAs [38]. CE endoscopic Doppler US works at high MI that does not require specific software and uses the UCA as a Doppler enhancing medium [40, 41]. Low MI CE-EUS has been introduced recently using the same contrast-specific modes as for transabdominal CEUS [42–44].

EUS will be performed first and CE-EUS can be added to characterise internal vasculature, to differentiate benign from malignant masses, and to improve staging and real-time guidance of diagnostic and therapeutic procedures.

9.2. Study procedures

9.2.1. Contrast enhanced high mechanical index EUS

In CE endoscopic Doppler US the colour Doppler window should include the whole tumour if possible. The Doppler frequency should be as high as possible, depending on the distance to the tumour. The Doppler scale should be between 3 and 8 cm/s assuming an insonation angle of 0° if directional colour Doppler is used [45]. The gain should be as high as possible without inducing artefacts. The flow velocity range (pulse repetition frequency, PRF) should be 5–15 cm/s if pulsed wave Doppler is used. The technique is the same as for transcutaneous US. CE endoscopic Doppler US scanning takes an extra 3–4 min [46].

9.2.2. Contrast enhanced low mechanical index EUS (low MI CE-EUS)

The technique is the same as described for the transcutaneous route. However, there are various settings that should be checked in accordance with the manufacturer. The MI used in published feasibility articles was variable [42, 43, 47], ranging from 0.08 to 0.3.

9.3. Image interpretation for pancreatic lesions

9.3.1 Discrimination of adenocarcinoma

CE endoscopic Doppler US can be used to differentiate between pancreatic neoplasms, mainly the hypoenhancing ductal adenocarcinoma and the iso- or hyperenhancing neuroendocrine tumours but also pseudo-solid lesions like serous microcystic cystadenoma [21, 37, 48]. The differential diagnosis

between ductal adenocarcinoma and mass-forming focal pancreatitis can be improved since adenocarcinomas mainly contain arterioles and hardly any venules whereas in focal pancreatitis both arterioles and venules are detectable during CE endoscopic Doppler US [45, 49–51]. The method can be improved further by estimation of the resistance index (RI) of the arterioles. The cut-off RI for suspected malignant lesions is >0.70 versus <0.70 for non-malignant, inflammatory lesions [52]. As for all other US applications, the limitations of CE endoscopic Doppler US are extensive calcifications and poor B-mode depiction of the lesion.

Low MI CE-EUS seems to be more powerful, but there is currently only minimal published data [53–55]. Analysis of the microvessel architecture seems to be an advantage over transcutaneous CEUS, e.g., the central feeding artery in serous cystadenoma [21]. The technique can be used in cases in which significant artefacts impede transcutaneous visualisation, especially for characterisation and follow-up of focal pancreatic lesions. The accuracy for the differential diagnosis of pancreatic adenocarcinoma is reported to be over 85% [53, 55, 56].

9.3.2 Discrimination of pancreatic pseudocysts from cystic tumours

Low MI CE-EUS can be also used for differential diagnosis in cystic pancreatic lesions [57] as described in the transcutaneous section. EUS has a clear advantage in small cystic lesions and in patients with impaired transcutaneous visibility.

9.4 Differential diagnosis of autoimmune pancreatitis

Both focal and diffuse autoimmune pancreatitis show hyperenhancement. Low MI CE-EUS is able to visualise hyperenhancement to discriminate ductal adenocarcinoma (which does not hyperenhance) from autoimmune pancreatitis [58] but experience is limited. 3D reconstruction might have a higher impact because of better visualisation of vessel patterns [58].

Recommended uses and indications

CE-EUS can be recommended for:

1. Discrimination of hypoenhancing ductal adenocarcinoma of the pancreas from other iso- or hyperenhancing lesions. Experience is mainly based on CE endoscopic Doppler US. (Recommendation Level: A;1b)
2. Discrimination of mass-forming chronic pancreatitis from ductal adenocarcinoma in patients with chronic pancreatitis. (Recommendation Level: A;1a)
3. Improved discrimination of cystic tumours from pancreatic pseudocysts. (Recommendation Level: A;1b)

10. Gastrointestinal Tract



10.1 Background

When examining the intestines, it is preferable to use frequencies above 7.5 MHz to enable optimal visualisation of wall layers, thickened bowel walls and lesions. Higher contrast doses (e.g. 2.4–4.8 ml SonoVue®) should be used. The arrival time in the intestinal capillaries is usually 10–20 sec after injection, particularly in the submucosal layer [59]. Peak enhancement is reached after 30–40 sec and this arterial phase is followed by a venous phase that lasts from 30 to approximately 120 sec.

10.2 Study procedure

Before i.v. UCA administration, the intestines must be examined in B-mode and Doppler US to detect any pathology. The difference in bowel wall microvasculature between healthy and diseased intestines can be recognised by CEUS [60].

10.3 Inflammatory Bowel Disease (IBD)

10.3.1 Image interpretation and evaluation

CEUS allows the quantification of bowel wall vascularity in patients with Crohn's disease [61] and correlates well with MRI of the intestinal wall [62, 63]. Additionally, CEUS visualises the microvasculature of the tissue surrounding the intestines. Time Intensity Curve (TIC) analysis may further help to quantify disease activity.

10.3.2 Disease activity

US can be used to study disease activity in IBD using bowel wall thickness and Doppler measurements as a marker of inflammation [64–66]. Adding a UCA improves reliability in estimating disease activity in Crohn's disease [67, 68]. Enhancement in different wall layers can be evaluated and quantified in Crohn's disease and correlates to clinical activity indices with good sensitivity and specificity [69–71]. Quantitative measurements of bowel enhancement obtained by CEUS also correlate with endoscopic severity [72] and histopathologic findings [71]. Furthermore, ultrasonographic evaluation of the changes of bowel wall enhancement during biological therapy (e.g. anti-TNF agents) promises to be a useful and relatively cheap imaging modality for the clinical monitoring of the activity of Crohn's disease [73].

10.3.3 Distinguishing between fibrous and inflammatory strictures

Preliminary studies indicate that the use of UCAs is effective for the recognition of predominantly cicatricial stenoses in patients with Crohn's disease [74]. In patients with bowel stricture and resultant obstruction, it is important to determine whether there is active inflammation at the site of stricture or if the stenotic segment is fibrotic. Using CEUS, the active inflammatory components enhance strongly whereas a fibrotic stricture enhances poorly [75].

10.3.4 Abscesses

Distinguishing abscesses from inflammatory infiltrates is an important clinical task in the management of Crohn's disease. If areas of a significant size close to or within an affected bowel wall are completely devoid of microbubble signals, these lesions likely represent abscesses rather than inflammatory infiltrates, particularly if adjacent tissue shows hyperenhancement [61]. Similar findings also apply to abscesses caused by other diseases, e.g. diverticulitis [76].

10.3.5 Fistula

Injecting a UCA into one of the orifices of a fistula improves visualisation of the course of the fistula in Crohn's disease [77]. The UCA can be diluted manifold with sterile saline before injection into orifices (see section on intracavitary applications).

10.4 Limitations

It is impossible to visualise all bowel segments using transabdominal US. Intestinal peristalsis can impair image quality and

the repeatability of quantitative measurement of bowel enhancement patterns. More studies are needed to establish the exact role of CEUS in the imaging of GI pathology [78].

Recommended uses and indications

CEUS is indicated in the following clinical situations:

1. Estimation of disease activity in inflammatory bowel disease. (Recommendation Level: B;1b)
2. Discerning between fibrous and inflammatory strictures in Crohn's disease. (Recommendation Level: C;4)
3. Characterisation of suspected abscesses. (Recommendation Level: C;4)
4. Confirming and following the route of fistulas. (Recommendation Level: C;4)

11 Spleen



11.1 Background

The indication for CEUS investigation of the spleen, other than in trauma (see section 15), is the characterisation of focal lesions [79]. Solid splenic lesions may be occasional incidental US findings in asymptomatic subjects. In this setting and when they are single or scanty, especially if they are hyperechoic on conventional US, they are benign in the large majority of cases. However, in cancer patients, especially when lesions are multiple, hypoechoic and of recent onset, they tend to be malignant. Unfortunately, the clinical information and US findings are not usually sufficient to provide a reliable distinction between benign and malignant masses. Fine needle biopsy of splenic masses may have complications, especially peritoneal bleeding, making a noninvasive diagnosis highly desirable. CEUS may increase confidence in suggesting a benign nature.

11.2 Study procedure

The peculiar splenic vascularisation [80] leads to a rapid and transiently inhomogeneous enhancement pattern, especially in congestive splenomegaly, resembling the “zebra” pattern seen on dynamic CECT or CEMRI. About 1 minute after injection, the parenchyma becomes homogeneous, showing strong and persistent late phase enhancement that lasts longer than 5 minutes [81].

11.3 Image interpretation

CEUS is useful for characterising ectopic splenic tissue (accessory spleens and post-splenectomy splenosis) [82]. Splenic hilar lymph nodes, adrenal lesions, pancreatic tail tumours, metastatic deposits, and other lesions show less enhancement than the normal splenic parenchyma in the late phase. Accessory spleens usually exhibit a typical location and appearance and further imaging is necessary only in a minority of cases. CEUS shows an enhancement pattern exactly paralleling that of the adjacent spleen [83], i.e. more intense than that of other organs in the late phase.

In splenic infarction, CEUS accurately demonstrates the shape and extent of the lesion as a wedge-shaped, non-enhancing area based on the spleen capsule and pointing towards the hilum [84].

A splenic abscess is a poorly- or completely non-enhancing lesion, best recognised in venous phase images, with an enhancing rim and septa. No contrast enhancement is seen within

the internal fluid, debris, or necrotic components. Intermediate and early stage lesions show mixed patterns, like those in the liver [85].

Typical findings for benign splenic lesions include either no contrast enhancement or rapid wash-in, followed by persistent enhancement in the late phase. If CEUS findings are consistent with a benign splenic lesion, CT seems to be of limited additional value [86]. In contrast, the combination of contrast enhancement (diffuse or peripheral) in the arterial phase followed by rapid and marked wash-out is typical for malignant lesions (metastases or lymphoma) [87–90]. However, the behaviour of malignant and some benign lesions partially overlap, since haemangiomas, hamartomas, as well as other uncommon splenic abnormalities, may show some degree of wash-out, mimicking a malignant pattern [90, 91].

11.4 Differential diagnosis and limitations

In patients with left upper quadrant pain and splenic inhomogeneity on conventional US, CEUS allows visualisation of the underlying splenic abnormalities [84] increasing operator confidence in establishing a diagnosis [92]. CEUS is particularly helpful when an infarcted region is barely recognisable on US or it is spherical and simulates a focal lesion. Additionally, CEUS can diagnose splenic tumour infiltration mimicking infarction on conventional US. Differentiating splenic abscesses from necrotic lymphomatous lesions remains a challenge, since both conditions may occur in the immunocompromised patient.

CEUS may be helpful when a splenic cyst with ill-defined margins and/or inhomogeneous content is identified with US. Echogenic splenic tumours incidentally found on US and assessed by CEUS can be diagnosed as haemangiomas and can be managed with follow-up examinations.

11.5 Splenic tumour detection

CEUS may aid in detecting focal lesions in the spleen [79]. Lesions that are not seen on baseline US can be revealed by CEUS, which has been found to be 90% sensitive and 100% specific compared to CT with respect to lesion detection in lymphoma patients [93]. In a retrospective study on splenic metastases, CEUS increased the detection rate by 38% [94]. Lesions found in patients with solid organ or haematological malignancies require whole-body imaging using CT and/or PET [95], but CEUS can be useful if they are inconclusive, particularly to rule out lesions when PET shows “non-specific uptake”. Finally, CEUS can be used in patients with splenic malignancies to monitor their response to treatment. When chemotherapy is successful, the lesion becomes almost non-enhancing on CEUS with absence of any intra-nodular vessels or microcirculation. These findings are seen early, paralleling the PET response. Long-term follow-up shows progressive disappearance of the lesions.

Recommended uses and indications

CEUS can be utilised:

1. To characterise splenic parenchymal inhomogeneity or suspected lesions on conventional US. (Recommendation Level: B;1b)
2. To confirm suspected splenic infarction. (Recommendation Level: B;2b)
3. To characterize suspected accessory spleens or splenosis. (Recommendation Level: B;2b)

4. To detect splenic malignant lesions in oncologic patients when CT and/or MRI and PET are contraindicated or inconclusive. (Recommendation Level: B;1b)

12. Kidney



12.1 Background and vascular anatomy

In most centres, ultrasonography is the preferred first imaging modality in patients with known or suspected renal disease. The main objectives are to measure renal size, to detect focal lesions and obstruction of the collecting system and to look for vascular disorders. However, US is not reliable in distinguishing between different types of tissue and benign and malignant lesions may be difficult to distinguish. Doppler helps to characterise renal blood flow, with limitations because of attenuation, poor sensitivity for very slow blood flow, and angle dependency.

12.2 Study procedure

Kidneys enhance quickly and intensively after microbubble administration. The arterial pedicle and main branches enhance first, followed within a few seconds by complete fill-in of the cortex. Unlike with Doppler US, signals from microbubbles are independent of the angle of insonation, and depiction of renal perfusion is excellent even at the renal poles. Medullary perfusion follows cortical perfusion, with the outer medulla enhancing first, followed by gradual fill-in of the pyramids [96]. There is no microbubble excretion into the urinary tract. As contrast concentration in the general circulation decreases, enhancement fades. The expert opinion is that contrast enhancement is less intense and fades earlier in patients with chronic renal disease.

12.3 Renal ischaemia

Several investigations, both in animal studies and in humans, have shown excellent diagnostic performance in the detection of renal parenchymal ischaemia, similar to that of CECT [97] and superior to colour Doppler US, making CEUS a recommended technique in case of suspicion of infarction. Infarcts appear as wedge-shaped non-enhancing areas within an otherwise enhanced kidney. The excellent spatial resolution of CEUS allows confident differentiation between renal infarction and cortical necrosis, which appears as non-enhancing cortical areas with preserved hilar vascularity [96, 98].

Another important application of CEUS in patients with renal ischaemia is differentiation between non-perfused, infarcted tissue and hypoperfused parenchymal regions. On Doppler US, both appear as areas lacking colour signal, but only infarcted areas completely lack contrast enhancement after microbubble injection.

12.4 Renal artery stenosis

UCAs can be injected to improve the sensitivity of conventional colour Doppler US in identifying the renal arteries, with an improvement of approximately 10% [99]. This allows correct positioning of the sample volume for the detection of Doppler spectral tracings with the aim of screening for renal artery stenosis. Routine use of UCA offers no significant advantage [99].

12.5 Renal focal lesions

12.5.1 Differential diagnosis between cystic and solid lesions

Thanks to its excellent sensitivity, CEUS is more sensitive than CECT in detecting blood flow in hypovascularized lesions [100] and can be utilised in the few cases in which the distinction between solid hypovascular tumours (showing enhancement, even if there is very little flow) and atypical cystic masses (no contrast perfusion at all) remains unresolved after CT and colour Doppler US.

12.5.2 Differential diagnosis between solid renal masses and pseudotumours

The enhancement in renal tumours differs from the surrounding parenchyma, with a difference in degree or distribution of enhancement in at least one vascular phase, in the majority of cases. This helps differentiation between tumours and pseudotumours, since the latter have the same enhancing characteristics as the surrounding parenchyma in all phases [96, 101]. Solid renal tumours do not show diagnostic perfusion patterns on CEUS, which is thus usually not able to differentiate between malignant and benign solid renal masses (e.g. carcinoma versus angiomyolipoma).

In expert hands, CEUS may help identify renal vein invasion by cancers with an accuracy comparable to CECT [102]. In addition, in the opinion of the experts, the arterial vascularisation of the thrombus in the renal vein promises to differentiate bland thrombus (non-enhancing) from tumour invasion (enhancing thrombus), but further studies are necessary.

12.5.3 Characterisation of complex cystic renal masses

CEUS allows the characterisation of renal cystic lesions as benign or malignant with at least the same accuracy as CECT. It is more sensitive than CT in detecting enhancement of the cystic wall, septa, and solid components [103–106]. Nonetheless, CT remains the reference method for staging patients with malignant cystic lesions. CEUS is very well suited for the follow-up of non-surgical lesions and might replace CT, in light of its lack of contraindications, wide availability and lack of ionizing radiation, all of which are particularly welcome in this setting.

12.5.4 Renal infections

Following the European Urology Association guidelines, diagnosis of acute uncomplicated pyelonephritis is based on the clinical picture and laboratory findings. Conventional B-mode US is used to rule out urinary obstruction and renal stones. Additional investigations should be considered if the patient remains febrile after 72 h of treatment. These recommendations have a low level of evidence, and are made despite the absence of directly applicable clinical studies of good quality. As a consequence, the role of CEUS and of imaging itself in patients with uncomplicated pyelonephritis is debated and no clear indications exist, despite the finding that CEUS depicts renal abscesses as non-enhancing regions and can be used to monitor their course [96].

12.6 Assessment of percutaneous ablation therapies

Percutaneous ablation plays an increasing role in the management of patients with renal tumours. Diagnostic imaging in these patients includes CECT and/or CEMRI imaging during pre-treatment work-up and at distinct time points during follow-up after treatment. Unenhanced US can be used to guide

ablation, but does not provide enough information about the outcome of ablation treatments. There is increasing evidence that, CEUS overcomes many of these limitations in patients undergoing renal tumour ablation [107]. It provides important information on lesion vascularity, and may improve visualisation of lesions that are poorly demonstrated on the baseline US scan. Guidance of the ablation needle into the lesion and assessment of the therapeutic results are improved [108, 109]. Similarly to the liver, the intra-procedural assessment must be delayed by 5–10 minutes after the end of the ablation to allow the heat-generated gas and the related artefacts to dissipate. Any contrast enhancement within the ablation zone is conventionally regarded as residual tumour. Larger vessels surrounding the ablated region may be misinterpreted as residual tumour. Meticulous comparison with pre-procedural examinations and evaluation of lesion morphology are therefore important to avoid misdiagnosis, since residual tumour presents as nodular or crescent-like enhancing regions, with enhancement remaining similar to what observed in the tumour before treatment [110]. In two recent series of 28 [111] and 66 [110] renal tumours with sufficiently long follow-up, CEUS provided similar overall accuracy to that of CT/MRI in confirming the adequacy of treatment.

Recommended uses and indications

CEUS is recommended in the following clinical situations:

1. Suspected vascular disorders, including renal infarction and cortical necrosis. (Recommendation Level: A;1a)
2. Differential diagnosis between solid lesions and cysts presenting with equivocal appearance at conventional US. (Recommendation Level: B;2b)
3. Differentiation between renal tumours and anatomical variations mimicking a renal tumour (“pseudo-tumours”) when conventional US is equivocal. (Recommendation Level: B;1b). However, both CEUS and CECT have limitations in rare very small isoenhancing tumours.
4. Characterisation of complex cystic masses as benign, indeterminate or malignant to provide information for the surgical strategy. (Recommendation Level: A;1b)
5. Additional aid, when necessary, in the follow-up of non-surgical complex masses. (Recommendation Level: C;5).
6. Identification of clinically-suspected renal abscesses in patients with complicated urinary tract infection. (Recommendation Level: C;5)
7. In patients undergoing renal tumour ablation under US guidance, CEUS may be used to improve lesion visualisation in difficult cases and to detect residual tumour either immediately or later after ablation. When CEUS is planned, pre-ablation assessment of lesion vascularity is important. (Recommendation Level: B;1b)

13 Vesico-Ureteric Reflux (VUR)



13.1 Background

In addition to intravascular use, UCAs are suitable for intracavitary administration. The intravesical administration of UCA for the diagnosis of vesico-ureteric reflux, voiding urosonography, has become a routine option that can completely replace reflux examinations using ionizing radiation (i.e. voiding cystourethrography) in girls. Comparative studies between voiding urosonography and cystourethrography have revealed sig-

nificantly higher sensitivity for urosonography in detecting reflux [112, 113].

Levovist® is licensed for VUR. SonoVue®, seems to perform at least as well [114] although it is not licensed for this indication.

13.2 Study procedure

The basic steps of voiding urosonography [112] are:

- (a) US evaluation of the kidneys and bladder;
- (b) intravesical administration of UCA diluted in normal sterile saline and
- (c) repeated scanning of the bladder and kidneys at low MI during and after bladder filling and, finally while voiding. During the last step, urethrosonography (transpubic and/or transperineal) is added in some centres.

UCAs can be administered via a transurethral bladder catheter or via suprapubic puncture (0.1–0.5 mL SonoVue® in 500 mL 0.9% saline [112, 115]), by slow instillation during CEUS monitoring, until strong enhancement of the bladder content has been achieved. The dose can be adjusted if there is excessive shadowing or insufficient signal. A full bladder is necessary for suprapubic puncture, and it is advisable to apply an anaesthetic plaster to the puncture site about one hour prior to the examination.

13.3 Diagnosis of vesico-ureteral reflux

Reflux is diagnosed when microbubbles appear in one or both ureters and/or the pelvicalyceal system. The severity of reflux is graded using 5 degrees (grade I–V) [116] comparable to the international reflux grading system of voiding cystourethrography. The US scan is continued during and after voiding with the child supine, prone, sitting, or standing, always scanning the kidneys alternately and also the bladder, if the patient's position allows [112].

13.4 Voiding urosonography

Voiding urosonography is also helpful for studying the urethra [117]. However, further studies on this application are needed. Voiding urosonography can be considered the method of choice for the initial study of suspected VUR in girls, in whom information about the urethra is less important, whereas voiding cystourethrography continues to be the first choice in boys, though voiding urosonography also shows potential in this setting [117]. Conventional cystography remains the reference technique in patients with abnormal urethral findings and/or to plan surgery.

13.5. Limitations

Voiding urosonography is not recommended as the primary imaging modality for reflux, if the bladder or one of the kidneys is not depicted on ultrasound and for specific urethral and/or bladder functional and anatomical evaluation [113].

Recommended uses and indications

Voiding urosonography is recommended in the following clinical situations:

1. First examination for vesicoureteral reflux in girls. (Recommendation Level: A;1a)
2. Follow-up examinations for vesicoureteral reflux in girls and boys after conservative or surgical therapy. (Recommendation Level: A;1a)
3. Screening high-risk patients for reflux (e.g. siblings, transplanted kidney). (Recommendation Level: A;1a)

4. The CEUS assessment of urethra in boys appears feasible and accurate, but not enough experience has been gained yet to recommend it in routine clinical practice. (Recommendation Level: 0;4)

14 Scrotum

14.1 Background

Ultrasonography is the imaging modality of choice for examination of the scrotum. Occasionally, however, sonographic findings are equivocal and this may be important as a misinterpretation can result in an unnecessary orchiectomy. A particular conundrum is the unequivocal differentiation between hypovascular and avascular lesions, presuming that an avascular lesion implies benign disease: this may be impossible using colour Doppler US. CEUS provides a practical solution by increasing the confidence of the interpretation of lesion vascularity and of scrotal cord vessels, allowing for appropriate clinical management.

14.2 Study procedure

A full B-mode and colour Doppler examination of the lesion with linear high frequency transducers should be performed and recorded to relate to the subsequent CEUS findings. The arterial phase at CEUS is the most important aspect of the examination. The testis and epididymis enhance rapidly but the arrival time varies between individuals. The arteries enhance first, followed within seconds by complete parenchymal enhancement. The scrotal wall tends to enhance to a lesser degree than the contents. There is no accumulation of microbubbles in the parenchyma of the testis and the enhancement declines over a variable period of time such that there is minimal residual enhancement by 3 minutes.

14.3 Patterns of disease

14.3.1 Torsion of the spermatic cord

CEUS may be used as a problem solving technique in children with small testes where conventional Doppler imaging methods provide suboptimal assessment of flow. There is no firm data currently to inform the use of CEUS in spermatic cord torsion. In a small series of men with torsion, CEUS confirmed absence of vascularisation, but failed to add any clinically significant information to unenhanced colour Doppler US [118].

14.3.2 Segmental infarction

The appearance of acute segmental testicular infarction on conventional B-mode and colour Doppler US is variable. Often the benign nature of the lesion is established by its wedge shape with markedly diminished or absent colour Doppler flow [119]. The main concern is the differentiation of a segmental infarct with a rounded configuration from a poorly vascularised tumour [120]. CEUS improves the characterisation of segmental infarction by showing one or more ischaemic parenchymal lobules separated by normal testicular vessels [121]. Subacute segmental infarction characteristically exhibits a perilesional rim of enhancement, which diminishes over time and is eventually lost with changes in lesion shape and shrinkage [121].

14.3.3 Trauma

Conventional B-mode and colour Doppler assessment of the testis in trauma is well established, but they under-estimate

the extent of injury. Besides integrity or interruption of the tunica albuginea, the most important information for the surgeon is the extent of viable testicular tissue. CEUS adds to the colour Doppler assessment with clear delineation of fracture lines, intratesticular haematomas, and the amount of viable testis [122].

14.3.4 Inflammation

Epididymo-orchitis is a clinical diagnosis and is usually easily confirmed on colour Doppler US. CEUS may be able to determine the development of an abscess (appearing as a non-enhancing region) at an earlier stage, or the extent of a large abscess, and allow for prompt treatment [118]. CEUS may be utilised in selected cases to increase the sensitivity in detecting thrombosis of the spermatic cord vessels, especially in funiculitis, and in detecting post-inflammatory parenchymal ischaemic changes.

14.3.5 Tumours and complex cysts

The current understanding is that testicular tumours with a diameter of less than 1.5 cm may not show flow on colour Doppler US and thus may be misinterpreted as a benign lesion, the purported hallmark of malignancy being an increase in vascularity. Simple testicular cysts are usually benign, but any wall irregularity or echogenic debris may be suggestive of a (rare) cystic testicular tumour [123, 124]. It is thought that virtually all testicular tumours display vascularisation on CEUS, with the exception of any cystic component and regions of necrosis [125]. Experience suggests that CEUS is able to confirm the absence of vascularity in benign complex and epidermoid cysts [126]. There is currently no evidence in the literature with regards to these findings.

Recommended uses and indications

CEUS for the testis can be currently recommended for:

1. Discrimination of focal testicular lesions into those that are vascular and those that show no enhancement, potentially identifying lesions without malignant potential. (Recommendation Level: B;2b)
2. Discrimination of areas of non-viable tissue in cases of testicular trauma. (Recommendation Level: B;4)
3. Detection and characterisation of segmental infarction. (Recommendation Level: B;2b)
4. Discrimination of abscess formation in severe epididymo-orchitis. (Recommendation Level: C;4)

15. Abdominal Trauma



15.1 Background

CECT is the modality of choice for the rapid detection and grading of neurological, skeletal, and thoraco-abdominal injuries in all cases of high-energy multitrauma. However, there is a wide range of severity among trauma patients who are admitted to an emergency unit, and the rate of positive findings on CT decreases with lower energy trauma. This should be weighed against the negative aspects of CT, including exposure to ionizing radiation and injection of iodinated contrast media. US is sensitive in detecting free peritoneal fluid as an indirect sign of injury (Focused Assessment with Sonography in Trauma – FAST) but it has poor sensitivity in detecting solid organ trauma and is even less useful for hollow viscus trauma.

CEUS can increase the conspicuity of traumatic injuries, with a closer correlation with CT [87, 127, 128]. In a large, multicentre study [129], CEUS was more sensitive than US and provided sensitivities of 69% (renal), 84% (liver) and 93% (spleen) compared to CT in the detection of solid organ injuries with very high specificity (over 90%).

15.2. Study procedure

Contrast enhancement lasts long enough to allow an adequate exploration of all parenchymal organs in the trauma patient. The kidneys have the earliest and most transient enhancement and the spleen is inhomogeneous initially and then becomes persistently and homogeneously enhanced. Consequently the examination sequence usually starts with the kidneys, then moves to the liver, and finally examines the spleen. An alternative is to split the contrast dose in two, using the first to explore the right kidney and then the liver, and the second for the left kidney and the spleen. However, in many instances the CEUS study directly targets the organ suspected or known to be injured.

15.3 Image interpretation of abdominal injuries

CEUS demonstrates the injuries as non-enhancing defects, sharply demarcated from the intensely enhanced, undamaged tissue, particularly during the venous phase. Contusion appears as an ill-defined area of subtle hypoenhancement. Lacerations are depicted as markedly hypoechoic bands, usually oriented perpendicular to the organ surface; sometimes the torn organ capsule is seen as a discontinuity. A haematoma is recognisable as a non-enhancing area without internal enhanced vessels. CEUS can detect changes that are not apparent on conventional US, such as infarcts, perilesional hyperaemia, pseudoaneurysm formation, as well as contrast extravasation, which appears as a pooling or as a jet of contrast enhancement outside blood vessels. The spread of contrast enhanced blood into the parenchyma, the peritoneal cavity, or the retroperitoneum is an important finding since it indicates on-going haemorrhage and the need for surgery. As shown both by experimental and clinical studies, CEUS can detect ongoing bleeding from a variety of traumatic and also non-traumatic sources [87].

Emergency CT scans of trauma patients can have artefacts and CEUS may be useful for better assessing unclear findings. Furthermore, CEUS may be used in patients not ideal for CECT, such as children (see section 7). CEUS may decrease the number of repeat US examinations and expedite patient discharge. Several published series have demonstrated that CEUS allows a confident exclusion of major abdominal injuries. Hence, many patients with minor trauma can be discharged after a period of observation, without being submitted to CT at all.

15.4 Limitations

Since UCAs are not excreted in the urine, CEUS cannot be used for detecting damage to the urinary excretory system.

Recommended uses and indications

CEUS can be employed consistently in trauma imaging, considering the wide spectrum of scenarios encountered in clinical practice.

1. As an alternative to CT in stable patients with isolated blunt moderate-energy abdominal trauma to rule out solid organ injuries, especially in children (Recommendation Level: A;1b)

2. To further evaluate uncertain CT findings (Recommendation Level: C;2b)
3. For the follow-up of trauma managed conservatively, because it may make it possible to reduce in the number of CT scans or increase confidence when the situation does not strictly require a CT scan. (Recommendation Level: B;1b)

16. Lung and Pleural Lesions



16.1 Background

US imaging of the healthy lung is impossible because the US beam is totally reflected at the lung surface. Consolidations can be visualised when they reach the pleura, are accessible via an acoustic window, and there is no subcutaneous emphysema or pneumothorax [130]. CEUS assessment of the lung is therefore addressed to lung consolidations.

Because of its dual arterial supply, the lung has similarities to the liver and CEUS allows the differentiation of the pulmonary from the systemic bronchial arterial supply of consolidations by assessing the timing and extent of enhancement [131].

16.2 Study procedure

For lung consolidation, a conventional convex abdominal transducer is most commonly used. Before injecting the UCA, the best probe position to visualise the consolidation should be determined using B-mode and colour Doppler US and then observed for at least the first 30 s after contrast administration [132].

16.3 Image interpretation

Contrast arrives in the right heart between 1 and 5 sec after injection and immediately thereafter enters the pulmonary artery (indicating the beginning of the time window of pulmonary arterial enhancement), and between 8 and 11 sec enters the left heart (determining the start of systemic bronchial arterial enhancement immediately thereafter) in healthy subjects. An arrival time in the consolidation under study of less than 10 seconds ("early arterial enhancement") indicates pulmonary arterial supply and a delayed arrival time over 10 seconds ("late arterial enhancement") indicates supply by the bronchial arteries. In patients with cardiac and/or pulmonary disease, the arrival time for pulmonary arterial supply may be longer than 10 seconds [131].

16.3.1 Pneumonia

Contrast arrives early in pneumonia (10 sec) and enhancement is marked [131] followed by a plateau caused by a combined supply from pulmonary and bronchial arteries [132]. In addition, CEUS allows demarcation of necrosis or abscess formations in the infiltrated lung tissue as regions of absent enhancement [131].

16.3.2 Pulmonary embolism

In embolic pulmonary infarcts, the arrival time is delayed and the degree of enhancement is minimal [131] within the first 30 seconds after UCA administration [132]. Such a decrease in enhancement is most evident early after pulmonary embolism and progressively recovers, so that infarctions are more clearly recognisable early after their onset. Quantification of contrast enhancement using dedicated software may provide more consistent information. Pleurisy or pneumonia can be

clearly differentiated from pulmonary embolism by early and intense pulmonary artery enhancement [131–133].

16.3.3 Pulmonary carcinoma and metastasis

The value of CEUS for lung cancer is the improved delineation of viable from non-viable tissue before biopsy compared to colour Doppler US [134]. Lung tumours may behave very variably as regards contrast distribution on CEUS, but on average the time of arrival is late arterial as the arterial supply is from the bronchial system and not from pulmonary arteries [131, 132].

16.3.4 Atelectasis

In atelectasis, the CEUS pattern is similar to pneumonia with early and marked enhancement (<10 sec) followed by a plateau [132]. An underlying central tumour may be better differentiated from the atelectasis by late enhancement [134].

Recommended uses and applications (applicable only to peripheral lesions visible on US)

1. CEUS is useful in differentiating inflammatory from embolic lung consolidation, especially in patients with equivocal CT findings. (Recommendation Level B;2b)
2. CEUS may be used in equivocal cases to diagnose lung abscesses within pneumonia, since CEUS appears better than conventional B-mode US or X-ray. (Recommendation Level C;5)

17. Vascular



17.1 Background

There are two major extracerebral vascular systems with common indications for CEUS. One is the cervical carotid artery and the other the abdominal aorta. Conventional US techniques are limited in demonstrating slow flow, especially in small vessels such as vasa vasorum or collaterals and flow in critical stenoses. UCAs help to overcome some of these limitations and might be used also in other extracerebral vascular districts, but such usage is less well established and is not reported herein.

17.2 Study Procedures

As for conventional investigations, CEUS of the carotid artery is carried out with linear probes working in the range of 5–10 MHz and the abdominal aorta with convex probes at 2.5–5 MHz.

17.3 Carotid artery

17.3.1 Stenosis

Duplex US is the first line imaging modality for suspected carotid artery disease [135–138]. CEUS improves the sensitivity of Doppler US and can be used for distinguishing occlusion from tight sub-occlusive stenosis, even with conventional US equipment. However, when a contrast-specific modality is available, low MI CEUS can be utilised to further improve the delineation of the endovascular border in difficult cases, making it possible to detect the shape of pre-stenotic, intra-stenotic and post-stenotic segments, especially in elongated vessels [139, 140]. This is also facilitated by the fact that high velocity and low-velocity flow phenomena are registered at the same time with CEUS without aliasing and blooming artefacts and without any angle dependence, which all affect Doppler US

[139, 140]. However, CEUS does not provide flow information, which may still be obtained by Doppler US, potentially facilitated by contrast injection. Plaque ulceration can be imaged using CEUS [141].

17.3.2 Follow-up after carotid stenting

CEUS is a reliable method for evaluating re-stenosis after internal carotid artery stenting [142]. CEUS has fewer intrastenotic flow artefacts compared to colour and power Doppler US, resulting in better visualisation and detection of the complete length and morphology of the stenosis [142].

17.3.3 Dissection

The pathognomonic imaging findings are mural haematomas and the depiction of a true and false lumen and small flaps. Blood flow is usually decreased in the false lumen [143], increasing the risk of thrombosis, eventually resulting in complete occlusion or emboli [144]. MRI is the reference standard in the diagnosis of cervical vessel dissections; when it is contraindicated, the diagnostic accuracy of US examinations can be improved by the use of CEUS [139, 140].

17.3.4 Complications after vascular intervention

Due to aliasing artefacts, correct visualisation of post-surgical fistula tracks can be difficult using conventional colour Doppler US. However, with CEUS, fistula tracks can be detected without aliasing or overwriting artefacts [145]. Additionally, CEUS may help to image flow in false aneurysms with greater precision than colour Doppler US.

17.3.5 Plaque characterisation

The most widely accepted predictor of stroke risk is the degree of carotid stenosis. However, other imaging features are becoming recognised as significant factors [146]. Plaque neovascularisation demonstrated by CEUS correlates well with histological findings [147, 148] and is a potential additional predictor of cerebral ischaemic events, best assessed by quantification software [141, 147–150], but any role in daily clinical practice is still to be demonstrated.

17.4 Abdominal aortic aneurysm (AAA)

CEUS can overcome some limitations of conventional US by improving the delineation of the aortic lumen and the detection of the main branching arteries. CEUS also improves the diagnosis of aortic rupture by detecting contrast extravasation [151].

17.4.1 Aortic dissections

Usually dissection of the abdominal aorta is an extension of thoracic aortic dissection [151]. Up to 38% of aortic dissections are missed on initial imaging examination and up to 28% of aortic dissections remain undetected until autopsy [152–155]. In most cases, the true and false lumen can be discriminated with CEUS, because both early (true lumen) and late (false lumen) contrast enhancement can be detected, provided the false lumen is not thrombosed [153, 155]. Vascular complications such as renal or splenic infarction can be evaluated [139].

17.4.2 Inflammatory Abdominal Aortic Aneurysm

Inflammatory aneurysm of the abdominal aorta is a variant of atherosclerotic aneurysm that is characterized by inflammatory and/or fibrotic changes in the periaortic regions of the

retroperitoneum [156, 157]. The triad of a thickened aneurysmal wall, extensive perianeurysmal and retroperitoneal fibrosis, with adhesions to adjacent abdominal organs, should suggest this diagnosis [158–160]. Contrast enhancement in the inflammatory aneurysm improves differentiation between covered aortic rupture and inflammatory aneurysm [161].

17.4.3 Endoleaks

Early and midterm results of endovascular repair of AAA are promising but long-term durability and outcomes of this technique are still unclear. Endoleaks represent blood flow outside the stent graft lumen but within the aneurysm sac and are conventionally detected by CT angiography, which however, does not allow detection of some types of endoleak [162]. Several authors have pointed out the usefulness of CEUS because it seems to identify and characterise endoleaks better than CT angiography, with analysis of velocity and flow direction [163–169]. CEUS enhancement quantification by TIC provides additional accuracy [168]. Once an aortic endoleak has been detected, CEUS can be used for the follow-up of patients [170].

17.5 Limitations

Limitations in the CEUS exploration of the carotid artery and abdominal aorta are any conditions which prevent adequate US penetration and which also limit conventional B-mode US exploration. Of particular regard are extensive wall calcification and subcutaneous emphysema after intervention or limited examination windows.

Recommended uses and indications

CEUS is recommended for the following indications:

1. Differentiation between total carotid occlusion and residual flow in tight stenoses by contrast enhanced Doppler or CEUS. (Recommendation Level: B;3)
2. Improvement of lumen delineation in technically difficult carotid arteries (contrast enhanced Doppler US can also provide useful information). (Recommendation Level: B;3)
3. Evaluation of carotid plaque neovascularisation. (Recommendation Level: B;1b)
4. Improving the detection of dissection of the common and internal carotid arteries, vertebral artery and aorta. (Recommendation Level: C;3)
5. Detection of aortic wall rupture. (Recommendation Level: B;3)
6. As an additional tool in the characterisation of suspected inflammatory AAA. (Recommendation Level: C;5)
7. Detection and characterisation of endoleaks after AAA repair. (Recommendation Level: A;1a)
8. Follow-up of AAA endoleaks. (Recommendation Level: A;1a)

18. Cerebral Vessels



18.1 Background

The major indication for CEUS in the examination of cerebral arteries is the poor signal-to-noise ratio using unenhanced Doppler US, which can prevent measurement of the Doppler traces for distinguishing no flow, slow flow or low flow [171]. Contrast enhanced transcranial colour-coded duplex sonography (CE-TCCS) is the best modality for simultaneously depicting B-mode brain anatomy as well as vessel detection and flow tracings.

18.2 Study procedures

Transducers for CEUS are the same as for CE-TCCS, namely sector 1.5–4 MHz probes. There are two applications using UCAs: main vessel, i.e. vascular imaging, and “perfusion imaging”. For vascular imaging, UCAs are utilised to enhance Doppler signals in transtemporal or transnuchal transverse axial planes (insonation depth 10–12 cm). Coronal transtemporal planes may also be used. In order to obtain adequate information, some technical artefacts should be considered: 1) bolus injection may cause blooming artefacts preventing accurate Doppler spectral measurements. This artefact can be reduced by reducing the total gain or by slow infusion of the UCA (1–2 mL SonoVue®/minute). 2) UCA injection leads to an artificial increase (15–36%) in maximum blood flow velocity [172]. This may affect velocity criteria in the classification of stenoses. In perfusion imaging, either low or high MI CEUS is performed with transtemporal insonation in the axial plane with an insonation depth of 10 to 15 cm. Other insonation planes may also be used.

18.3 Main intracerebral vessel imaging: interpretation and evaluation

18.3.1 Vascular imaging

Most importantly, CE-TCCS is used to differentiate vessel occlusion in poor insonation conditions, and to detect of very slow blood flow velocities and low flow volumes (small vessels, vessel pseudo-occlusion). The Doppler spectrum adds haemodynamic information to the anatomical information provided by colour Doppler US.

18.3.2 Examination of the anterior circulation

A poor temporal bone window, as seen in up to 45% of elderly patients, can usually be overcome with CE-TCCS. In over 85% of such cases the basal arteries of the circle of Willis can be depicted satisfactorily after UCA administration [173]. According to expert opinion, CEUS with SonoVue® infusion can be used in patients with poor acoustic windows for transcranial Doppler monitoring to test cerebral autoregulation as well as language lateralisation for surgical planning.

18.3.3 Examination of the posterior circulation

CE-TCCS through the foramen magnum can increase the depth at which the intracranial vertebral arteries, the basilar artery, and the cerebellar artery segments can be identified and thus improve diagnostic confidence [172].

18.3.4. UCAs in patients with internal carotid artery stenosis

Characterisation of flow in the circle of Willis in patients with internal carotid artery stenosis and poor bone windows is important for estimating the risk of ipsilateral border zone infarction. Patients without collateral flow are particularly vulnerable to cross-clamping during carotid endarterectomy. The use of UCA in these patients can provide valuable information for patient management [174].

18.3.5 UCAs in stroke patients

In acute stroke, the basal cerebral arteries can only be detected in 55–80% of cases with unenhanced TCCS. Fortunately, reliable diagnoses can be obtained in more than 85% of these patients after contrast enhancement, with correlative findings on angiography (MR, CTA or conventional angiography) in over 95% of cases [171].

18.4 Perfusion imaging

CEUS is performed with transtemporal insonation in the axial plane with an insonation depth of 10 to 15 cm in perfusion imaging. Other insonation planes may also be used. CEUS perfusion imaging has been shown to improve prognostic assessment in the acute phase and to provide comparable results to CT [175, 176] and MRI [177]. After bolus injection, TICs can be generated to extract features (time to peak intensity, peak intensity, area under the curve, etc.) that describe the perfusion characteristics quantitatively in standardised regions of interest [171, 178].

18.5 Limitations

Despite UCA administration, only the proximal basilar artery can be evaluated. The distal portion can be depicted transtemporally, leaving the middle portion as a diagnostic gap for CE-TCCS. The quality of transtemporal precontrast scans is strongly predictive of the potential diagnostic benefit from the administration of an UCA. In patients without visible intracranial structures and vessels on conventional B-mode and colour Doppler US, there is little chance that CEUS will provide satisfactory diagnostic information.

The combination of systemic thrombolysis and repeated administration of a UCA over an hour in patients with middle cerebral artery occlusion accelerates recanalisation but also increases haemorrhage into the infarct [179]. While of greatest interest as a way to enhance therapy (which has not yet been fully evaluated) this is a potential risk when repeated CEUS studies are performed.

The clinical value of the quantification of enhancement is limited by both physical and technical factors. Up to now, they can only reliably characterise the absence of enhancement rather than the exact degree of blood supply impairment.

Recommended uses and indications

1. Contrast enhanced transcranial colour duplex sonography can be diagnostic in patients with unsatisfactory intracerebral information with non-enhanced transcranial colour duplex sonography. (Recommendation Level: A:1b).
2. CEUS perfusion imaging based on quantification of brain enhancement provides prognostic information in acute stroke. (Recommendation Level: C:4).

19 Inflammatory Joint Diseases



19.1 Background

Colour/power Doppler US can detect the vascularity in synovial proliferation reflecting inflammatory activity. However, these techniques have limited sensitivity and they benefit from the addition of UCAs.

19.2. Study procedure

Reports on the use of UCAs in inflammatory joint disease are mainly about the enhancement of signals detected by conventional colour/power Doppler US (CE Doppler US), rather than by using low MI CEUS. The standard probes and equipment used for the second level investigation of joints are also utilised for CEUS.

19.3 Image interpretation

19.3.1 Arthritis and synovitis

Microscopic examination of synovial biopsies shows angiogenesis from the earliest stages of inflammatory disease. Proliferation of hypervascularised pannus can be detected before joint destruction. It correlates with disease activity and appears to be crucial to its invasive and destructive behaviour [180]. Moreover, the development of novel biological therapies (e.g. tumour necrosis factor-alpha inhibitors), which target the microvasculature, have created a demand for more sensitive vascular imaging in order to assess response to treatment [180–184]. The addition of UCAs to Doppler US significantly improves the detection of vascularity in active rheumatoid arthritis [185, 186]. Following CE Doppler US, therapy was modified in up to 24% of patients in a dedicated study [185]. There is also evidence that CE power Doppler US helps to differentiate between active and inactive disease in subclinical juvenile rheumatoid arthritis of the knee [187]. CE Doppler US correlates with the findings of CEMRI, indicating the degree of inflammation in patients with synovitis [188]. CE Doppler US is also more useful in the diagnosis of sacro-iliitis than conventional unenhanced Doppler US [182, 189]. Overall, improved diagnostic accuracy in assessing the degree of inflammation can be achieved by the addition of UCA in large and small joints.

19.3.2. Differentiation between synovial pannus and fluid

MRI studies have demonstrated that the presence and amount of synovitis is a prognostic factor for bone damage [190]: no bone damage occurs in joints without synovitis. Therefore, early detection of vascularised synovia is a primary goal in assessment of inflammation. CE Doppler US improves the differentiation between active synovitis and other articular thickenings such as fibrotic pannus and articular fluid [191, 192].

19.3.3. Bursae and tendons

Contrast administration can highlight peripheral enhancement on Doppler US corresponding to the vascularised synovial lining of an inflamed bursa and can better differentiate between fluid, fibrous and hypervascular synovial thickening in comparison to non-enhanced Doppler US [193, 194].

19.3.4 Therapeutic follow-up

Successful treatment results in a decrease in synovial thickening and necrosis of the pannus with reduction of vascularity and thus of Doppler signals. The distinction between fibrous pannus and active synovial proliferation is one of the most important questions during follow-up, because the volume of the synovium itself is not clinically significant, as it may contain varying amounts of fibrous tissue [190]. On unenhanced power Doppler US, fibrotic pannus shows no vascularity as also after addition of UCA into fibrotic pannus shows no vascularity, as it also does after the addition of UCA and, with CEUS, lacks enhancement [195–199].

Recommended uses and indications

Contrast enhanced colour/power Doppler US:

1. Can be utilised for further assessment of the degree of vascularisation in joints of patients with rheumatoid arthritis. (Recommendation Level: C;2b)
2. Repeat contrast enhanced Doppler US may provide useful information on the response to treatment, to guide therapeutic

strategy. The technique has the potential to be utilised within dedicated centres using standardised methodology. (Recommendation Level: C;2b)

20. Intracavitary Uses



20.1. Introduction

Reports on numerous off-label extravascular or intracavitary administrations of SonoVue® have been published and those considered of more general use and most consistent are reported. Other potential applications have been occasionally described as case reports and congress abstracts.

20.2. Study procedure

To date, no standard dosage of UCA has been established for intracavitary injection. The reported range is 0.1 mL–1 mL SonoVue® (most commonly just a few drops) diluted in 10 mL or more of 0.9% saline; a higher content of SonoVue® may be needed for high frequency US probes.

20.3 Injection into Physiological Cavities

20.3.1 Voiding US for vesicoureteral reflux

This topic is described in section 13.4.

20.3.2 Imaging of tubal patency – contrast enhanced hystero-salpingo-contrast-sonography (CE-HyCoSy)

Originally performed using shaken saline infused into the uterine cavity, hystero-salpingo-sonography suffers from a false negative rate of patency of about 12% [200]. CEUS with SonoVue® provides better results [200–202] with higher specificity, but the positive predictive value for the diagnosis of “occluded tube” remains low [200]. The high negative predictive value of conventional hystero-salpingo-contrast-sonography leads authors to suggest performing contrast enhanced hystero-salpingo-contrast-sonography only if conventional hystero-salpingo-contrast-sonography does not show patency.

20.3.3 Detection of peritoneo-pleural communication for the diagnosis of hepatic hydrothorax

The detection of direct communication between the abdominal and pleural cavities is the main indication reported so far [203, 204]. Confirmation of the suspected diagnosis of hepatic hydrothorax can be established in cirrhotic patients by injecting SonoVue® into the peritoneal cavity, at best early (<2 days) after thoracentesis and demonstrating its passage into the pleural cavity.

20.3.4 Bile ducts

CEUS-guided percutaneous cholangiography was first described in 2009 [205]. A later case report on UCA injection into a surgically placed T-tube followed [206]. It is expert opinion that the advantage of CEUS-guided percutaneous cholangiography and drainage is that external drainage for biliary obstruction in patients with severe cholangiosepsis can be performed in the intensive care unit without X-ray guidance. UCA for endoscopic retrograde cholangiography has been reported [207].

20.3.5 Salivary glands

UCA injected into the main duct of a salivary gland could become a supplementary diagnostic method added to sialogra-

phy to classify obstructive diseases of the salivary glands. The salivary gland is cannulated with appropriate dilators and the plastic tube of a peripheral vein catheter is inserted [208].

20.4 Injection into Non-Physiological Cavities

20.4.1 CEUS for imaging of fistula

CEUS detection and classification of fistulas, whatever the initial disease, has been proven to be effective. The following conditions have been reported: rectovaginal fistulas via a transvaginal approach [77], vesicointestinal fistulas via a trans-abdominal approach [209] and anal fistulas via the transrectal approach [210].

20.5 Other intracavitary indications for CEUS

In principle, UCAs can be instilled into any sonographically accessible physiological or pathological body cavity to assess morphology of the cavity and potential communications with adjacent structures or organs. Clinical applications include: abscesses, pancreatic pseudocysts and other complications of pancreatitis, intestinal and other fistulas, gastro-oesophageal reflux, gastric lumen and intestinal stenoses.

Recommended uses and indications

No definite recommendation can be made for these indications. Use of CEUS must be decided on a case-by-case basis, usually resorting to CEUS because of inconclusive standard diagnostic techniques or when patients are not suitable for these or because they have higher risks (for instance, use of ionizing radiation on sensitive organs, or moving the patient out of intensive care units) or more complex logistic situations.

21 Lymph Nodes

21.1 Background

The differential diagnosis of superficial lymphadenopathy in cancer patients has been the object of various studies with high-resolution US. Their shape, appearance and vascular pattern have been analysed to discriminate benign from malignant nodes, with a wide range of sensitivities and specificities [211, 212]. CEUS has been shown to increase the accuracy of the analysis of the vascular pattern (angioarchitecture) [213]. Contrast enhanced investigations were first performed with high MI US using Doppler and later with low MI CEUS.

21.2 Study procedure

The same probes as for conventional B-mode US are utilised but with contrast-specific modalities and a full vial of SonoVue®, as for other superficial applications.

21.3 Image interpretation and differential diagnosis of benign and malignant lymph nodes

Demonstration of malignant neovascularisation, seen as vessels penetrating the node's capsule away from the hilum, has been used in most reports as the characteristic feature of metastatic lymph nodes. Confirmation of the reactive nature of lymph nodes relies on their preserved morphology and vascular anatomy, with a single vascular pedicle at the hilum containing arteries and veins vessels, regularly branching towards the periphery of the lymph node. Display of vascular anatomy can be facilitated by the addition of UCAs during colour Doppler US. Conventional CEUS using low MI can improve on the results

of Doppler US with a sensitivity, specificity and accuracy rate of up to 84%, 79% and 80% [214–223].

However, the US study of lymph node vascularisation has limitations. Most studies were made in special clinical settings (known head and neck or gynaecologic cancer). Vessel distribution analysis is usually satisfactorily informative if the whole lymph node is involved. This is not always the case, because of the possibility of focal cancer metastases or necrosis. Lymphoma must be considered separately because there is evidence that the vascular pattern of lymphoma lymph nodes resembles that of non-malignant nodes [224, 225].

21.4 Sentinel lymph nodes

CEUS can be used for detecting sentinel lymph nodes in cancer patients. One mL of SonoVue® is injected subcutaneously near the tumour site and the enhanced lymphatics are traced to the sentinel node [226–231]. Initial experiences indicate that the method is not toxic and performs as well as the blue dye or radioisotope methods [231].

Recommended uses and indications

1. CEUS appears to be capable of discriminating benign from malignant superficial lymph nodes only in special clinical settings. Therefore, despite some positive publications, it is the opinion of the experts that CEUS is not recommended for routine discrimination of benign from malignant lymph nodes. (Recommendation Level: C;5)
2. CEUS with subcutaneous injection of contrast agent to identify the sentinel lymph node is a field of ongoing research and can therefore not be recommended for clinical practice to date. (Recommendation Level: C;5)

22. Tumour Response Assessment

22.1 Background

The advent of novel therapies targeting tumour angiogenesis and vascularity has highlighted the need for accurate and reproducible quantitative techniques to assess early changes in tumour vascularity [232]. However, as these therapies are predominantly cytostatic, current response assessment which is based on interval evaluation of the tumour size using the *Response Evaluation Criteria In Solid Tumours* (RECIST) [233] is inadequate as it reflects only late changes and is unable to identify non-responders at an early time-point [234].

22.2 Study procedure

Dynamic contrast enhanced US (DCE-US) can be performed using two different approaches with different results and evidence produced so far:

- (a) bolus injection of UCA with TIC analysis; single plane imaging is usually performed at 10–20 frames per second for the duration of the enhancement. The average intensity within a region of interest (ROI) can be displayed as a function of time, i.e. a TIC which describes the wash-in and wash-out of the UCA in the ROI [235]. In addition, a second ROI can be placed in a reference tissue for comparison purposes [236]. The majority of clinical studies to date are based on this method.
- (b) intravenous infusion of UCA with disruption-replenishment analysis. The UCA is administered using a pump or drip over 5 to 20 minutes. UCA is first imaged without being disrupted at a low MI, then the MI is increased for a few frames, causing

bubble disruption. Immediately after that, the MI is returned to the non-disrupting level to observe the replenishment of the microbubbles into the ROI. Various models describe the echo-signal dynamics during the UCA-replenishment phase, which can be used for flow analysis [237].

Initially monitoring for tumour response with UCAs relied on qualitative analyses [238], but new methodologies have been developed to produce more robust and semi-quantitative indices. Analyses of the TIC, including wash-in and wash-out times, can be performed with curve fitting to determine functional indices [239]. The main indices include: peak intensity (PI); area under the curve (AUC); area under the wash-in (AUWI); area under the wash-out (AUWO; all corresponding to blood volume); time to peak intensity (TPI); slope of the wash-in (SWI; both corresponding to blood flow); and mean transit time (MTT). No permeability information can be obtained because of the pure blood pool nature of microbubbles. A more extensive EFSUMB introduction to quantitative enhancement indices is being prepared.

22.3 Clinical application of DCE-US

Early clinical trials employed qualitative analysis in the assessment of the response of different tumours such as gastrointestinal stromal tumour (GIST) or renal cell carcinoma [240–243]. More recently, there have been studies using semi-quantitative techniques with UCA bolus injection in renal cell carcinoma, hepatocellular carcinoma (HCC) and GIST [244–246]. Studies from the French group showed that two indices representing blood volume correlated with the RECIST response. For one study on renal cell carcinoma the authors demonstrated a correlation of such indices with Progression Free Survival and Overall Survival [244]. The same results could not be reproduced in a Canadian study using the disruption-replenishment technique tested versus Progression Free Survival assessed by the RECIST method [237].

A French multicentre study of various types of tumours, approximately half of which were located outside the liver (including more than 400 patients), such as metastatic renal cell carcinoma, GIST, colon cancer, melanoma, breast cancer and HCC, treated with anti-angiogenic therapies has been running, but not yet reported in its complete form. The preliminary results found that the AUC is one of the features correlated to response at 6 months in good and poor responders [247], but the full results of the data set are not yet available. There is now emerging evidence that DCE-US may be used with appropriate tools to differentiate between responders and non-responders at an earlier stage than conventional methods and this potentially allows tailoring of the treatment regimen, particularly changing treatment for non-responders. DCE-US has been endorsed by the European Medical Oncology Society to assess response under biological therapy for GIST [248].

Recommended uses and indications

1. DCE-US can be utilised to assess response to biologic therapy in metastatic GIST and other metastatic tumours, e.g. renal cell carcinoma, in dedicated centres with appropriate software for contrast signal quantification. (Recommendation Level: A;1b)

23. Breast



The application of CEUS to the differential diagnosis of breast masses was one of the first [249] and the initial results were very encouraging. Sadly, this early promise has not been fulfilled, despite numerous studies using modern methods [250] (summarised in [251]) including temporal accumulation methods (microvascular imaging) [252]. No specific pattern indicating malignancy has been identified. Thus, CEUS of the breast remains an important topic for research but cannot be recommended for routine clinical use. Among the different fields of research, that on contrast quantification appears the most promising [253].

24. Adrenal Glands



So far, no CEUS criteria that can reliably differentiate between benign (endocrine tumours and adenomas) and malignant adrenal masses are known and indeed, the specificity of CEUS in the diagnosis of malignant adrenal masses was reported to be below 70% [254]. Malignant adrenal tumours may infiltrate and occlude the adrenal vein. The vascularity of a tumour thrombus can be shown by UCA and thus its character be demonstrated.

CEUS may demonstrate characteristic hypervascularity of some adrenal gland tumours, e.g. pheochromocytoma, which typically also have necrotic regions with no contrast enhancement [255].

25 Emerging Perspectives and Potential Future Applications for CEUS



25A. Obstetrics and Gynaecology

25A.1 Obstetrics

The use of UCAs in obstetrics is not indicated because of lack of testing and underlying fears of toxicity. There is older literature in humans on the topic but none that is recent in animal models. It is unknown whether the microbubbles pass through the placenta, though this seems unlikely. CEUS to assess a pregnant mother should be balanced against the risk of other modalities. The opportunities seem very limited and the subject is not considered further here.

25A.2 Gynaecology

25A.2.1 Uterus

Research has included uterine and cervical tumours [256], flow differences between endometrial polyps and cancer [257], and CEUS during uterine artery embolisation to treat leiomyomas [258]. So far, no prospective trials confirm the value of CEUS to assess uterine tumours and thus there is no proven clinical indication for its use in examining the endometrium or the myometrium.

25A.2.2 Adnexa

Differentiation of benign from malignant adnexal masses was attempted by visual assessment of contrast distribution and by quantification of enhanced Doppler signals but, despite some difference in average values for some variables, no feature with sufficient clinical potential was obtained [259].

By using CEUS it was demonstrated that adnexal masses without internal enhancement are invariably benign, and this feature was detected with high intra- and interobserver reproducibility [258], but the presence of enhancement is not a specific sign of malignancy [256]. CEUS does not greatly improve the accuracy of colour Doppler US for the diagnosis of malignancy in adnexal masses [260]. A large multicentre study on the diagnosis of malignancy in adnexal masses, including quantitative CEUS features, confirmed that CEUS is not superior to conventional US, despite being statistically more accurate [260]. Both also have difficulty in distinguishing between benign and borderline tumours.

At present, there are no recommended gynaecological clinical indications for the use of CEUS, despite the finding that absence of any enhancement in adnexal masses corresponds to benign lesions. (Recommendation Level: A;2b).

25B. Perineum

CE perineal US is an effective, easily available but so far not well known diagnostic tool. Perineal US is particularly useful if clinical examination, endorectal US or MRI with endorectal coils cannot be performed (e.g., due to severe pain when introducing the probe). CE perineal US requires good knowledge of the anatomy of the pelvic floor and the sphincters. No patient preparation is required. The location of inflammatory and neoplastic lesions should be described in relation to the sphincter apparatus. Fistulas can be further differentiated by US examination into intersphincteric, transsphincteric and extrasphincteric forms. Conventional B-mode perineal US is inadequate for complex fistulas, as its sensitivity for the complex branching structure is poor. However, discrimination of fistulas and abscesses with CE perineal US is possible in most cases, but studies have not been published so far. Additionally, the extent of a fistula can be imaged by instillation of UCA into its external ostium. CE Doppler US has shown a higher resistance index (RI) in neoplasia compared to inflammation, but further studies are needed.

25C. Urinary Bladder

25C.1 Background

In patients with urinary bladder tumours, noninvasive diagnostic imaging may play a role, even though it cannot replace cystoscopy and pathologic staging. The depth of wall invasion, as well as the histological grade and the extension outside the bladder are the three main factors determining prognosis and therapeutic approach.

25C.2 Study procedure

Optimal bladder filling (approximately two thirds of the total bladder volume) is critical [261]. Insufficient filling prevents lesion detection, while excessive distension results in bladder wall thinning and reduced conspicuity of the wall layer and may make it more difficult to differentiate a superficial tumour from an infiltrating lesion.

The layers of the bladder wall can be differentiated after microbubble injection. The mucosa, and especially the submucosal layer, exhibit early and intense enhancement that persists for 1–2 minutes. The muscular layer has lesser and delayed enhancement [261].

25C.3 Image interpretation

25C.3.1 Characterisation of mural masses

CEUS improves the differential diagnosis of intraluminal echoic masses, allowing the detection of tumours, which are vascularised and thus enhance [262], while clots do not enhance [263]. In a group of 35 patients in whom cystoscopic biopsy was the reference standard, CEUS correctly assessed the presence or absence of tumour in 88% of cases [263].

25C.3.2 Bladder tumour staging

CEUS is superior to conventional B-mode US in identifying infiltration of the muscle layer [261], but MRI and CT are the imaging modalities of choice for local staging of bladder tumours. Attempts to predict tumour grading by the pattern of CEUS enhancement is still a research topic [262].

25C.4 Limitations

Similarly to other imaging modalities, the most important limitation of CEUS in bladder tumour detection is the difficulty in identifying subcentimetre lesions. Flat, plaque-like tumours may also be difficult to detect, even when large. Tumour position can affect the quality of depiction at CEUS, and therefore the accuracy of staging. Tumours in the anterior portion of the bladder dome are sometimes difficult to visualise. Columnar hypertrophy of the bladder wall associated with benign prostatic hypertrophy can hide or mimic urothelial polypoid projections, as well as prostate hypertrophy itself [261]. Benign tumours and focal cystitis are other uncommon conditions that present with focal bladder wall enhancement and can mimic a malignant lesion. Finally, CEUS is not panoramic as CT and MR are.

To summarize, the most useful application of CEUS is the differential diagnosis of bladder cancer from clots in patients with haematuria when the diagnosis is equivocal on conventional B-mode and Doppler US. (Recommendation Level: C;2b). In patients with anatomical situations leading to poor urinary bladder visualisation, CEUS often does not provide the desired information. (Recommendation Level: X;5).

25D. Transplanted Kidney

Progressive vascular remodelling in the transplanted kidney, from a variety of mechanisms, compromises renal perfusion and accounts for the majority of allograft failures. CEUS has the potential to investigate perfusion abnormalities in renal transplants and to obtain information on blood flow based on the quantification of contrast enhancement or on the depiction of devascularised regions (the latter with the same significance as in native kidneys, so that CEUS use for this indication can be considered as established also in transplanted kidneys). Different quantitative features have been assessed, all related to impaired parenchymal perfusion (e.g. longer time to peak, lower wash-in slopes, longer mean-transit time) and associated with a worse prognosis of graft function and survival [264].

Although these preliminary results are promising, further studies are needed to assess whether detecting haemodynamic changes in renal grafts affects the management of patients with poorly functioning transplants; consequently the quantification of CEUS is still considered a research field in transplant assessment.

25E. Prostate Cancer

Conventional B-mode and Doppler transrectal US imaging have a limited role in the detection of prostate cancer because of poor sensitivity and specificity (approximately 50–60%). However, there is a correlation between microvascular density and the presence of prostate cancer, its stage and survival. Therefore, attempts were made with CE transrectal US with colour-Doppler to improve the detection of additional cancer nodules; with this modality the detection rate of targeted biopsies increased by almost 50% compared to systematic biopsies in some studies [265, 266]. Low MI transrectal CEUS became available only recently when contrast specific modalities were implemented on endocavitary probes. Preliminary single centre results appeared to confirm the findings of CE Doppler US, despite the lack of specificity of enhancing areas and of any other pattern [267–269]. The evidence achieved so far with CEUS modalities is, however, still too limited and not sufficiently confirmed in clinical practice in other centres, so that the role of CEUS in prostate cancer should still be considered a research topic, with hopes of improvements as new techniques are becoming available, such as 4D contrast enhanced transrectal US imaging.

25F. Aorto-Caval Fistula

Perioperative mortality of abdominal aortal aneurysms complicated by aorto-caval fistulas undergoing open surgery is up to 60% and the additional retroperitoneal rupture of the aneurysm considerably raises the mortality [270]. The diagnosis can be made by noninvasive testing, such as US scanning, including CEUS, which improves visualisation of the fistula track and of the number of fistulas, avoiding the aliasing or the overwriting artefacts typical of Doppler US.

25.G Free Tissue Transplants

25G.1. Background

Free flap reconstruction of complex defects after trauma, tumour resection, burns, or wound healing disturbances has revolutionized plastic, reconstructive, and microsurgery, giving the unprecedented potential to provide form, function, and volume for defects in every body region. However, despite refinements in this technique over the last several decades that have resulted in a decreased rate of flap loss of less than 5–10%, in general, the loss of free flaps because of vascular impairment remains a serious complication. Early identification of vascular deterioration and prompt revision could save up to 33–57% of failing flaps. CEUS offers the possibility of earlier detection [271–273].

25G.2 Study procedure

Standard doses (2.4–4.8 mL of SonoVue®) and administration methods are used together with high frequency probes (≥ 6 MHz) to evaluate the microcirculation of the cutaneous, subcutaneous, and deeper layers of free flaps. Beside the standard visual evaluation, improved diagnostic assessment is obtained by contrast specific software working on the acquired information, including the production of TIC in different tissue layers by demarcation of different ROIs to quantify enhancement (274). Postoperative TIC analysis allows calculation of peak and time to peak of enhancement and regional blood volume. Exported cine-loops allow colour-coded depiction of these features with dedicated software [275, 276].

25G.3 Image Interpretation

25G.3.1 Preoperative planning of tissue transplants

The blood vessels in the transplanted free flap are small (at most 1–2 mm). The surgeon needs to know the precise number, course and position of these blood vessels as well as the flow in order to estimate the proportion with a good blood supply.

25G.3.2 Intraoperative imaging

CEUS enables the identification of perforator vessels intra-operatively, and helps to determine if there are any abnormalities. The surgeon can thus make a more accurate decision as to whether the entire flap is perfused and if the estimated flap size is correct.

25G.3.3 Postoperative monitoring of tissue transplants

The feeding vessels or, if there is a connection to a bypass, the anastomosis, and the transplant's own vessels can also be examined even if the vessel diameter is very small. CEUS can provide valuable information about a vascular compromise (thrombosis, embolism, twisting, kinking, or compression) and demonstrate successful surgical salvage [274, 277].

25G.3.4 Critical microvascularisation of free flaps

A significant difference between normally vascularised and compromised flaps can be observed and the Time to Peak and Regional Blood Flow appear to be the most useful indices [278]. For CEUS and CEMRI, the mean signal increase of the TIC was significantly higher in ROIs of normally perfused flaps compared to compromised flaps [275, 276, 279, 280]. With CEUS, the exact size of the necrotic regions can be evaluated by analysing the entire flap. A haematoma or seroma can be detected early with CEUS, by the absent perfusion.

25G.4 Limitations

The main limitation for the evaluation of flap perfusion is the fact that CEUS does not allow for continuous monitoring after bolus injection. Continuous infusion might be a better method, but remains to be explored.

To summarise, high-resolution CEUS is promising for confirming a clinical suspicion of malperfusion of free tissue transplants as well as for determining the cause. (Recommendation Level: B;2b).

25 H. Biliary disease

25 H.1 Background

The vascular phases of the gallbladder are different from those of the liver because the blood supply is provided entirely by the cystic artery and not by portal vein branches. The arterial phase is followed by the venous phase, which is shorter than that of the liver.

25 H.2. Image interpretation

25 H.2.1 Acute cholecystitis

In acute cholecystitis, the detection or exclusion of abscess formation in the surrounding liver parenchyma is important and can be performed with CEUS, but published evidence is sparse so far. Interruption of the gallbladder wall suggests perforation, which can be confirmed by the absence of enhancement of the perforated wall.

25 H.2.2 Extrahepatic biliary tumours

The absence of enhancement in biliary sludge (whether in the gallbladder or in a dilated biliary tree) allows differentiation from a tumour, which enhances, in almost all cases using CEUS.

Gallbladder carcinomas are typically hyperenhancing in the arterial phase and hypoenhancing in the venous phase. The differentiation between benign and malignant lesions is mainly determined by clinical features and size and enlargement of polyps to >10mm is an indication for cholecystectomy. More sophisticated classification of the vascular and enhancement pattern of gallbladder lesions, including that provided by CEUS, has not been introduced so far in the clinical routine and CEUS currently has no role in differentiating benign from malignant gallbladder polyps.

The most important task of CEUS and other imaging methods is to detect infiltration of the surrounding liver parenchyma and to exclude liver metastases.

Transabdominal CEUS has no proven role when extrahepatic cholangiocarcinoma is suspected, although promising findings have been observed e.g., determining the depth of wall infiltration and surrounding tissue mainly by using CE-EUS.

Intrabiliary administration of UCA is discussed in 20.3.4.

26. Use of CEUS in Patients with Renal Failure

The use of iodinated/Gadolinium-containing contrast agents for CT and MR, respectively, potentially exposes patients with renal failure to severe complications [281, 282]. Assay of serum creatinine level and calculation of the estimated glomerular filtration rate before injection is mandatory in patients who may have impaired renal function (diabetes mellitus, age >70 years, history suggesting possible reduced eGFR, congestive heart failure, intensive diuretic treatment, dehydration, etc). Recommended guidelines to avoid contrast-induced nephrotoxicity from iodinated contrast agents [281] are available. However, none can guarantee completely successful prevention.

The risk of nephrotoxicity is very low with MRI contrast agents, even in patients with impaired renal function. However, these agents can induce nephrogenic systemic fibrosis (NSF), a rare but severe complication [282]. The risk of NSF depends upon the degree of impairment of the patient's renal function and the type of agent (stability of the Gadolinium bound to chelate).

Thus in patients with renal failure, it is recommended to consider an alternative imaging method that does not use iodinated or Gadolinium-containing contrast media. Since UCAs are not nephrotoxic (and no renal function assessment is required), CEUS should be considered in every case, especially if it offers the possibility of achieving enough diagnostic information, even with off-label CEUS uses. This is particularly the case in patients with severe renal failure, in whom CT or MRI should only be used in case of inconclusive examinations and strong clinical need.

27. Technical Appendices

The number of systems capable of CEUS imaging has increased greatly in recent years and almost all manufacturers have im-

plemented this technique in top level as well as, in many instances, in lower level machines. The technical details of the modalities which produce CEUS imaging are rapidly and continuously evolving so that any written list of information would not be complete. Accordingly, it is preferable that readers access such technical information directly from the websites of each manufacturer who supported this project. The links can be found on the EFSUMB webpage (<http://www.efsumb.org/guidelines/ceus-manufacturers-links.pdf>), but the content remains the responsibility of the respective manufacturers.

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