# CONTRAST-ENHANCED ULTRASOUND OF THE ABDOMEN INCLUDING THE KIDNEYS

*A FREE Continuing Education Monograph*


**FACULTY**

**Richard G. Barr, MD, PhD**

Professor of Radiology
Northeast Ohio Medical University
Director, Southwoods Imaging
Department of Radiology
Surgical Hospital at Southwoods
Youngstown, Ohio

**Edward G. Grant, MD, FACR**

Professor and Chairman
Department of Radiology
Keck Hospital of USC
USC Norris Comprehensive Cancer Center
University of Southern California
Los Angeles, California



This activity is jointly provided by:

MEDICAL EDUCATION RESOURCES and abc MEDICAL EDUCATION

This activity is tracked by CME tracker

This activity can be found at **www.ImagingEducation.com**, scroll to **Ultrasound**

IMAGING Education™

This activity is supported by an educational grant from Bracco Diagnostics Inc.

## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 3-D | 3-dimensional |
| ACR | American College of Radiology |
| APHE | arterial phase hyperenhancement |
| CECT | contrast-enhanced computed tomography |
| CEMRI | contrast-enhanced magnetic resonance imaging |
| CEUS | contrast-enhanced ultrasound |
| CT | computed tomography |
| EFSUMB | European Federation of Societies for Ultrasound in Medicine and Biology |
| FAST | focused assessment with sonography in trauma |
| FDA | U.S. Food and Drug Administration |
| FLL | focal liver lesion |
| GBCA | gadolinium-based contrast agent |
| GI | gastrointestinal |
| HCC | hepatocellular carcinoma |
| IBD | inflammatory bowel disease |
| LI-RADS | Liver Imaging Reporting and Data System |
| MI | mechanical index |
| MRI | magnetic resonance imaging |
| NICE | National Institute for Health and Care Excellence |
| NPV | negative predictive value |
| PPV | positive predictive value |
| UCA | ultrasound contrast agent |
| US | ultrasound |

## TARGET AUDIENCE

This activity is designed for radiologists, sonographers, emergency department physicians, radiology nurses, and other healthcare professionals to provide them with medically relevant education on the role of contrast-enhanced ultrasound (CEUS) of the abdomen in the diagnosis and therapy decision-making for diseases of the liver, pancreas, kidneys, spleen, gallbladder and biliary tree, and gastrointestinal tract.

## EDUCATIONAL OBJECTIVES

After completing this activity, participants should be better able to:

- Summarize indications, recommendations, and clinical trials demonstrating the clinical utility of CEUS of the abdomen, including the liver, pancreas, kidneys, spleen, gallbladder and biliary tree, and gastrointestinal tract
- Explain the fundamental physics of CEUS of the abdomen
- Interpret the safety, efficacy, and pharmacoeconomics of CEUS of the abdomen

## STATEMENT OF NEED/PROGRAM OVERVIEW

- Contrast-enhanced ultrasound (CEUS) of the abdomen is currently an underutilized imaging modality in the United States, although it is a well-established, noninvasive, real-time imaging technique for evaluating known or suspected abdominal pathology of the liver, pancreas, kidneys, spleen, gallbladder, and gastrointestinal tract. Ultrasound contrast agents (UCAs) act as true blood-pool tracers, providing unique, characteristic contrast washin/washout kinetics and enhancement patterns that can be used to characterize various lesions that may not be detected by other imaging modalities.
- CEUS has several advantages over contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMRI). In addition to having a lack of exposure to ionizing radiation, CEUS can be used in patients with renal and hepatic insufficiency and in pregnant women. The cost of CEUS is significantly lower than CECT and CEMRI, and CEUS is portable and thus can be performed at the bedside. Education in regard to the indications and benefits of CEUS of the abdomen is greatly needed to increase patient safety and lower healthcare resource utilization.

## ACCREDITATION FOR PHYSICIANS AND NURSES

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by Medical Education Resources (MER) and ABC Medical Education. MER is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council or Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

### Interprofessional Continuing Education (IPCE)

This activity was planned by and for the healthcare team, and learners will receive 1 Interprofessional Continuing Education (IPCE) Credit for learning and change.

### Physician Accreditation

MER designates this enduring activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Nursing Accreditation**

MER designates this enduring activity for a maximum of 1 ANCC nursing contact hour.

Nurses will be awarded 1 contact hour upon successful completion of the activity.

MER is a provider of continuing nursing education by the California Board of Registered Nursing, Provider #CEP 12299, for 1 contact hour.

## INSTRUCTIONS FOR RECEIVING CONTINUING MEDICAL EDUCATION (CME) CREDIT AND CONTINUING NURSING EDUCATION (CNE) CREDIT

**Physicians and Nurses**

**Original Release Date:** November 2020

**Re-review Date:** November 2022

**Expiration Date:** November 2024

**Physicians CME Credit:** 1 *AMA PRA Category 1 Credit*™

**Nurses CNE Credit:** 1 ANCC Contact Hour

There are no fees for participating in and receiving CME credit for this activity.

The participants must

- Study the activity in its entirety
- Complete the online posttest and evaluation at **www.ImagingEducation.com**, scroll down to **Ultrasound**
- Click on the activity ***Contrast-Enhanced Ultrasound of the Abdomen Including the Kidneys***. PDF will open
- Click on **CE Credit - Posttest** button at the top of your screen to access the posttest
- A statement of credit will be issued only upon receipt of a completed activity evaluation and a completed posttest with a score of 70% or better. A statement of credit will be issued upon completion via email

## ACCREDITATION FOR SONOGRAPHERS

Approved by the Society of Diagnostic Medical Sonography (SDMS) for 1 SDMS CME Credit. SDMS CME Credit is accepted by the American Registry for Diagnostic Medical Sonography (ARDMS), American Registry of Radiologic Technologists (ARRT), Canadian Sonography, and Cardiovascular Credentialing International (CCI) toward their continuing education requirements. The SDMS had no involvement in the development of this CME activity.

## INSTRUCTIONS FOR RECEIVING SDMS CME CREDIT

**Release Date:** February 1, 2024

**Expiration Date:** January 31, 2025

**1 SDMS CME Credit**

There are no fees for participating in and receiving CME credit for this activity.

The participants must

- Study the activity in its entirety
- Complete the online posttest at **www.ImagingEducation.com**, scroll down to **Ultrasound**
- Click on the activity ***Contrast-Enhanced Ultrasound of the Abdomen Including the Kidneys***. PDF will open
- Click on **CE Credit - Posttest** button at the top of your screen to access the posttest
- SDMS CME credit will be issued only upon receipt of a completed posttest with a score of 70% or better
- The *SDMS CME Management System* will create a SDMS CME certificate that will automatically be emailed to a participant's login email

Please contact ABC Medical Education at chris@abcmeded.com should you have any questions.

## DISCLOSURE OF CONFLICTS OF INTEREST

The ***faculty*** reported the following financial relationships with commercial interests whose products or services may be mentioned in this CME activity:

| Faculty | Reported Financial Relationship |
|---|---|
| Richard G. Barr, MD, PhD | Grant/research support from BK Ultrasound, GE Ultrasound, Philips Ultrasound, and Siemens Ultrasound. Consulting fees from Bracco Diagnostics Inc. and Lantheus Medical Imaging. Speakers' bureau for Bracco Diagnostics Inc., Lantheus Medical Imaging, and Philips Ultrasound. Royalty from Thieme Publishers. |
| Edward G. Grant, MD, FACR | Grant/research support from GE Healthcare. |

The ***content manager*** reported the following financial relationships with commercial interests whose products or services may be mentioned in this CME activity:

| Content Manager | Reported Financial Relationship |
|---|---|
| Andy Galler (ABC Medical Education) | No financial relationships to disclose. |

## DISCLAIMER

The content and views presented in this educational activity are those of the authors and do not necessarily reflect those of ABC Medical Education, and/or Bracco Diagnostics Inc. The authors have disclosed if there is any discussion of published and/or investigational uses of agents that are not indicated by the FDA in their presentations. The opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of ABC Medical Education, and/or Bracco Diagnostics Inc. Before prescribing any medicine, primary references and full prescribing information should be consulted. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities. The information presented in this activity is not meant to serve as a guideline for patient management.

## INTRODUCTION

Contrast-enhanced ultrasound (CEUS) is a well-established, noninvasive, imaging technique for evaluating the liver and other abdominal organs, providing continuous, real-time imaging with high-temporal resolution.[1,2] Ultrasound contrast agents (UCAs) are used to improve visualization and characterization of anatomic structures and lesions.[2–8] CEUS of the abdomen is most often performed transabdominally, but can also be performed endoscopically. Current abdominal applications for CEUS include imaging of the liver,[2] pancreas,[1,9,10] kidneys,[11,12] spleen,[13] hepatobiliary system,[2] and gastrointestinal (GI) tract.[5,14,15] In the liver, CEUS is particularly useful for characterization of focal lesions, monitoring radiofrequency ablation therapy, evaluating response to anti-angiogenic agents, and quantitative perfusion of lesions.[2] CEUS is also invaluable in the characterization of renal masses[16–18] and in the evaluation of inflammatory bowel disease.[14,15,19]

CEUS has several advantages over contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMRI),[1,2] including a lack of exposure to ionizing radiation; an absence of potential harmful effects on the kidney and liver, allowing its use in patients with renal failure; wider accessibility and portability (including bedside); increased cost-effectiveness compared with CT and MRI; real-time assessment of organ/lesion vascularity; and improved patient comfort. For pediatric patients, CEUS has the additional benefit that the patient does not need to be sedated. Here we review in detail the principles of CEUS, as well as the efficacy and safety of UCAs for abdominal imaging.

## UCAs

UCAs are characterized by a microsphere structure in which a gaseous core is encapsulated by a stabilizing shell.

Currently available, second-generation UCAs are 1.1–4.5 μm, gas-filled microspheres with a soluble gas (perflutren or sulfur hexafluoride) in the core and an external stabilizing shell comprised of albumin, lipid, or phospholipid[20] (**Table 1**). These UCAs are smaller than red blood cells (ie, <7 μm in diameter) and pass easily through capillary beds. Unlike CT and MRI contrast agents, UCAs behave as purely intravascular contrast agents, with no penetration into the interstitial space.[3] Because UCAs are not excreted through the kidneys, nephrotoxicity does not occur, making CEUS a good imaging option for patients with renal disease.[21] In addition, because UCAs act as a true blood-pool tracer, they provide unique, characteristic contrast washin/washout kinetics and enhancement patterns that can be used to characterize various lesions.

**Table 1.** Currently Available, FDA-Approved Ultrasound Contrast Agents[22–24]

| Name | Manufacturer | Mean Diameter | Shell | Gas | FDA-Approved Indication(s) |
|---|---|---|---|---|---|
| Definity® (perflutren lipid microsphere) | Lantheus Medical Imaging | 1.1–3.3 μm (max 20 μm; 98% <10 μm) | Lipid | Perflutren | • For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border |
| Lumason® (sulfur hexafluoride lipid-type A microspheres) | Bracco Diagnostics | 1.5–2.5 μm (max 20 μm; 99% ≤10 μm) | Phospholipid | Sulfur hexafluoride ($SF_6$) | • For use in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult patients with suboptimal echocardiograms<br>• For use in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients<br>• For use in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients |
| Optison™ (perflutren protein-type A microspheres) | GE Healthcare | 3.0–4.5 μm (max 32 μm; 95% <10 μm) | Human albumin | Perflutren | • For use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders |

Currently, 3 UCAs are approved by the U.S. Food and Drug Administration (FDA) and available for use in the United States: Optison™ (perflutren protein-type A microspheres), Definity® (perflutren lipid microsphere), and Lumason® (sulfur hexafluoride lipid-type A microspheres).[22–24] When administered intravenously and used with low mechanical index (MI) CEUS techniques, the nonlinear acoustic effects of the microspheres amplify signals from blood flow,[25] resulting in real-time, high-resolution images of both macrovasculature and microvasculature (ie, capillary beds).[2,26–28] The ability to depict microvasculature structures is particularly beneficial, as these vessels may be too small and/or have insufficient blood-flow velocity to be visualized on color or power Doppler images: Doppler ultrasound can image blood vessels as small as 100 µm, while CEUS can depict vessels as small as 40 µm.[2]

All 3 of the currently approved UCAs are approved for echocardiography use. Lumason is the only UCA with FDA approval for use in ultrasonography of the liver for characterization of focal liver lesions (FLLs) in adult and pediatric patients.[24] This approval was obtained in March 2016. More recently, in December 2016, Lumason was also approved for evaluation of vesicoureteral reflux in pediatric patients. While at the time of this writing, neither Definity nor Optison has been approved for the characterization of FLLs in adult and pediatric patients, nor for the evaluation of vesicoureteral reflux in pediatric patients, clinicians could choose to use one of these agents off-label.

## GUIDELINES FOR CEUS OF THE ABDOMEN

International guidelines for CEUS of the abdomen have evolved over time.[29] The first edition of guidelines by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) was issued in 2004.[3] This guideline was the first scientific endorsement of the clinical use of UCAs for the workup of FLLs and for evaluation of all phases of liver tumor ablation. In 2008, the second edition of guidelines was published,[4] updating the earlier guidelines and adding recommendations for applications of CEUS in kidney and urinary tract (including vesicoureteral reflux), pancreas, and abdominal trauma. These guidelines and recommendations for nonhepatic and hepatic applications of CEUS were further updated in 2011 and 2012, and new guidelines were released in 2018 for nonhepatic applications of CEUS.[2,5,30] The nonhepatic component further emphasized the inclusion of extrahepatic applications for CEUS, introducing a grading system (type/level of evidence) for each recommendation.[5] The hepatic component, a joint global effort by several scientific groups, including worldwide consensus (WFUMB [World Federation for Ultrasound in Medicine and Biology]-EFSUMB Initiative in Cooperation with Representatives of AFSUMB [Asian Federation of Societies for Ultrasound in Medicine and Biology], the AIUM [American Institute of Ultrasound in Medicine], the ASUM [Australasian Society for Ultrasound in Medicine], the FLAUS [Latin-American Federation of Societies for Ultrasound in Medicine and Biology], and ICUS [International Contrast Ultrasound Society]), provided detailed recommendations for the use of CEUS and interpretation of enhancement patterns for liver applications.[31] The American College of Radiology (ACR) Manual on Contrast Media now includes a short chapter on ultrasound contrast media.[32]

To standardize the reporting and data collection of CT and MRI for hepatocellular carcinoma (HCC), the ACR developed the Liver Imaging Reporting and Data System (LI-RADS). More recently, the ACR also published the CEUS LI-RADS.[33] Developed by a consortium of diagnostic radiologists and hepatologists with expertise in hepatobiliary ultrasound, this 27-page document provides a lexicon of controlled terminology, schematic illustrations, and a categorization algorithm for assessment of liver lesions with CEUS. **Tables 2** and **3** provide the CEUS LI-RADS–suggested imaging parameters and the indications for and advantages of CEUS for evaluation of the liver, respectively. **Table 4** provides a comparison of the different features of CEUS LI-RADS and CT/MRI LI-RADs.

### **Table 2.** CEUS LI-RADS Suggested Imaging Parameters[33]

| |
|---|
| • **Low-MI contrast agent–specific imaging modes should be used** (refer to vendor instructions and when necessary, obtain additional technical support from vendor to ensure proper system settings before undertaking CEUS studies) |
| • **Dual screen imaging with separate contrast mode and B-mode imaging is helpful to guide exams** |
| • **Use of simultaneous caliper display on both screens is ideal for observation/nodule localization** |
| • **Arterial phase and beginning of portal phase should be performed continuously and without interruption** (up to 60 seconds after contrast injection) |
| • **After 1 minute post-injection, imaging can be performed using intermittent scanning to minimize microsphere destruction** |
| • **Exam should be continued until near complete clearance of contrast to better characterize washout that is late onset and mild in degree** (~5–6 minutes after the injection) |

CEUS=contrast-enhanced ultrasound; LI-RADS=Liver Imaging Reporting and Data System; MI=mechanical index.

**Table 3.** LI-RADS Indications for and Advantages of CEUS[33]

| |
|---|
| • Assess nodules ≥10 mm detected on surveillance US |
| • Assess LR-3, LR-4, and LR-M observations detected on prior CT or MRI |
| • Detect APHE when mistiming is suspected as the reason for its absence on prior CT or MRI |
| • Assess biopsied observations with inconclusive histology |
| • Guide biopsy or treatment of observations difficult to visualize with precontrast US |
| • Help select appropriate observation(s) or observation component(s) for biopsy |
| • Monitor changes in enhancement pattern over time for selected CEUS LR-3 or CEUS LR-4 observations |
| • Differentiate tumor in vein ("tumor thrombus") from bland thrombus |

APHE=arterial phase hyperenhancement; CEUS=contrast-enhanced ultrasound; CT=computed tomography; HCC=hepatocellular carcinoma; LI-RADS=Liver Imaging Reporting and Data System; MRI=magnetic resonance imaging; US=ultrasound.

**Table 4.** Key differences between CEUS LI-RADS and CT/MRI LI-RADS[33]

| Parameters | CEUS LI-RADS v2017 | CT/MRI LI-RADS v2017 |
|---|---|---|
| Operator expertise | High expertise required | High expertise NOT required |
| Observation visibility | Precontrast visibility required | Precontrast visibility NOT required |
| Number of observations | One to few | One to many |
| Context | Diagnosis | Diagnosis, staging, response to therapy |
| Type of contrast agent | Blood pool (microsphere) | Iodinated or GBCA |
| Permitted contrast injections | One to multiple (if needed) | Usually only one |
| Size thresholds for APHE | <10 mm, ≥10 mm | <10 mm, 10–19 mm, ≥20 mm |
| APHE | High temporal resolution | Single or a few time points |
| Washout phenomenon | Washout is true washout | Washout may be apparent, not true washout |
| Washout characterization | Onset and degree are critical | Onset and degree are NOT critical |
| "Capsule": type of feature | Not a CEUS feature | Major feature |
| Growth: type of feature | Ancillary feature | Major feature (if exceeds threshold) |
| Number of ancillary features | Few | Many |

APHE=arterial phase hyperenhancement; CEUS=contrast-enhanced ultrasound; CT=computed tomography; GBCA=gadolinium-based contrast agent; LI-RADS=Liver Imaging Reporting and Data System; MRI=magnetic resonance imaging.

## CEUS OF THE ABDOMEN IN CLINICAL PRACTICE

### Liver

*Characterization of FLLs*

CEUS of the liver is primarily for the characterization of FLLs. FLL characterization using CEUS is based on real-time evaluation of contrast enhancement of the lesion (hypoenhancing, isoenhancing, hyperenhancing) versus the surrounding liver parenchyma,[34] as assessed during the arterial, portal-venous, and late phases. The 2012 WFUMB-EFSUMB guidelines recommend the following steps and suggestions[2]:

1. The examination should start with conventional B-mode and Doppler techniques
2. After identification of the target lesion, the transducer is held still while the scanner is switched to low-MI contrast-specific imaging
3. Use of the dual screen format showing a low-MI B-mode image alongside the contrast-only display aids anatomic guidance
4. Contrast is administered as a bolus injection followed by a flush with normal saline 0.9%
5. A timer should be started at the time of UCA injection
6. Because of the dynamic nature of real-time CEUS, essential clips for each vascular phase should be recorded
7. Assessment of the arterial and portal-venous phases should be carried out without interruption
8. For the late phase, intermittent scanning may be used until the disappearance of contrast from the liver's microvasculature
9. Injection of contrast can be repeated when a lesion has been detected in the portal-venous phase or in the late phase to study the arterial phase, and in the case of multiple FLLs. Reinjection should be delayed until most microbubbles have vanished and the CEUS screen is almost black again

Typical contrast enhancement patterns for common benign and malignant lesions in the arterial and portal-venous/late phases are shown in **Figure** 1.[2,35–37]

Solid benign lesions tend to be isoenhancing or hyperenhancing relative to the surrounding parenchyma in the arterial phase. Specifically, for hemangiomas,[38–40] the most common findings on CEUS are peripheral nodular enhancement in the arterial phase, followed by partial or complete centripetal fill-in (**Figure 2**). Focal nodular hyperplasia[20] is hyperenhancing in the arterial and portal-venous phases in more than 90% of cases, with a central vascular supply that is often visible when imaging. Hepatic adenomas[40–43] typically show rapid arterial hyperenhancement that progresses from the periphery to the center. Focal fatty lesions (focal fatty infiltration) may simulate neoplasia on unenhanced US[2,4] and show similar enhancement patterns to those of the adjacent liver parenchyma in all phases. The enhancement pattern of abscesses is dependent on lesion maturity[44–46]: early lesions tend to be hyperenhancing, while mature lesions develop hypo- or nonenhancing foci centrally. For hematomas,[5,47–50] CEUS is particularly helpful. These lesions will be completely or almost completely avascular with CEUS because UCAs are purely intravascular; thus, identifying hematomas is easier on CEUS than on CECT images.

Malignant lesions are characterized by their washin/washout kinetics. The timing of the washout varies with the lesion etiology. Metastatic lesions tend to have rapid (<1 min) and intense washout. HCCs tend to have delayed and less intense washout. The washout in HCC may not occur until 5 minutes. Cholangiocarcinomas tend to washout faster than HCC and have stronger washout.[51–53] The most common primary malignant lesion of the liver is HCC. In patients without cirrhosis, HCC is typically hyperenhancing in the arterial phase with a chaotic vascular pattern, and isoenhancing in portal-venous and late phases (**Figure 3**).[2,41,54,55] Several studies have shown contrast washout kinetics to be indicative of HCC histologic differentiation in patients with liver cirrhosis.[51,52,56–60] In patients with cirrhosis, the development of HCC is accompanied by decreases in both normal arterial and portal blood flow and a concurrent disappearance of normal intranodular vessels. Also concurrent with the decline in normal vascularity is a progressive increase in arterial flow from newly formed tumor vessels—neoangiogenesis. Therefore, hyperenhancement in the arterial phase can be seen in HCC and these changes are important components in the characterization of hepatocellular nodules in cirrhosis during the vascular phases of contrast enhancement.[2]

**Figure 1.** Typical vessel architecture and contrast enhancement pattern for (a) focal nodular hyperplasia; (b) hemangioma; (c) metastatic liver lesion; and (d) hepatocellular carcinoma.[37]

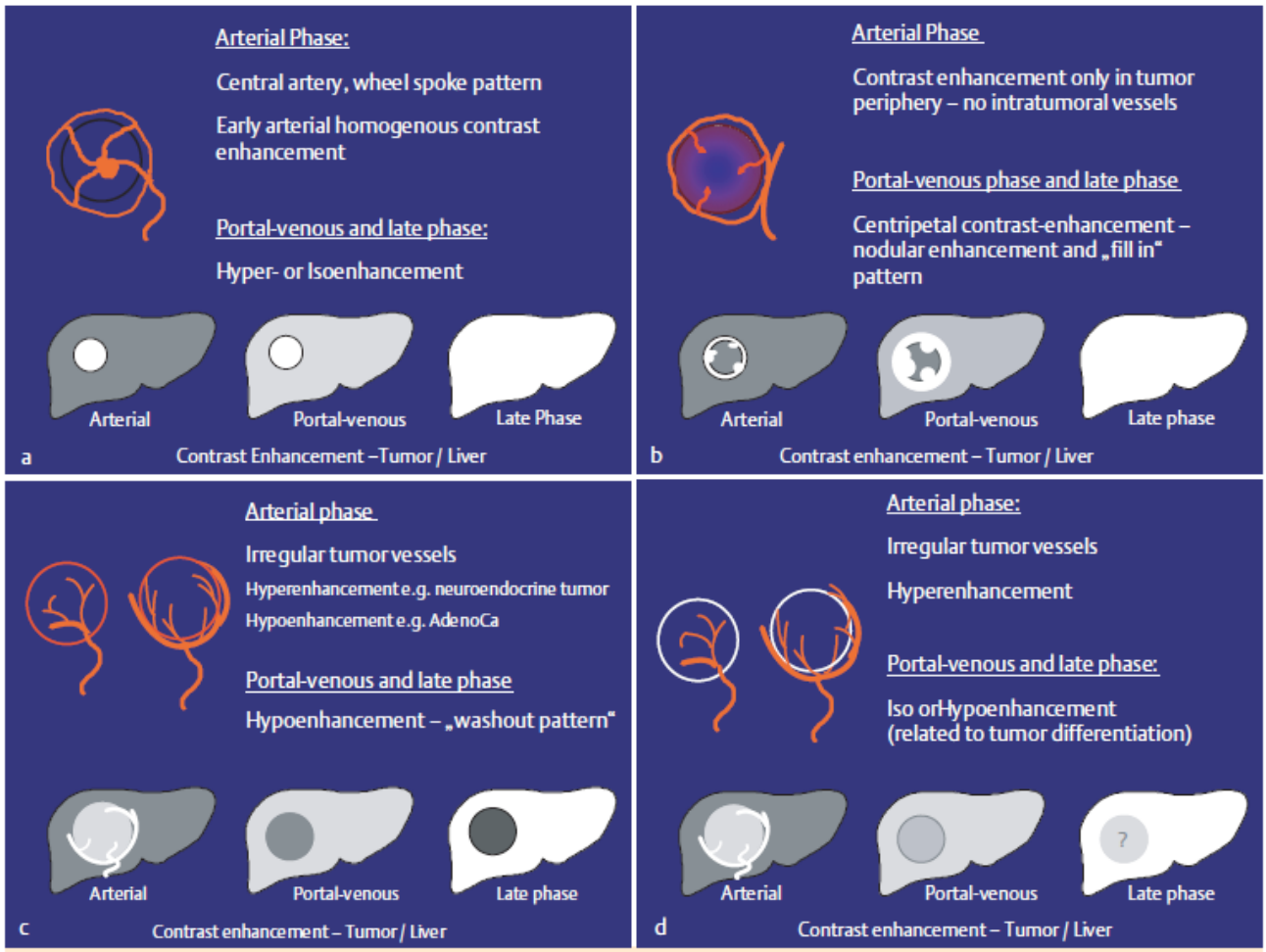
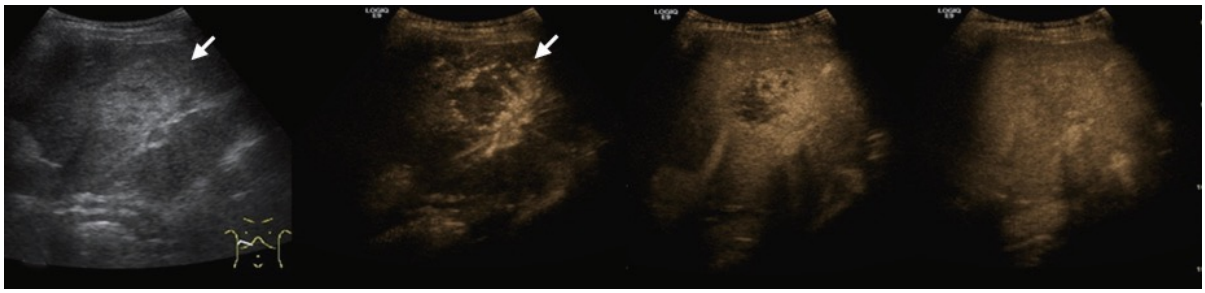



**Figure 2.** Hemangioma enhancement patterns are similar with (a) CEUS and (b) dynamic liver CT, with peripheral nodular enhancement in the arterial phase and gradual filling of the entire mass in later phases.[40] CEUS=contrast-enhanced ultrasound; CT=computed tomography.

**(a)**



**(b)**

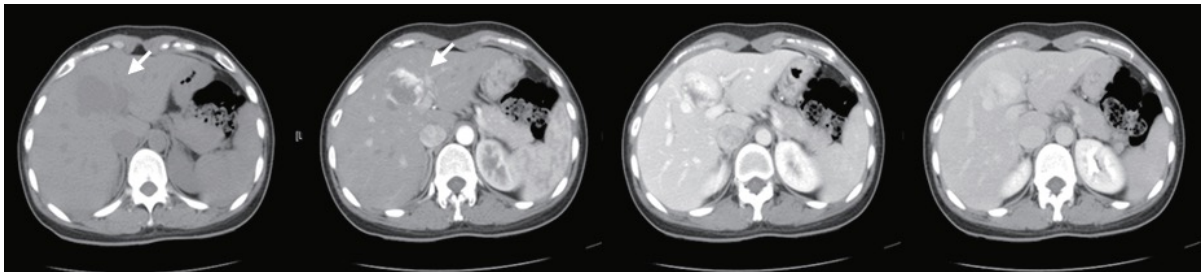
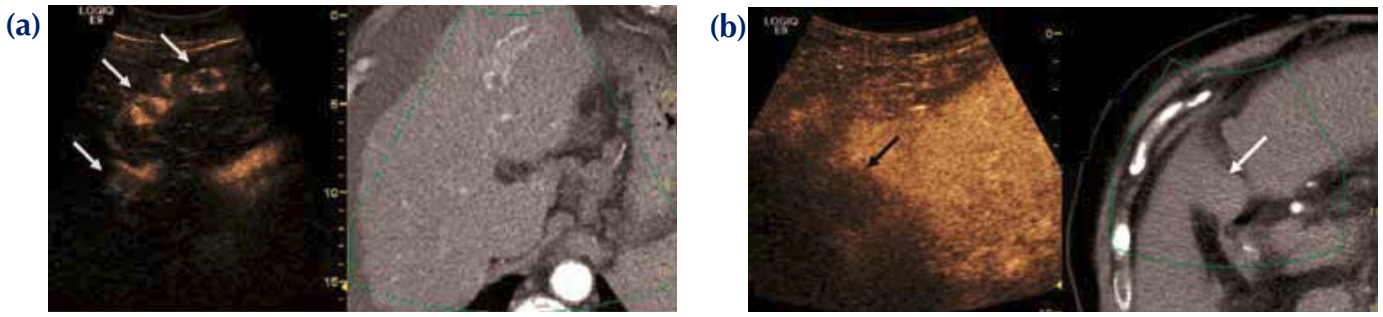


**Figure 3.** Because of the purely vascular distribution of the contrast agent, (a) arterial enhancement and (b) portal-venous washout of HCC are better visualized with CEUS (left images) than CT (right images). CEUS=contrast-enhanced ultrasound; CT=computed tomography; HCC=hepatocellular carcinoma. Images courtesy of Prof. Jung, University Clinic Regensburg, Germany.




Intrahepatic cholangiocarcinoma is occasionally detected during HCC surveillance, and is considered a mimic of HCC. Therefore, recognizing findings suggestive of cholangiocarcinoma is important—ie, a hypoattenuating mass with peripheral enhancement, progressive enhancement in dynamic contrast imaging, the presence of capsular retraction, and frequent biliary dilatation.[61] Metastases tend to show variable enhancement during the arterial phase, but are almost always hypoenhancing during the portal-venous and late phases (early washout).[40] CEUS efficacy in detection of liver metastases has been shown to be similar to that of CT and MRI.[2,21,62]

For the characterization of FLLs as malignant, CEUS is superior to unenhanced ultrasound (**Table 5**),[63–66] and has been shown to be similar (or at times superior) to CECT and CEMRI for this application. Comparing CEUS vs CECT and/or CEMRI in these studies, the sensitivity range is 90%–98.2% for CEUS vs 9%–90.6% for CECT vs 81.8%–91% for CEMRI; the specificity range is 66.7%–93% for CEUS vs 37.5%–81.6% for CECT vs 42.9%–93% for CEMRI (**Table 6**).[63,67–70]

A meta-analysis encompassing 21 studies and 3376 patients comparing CEUS with other imaging modalities[71] showed that CEUS had high pooled sensitivity (88%) and specificity (81%). For CECT, sensitivity was 90% and specificity was 77%; for CEMRI, sensitivity was 86% and specificity was 81%. The meta-analysis found no significant differences in diagnostic value for characterization of FLLs with CEUS as compared with CECT and CEMRI.

**Table 5.** CEUS vs Nonenhanced US Sensitivity and Specificity[63–66]

| | Quaia 2004 | Dai 2007 | Quaia 2007 | Trillaud 2009 |
|---|---|---|---|---|
| **Number of lesions** | 452 | 554 | 236 | 123 |
| Malignant, n | 323 | 346 | 96 | 68 |
| Benign, n | 129 | 208 | 140 | 55 |
| **Sensitivity, %** | | | | |
| CEUS | 81–85 | 88.7–92.5 | 78–86 | 98.2 |
| US | 52–54 | 42.5–53.8 | 23–38 | 40.0 |
| **Specificity, %** | | | | |
| CEUS | 95 | 78.4–86.5 | 58–61 | 88.2 |
| US | 40–43 | 22.1–23.1 | 21–28 | 36.8 |

CEUS=contrast-enhanced ultrasound; US=ultrasound.

**Table 6.** CEUS vs CECT and/or CEMRI Sensitivity and Specificity[63,67–70]

| | Trillaud 2009 | Seitz 2009 (DEGUM) | Seitz 2010 (DEGUM) | Quaia 2014 | D'Onofrio 2014 |
|---|---|---|---|---|---|
| **Number of lesions** | 121[a]/30[b] | 158[c] | 82[e] | 55[f] | 147 |
| Malignant, n | 54/21 | 109 | 55 | 22 | 105 |
| Benign, n | 67/8 | 49[d] | 27 | 33 | 42 |
| **Sensitivity, %** | | | | | |
| CEUS | 98.2/95.5 | 95.3 | 90.9 | 95 | 90 |
| CECT | – /72.7 | 90.6 | — | 9 | — |
| CEMRI | – /81.8 | — | 81.8 | — | 91 |
| CT + MRI | 68.5/ – | — | — | — | |
| **Specificity, %** | | | | | |
| CEUS | 88.1/75.0 | 83.7 | 66.7 | 84–90 | 93 |
| CECT | – /37.5 | 81.6 | — | 54–66 | — |
| CEMRI | – /42.9 | — | 63.0 | — | 93 |
| CT + MRI | 74.6/ – | — | — | — | — |

CECT=contrast-enhanced computed tomography; CEMRI=contrast-enhanced magnetic resonance imaging; CEUS=contrast-enhanced ultrasound.

[a] Total study population included 127 patients. This subgroup (n=121) includes patients for whom comparison of CEUS vs CT/MRI could be performed, evaluation of the target lesion could be obtained, and accuracy of CEUS vs a final reference diagnosis could be calculated.

[b] Subgroup of lesions in patients who underwent CT and MRI (n=30) and who had complete histological diagnosis available.

[c] Total study population included 267 patients with 269 lesions. Only subgroup B lesions (n=158) with complete histological diagnosis available (allowing for full statistical analysis) are included here.

[d] Includes 4 lesions diagnosed as "without defined entity."

[e] Further category of subgroup B lesions in patients who underwent CEMRI (n=84) and for whom complete histological diagnosis was available.

[f] Indeterminate on CT.

*Other Hepatic Clinical Applications of CEUS*

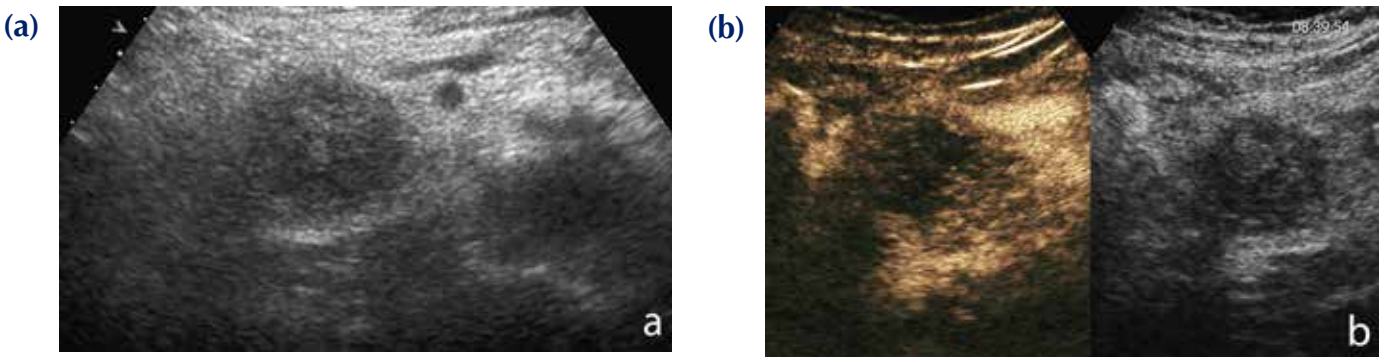
Clinical uses of CEUS other than FLL characterization include ultrasound-guided biopsies of FLL: CEUS-guided liver biopsies have a higher diagnostic accuracy (95%) than unenhanced ultrasound (87%).[72] CEUS is also useful for treatment planning.[2] Specifically, transcutaneous CEUS is useful to plan radiofrequency ablation. CEUS is also extremely useful to differentiate between venous thrombosis and tumor infiltration of hepatic vessels. Intraoperative CEUS has been shown to be more sensitive, specific, and accurate than intraoperative unenhanced ultrasound, CECT, or CEMRI for assessing tumor resectability,[73–77] and has been shown to lead to a change in surgical management in up to 30% of cases.[75,76,78] CEUS can be used after treatment with ablation or chemotherapy/radioembolization to assess initial treatment response and to assess signs of tumor progression.[2] Finally, CEUS is used in the setting of liver transplantation—presurgically to assess patency of the hepatic artery and portal vein and postsurgically for the noninvasive detection of vascular complications.[79,80]

## Pancreas

Similar to CEUS of the liver, CEUS of the pancreas provides high-detail resolution and real-time imaging of the pancreas, permitting visualization of intrapancreatic vessels and microvessels. Transabdominal CEUS and endoscopic CEUS are both useful for evaluation of pancreatic neoplasia and inflammatory lesions[5,81]; however, endoscopic CEUS may permit visualization of lesions that cannot be seen adequately with transcutaneous CEUS.[10,81–83] As is the case with FLLs, focal pancreatic lesions are identified by comparison with adjacent (healthy) pancreatic tissue. Healthy pancreatic parenchyma shows an early arterial phase (10–30 seconds) and a transient venous phase (30–120 seconds) after contrast injection.[4,5]

Differentiation of pancreatic ductal adenocarcinoma (the most common solid primary pancreatic neoplasia) from other solid tumors is one of the main indications for pancreatic CEUS. Most ductal adenocarcinomas (90% of cases) are hypoenhancing in all phases, and characterized by a relatively low mean vascular density (**Figure 4**).[84–88] Almost all other solid pancreatic lesions are hyperenhancing due to hypervascularity,[9,86–92] including neuroendocrine tumors, serous microcystic neoplasia, hamartomas, focal pancreatitis, autoimmune pancreatitis, intrapancreatic accessory spleen, metastases, and other rare neoplastic focal pancreatic lesions. Another indication is differentiating among the various pancreatic cystic lesions, such as a pseudocyst or walled-off pancreatic necrosis, a serous cystadenoma, a mucinous cystic neoplasm, a mucinous cystadenocarcinoma, and an intraductal papillary mucinous neoplasm.

**Figure 4.** Pancreatic ductal adenocarcinoma: (a) a solid hypoechoic rounded lesion with ill-defined margins in the pancreatic head on B-mode US, and (b) the typical markedly hypovascular pattern of ductal adenocarcinoma on CEUS.[84] CEUS=contrast-enhanced ultrasound; US=ultrasound.



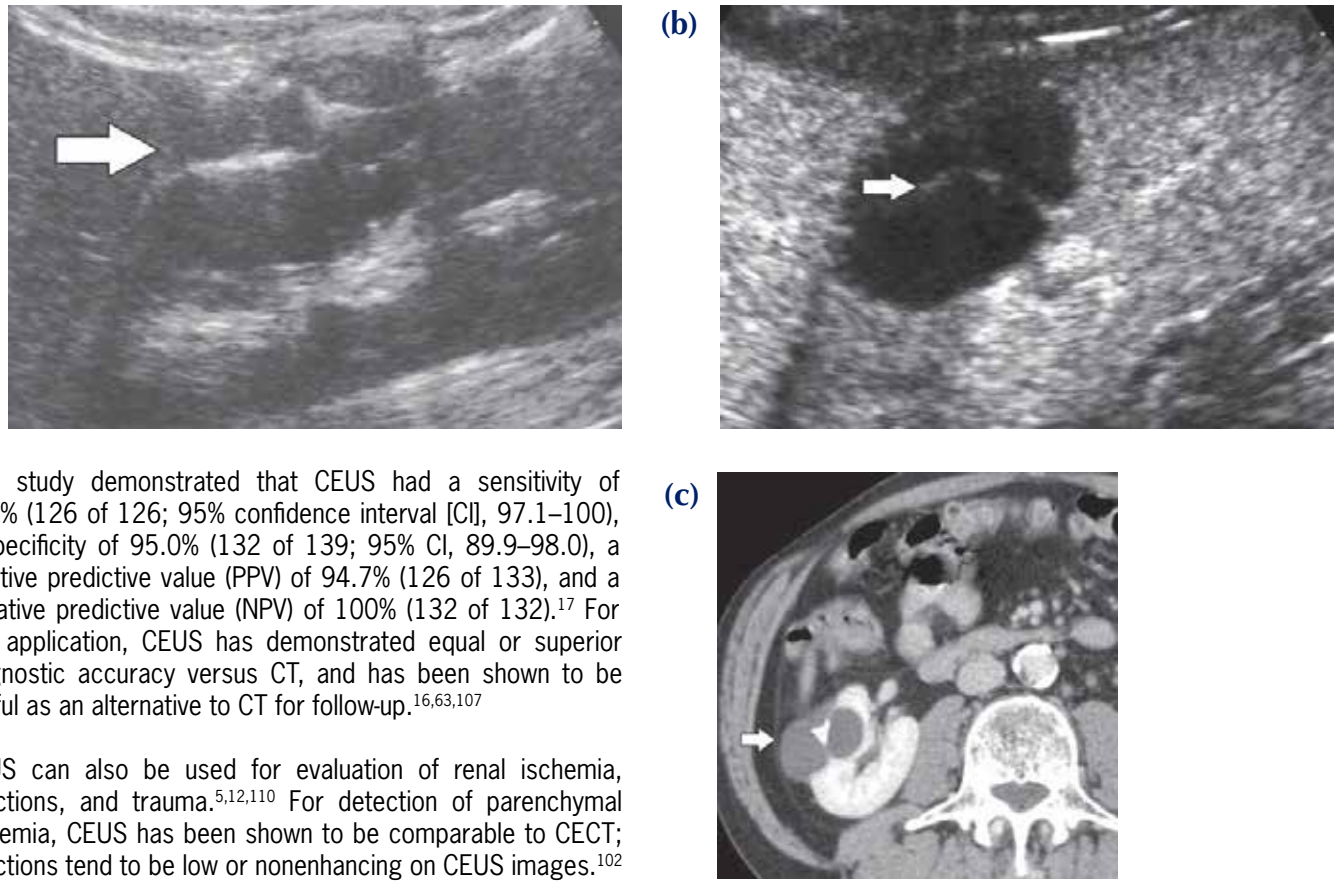

Evaluation of pancreatitis is another main indication for CEUS. Acute pancreatitis is associated with organ failure and necrosis, and CEUS can help identify necrotic areas as nonenhancing regions[93,94]; however, the appearance of chronic pancreatitis depends on the stage of disease. Evaluation of autoimmune pancreatitis is also complicated, with 3 recognized patterns: diffuse, focal, and multifocal.[95,96] For better visualization of vascular patterns, 3-dimensional (3-D) reconstruction has been shown to be useful.[97]

For diagnosis of pancreatic malignancy, the efficacy of CEUS is excellent, with a sensitivity of about 82% to 100% and a specificity of 90% to 100%.[9,89,98] In 2012, D'Onofrio published the results of the Pancreatic Multicenter Ultrasound Study,[98] a large study evaluating CEUS versus pathology for diagnosis of pancreatic lesions in 1439 patients. In this study, the following sensitivities and specificities were found: for solid lesions, 88% sensitivity and 88% specificity; for neuroendocrine tumors, 74% sensitivity and 93% specificity; and for cystic lesions, 78% sensitivity and 100% specificity. In another study focused on cystic pancreatic lesions,[99] the sensitivity for diagnosing pseudocysts was 94% and the specificity was 77%. Finally, CEUS is useful for assessment of percutaneous ablation therapy assessment in the pancreas, both for confirmation of treatment results and for evaluation of residual tumor vascularity.[18,100,101]

## Kidneys

CEUS is important for studying a wide variety of kidney pathologies.[102] CEUS enables dynamic assessment and quantification of both macro- and microvascularization without affecting renal function. A main indication for CEUS of the kidney is differentiating between solid renal masses and pseudotumors,[5,11,12] again based primarily on differences in tumor vascularity versus normal parenchyma. Identification of a normal, hypovascular renal pyramid within the lesion during the nephrographic phase essentially confirms the diagnosis of pseudotumor. CEUS is also used to differentiate between solid lesions and cystic lesions[5,103,104]: solid hypovascular tumor enhancement is minimal, while debris is completely nonenhancing. For diagnosis of cystic renal cell carcinoma, CEUS has been shown to be superior to both CT and MRI.[105,106] Another indication is characterization of complex cystic renal masses (**Figure 5**).[16,107–109] A retrospective performance study covering 1999 to 2010 included 721 patients with 1018 indeterminate renal masses referred for CEUS after inconclusive findings from other studies, which could have been unenhanced CT, CECT, unenhanced MRI, CEMRI, or unenhanced ultrasound.[17] The initial studies were performed using existing protocols at the institution where the study was performed. Each study performed before the CEUS examination was classified prospectively using the Bosniak scoring system. Diagnostic accuracy measures were calculated by using pathologic diagnosis as the reference standard, as well as lesion stability at 3 and 5 years.

**Figure 5.** Complex benign cystic renal mass on right kidney in 47-year-old woman on (a) baseline sonography image, (b) CEUS, and (c) CECT. Baseline sonography shows 4-cm multiloculated cystic mass (arrow, a) with several thin septa. CEUS during the arterial phase (with software suppression of tissue background) shows almost complete cancellation of intracystic septa and evidence of only slight enhancement in thin intracystic septa (arrow, b). CECT during the nephrographic phase shows evident septa and intracystic septal calcification. The cystic lesion (arrow, c) was classified as benign after review of CEUS scan.[107] CECT=contrast-enhanced computed tomography; CEUS=contrast-enhanced ultrasound.



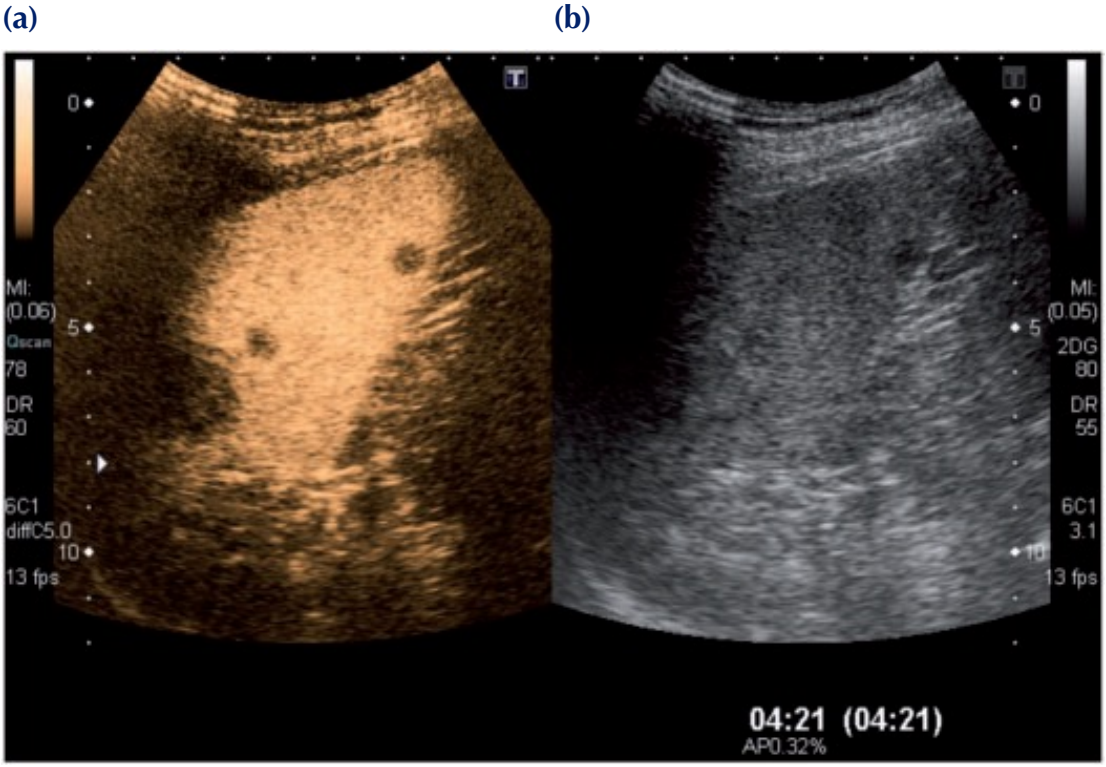

This study demonstrated that CEUS had a sensitivity of 100% (126 of 126; 95% confidence interval [CI], 97.1–100), a specificity of 95.0% (132 of 139; 95% CI, 89.9–98.0), a positive predictive value (PPV) of 94.7% (126 of 133), and a negative predictive value (NPV) of 100% (132 of 132).[17] For this application, CEUS has demonstrated equal or superior diagnostic accuracy versus CT, and has been shown to be useful as an alternative to CT for follow-up.[16,63,107]

CEUS can also be used for evaluation of renal ischemia, infections, and trauma.[5,12,110] For detection of parenchymal ischemia, CEUS has been shown to be comparable to CECT; infections tend to be low or nonenhancing on CEUS images.[102]

## Spleen

Conventional gray-scale and Doppler ultrasound are frequently unable to characterize focal splenic lesions, and CEUS is often needed to make a definitive and/or differential diagnosis.[13] Current recommended applications include[5,13] characterization of splenic parenchymal inhomogeneity or suspected lesions on conventional ultrasound (**Figure 6**); confirmation of suspected splenic infarction; characterization of accessory spleens or splenosis; and detection of splenic malignant lesions in oncologic patients when CT, MRI, and/or positron emission tomography are contraindicated or inconclusive.

**Figure 6.** Discrete melanoma metastases identified on (a) CEUS that were seen only as inhomogeneous splenic parenchyma on (b) conventional ultrasound.[13] CEUS=contrast-enhanced ultrasound.



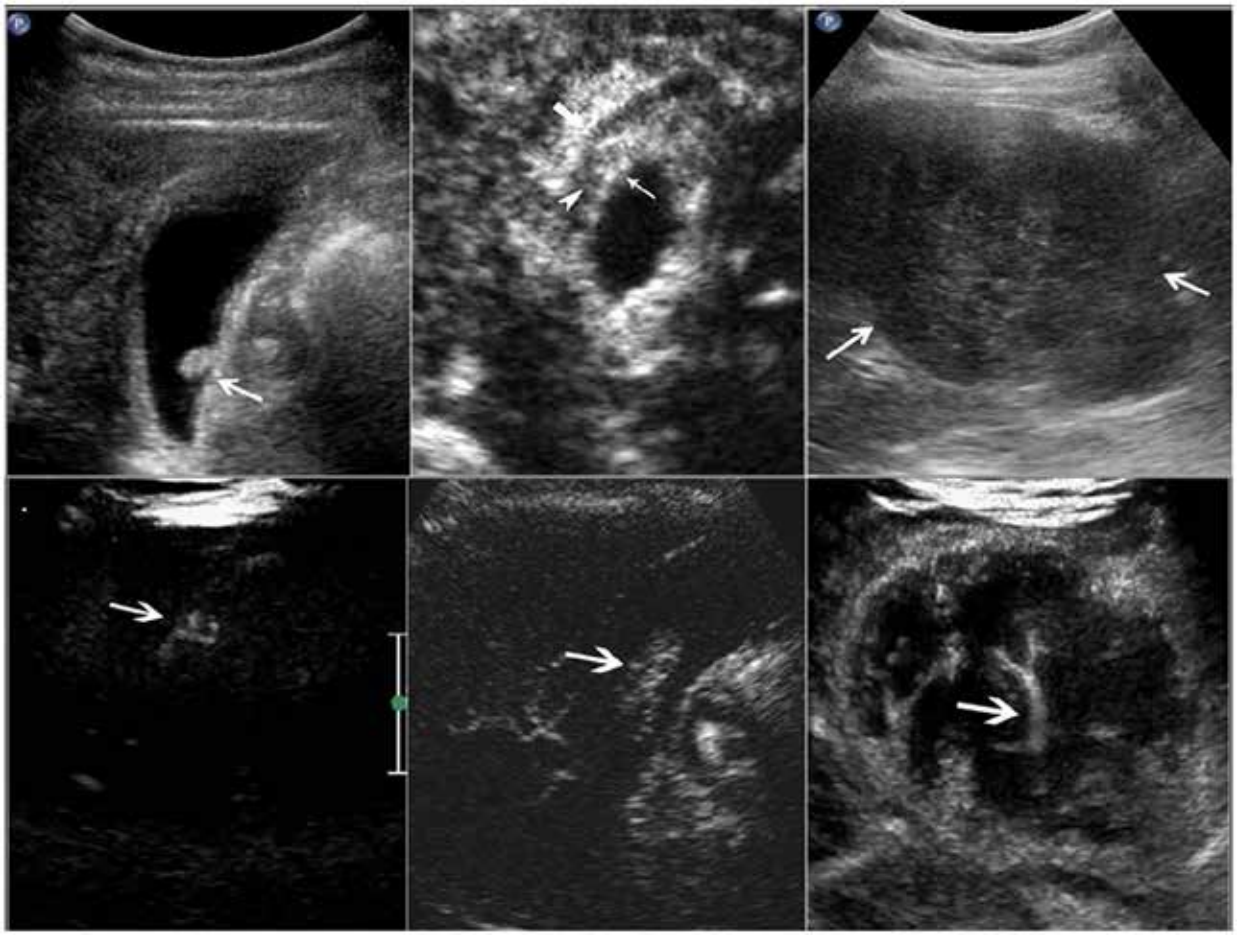

As with other abdominal lesions, enhancement patterns in various phases are used to characterize benign versus malignant splenic lesions.[5,13] Benign lesions are associated with absence of enhancement in any phase, or arterial phase hyperenhancement accompanied by persistent late-phase enhancement, whereas malignant lesions are characterized by arterial phase hypoenhancement followed by washout in the late phase. However, hypoenhancement followed by washout in the late phase can also be seen in atypical benign lesions; if present, further imaging and/or biopsy is indicated.

Although CT is usually used to image splenic trauma, focused ultrasound is sometimes used in the initial triage of patients with abdominal trauma (focused assessment with sonography in trauma [FAST] US), particularly when administration of iodinated contrast media is not recommended.[13] However, splenic lacerations and hematomas are often isoechoic, making them difficult to identify with conventional ultrasound. On CEUS, such lesions have reduced or absent perfusion in the late phase, making them more easily identifiable. In one study of patients with solid-organ injuries detected by CT, CEUS successfully identified all splenic injuries.[111] Current EFSUMB guidelines[30] recommend CEUS (1) as an alternative to CT to rule out solid-organ injuries (especially in children) in stable patients with isolated, moderate-energy abdominal trauma, (2) for further evaluation of equivocal CT findings, and (3) for follow-up of injuries when conservative management is the preferred strategy.

### Gallbladder and Biliary Tree

Because ultrasound provides real-time scanning with no radiation, high-resolution images, and cost-effectiveness, ultrasound is the primary imaging modality for assessment of gallbladder disease.[112] A primary use for CEUS in the gallbladder is the differentiation of neoplasia from biliary sludge and debris, and to detect tumor infiltration of surrounding structures.[5] In one study of 192 patients with gallbladder disease, CEUS was successfully used to identify findings associated with benign versus malignant lesions. Specifically, branched versus linear intralesional vessels and destruction of gallbladder wall on CEUS were found to be highly suggestive of gallbladder malignancy (**Figure 7**).[112]

**Figure 7.** Morphological types and intralesional blood vessels of gallbladder lesions. Upper left, polypoid type; upper middle, thickened-wall type; upper right, mass-forming type. Lower left, scattered blood vessels; lower middle, linear blood vessels; lower right, branched blood vessels.[112]



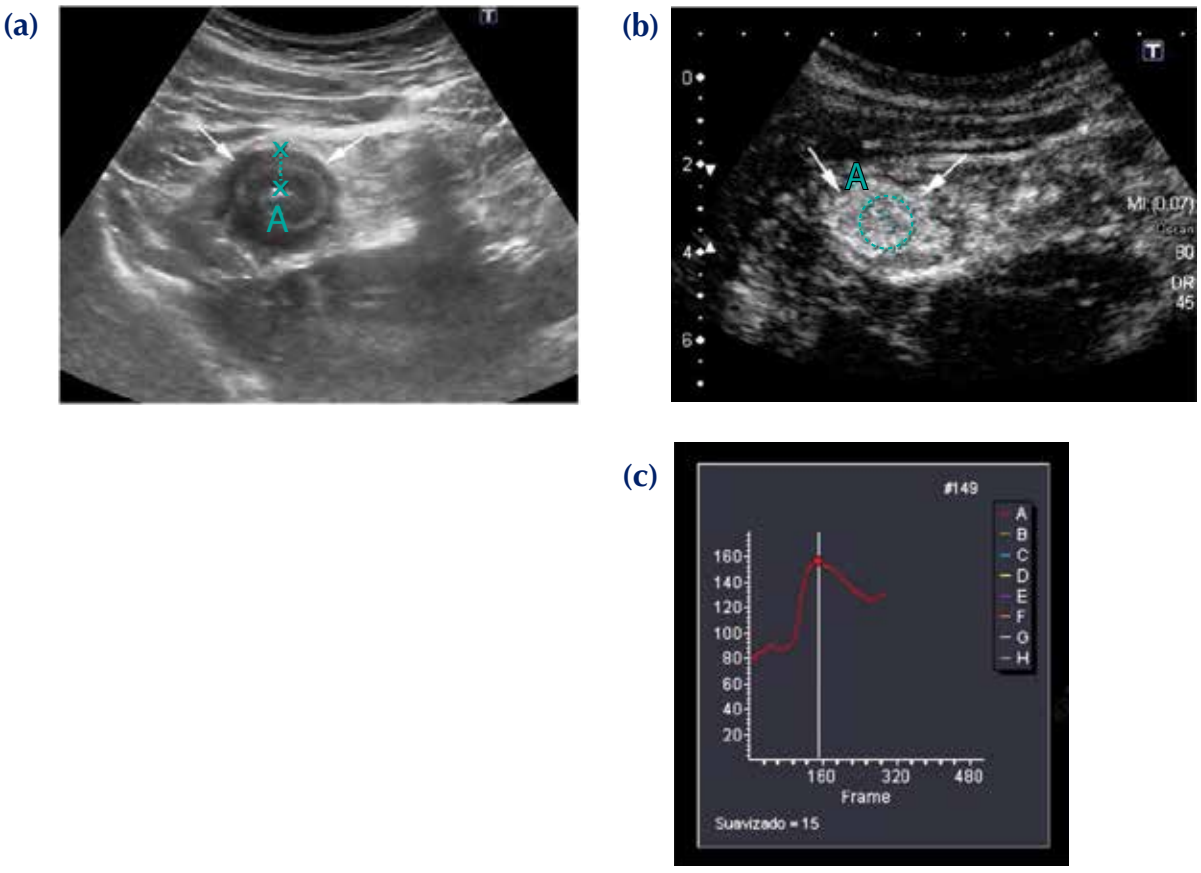
Vascular phases in the gallbladder differ from those in the liver: in the gallbladder, blood supply is provided entirely by the cystic artery and not by portal vein branches.[5, 113] Therefore, in this organ, the arterial phase is followed directly by the venous phase.[5] Gallbladder carcinomas are typically hyperenhancing in the arterial phase and hypoenhancing in the venous phase. In the biliary tree, CEUS is useful to evaluate patients with cholangiocarcinoma. In the case of extrahepatic cholangiocarcinoma, endoscopic CEUS is particularly useful to determine the depth of tumor infiltration and to detect involvement of surrounding tissue.[36,85,113]

## GI Tract

In the GI tract, CEUS is useful to evaluate bowel wall and peri-intestinal structures. For GI tract examination, higher frequency transducers (7.5 MHz) are typically used. The arterial phase lasts until 30 to 40 seconds after injection, followed by a venous phase, lasting until approximately 120 seconds.[5,15]

A main indication is evaluation of inflammatory bowel disease (IBD). IBD is more often evaluated by CT or MRI, but CEUS can help assess activity in Crohn's disease.[5,14,19,85] In the case of Crohn's disease, CEUS is useful to differentiate between fibrous and inflammatory strictures, and to quantify bowel wall vascularity (a marker of inflammatory activity).[114] Contrast kinetics (ie, time-intensity curve analysis) are useful to further quantify disease activity.[5] Based on patterns of contrast enhancement, CEUS has a sensitivity of 81% and a specificity of 63% for detecting active Crohn's disease.[114] In addition, in a study of 105 patients with Crohn's disease, CEUS was shown to be more sensitive than magnetic resonance enterography (100% vs 87%, respectively), with similar specificity (92% vs 100%, respectively) for detecting terminal ileal inflammation (using ileoscopy as the gold standard).[115] Finally, in a study of 60 patients with Crohn's disease, the authors assessed whether CEUS could increase the value of ultrasound, and found that the addition of contrast resulted in improved sensitivity (98%), specificity (100%), and accuracy (98.3%) for evaluation of postoperative recurrence (**Figure 8**).[116]

**Figure 8.** A 25-year-old man with previous ileocolonic resection for Crohn's disease with recurrence at the neoterminal ileum. Transverse US image (a) shows circumferential thickening of the neoterminal ileum (arrows). CEUS (b) shows marked enhancement of the neoterminal ileum. (c) Brightness–time curve shows a percentage of increase of enhancement of 100%.[116] A=region of interest placed in bowel wall; CEUS=contrast-enhanced ultrasound; US=ultrasound.




CT is the gold standard for diagnosis of acute appendicitis; however, because ultrasound is faster and avoids radiation and iodinated contrast, ultrasound can be preferable over CT in patients requiring avoidance of radiation and/or iodinated contrast.[117] As such, CEUS is useful both for diagnosis of acute appendicitis and determination of inflammation stage[118]: on CEUS, early stages of acute appendicitis are associated with hypervascularity, versus abscess and necrosis, which are associated with hypovascularity.[119]

### CEUS of the Abdomen in Children

CECT exposes children to ionizing radiation and potentially nephrotoxic iodinated contrast, and CEMRI involves gadolinium contrast administration and often, in children, sedation – all concerns in this vulnerable population, particularly in children requiring serial examinations. In contrast, CEUS is a real-time, noninvasive, relatively low-cost examination without ionizing radiation that requires no sedation. An additional advantage is that CEUS can be performed in a variety of settings, from bedside to operating room.[120]

Of the available UCAs, only Lumason is approved for use in ultrasonography of the liver for characterization of FLLs in pediatric patients[24]; therefore, use of this agent for this application in children is not off-label. Recent studies using second-generation UCA in children suggest that CEUS is safe and effective for hepatic applications.[120–122] In addition, a recent literature review showed CEUS in children is comparable to CT and MRI, with a specificity of 98% for identifying benign lesions and an NPV of 100%.[120] Nonhepatic applications in children include evaluation for appendicitis, Crohn's disease, intussusception, and pyloric stenosis.[123]

In a European survey of pediatric radiologists with experience using a second-generation UCA, 45 centers reported 5079 examinations in children (mean age 2.9 years; range birth–18 years).[124] Of these examinations, 4131 (81%) in 29 centers were intravesical applications and 948 (19%) in 30 centers were intravenous applications. Six (0.52%) minor adverse events (AEs; skin reaction, unusual taste, and hyperventilation) were reported after 5 intravenous studies, and no AEs were reported after intravesical use, suggesting a favorable safety profile for this second-generation UCA in children. A large (N=305) safety and economic study in children receiving CEUS, most with liver lesions or trauma, demonstrated no immediate AEs, and delayed AEs in 2 patients (0.7%; transient hypertension and transient tachycardia, neither symptomatic).[122] In this same study, use of CEUS avoided 97 MRI examinations and 71 CT examinations, resulting in potential cost savings of $180 versus MRI (not including anesthesia) and $74 versus CT.

## CEUS SAFETY

UCAs are considered safe, and associated with a low incidence of AEs[2]; the AE rates reported with UCAs are lower than those for CT contrast agents and comparable to those for MRI contrast agents.[125] Because UCAs are excreted via the lungs, no nephrotoxic effects occur, and no laboratory tests are needed to assess liver or kidney function prior to administration.[1] In addition, UCAs contain no iodine, so they are not associated with any thyroid effects.[1] Life-threatening anaphylactoid reactions are rare in abdominal CEUS applications (0.001%–0.002%), with no deaths reported in a series of more than 23,000 patients. The severe reaction rate to UCA is significantly lower than severe reactions to iodinated contrast agents used for CT and gadolinium-based contrast agents used for MRI.[126,127] Nevertheless, healthcare providers administering UCAs should receive training in resuscitation and have appropriate facilities available in the event of a severe AE.

Older FDA labeling contained a contraindication for UCAs in patients with severe cardiopulmonary disease and imposed patient monitoring for 30 minutes after injection; however, the contraindications were downgraded to warnings in 2008 and, in 2011, the requirement to observe patients for 30 minutes after injection was removed.[2] In 2016, the FDA removed the contraindication that UCAs should not be used in patients with known or suspected right-to-left, bidirectional, or transient right-to-left cardiac shunts.[22–24,128]

Data from small animal models suggest that microvascular disruption can occur when microspheres are insonated.[129] Therefore, low-MI technique is recommended for CEUS. Where high-MI sequences are deemed necessary, the risks should be considered in light of the potential benefits.[2] Data are limited on the use of UCA during pregnancy or breastfeeding.[2,130]

## PHARMACOECONOMICS OF CEUS

In general, ultrasound is widely believed to be more accessible and less costly than CT or MRI, and several studies have demonstrated cost savings when CEUS was compared with CECT or CEMRI.[131–135] In a study to assess the diagnostic impact and cost of CEUS, CT, and MRI for characterization of FLLs in 157 patients, CEUS led to a change in the diagnostic workup in 131 patients (83.4%) and in the therapeutic workup in 93 patients (59.2%).[136] In addition, CEUS allowed for the final diagnosis to be established in 133 patients (84.7%). In addition, the cost of CEUS was found to be lower than that of CECT and MRI. A large systematic review conducted in 2013 found that CEUS was a cost-effective alternative to CECT for surveillance of cirrhosis and for characterization of incidentally detected FLLs.[137] The NICE (National Institute for Health and Care Excellence) diagnostic guidance publication on SonoVue for CEUS of the liver found that the lower cost combined with slightly better performance meant that CEUS was more cost effective than either CECT or CEMRI.[138] Importantly, cost savings associated with CEUS were found to be considerably greater when CEUS was performed at specialized centers.[139] While this analysis cannot be fully extrapolated into US dollar savings, it does provide insights into how CEUS—whether using SonoVue or another UCA—can potentially improve diagnostic outcomes while reducing costs.

## SUMMARY AND CONCLUSIONS

The use of second-generation UCAs together with contrast-specific ultrasound modes permit detection and characterization of a wide variety of pathologies associated with abdominal organs, with high sensitivity and specificity. A primary use is real-time evaluation of FLLs on the basis of characteristic contrast enhancement patterns and washin/washout kinetics. Current guidelines include a number of extrahepatic applications of CEUS, including evaluation of the pancreas, kidneys, gallbladder, and GI tract. The advantages of CEUS over other noninvasive imaging modalities are numerous, and include a lack of ionizing radiation, increased accessibility and portability (including the potential for point-of-care, bedside use) and improved patient comfort. Studies also show that relative to CT and MRI, CEUS is associated with lower costs, especially when performed in a specialized setting. Finally, the benefits of CEUS are particularly significant in patients with renal dysfunction: the potential clinical outcomes of iodinated contrast (nephrotoxicity) and gadolinium-based contrast (nephrogenic systemic fibrosis) in patients with poor renal function is an important consideration when selecting an imaging modality.

## REFERENCES


1. Chung YE, Kim KW. Contrast-enhanced ultrasonography: advance and current status in abdominal imaging. *Ultrasonography*. 2015;34(1):3-18.
2. Claudon M, Dietrich CF, Choi BI, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver—update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol*. 2013;39(2):187-210.
3. Albrecht T, Blomley M, Bolondi L, et al; EFSUMB Study Group. Guidelines for the use of contrast agents in ultrasound. January 2004. *Ultraschall Med*. 2004;25(4):249-256.
4. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)—update 2008. *Ultraschall Med*. 2008;29(1):28-44.
5. Piscaglia F, Nolsøe C, Dietrich CF, et al. The EFSUMB guidelines and recommendations on the clinical practice of contrast enhanced ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med*. 2012;33(1):33-59.
6. Dietrich CF, Averkiou MA, Correas JM, Lassau N, Leen E, Piscaglia F. An EFSUMB introduction into dynamic contrast-enhanced ultrasound (DCE-US) for quantification of tumour perfusion. *Ultraschall Med*. 2012;33(4):344-351.
7. Wilson SR, Burns PN. Microbubble-enhanced US in body imaging: what role? *Radiology*. 2010;257(1):24-39.
8. Wilson SR, Greenbaum LD, Goldberg BB. Contrast-enhanced ultrasound: what is the evidence and what are the obstacles? *AJR Am J Roentgenol*. 2009;193(1):55-60.
9. Dietrich CF, Ignee A, Braden B, Barreiros AP, Ott M, Hocke M. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. *Clin Gastroenterol Hepatol*. 2008;6(5):590-597.
10. Faccioli N, D'Onofrio M, Malagò R, et al. Resectable pancreatic adenocarcinoma: depiction of tumoral margins at contrast-enhanced ultrasonography. *Pancreas*. 2008;37(3):265-268.
11. Correas JM, Claudon M, Tranquart F, Hélénon AO. The kidney: imaging with microbubble contrast agents. *Ultrasound Q*. 2006;22(1):53-66.
12. Nilsson A. Contrast-enhanced ultrasound of the kidneys. *Eur Radiol*. 2004;14(8):P104-P109.
13. Omar A, Freeman S. Contrast-enhanced ultrasound of the spleen. *Ultrasound*. 2016;24(1):41-49.
14. Dietrich CF. Significance of abdominal ultrasound in inflammatory bowel disease. *Dig Dis*. 2009;27(4):482-493.
15. Plikat K, Klebl F, Buchner C, Schölmerich J, Schlottmann K. Evaluation of intestinal hyperaemia in inflamed bowel by high resolution contrast harmonic imaging (CHI) [in German]. *Ultraschall Med*. 2004;25(4):257-262.
16. Ascenti G, Mazziotti S, Zimbaro G, et al. Complex cystic renal masses: characterization with contrast-enhanced US. *Radiology*. 2007;243(1):158-165.
17. Barr RG, Peterson C, Hindi A. Evaluation of indeterminate renal masses with contrast-enhanced US: a diagnostic performance study. *Radiology*. 2014;271(1):133-142.
18. Ignee A, Straub B, Schuessler G, Dietrich CF. Contrast enhanced ultrasound of renal masses. *World J Radiol*. 2010;2(1):15-31.
19. Dietrich CF, Jedrzejczyk M, Ignee A. Sonographic assessment of splanchnic arteries and the bowel wall. *Eur J Radiol*. 2007;64(2):202-212.
20. Piscaglia F, Lencioni R, Sagrini E, et al. Characterization of focal liver lesions with contrast-enhanced ultrasound. *Ultrasound Med Biol*. 2010;36(4):531-550.
21. Quaia E, D'Onofrio M, Palumbo A, Rossi S, Bruni S, Cova M. Comparison of contrast-enhanced ultrasonography versus baseline ultrasound and contrast-enhanced computed tomography in metastatic disease of the liver: diagnostic performance and confidence. *Eur Radiol*. 2006;16(7):1599-1609.
22. Optison [package insert]. Marlborough, MA: GE Healthcare Inc; revised January 2017.
23. Definity [package insert]. North Billerica, MA: Lantheus Medical Imaging; revised October 2017.
24. Lumason [package insert]. Monroe Township, NJ; Bracco Diagnostics; December 2016.
25. Greis C. Technology overview: SonoVue (Bracco, Milan). *Eur Radiol*. 2004;14(suppl 8):P11-P15.
26. Celli N, Gaiani S, Piscaglia F, et al. Characterization of liver lesions by real-time contrast-enhanced ultrasonography. *Eur J Gastroenterol Hepatol*. 2007;19(1):3-14.
27. von Herbay A, Vogt C, Willers R, Häussinger D. Real-time imaging with the sonographic contrast agent SonoVue: differentiation between benign and malignant hepatic lesions. *J Ultrasound Med*. 2004;23(12):1557-1568.

28. Nicolau C, Vilana R, Catal V, et al. Importance of evaluating all vascular phases on contrast-enhanced sonography in the differentiation of benign from malignant focal liver lesions. *AJR Am J Roentgenol.* 2006;186(1):158-167.

29. Nolsøe CP, Lorentzen T. International guidelines for contrast-enhanced ultrasonography: ultrasound imaging in the new millennium. *Ultrasonography*. 2016;35(2):89-103.

30. Sidhu PS, Cantisani V, Dietrich CF, et al. The EFSUMB guidelines and recommendations for the clinical practice of contrast-enhanced ultrasound (CEUS) in non-hepatic applications: update 2017 (long version). *Ultraschall Med.* 2018;39(2):e2-e44.

31. International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology*. 2009;49(2):658-664.

32. American College of Radiology (ACR) Committee on Drugs and Contrast Media. *ACR Manual on Contrast Media*. Version 10.3. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Published 2018. Accessed August 21, 2018.

33. American College of Radiology. CEUS LI-RADS® v2017 CORE. https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/CEUS-LI-RADS-2017-Core.pdf?la=en. Accessed June 4, 2018.

34. Wilson SR, Burns PN. An algorithm for the diagnosis of focal liver masses using microbubble contrast-enhanced pulse-inversion sonography. *AJR Am J Roentgenol.* 2006;186(5):1401-1412.

35. Dietrich CF, Cui XW, Boozari B, Hocke M, Ignee A. Contrast-enhanced ultrasound (CEUS) in the diagnostic algorithm of hepatocellular and cholangiocellular carcinoma, comments on the AASLD guidelines. *Ultraschall Med.* 2012;33(suppl 1):S57-S66.

36. Barreiros AP, Piscaglia F, Dietrich CF. Contrast enhanced ultrasound for the diagnosis of hepatocellular carcinoma (HCC): comments on AASLD guidelines. *J Hepatol.* 2012;57(4):930-932.

37. Strobel D, Seitz K, Blank W, et al. Contrast-enhanced ultrasound for the characterization of focal liver lesions—diagnostic accuracy in clinical practice (DEGUM multicenter trial). *Ultraschall Med.* 2008;29(5):499-505.

38. Dietrich CF, Maddalena ME, Cui XW, Schreiber-Dietrich D, Ignee A. Liver tumor characterization—review of the literature. *Ultraschall Med.* 2012;33(suppl 1):S3-S10.

39. Dietrich CF, Mertens JC, Braden B, Schuessler G, Ott M, Ignee A. Contrast-enhanced ultrasound of histologically proven liver hemangiomas. *Hepatology*. 2007;45(5):1139-1145.

40. Jang JY, Kim MY, Jeong SW, et al. Current consensus and guidelines of contrast enhanced ultrasound for the characterization of focal liver lesions. *Clin Mol Hepatol.* 2013;19(1):1-16.

41. Dietrich CF, Jenssen C. Focal liver lesion, incidental finding [in German]. *Dtsch Med Wochenschr*. 2012;137(41):2099-2116.

42. Dietrich CF, Schuessler G, Trojan J, Fellbaum C, Ignee A. Differentiation of focal nodular hyperplasia and hepatocellular adenoma by contrast-enhanced ultrasound. *Br J Radiol.* 2005;78(932):704-707.

43. Kim TK, Jang HJ, Burns PN, Murphy-Lavallee J, Wilson SR. Focal nodular hyperplasia and hepatic adenoma: differentiation with low-mechanical-index contrast-enhanced sonography. *AJR Am J Roentgenol.* 2008;190(1):58-66.

44. Catalano O, Sandomenico F, Nunziata A, Raso MM, Vallone P, Siani A. Transient hepatic echogenicity difference on contrast-enhanced ultrasonography: sonographic sign and pitfall. *J Ultrasound Med.* 2007;26(3):337-345.

45. Catalano O, Sandomenico F, Raso MM, Siani A. Low mechanical index contrast-enhanced sonographic findings of pyogenic hepatic abscesses. *AJR Am J Roentgenol.* 2004;182(2):447-450.

46. Liu GJ, Lu MD, Xie XY, et al. Real-time contrast-enhanced ultrasound imaging of infected focal liver lesions. *J Ultrasound Med.* 2008;27(4):657-666.

47. Thorelius L. Contrast-enhanced ultrasound in trauma. *Eur Radiol.* 2004;14(suppl 8):P43-P52.

48. Thorelius L. Contrast-enhanced ultrasound: beyond the liver. *Eur Radiol.* 2003;13(suppl 3):N91-N108.

49. Nilsson A, Lorén I, Nirhov N, Lindhagen T, Nilsson P. Power Doppler ultrasonography: alternative to computed tomography in abdominal trauma patients. *J Ultrasound Med.* 1999;18(10):669-672.

50. Cagini L, Gravante S, Malaspina CM, et al. Contrast enhanced ultrasound (CEUS) in blunt abdominal trauma. *Crit Ultrasound J.* 2013;5(suppl 1):S9.

51. Jang HJ, Kim TK, Wilson SR. Small nodules (1-2 cm) in liver cirrhosis: characterization with contrast-enhanced ultrasound. *Eur J Radiol.* 2009;72(3):418-424.

52. Jang HJ, Kim TK, Burns PN, Wilson SR. Enhancement patterns of hepatocellular carcinoma at contrast-enhanced US: comparison with histologic differentiation. *Radiology*. 2007;244(3):898-906.

53. Jo PC, Jang HJ, Burns PN, Burak KW, Kim TK, Wilson SR. Integration of contrast-enhanced US into a multimodality approach to imaging of nodules in a cirrhotic liver: how I do it. *Radiology*. 2017;282(2):317-331.

54. Dietrich CF, Sharma M, Gibson RN, Schreiber-Dietrich D, Jenssen C. Fortuitously discovered liver lesions. *World J Gastroenterol.* 2013;19(21):3173-3188.

55. Bernatik T, Seitz K, Blank W, Schuler A, Dietrich CF, Strobel D. Unclear focal liver lesions in contrast-enhanced ultrasonography—lessons to be learned from the DEGUM multicenter study for the characterization of liver tumors. *Ultraschall Med.* 2010;31(6):577-581.

56. Boozari B, Soudah B, Rifai K, et al. Grading of hypervascular hepatocellular carcinoma using late phase of contrast enhanced sonography—a prospective study. *Dig Liver Dis.* 2011;43(6):484-490.

57. Liu GJ, Xu HX, Lu MD, et al. Correlation between enhancement pattern of hepatocellular carcinoma on real-time contrast-enhanced ultrasound and tumour cellular differentiation on histopathology. *Br J Radiol.* 2007;80(953):321-330.

58. Nicolau C, Catalá V, Vilana R, et al. Evaluation of hepatocellular carcinoma using SonoVue, a second generation ultrasound contrast agent: correlation with cellular differentiation. *Eur Radiol.* 2004;14(6):1092-1099.

59. Bhayana D, Kim TK, Jang HJ, Burns PN, Wilson SR. Hypervascular liver masses on contrast-enhanced ultrasound: the importance of washout. *AJR Am J Roentgenol.* 2010;194(4):977-983.

60. Kim TK, Lee KH, Jang HJ, et al. Analysis of gadobenate dimeglumine-enhanced MR findings for characterizing small (1-2-cm) hepatic nodules in patients at high risk for hepatocellular carcinoma. *Radiology.* 2011;259(3):730-738.

61. Kim TK, Lee E, Jang HJ. Imaging findings of mimickers of hepatocellular carcinoma. *Clin Mol Hepatol.* 2015;21(4):326-343.

62. Dietrich CF, Kratzer W, Strobe D, et al. Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT and MRI. *World J Gastroenterol.* 2006;12(11):1699-1705.

63. Trillaud H, Bruel JM, Valette PJ, et al. Characterization of focal liver lesions with SonoVue-enhanced sonography: international multicenter-study in comparison to CT and MRI. *World J Gastroenterol.* 2009;15(30):3748-3756.

64. Dai Y, Chen MH, Yin SS, et al. Focal liver lesions: can SonoVue-enhanced ultrasound be used to differentiate malignant from benign lesions? *Invest Radiol.* 2007;42(8):596-603.

65. Quaia E, D'Onofrio M, Cabassa P, et al.. Diagnostic value of hepatocellular nodule vascularity after microbubble injection for characterizing malignancy in patients with cirrhosis. *AJR Am J Roentgenol.* 2007;189(6):1474-1483.

66. Quaia E, Calliada F, Bertolotto M. Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. *Radiology.* 2004;232:420-430.

67. Seitz K, Bernatik T, Strobel D, et al. Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions in clinical practice (DEGUM Multicenter Trial): CEUS vs. MRI—a prospective comparison in 269 patients. *Ultraschall Med.* 2010;31(5):492-499.

68. Seitz K, Strobel D, Bernatik T, et al. Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions - prospective comparison in clinical practice: CEUS vs. CT (DEGUM multicenter trial). Parts of this manuscript were presented at the Ultrasound Dreilandertreffen 2008, Davos. *Ultraschall Med.* 2009;30(4):383-389.

69. D'Onofrio M, Crosara S, De Robertis R, et al. Malignant focal liver lesions at contrast-enhanced ultrasonography and magnetic resonance with hepatospecific contrast agent. *Ultrasound.* 2014;22(2):91-98.

70. Quaia E, De Paoli L, Angileri R, Cabibbo B, Cova MA. Indeterminate solid hepatic lesions identified on non-diagnostic contrast-enhanced computed tomography: Assessment of the additional diagnostic value of contrast-enhanced ultrasound in the non-cirrhotic liver. *Eur J Radiol.* 2014;83(3):456-462.

71. Guang Y, Xie L, Ding H, Cai A, Huang Y. Diagnosis value of focal liver lesions with SonoVue®-enhanced ultrasound compared with contrast-enhanced computed tomography and contrast-enhanced MRI: a meta-analysis. *J Cancer Res Clin Oncol.* 2011;137(11):1595-1605.

72. Wu W, Chen MH, Yin SS, et al. The role of contrast-enhanced sonography of focal liver lesions before percutaneous biopsy. *AJR Am J Roentgenol.* 2006;187(3):752-761.

73. Arita J, Hasegawa K, Takahashi M, et al. Correlation between contrast-enhanced intraoperative ultrasound using Sonazoid and histologic grade of resected hepatocellular carcinoma. *AJR Am J Roentgenol.* 2011;196(6):1314-1321.

74. Nakano H, Ishida Y, Hatakeyama T, et al. Contrast-enhanced intraoperative ultrasonography equipped with late Kupffer-phase image obtained by Sonazoid in patients with colorectal liver metastases. *World J Gastroenterol.* 2008;14(20):3207-3211.

75. Torzilli G. Advances in the surgical treatment of colorectal cancer liver metastases through ultrasound. *Surg Today.* 2011;41(9):1184-1189.

76. Donadon M, Torzilli G. Intraoperative ultrasound in patients with hepatocellular carcinoma: from daily practice to future trends. *Liver Cancer.* 2013;2(1):16-24.

77. Leen E, Ceccotti P, Moug SJ, et al. Potential value of contrast-enhanced intraoperative ultrasonography during partial hepatectomy for metastases: an essential investigation before resection? *Ann Surg.* 2006;243(2):236-240.

78. Leen E, Ceccotti P, Kalogeropoulou C, Angerson WJ, Moug SJ, Horgan PG. Prospective multicenter trial evaluating a novel method of characterizing focal liver lesions using contrast-enhanced sonography. *AJR Am J Roentgenol*. 2006;186(6):1551-1559.

79. Ren J, Wu T, Zheng BW, Tan YY, Zheng RQ, Chen GH. Application of contrast-enhanced ultrasound after liver transplantation: current status and perspectives. *World J Gastroenterol*. 2016;22(4):1607-1616.

80. Clevert DA, Stickel M, Minaifar N, et al. Contrast-enhanced ultrasound in liver transplant: first results and potential for complications in the postoperative period. *Clin Hemorheol Microcirc*. 2009;43(1-2):83-94.

81. D'Onofrio M, Malagò R, Zamboni G, et al. Contrast-enhanced ultrasonography better identifies pancreatic tumor vascularization than helical CT. *Pancreatology*. 2005;5(4-5):398-402.

82. D'Onofrio M, Megibow AJ, Faccioli N, et al. Comparison of contrast-enhanced sonography and MRI in displaying anatomic features of cystic pancreatic masses. *AJR Am J Roentgenol*. 2007;189(6):1435-1442.

83. Numata K, Ozawa Y, Kobayashi N, et al. Contrast-enhanced sonography of pancreatic carcinoma: correlations with pathological findings. *J Gastroenterol*. 2005;40(6):631-640.

84. De Robertis R, D'Onofrio M, Crosara S, et al. Contrast-enhanced ultrasound of pancreatic tumours. *Australas J Ultrasound Med*. 2014;17(3):96-109.

85. Dietrich CF, Cui XW, Schreiber-Dietrich DG, Ignee A. EFSUMB guidelines 2011: comments and illustrations. *Ultraschall Med*. 2012;33(suppl 1):S11-S21.

86. Mäkinen K, Loimas S, Nuutinen P, Eskelinen M, Alhava E. The growth pattern and microvasculature of pancreatic tumours induced with cultured carcinoma cells. *Br J Cancer*. 2000;82(4):900-904.

87. Ryschich E, Schmidt E, Maksan SM, Klar E, Schmidt J. Expansion of endothelial surface by an increase of vessel diameter during tumor angiogenesis in experimental and hepatocellular and pancreatic cancer. *World J Gastroenterol*. 2004;10(21):3171-3174.

88. Schmidt J, Ryschich E, Daniel V, et al. Vascular structure and microcirculation of experimental pancreatic carcinoma in rats. *Eur J Surg*. 2000;166(4):328-335.

89. Dietrich CF, Braden B, Hocke M, Ott M, Ignee A. Improved characterisation of solitary solid pancreatic tumours using contrast enhanced transabdominal ultrasound. *J Cancer Res Clin Oncol*. 2008;134(6):635-643.

90. D'Onofrio M, Zamboni G, Tognolini A, et al. Mass-forming pancreatitis: value of contrast-enhanced ultrasonography. *World J Gastroenterol*. 2006;12(26):4181-4184.

91. Kersting S, Konopke R, Kersting F, et al. Quantitative perfusion analysis of transabdominal contrast-enhanced ultrasonography of pancreatic masses and carcinomas. *Gastroenterology*. 2009;137(6):1903-1911.

92. Ryschich E, Schmidt J, Loeffler T, et al. Different radiogenic effects on microcirculation in healthy pancreas and in pancreatic carcinoma of the rat. *Ann Surg*. 2003;237(4):515-521.

93. Rickes S, Rauh P, Uhle C, Ensberg D, Mönkemüller K, Malfertheiner P. Contrast-enhanced sonography in pancreatic diseases. *Eur J Radiol*. 2007;64(2):183-188.

94. Ripollés T, Martínez MJ, López E, Castelló I, Delgado F. Contrast-enhanced ultrasound in the staging of acute pancreatitis. *Eur Radiol*. 2010;20(10):2518-2523.

95. Crosara S, D'Onofrio M, De Robertis R, et al. Autoimmune pancreatitis: multimodality non-invasive imaging diagnosis. *World J Gastroenterol*. 2014;20(45):16881-16890.

96. Mauch M, Blank W, Kunze G, et al. Importance of abdominal ultrasound in 17 patients with histologically confirmed autoimmune pancreatitis (AIP). *Ultraschall Med*. 2015;36(3):248-254.

97. Hocke M, Ignee A, Dietrich CF. Contrast-enhanced endoscopic ultrasound in the diagnosis of autoimmune pancreatitis. *Endoscopy*. 2011;43(2):163-165.

98. D'Onofrio M, Barbi E, Dietrich CF, et al. Pancreatic multicenter ultrasound study (PAMUS). *Eur J Radiol*. 2012;81(4):630-638.

99. Beyer-Enke SA, Hocke M, Ignee A, Braden B, Dietrich CF. Contrast enhanced transabdominal ultrasound in the characterisation of pancreatic lesions with cystic appearance. *JOP*. 2010;11(5):427-433.

100. Hoeffel C, Pousset M, Timsit MO, et al. Radiofrequency ablation of renal tumours: diagnostic accuracy of contrast-enhanced ultrasound for early detection of residual tumour. *Eur Radiol*. 2010;20(8):1812-1821.

101. Meloni MF, Bertolotto M, Alberzoni C, et al. Follow-up after percutaneous radiofrequency ablation of renal cell carcinoma: contrast-enhanced sonography versus contrast-enhanced CT or MRI. *AJR Am J Roentgenol*. 2008;191(4):1233-1238.

102. Cokkinos DD, Antypa E, Kalogeropoulos I, et al. Contrast-enhanced ultrasound performed under urgent conditions. Indications, review of the technique, clinical examples and limitations. *Insights Imaging*. 2013;4(2):185-198.

103. Roy C, Gengler L, Sauer B, Lang H. Role of contrast enhanced US in the evaluation of renal tumors. *J Radiol*. 2008;89(11): 1735-1744.

104. Tamai H, Takiguchi Y, Oka M, et al. Contrast-enhanced ultrasonography in the diagnosis of solid renal tumors. *J Ultrasound Med*. 2005;24(12):1635-1640.

105. Park BK, Kim B, Kim SH, Ko K, Lee HM, Choi HY. Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. *Eur J Radiol*. 2007;61(2):310-314.

106. Clevert DA, Minaifar N, Weckbach S, et al. Multislice computed tomography versus contrast-enhanced ultrasound in evaluation of complex cystic renal masses using the Bosniak classification system. *Clin Hemorheol Microcirc*. 2008;39(1-4):171-178.

107. Quaia E, Bertolotto M, Cioffi V, et al. Comparison of contrast-enhanced sonography with unenhanced sonography and contrast-enhanced CT in the diagnosis of malignancy in complex cystic renal masses. *AJR Am J Roentgenol*. 2008;191(4):1239-1249.

108. Robbin ML, Lockhart ME, Barr RG. Renal imaging with ultrasound contrast: current status. *Radiol Clin North Am*. 2003;41(5):963-978.

109. Robbin ML. Ultrasound contrast agents: a promising future. *Radiol Clin North Am*. 2001;39(3):399-414.

110. Bertolotto M, Martegani A, Aiani L, Zappetti R, Cernic S, Cova MA. Value of contrast-enhanced ultrasonography for detecting renal infarcts proven by contrast enhanced CT. A feasibility study. *Eur Radiol*. 2008;18(2):376-383.

111. Mihalik JE, Smith RS, Toevs CC, Putnam AT, Foster JE. The use of contrast-enhanced ultrasound for the evaluation of solid abdominal organ injury in patients with blunt abdominal trauma. *J Trauma Acute Care Surg*. 2012;73(5):1100-1105.

112. Liu LN, Xu HX, Lu MD, et al. Contrast-enhanced ultrasound in the diagnosis of gallbladder diseases: a multi-center experience. *PLoS One*. 2012;7(10):e48371.

113. Cui XW, Ignee A, Braden B, Woenckhaus M, Dietrich CF. Biliary papillomatosis and new ultrasound imaging modalities. *Z Gastroenterol*. 2012;50(2):226-231.

114. Serra C, Menozzi G, Labate AM, et al. Ultrasound assessment of vascularization of the thickened terminal ileum wall in Crohn's disease patients using a low-mechanical index real-time scanning technique with a second generation ultrasound contrast agent. *Eur J Radiol*. 2007;62(1):114-121.

115. Horjus Talabur Horje CS, Bruijnen R, Roovers L, Groenen MJ, Joosten FB, Wahab PJ. Contrast enhanced abdominal ultrasound in the assessment of ileal inflammation in Crohn's disease: a comparison with MR enterography. *PLoS One*. 2015;10(8):e0136105.

116. Paredes JM, Ripollés T, Cortés X, et al. Contrast-enhanced ultrasonography: usefulness in the assessment of postoperative recurrence of Crohn's disease. *J Crohns Colitis*. 2013;7(3):192-201.

117. Reich B, Zalut T, Weiner SG. An international evaluation of ultrasound vs. computed tomography in the diagnosis of appendicitis. Int *J Emerg Med*. 2011;4:68.

118. Incesu L, Yazicioglu AK, Selcuk MB, Ozen N. Contrast-enhanced power Doppler US in the diagnosis of acute appendicitis. *Eur J Radiol*. 2004;50(2):201-209.

119. Mostbeck G, Adam EJ, Nielsen MB, et al. How to diagnose acute appendicitis: ultrasound first. *Insights Imaging*. 2016;7(2):255-263.

120. Laugesen NG, Nolsoe CP, Rosenberg J. Clinical applications of contrast-enhanced ultrasound in the pediatric work-up of focal liver lesions and blunt abdominal trauma: a systematic review. *Ultrasound Int Open*. 2017;3(1):E2-E7.

121. Coleman JL, Navid F, Furman WL, McCarville MB. Safety of ultrasound contrast agents in the pediatric oncologic population: a single-institution experience. *AJR Am J Roentgenol*. 2014;202(5):966-970.

122. Yusuf GT, Sellars ME, Deganello A, Cosgrove DO, Sidhu PS. Retrospective analysis of the safety and cost implications of pediatric contrast-enhanced ultrasound at a single center. *AJR Am J Roentgenol*. 2017;208(2):446-452.

123. Gale HI, Gee MS, Westra SJ, Nimkin K. Abdominal ultrasonography of the pediatric gastrointestinal tract. *World J Radiol*. 2016;8(7):656-667.

124. Riccabona M. Application of a second-generation US contrast agent in infants and children—a European questionnaire-based survey. *Pediatr Radiol*. 2012;42(12):1471-1480.

125. Sidhu PS, Choi BI, Nielsen MB. The EFSUMB guidelines on the non-hepatic clinical applications of contrast enhanced ultrasound (CEUS): a new dawn for the escalating use of this ubiquitous technique. *Ultraschall Med*. 2012;33(1):5-7.

126. Piscaglia F, Bolondi L; Italian Society for Ultrasound in Medicine and Biology (SIUMB) Study Group on Ultrasound Contrast Agents. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. *Ultrasound Med Biol*. 2006;32(9):1369-1375.

127. ter Haar G. Safety and bio-effects of ultrasound contrast agents. *Med Biol Eng Comput*. 2009;47(8):893-900.

128. The FDA removes the contraindication for use of Bracco Diagnostics Inc.'s Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use or intravesical use, in patients with cardiac shunts [press release]. January 11, 2017. https://imaging.bracco.com/sites/braccoimaging.com/files/technica_sheet_pdf/us-en-2017-01-11-pr-lumason-contraindication.pdf. Accessed June 4, 2018.

129. Skyba DM, Price RJ, Linka AZ, Skalak TC, Kaul S. Direct in vivo visualization of intravascular destruction of microbubbles by ultrasound and its local effects on tissue. *Circulation.* 1998;98(4):290-293.

130. Piskunowicz M, Kosiak W, Irga N. Primum non nocere? Why can't we use second generation ultrasound contrast agents for the examination of children? *Ultraschall Med.* 2011;32(1):83-86.

131. Tranquart F, Correas JM, Ladam Marcus V, et al. Real-time contrast-enhanced ultrasound in the evaluation of focal liver lesions: diagnostic efficacy and economical issues from a French multicentric study [in French]. *J Radiol.* 2009;90(1 pt 2):109-122.

132. Romanini L, Passamonti M, Aiani L, et al. Economic assessment of contrast-enhanced ultrasonography for evaluation of focal liver lesions: a multicentre Italian experience. *Eur Radiol.* 2007;17(suppl 6):F99-F106.

133. Faccioli N, D'Onofrio M, Comai A, Cugini C. Contrast-enhanced ultrasonography in the characterization of benign focal liver lesions: activity-based cost analysis [in English, Italian]. *Radiol Med.* 2007;112(6):810-820.

134. Piscaglia F, Leoni S, Cabibbo G, et al. Cost analysis of recall strategies for non-invasive diagnosis of small hepatocellular carcinoma. *Dig Liver Dis.* 2010;42(10):729-734.

135. Sirli R, Sporea I, Martie A, Popescu A, Danila M. Contrast enhanced ultrasound in focal liver lesions—a cost efficiency study. *Med Ultrason.* 2010;12(4):280-285.

136. Lorusso A, Quaia E, Poillucci G, Stacul F, Grisi G, Cova MA. Activity-based cost analysis of contrast-enhanced ultrasonography (CEUS) related to the diagnostic impact in focal liver lesion characterisation. *Insights Imaging.* 2015;6(4):499-508.

137. Westwood M, Joore M, Grutters J, et al. Contrast-enhanced ultrasound using SonoVue® (sulphur hexafluoride microbubbles) compared with contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging for the characterisation of focal liver lesions and detection of liver metastases: a systematic review and cost-effectiveness analysis. *Health Technol Assess.* 2013;17(16):1-243.

138. National Institute for Health and Care Excellence (NICE). SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. Diagnostics guidance 5. https://www.nice.org.uk/guidance/dg5. Published August 29, 2012. Accessed June 4, 2018.

139. Giesel FL, Delorme S, Sibbel R, Kauczor HU, Krix M. Contrast-enhanced ultrasound for the characterization of incidental liver lesions—an economical evaluation in comparison with multi-phase computed tomography [in German]. *Ultraschall Med.* 2009;30(3):259-268.

This activity can be found at
**www.ImagingEducation.com**,
scroll to **Ultrasound**

IMAGING Education™

©2020-2024 All Rights Reserved. ABC Medical Education LLC.