Contrast-enhanced US Assessment of Focal Liver Lesions in Children[1]

Sudha A. Anupindi, MD
David M. Biko, MD
Aikaterini Ntoulia, MD, PhD
Laura Poznick, RDMS
Trudy A. Morgan, RDMS
Kassa Darge, MD, PhD
Susan J. Back, MD

Abbreviations: CEUS = contrast-enhanced US, FDA = U.S. Food and Drug Administration, FNH = focal nodular hyperplasia, MI = mechanical index

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[1]From the Department of Radiology, The Children's Hospital of Philadelphia, University of Pennsylvania, Perelman School of Medicine, 3401 Civic Center Blvd, Philadelphia, PA 19104. Recipient of a Certificate of Merit award for an education exhibit at the 2016 RSNA Annual Meeting. Received March 31, 2017; revision requested May 11 and received June 8; accepted June 15. For this journal-based SA-CME activity, the authors, editor, and reviewers have disclosed no relevant relationships. **Address correspondence to** S.A.A. (e-mail: *Anupindi@email.chop.edu*).

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

■ Understand the available types of intravenous US contrast agents, as well as their composition, physiologic properties, and safety profiles for use in children.

■ Describe the applications for using intravenous US contrast agents to assess focal liver lesions in children.

■ Recognize the enhancement patterns of common liver lesions on CEUS images obtained in pediatric patients.

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Ultrasonography (US) is often the first line of imaging for the examination of children suspected of having liver lesions. However, gray-scale US with color Doppler imaging has limitations. The use of US contrast agents has recently been approved by the U.S. Food and Drug Administration (FDA). Compared with other imaging modalities, contrast material–enhanced US (CEUS) enables the assessment of contrast enhancement patterns with a higher temporal resolution and is therefore becoming a valuable alternative imaging technique. CEUS is advantageous owing to its high safety profile; lower cost, compared with the costs of conventional contrast-enhanced computed tomographic and magnetic resonance imaging examinations; reliability; and reproducibility. Furthermore, US examinations obviate the use of sedation, ionizing radiation, and iodinated or gadolinium-based contrast agents. All of these are desirable attributes for an imaging examination for children, the most vulnerable of patients. Focal liver lesions in children are commonly discovered incidentally, and this can pose a dilemma in terms of diagnosis and management. Owing to the FDA's recent approval of the use of a specific US contrast agent for evaluation of focal liver lesions in pediatric patients, CEUS can now be used as a problem-solving tool that complements conventional imaging examinations and aids in the follow-up of lesions. The temporal resolution with CEUS enables US images to readily depict the real-time internal vascularity of a lesion. The characterization of a lesion during different phases of enhancement improves diagnostic confidence and treatment. In this article, the authors review the composition, physiologic properties, and safety profile of CEUS; describe the technique for performing CEUS; and highlight the utility of this examination in the assessment of common focal liver lesions in children.

Online supplemental material is available for this article.

Introduction

Ultrasonography (US) is often the first line of imaging for the examination of children suspected of having liver lesions (1,2). However, gray-scale US with color Doppler imaging can be insufficient for rendering a diagnosis. Although magnetic resonance (MR) imaging yields additional information to further characterize a hepatic lesion, it may not be readily available and young children must be sedated to undergo this examination. In addition, MR imaging–based diagnosis can be limited by motion degradation and small lesion size (1–3). The U.S. Food and Drug Administration (FDA) recently approved the use of an intravenous US contrast agent for liver imaging and intravesical applications in pediatric patients. Owing to this approval, contrast material–enhanced US (CEUS) is becoming a valuable alternative to standard US and contrast-enhanced computed tomography (CT) and MR imaging examinations. It offers

TEACHING POINTS

- Contrast material–enhanced US (CEUS) is becoming a valuable alternative to standard US and contrast-enhanced computed tomography (CT) and MR imaging examinations. It offers the advantages of a high safety profile; lower cost, compared with the costs of conventional contrast-enhanced CT and MR imaging examinations; diagnostic reliability; and reproducibility.
- For pediatric liver applications, the FDA-approved dose of sulfur hexafluoride lipid–type A microspheres (Lumason) is 0.03 mL/kg, with a maximum of 2.4 mL per dose.
- In cases in which a focal liver lesion cannot be readily classified as benign or malignant, it is classified as indeterminate. In these situations, CEUS can be used to characterize the enhancement pattern of the lesion.
- The reference-standard finding of malignant lesions at intravenous CEUS is early intense arterial enhancement (ie, hypervascularity), which sometimes manifests with visible abnormal vessels feeding the mass and early contrast agent washout during the portal venous phase.
- CEUS cannot replace CT for the examination of patients who are hemodynamically unstable and/or have sustained a polytrauma. Rather, it is useful for screening children who have sustained a low-energy impact isolated to the abdomen and are hemodynamically stable, evaluating solid-organ injuries, and monitoring lesions that are being managed conservatively.

the advantages of a high safety profile; lower cost, compared with the costs of conventional contrast-enhanced CT and MR imaging examinations; diagnostic reliability; and reproducibility (3–5). In addition, performing CEUS obviates the use of sedation, ionizing radiation, and iodinated or gadolinium-based contrast agents (3–5). US is a child- and family-friendly examination, as it can be performed with a family member (or family members) next to the child to ease stress. With CT and MR imaging, the equipment prohibits close contact between the child and his or her family during the procedure. Also, US can be performed at the point of care. The technique for performing intravenous CEUS has been well described (4). Leading US system vendors provide contrast agent–specific software that has facilitated the introduction of CEUS into clinical practice. US contrast agents can be administered through a vein, the urinary bladder, or a body cavity. However, this article is focused on intravenous applications in the liver.

The tolerability and safety of US contrast agents in adults and children are summarized in recent publications and European consensus guidelines (5,6). The majority of adverse reactions documented in pediatric publications have been minor, and to date, there has been only one report of US contrast agent–related pediatric anaphylaxis—to our knowledge (6). US contrast agents are not nephrotoxic and therefore are safe for patients with renal impairment.

Focal liver lesions are often discovered incidentally in children, posing a dilemma in terms of diagnosis and management. A focal liver lesion is the most common indication for intravenous CEUS in children (3,7). The recent FDA approval of sulfur hexafluoride lipid–type A microspheres (Lumason; Bracco Diagnostics, Monroe Township, NJ) for the evaluation of focal liver lesions in children has enabled the use of CEUS as a problem-solving tool that complements conventional imaging examinations and aids in lesion follow-up (3,8). CEUS can readily depict the real-time internal vascularity of a lesion and can be performed at the patient's bedside. The appearance of a lesion during different phases of contrast enhancement improves diagnostic confidence and treatment.

In this article, we review the composition, physiologic properties, and safety profile of US contrast agents and describe our technique for performing CEUS, highlighting its utility in the assessment of common focal liver lesions in children. We also review the CEUS enhancement patterns of common hepatic pathologic processes encountered in children—specifically, hemangioma, focal nodular hyperplasia (FNH), focal fat, hepatic adenoma, regenerative nodules, hepatic malignancy, and trauma.

US Contrast Agents

Second-generation US contrast agents (Table 1) were introduced in the late 1990s. The second-generation US contrast agent used most commonly worldwide is sulfur hexafluoride lipid–type A microspheres (SonoVue; Bracco, Milan, Italy). In October 2014, this agent became commercially available in the United States with a new trade name (Lumason). The initial FDA-approved application for this agent was improved visualization of the ventricular walls during contrast-enhanced echocardiography in adult patients. In April 2016, the FDA revised the application labeling for this contrast material to include evaluation of liver lesions in adults and children (8). Two other second-generation US contrast agents marketed in the United States, perflutren protein–type A microspheres (Optison; GE Healthcare, Pittsburgh, Pa) and perflutren lipid microspheres (Definity; Lantheus Medical Imaging, North Billerica, Mass), are FDA approved for echocardiographic use in adults. Although noncardiac adult and pediatric applications are currently designated as off-label uses of these agents, both of these materials have been used for intravenous CEUS in children (9,10).

Composition, Storage, Handling, and Physical-Chemical Properties

Second-generation US contrast agents are suspensions of tiny gas-filled microbubbles that are

encapsulated within an outer shell. The gas core comprises most of the microbubble's volume, and although the type of contained gas varies among different US contrast agents, in all cases, it is a high–molecular-weight inert gas with low solubility in a liquid environment. The outer shell is composed of a stable, highly elastic, biocompatible solid coating that also is of variable composition (11,12).

The sulfur hexafluoride lipid–type A microbubbles are composed of sulfur hexafluoride gas, and the shell is a monolayer of phospholipids (8). The product is supplied as a three-part kit that is stored at room temperature. The kit consists of a 5-mL glass vial of the microspheres, an injection syringe prefilled with a 5-mL diluent of 0.9% sodium chloride, and a minispike. At visual inspection, each vial contains a lower layer of white lyophilized powder and a headspace filled with sulfur hexafluoride gas. To reconstitute this contrast agent, the prefilled syringe contents are injected into the vial. It is important to correctly connect the three components of the kit according to the manufacturer's instructions (8). Connecting these parts in this order ensures that the microbubbles do not escape from the vial.

The perflutren protein–type A microbubbles contain perflutren gas, and the shell is composed of human plasma albumin (13). This product is supplied as a 3-mL glass vial, which must be refrigerated. However, each vial should reach room temperature before it is used. At visual inspection, the vial contains a lower layer of a liquid with a biphasic clear-white appearance, and a headspace filled with perflutren gas.

The perflutren lipid microbubbles contain perflutren gas, and the outer shell is composed of a blend of three different lipids. The product is supplied as a 2-mL glass vial that must be refrigerated; however, the vial should reach room temperature before it is used. At visual inspection, the vial, before reconstitution, contains a lower layer of a clear colorless liquid and a headspace filled with perflutren gas. This contrast agent is reconstituted by means of vial agitation for 45 seconds in a specifically designed activation device (Table 1). Using this device to control the rate and duration of the vial shaking ensures reproducible reconstitution of the contrast agent.

When these US contrast agents are appropriately reconstituted, each has a homogeneous white milky appearance and is ready for use. If the reconstituted agent is not used immediately, however, resuspension of the microspheres by means of hand agitation is required just before administration. Differences in the composition, storage, handling requirements, and pharmacokinetic properties among the three described US contrast agents are outlined in Table 1.

Microbubbles are sensitive to pressure and shear forces. Although they can be handled and administered through needles and catheters smaller than 20 gauge, microbubble loss can occur and the smallest (gauge) catheter that can be used is agent specific (14). The contrast agent administration should be immediately followed by a normal saline flush, which is performed by using a three-way stop-cock valve. The US contrast agent should be administered through the stop-cock port that is parallel (180°) to the intravenous tubing to avoid the microbubble destruction that occurs when the microbubbles are injected through the 90° port (14,15). Some equipment associated with catheter use also may affect the microbubbles. Neutral displacement connectors are needleless attachments to the vascular access catheter that are used at some institutions to minimize the risk of infection and clotting; however, they can also destroy bubbles (15). The term *neutral* refers to the direction of blood flow relative to the vascular catheter when it is disconnected from the Luer lock of the connector. Neutral connectors are improvements upon negative connectors, with which the blood refluxes into the catheter and poses a risk of infection and line clotting.

The overall diameters of the microbbubles in US contrast agents range from 1 to 10 μm and are equal in size to or smaller than an erythrocyte. Because of this size, microbubbles circulate freely within the bloodstream, are confined within the vascular system without diffusing into the extracellular space, and are capable of transpulmonary passage (16). Therefore, these agents enhance the intravascular compartment (containing the blood pool contrast agent) exclusively and enable us to characterize the perfusion of solid organs and the lesions within them.

The median duration of contrast enhancement is in the order of minutes, but it varies with each US contrast agent and can be influenced by related coexistent hepatic and pulmonary morbidities and several technical parameters related to the scanning technique, including the brand and/or model of the US unit (16,17).

Once the microbubbles are destroyed, the gas is slowly diffused into the blood and then eliminated through the lungs by way of exhalation. The usual route for metabolism of the phospholipid and albumin shell components is through the liver. Therefore, there is no metabolic burden on the kidneys with these agents, so they are ideal for use in patients with renal impairment (3,16).

Table 1: Differences among Three Second-Generation US Contrast Agents

Parameter	Sulfur Hexafluoride Lipid–Type A Microspheres	Perflutren Protein–Type A Microspheres	Perflutren Lipid Microspheres
Trade name and distributing company	Lumason, Bracco Diagnostics	Optison, GE Healthcare	Definity, Lantheus Medical Imaging
FDA approved for pediatric applications?	Yes	No	No
FDA-approved pediatric application	Intravenous liver and intravesical applications	Not applicable	Not applicable
Commercial packaging	Single vial	Three-part kit	Single vial
Storage conditions	Controlled room temperature	Refrigerated	Refrigerated
Storage temperature	15°–30°C (59°–86°F)	2°–8°C (36°–46°F)	2°–8°C (36°–46°F)
Volume in each vial	5 mL	3 mL	2 mL
Microbubble gas composition	Sulfur hexafluoride	Perflutren	Perflutren
Microbubble shell composition	Lipid	Human albumin	Lipid blend*
Number of microbubbles in each vial	$(1.5–5.6) \times 10^8$ mL	$(5.0–8.0) \times 10^8$ mL	1.2×10^{10} mL
Dosage	0.03 mL per kilogram of body weight	0.3 mL for children weighing <20 kg, 0.5 mL for children weighing ≥20 kg†	0.2–0.3 mL†
Maximal dosage per single dose	2.4 mL	2.15 mL/m²†	10 μL/kg†
Method used to activate microspheres in vial‡	Hand agitation	Hand agitation	Mechanical agitation device
Withdrawal syringe provided?	Yes	No	No

*The lipid blend consists of the following: (R) – hexadecanoic acid, 1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt; (R) - 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt; and (R)-α-[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl]-ω-methoxypoly (ox-1,2-ethanediyl), monosodium salt.
†Based on dosage data in the available literature.
‡Activation of the microspheres, by means of hand or mechanical agitation, results in a reconstituted suspension of homogeneous white milky liquid. A mechanical agitation device (Vialmix; Lantheus Holdings, North Billerica, Mass) is used to activate the perflutren lipid microspheres in the vial.

Mechanism of Action

Although the type of encapsulated gas, composition of the outer shell, and size and concentration of the microbubbles differ among US contrast agents, they all act according to similar basic principles of the interaction between the microbubbles and the US wave.

During each US wave cycle, microbubbles oscillate, repeatedly contracting with positive pressure and expanding with negative pressure, when they are exposed to frequencies in the diagnostic imaging range (11,12,18,19). The *mechanical index* (MI), defined as the ratio of the peak negative pressure divided by the incidence frequency, affects the microbubble response to the acoustic pressures. The higher the MI, the greater the negative pressure and thus the expansible force that will be exerted on the microbubbles (20). At a low MI (<0.1), the bubbles oscillate symmetrically and emit a linear signal with a frequency that is equal to that of the transmitted wave; this is the fundamental frequency. At an increased MI (between 0.2 and 0.6), the bubble resonance is asymmetric, with greater expansion than contraction at each cycle. This asymmetry causes a nonlinear signal, which contains not only the fundamental frequency of the transmitted US wave but also signals from harmonic frequencies that are integer multiples of the fundamental frequency and improve image quality. If the bubbles are exposed to an even higher MI (>0.6), the expansion force is so strong that it results in microbubble disruption, or cavitation, which produces a strong but transient harmonic signal. Similar to microbubbles, biologic tissue oscillates upon interaction with US waves. However, the amplitude of the oscillations generated by the flexible microbubbles is higher than that of the oscillations created by the less compressible biologic tissue. The inherent difference in acoustic impedance that occurs at the boundary of two materials with different attenuation coefficients, such as the gas-blood or

gas–soft tissue interface, coupled with the microbubble oscillations further contributes to the strong backscatter signal from the reflection of the US waves at the microsphere-blood interface (12). The sensitivity of the US system to detect microbubbles depends on the capability of the system to differentiate between the signal from the microbubbles and the signal from the background tissue (18). Most modern US units use embedded contrast harmonic imaging software to improve microbubble detection and low-MI technology to enable continuous visualization of the microbubbles and prevent their destruction (21). The overall intensity of the contrast agent signal depends on the power and frequency of the insonation and the concentration of microspheres.

In addition, selecting the appropriate display mode can lead to further improved microbubble visualization. There are three main display options: *(a)* gray-scale display alone, *(b)* gray-scale display with microbubbles visualized as a color overlay, and *(c)* contrast-only display, whereby the signal from the background tissue is suppressed such that only the microbubbles appear—as bright spots (22). A dual screen on which contrast-only and gray-scale images are displayed side by side also may be used.

Intravenous CEUS Examination

Technique

No blood or urine tests are required to assess renal function before intravenous CEUS is performed. Initially, a baseline nonenhanced abdominal US examination of the lesion(s) or organ(s) of concern is performed. If a focal parenchymal lesion is a concern, the lesion should be viewed on the gray-scale portion of a dual gray-scale–contrast-only display screen, with the image settings optimized. The contrast agent is injected, and a saline flush is administered immediately thereafter. A timer on the US unit is started when the contrast material is administered. For evaluation of focal liver lesions, continuous low-MI imaging is performed for 1–2 minutes as a cinematic clip; then, static images are obtained for 5 minutes or longer to capture all phases of contrast enhancement. Depending on the quality of the imaging examination and the number of lesions, more than one injection may be required. The performance of CEUS can deteriorate owing to low bubble concentration, tissue motion, slow perfusion, or inappropriate settings of the technical parameters. The image clips are reviewed frame by frame for clear visualization of all phases of the lesion's contrast perfusion. Static images of important diagnostic phases can be saved from these clips.

Contrast Agent Dosing

For pediatric liver applications, the FDA-approved dose of sulfur hexafluoride lipid–type A microspheres (Lumason) is 0.03 mL/kg, with a maximum of 2.4 mL per dose. Before the FDA approved the use of this agent, several dosing schemes for intravenous applications were proposed and used, and they varied according to the age or weight of the patient, US unit and transducer used, and indication for the examination. The dose might need to be increased when high-frequency transducers are used, the lesion is deep, and/or the patient is obese. An increased dose may also be required when structures with small vessels or relatively little blood flow, as compared with the liver or other large abdominal organs, are imaged (3). The following are the most commonly proposed dosing schemes for sulfur hexafluoride lipid–type A microspheres: *(a)* 0.6 mL for children younger than 6 years, 1.2 mL for children aged 6–12 years, and 2.4 mL for children older than 12 years (23); *(b)* 0.1 mL per each year of age (24); *(c)* 0.1 mL/kg for children weighing up to 24 kg and the standard dose of 2.4 mL for children weighing more than 24 kg (25); and *(d)* fixed doses of 0.1, 0.5, 1.2, 2.4, and 4.8 mL each (6,26,27).

For perflutren protein–type A microspheres (Optison), the most commonly reported dosing scheme is 0.3 mL for children weighing less than 20 kg and 0.5 mL for those weighing 20 kg or more (10,28,29).

To our knowledge, there have been no dedicated studies on the use of perflutren lipid microspheres (Definity) conducted exclusively with children. There have been a few studies (30–33) involving limited experiences with the intravenous use of this agent for cardiac, neuroimaging, and liver applications in mixed adult and pediatric populations. The proposed dosing scheme in these studies was a fixed injection of 0.2–0.3 mL. However, the published accounts of these studies do not include specific information regarding the number of children included or whether dose adjustments specifically for children were performed.

Contrast agent doses may also vary according to the US machine, contrast agent–specific software, or transducer used; the location of the lesion; and/or whether the examination involves organs with small blood vessels and slower blood flow (3).

Safety of Intravenous Contrast Agent Administration

In a recently published review (34), the authors describe their analysis of original research and five case studies of the intravenous administration of sulfur hexafluoride lipid–type A microspheres exclusively in pediatric populations. Overall, 502

Table 2: Common Reasons for Performing Intravenous CEUS in Children at the Authors' Institution

Evaluation of incidentally discovered focal liver lesions
Problem solving
Examination after blunt abdominal trauma
MR imaging is contraindicated
Compromised renal function
Patient at high risk of requiring sedation or general anesthesia

children underwent 655 intravenous CEUS examinations; 583 (89%) of these examinations were performed with sulfur hexafluoride lipid–type A microspheres, and 66 (10%) were performed with perflutren protein–type A microspheres. Ten children (2%) experienced adverse events related to the US contrast agent administration: one severe reaction and nine mild reactions (34).

Piskunowicz et al (6) described one acute severe event in a large safety study dedicated to pediatrics. In that study, 137 children underwent a total of 161 intravenous CEUS examinations, and one case of severe anaphylactic shock directly related to intravenous administration of the sulfur hexafluoride lipid–type A microsphere agent occurred in an 11-year-old girl. The nine mild adverse events in that study included three headaches and three cases of altered taste buds, with less frequently reported symptoms of nausea, tinnitus, and lightheadedness. Others have reported rare delayed adverse reactions, including transient hypertension and transient tachycardia (9,23–25). Thus far, no severe adverse events associated with intravenous administration of perflutren protein–type A microspheres in children have been reported.

The frequency of adverse events associated with the intravenous use of US contrast agents is lower than that associated with the use of iodinated contrast material at CT and similar to that associated with the use of gadolinium-based contrast agents. However, the long-term effects of gadolinium-based contrast material deposition in tissue are unknown (35,36). In addition, the absence of ionizing radiation exposure, sedation, and nephrotoxicity makes the overall safety profile of US contrast agents very favorable.

Cost Benefits

There are few published works that address the financial benefits of performing CEUS in adults or children. The available data are primarily from European centers (23,37–39). An analysis and review of the use of intravenous CEUS for assessment of focal liver lesions conducted in two separate adult studies (38,39) revealed that CEUS, as compared with contrast-enhanced CT and contrast-enhanced MR imaging, has similar diagnostic performance and is cost-effective according to institutional and regional health care economic parameters. Yusuf et al (23) had similar findings in a recent pediatric study; however, they also emphasized that using CEUS for the evaluation of focal liver lesions led to a reduced number of CT examinations and thereby decreased the radiation burden, to which a cost cannot be assigned. Although the overall cost savings associated with performing CEUS cannot be compared across different continents and practices, the main points regarding the cost-effectiveness of CEUS communicated by these investigators are promising.

Indications and Advantages

At our institution, intravenous CEUS has been used to evaluate various organs, including but not limited to the liver, kidneys, pancreas, testes, and uterus. However, a focal liver lesion is by far the most common indication for intravenous CEUS (3,7,34). Focal liver lesions are often incidentally discovered during abdominal imaging performed for other reasons, such as to determine the cause of vomiting or nonspecific abdominal pain. In cases in which a focal liver lesion cannot be readily classified as benign or malignant, it is classified as indeterminate (26). In these situations, CEUS can be used to characterize the enhancement pattern of the lesion. Investigators in a pediatric study (26) involving 44 patients reported intravenous CEUS to have a specificity of 98% for the classification of an indeterminate lesion as benign. This group found agreement between the CEUS-based interpretations of focal liver lesion findings and both the reference imaging– and histologic analysis–based interpretations in 85% of cases (26).

In children with chronic liver disease and cirrhosis, surveillance MR imaging can depict small indeterminate lesions for which further evaluation is required, and in these cases, intravenous CEUS can be used for problem solving (Table 2) (40,41). CEUS is ideal for children who are at high risk of requiring sedation or general anesthesia, have implants or devices that make them ineligible to undergo MR imaging, and/or are too critically ill to travel to the radiology facility. Patients with renal impairment who cannot receive iodinated or gadolinium-based contrast material can safely undergo intravenous CEUS at the bedside if needed, as the contrast agents are not nephrotoxic (Table 2). CEUS is often readily available, it can be scheduled more easily than can CT or MR imaging, and immediate results

and feedback can be delivered to the patient or parent(s) and the referring physician (Table 3).

The main limitations of CEUS are those that are inherent to the US modality, including poor visibility of lesions in patients with a large body habitus and lesions that are deep in the liver. CEUS might not have the capability to depict the width of disease burden, especially in cases of malignancy. In these cases, further cross-sectional imaging with CT and MR imaging is helpful for enabling a more comprehensive assessment of the disease burden and appropriate disease staging in patients diagnosed with a primary malignancy. Although CEUS is operator dependent and there is variability among vendor contrast agent–specific software packages, with training and education, operators can obtain excellent results. The current indications for intravenous CEUS in our department and the advantages of using intravenous CEUS are listed in Tables 2 and 3, respectively.

Table 3: Advantages of Performing Intravenous CEUS in Children

High safety profile (no ionizing radiation, sedation, or nephrotoxicity)
No *nil per os* (nothing by mouth) requirement
Portable examination
Patient and family friendly
High resolution
Lower cost than CT and MR imaging
Can be scheduled more easily than CT and MR imaging
Timely feedback to patient, parent(s), and physician

Focal Liver Lesions

In our practice, as in previously published pediatric studies (3,4,26,42), the most common focal liver lesions evaluated by using intravenous CEUS are hemangioma, FNH, focal fat, regenerative nodules, and hepatic trauma. In this article, we describe the CEUS findings and appearances of these lesions, as well as those of malignant focal liver lesions and the rare hepatic adenoma. Newly identified benign lesions can be easily followed up with CEUS in short 3–6-month intervals for up to a year. Once the stability of the lesion is established, a yearly gray-scale US examination may suffice. Unless otherwise stated, all of the CEUS examinations described herein were performed with sulfur hexafluoride lipid–type A microspheres (Lumason).

Hemangioma

Hemangioma is the most common benign vascular tumor of infancy (2,43,44). There are three subtypes of infantile hepatic hemangioma: focal, multifocal, and diffuse (2,44,45). Focal infantile hemangioma may be the hepatic form of the rapidly involuting congenital hemangioma; however, the relationship between these two entities is controversial (44,46). Focal infantile hepatic hemangioma is not associated with cutaneous hemangiomas, is typically diagnosed in patients at birth, and involutes when the patient is aged 12–14 months (2,45). Multifocal infantile hemangioma is associated with cutaneous hemangiomas and manifests in children aged approximately 6 months. With the diffuse form of infantile hemangioma, there is nearly complete replacement of the liver by hemangiomas (45).

The imaging characteristics of focal, multifocal, and diffuse hemangiomas are variable. With focal infantile hemangiomas, the US appearance of smaller infantile hemangiomas is homogeneous in echotexture, whereas the appearance of larger lesions is heterogeneous (2,47). Echogenic foci with posterior acoustic shadowing that represents calcification can be seen with focal infantile hemangioma (2,44,47). Arteriovenous or portovenous shunts may be present (48). With multifocal disease, there are multiple spherical lesions with normal intervening liver parenchyma (44). The presence of enlarged hepatic arteries or veins, with or without distal aortic tapering, may indicate an arteriovenous shunt, which can cause high-output cardiac failure (48). With diffuse disease, the liver may be either large without discrete masses or replaced by multiple hypoechoic masses (2,44,47,48).

There is a paucity of data on the enhancement patterns of infantile hemangiomas at CEUS. However, the enhancement patterns of these lesions, similar to those of other liver lesions, should have the same characteristics as those of lesions seen on multiphase CT and MR images. The typical enhancement pattern of a focal infantile hemangioma at CEUS has been described as peripheral and nodular, with centripetal progression during the portal venous phase and progression to complete enhancement (24,47,49) (Figs 1, 2; Movie 1). This is similar to the enhancement pattern seen on multiphase CT and MR images, where both focal and multifocal infantile hemangiomas demonstrate peripheral centripetal enhancement (47,48). Focal lesions may have central heterogeneous enhancement due to necrosis, hemorrhage, or thrombosis (48). The enhancement pattern of diffuse disease also has been described as that involving innumerable lesions with centripetal enhancement (48).

Focal Nodular Hyperplasia

FNH is a benign epithelial tumor arising from a polyclonal proliferation of Kupffer cells, hepatocytes, vascular structures, and biliary ductules

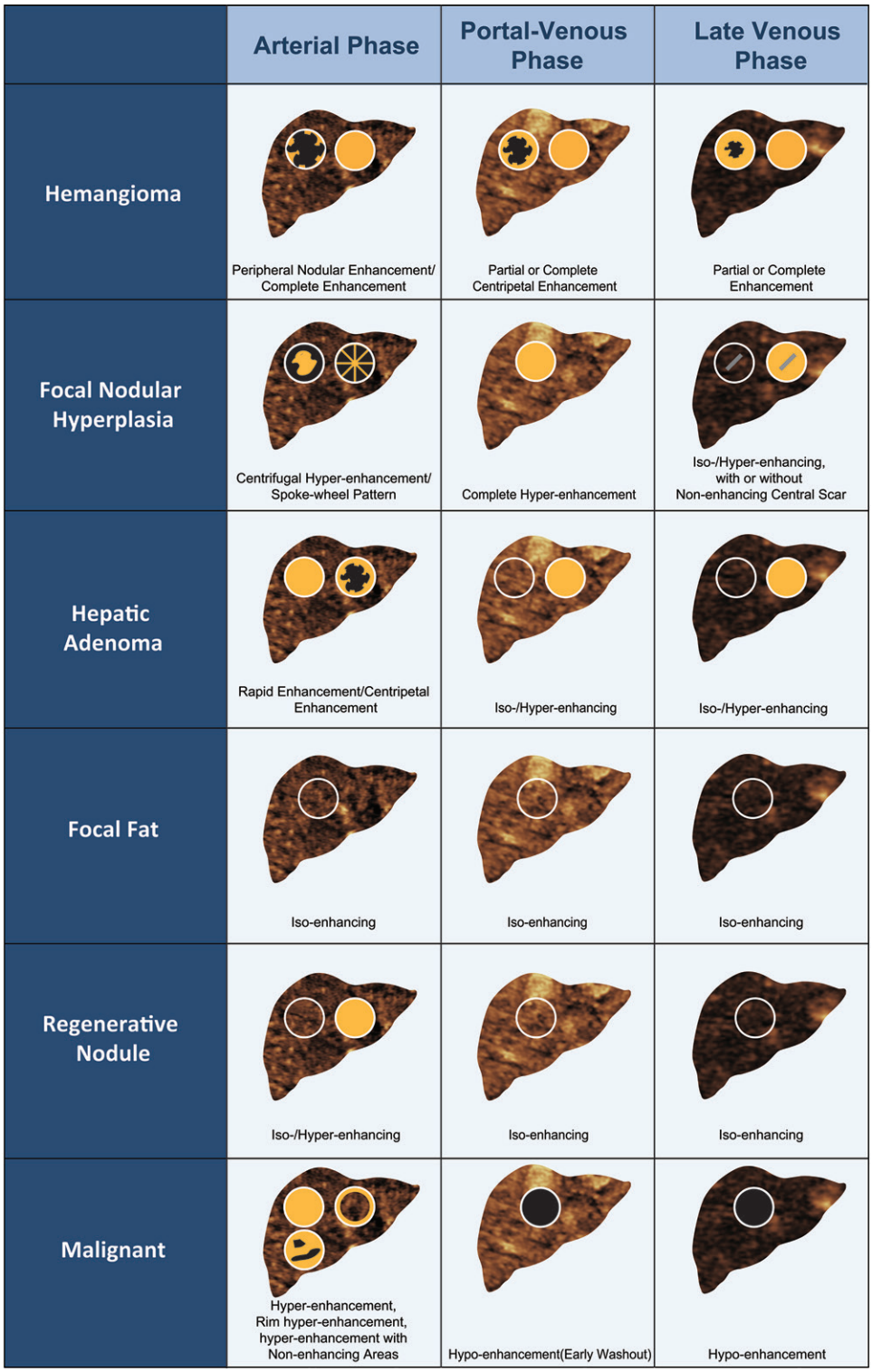


Figure 1. Schematic diagram illustrates the intravenous CEUS enhancement patterns of pediatric focal liver lesions during the arterial, portal venous, and late venous phases. Each circle represents a focal liver lesion. The different potential enhancement patterns for a particular lesion are illustrated with two or more circles. In the circles, orange shading represents contrast enhancement; black shading, nonenhancement or hypoenhancement; and a linear gray line, central scarring. *Nonenhancing* refers to an area without contrast enhancement (eg, due to blood or necrosis). *Hypoenhancement* refers to an area with enhancement lower than that of the liver parenchyma during the given phase; this is usually a lesion with early contrast material washout.

(2,50). FNH accounts for 2%–4% of pediatric liver tumors and is the most common benign nodular hepatic lesion that develops after treatment of childhood cancer (2,50,51). It is most commonly diagnosed as an incidental finding in pediatric patients aged 2–5 years (2,52).

The US findings of FNH are often nonspecific. These hyperplasias are most often well-circumscribed masses, but they may be hypoechoic, hyperechoic, or isoechoic. A central scar is present in approximately 20% of cases and, if seen, is hyperechoic relative to the remainder of the lesion (2,50,52,53). Evaluation with color Doppler US reveals a central feeding artery with a spoke-wheel or stellate pattern (2,52).

At CEUS, FNH typically demonstrates centrifugal or homogeneous enhancement during the arterial and portal venous phases (49,54–56)

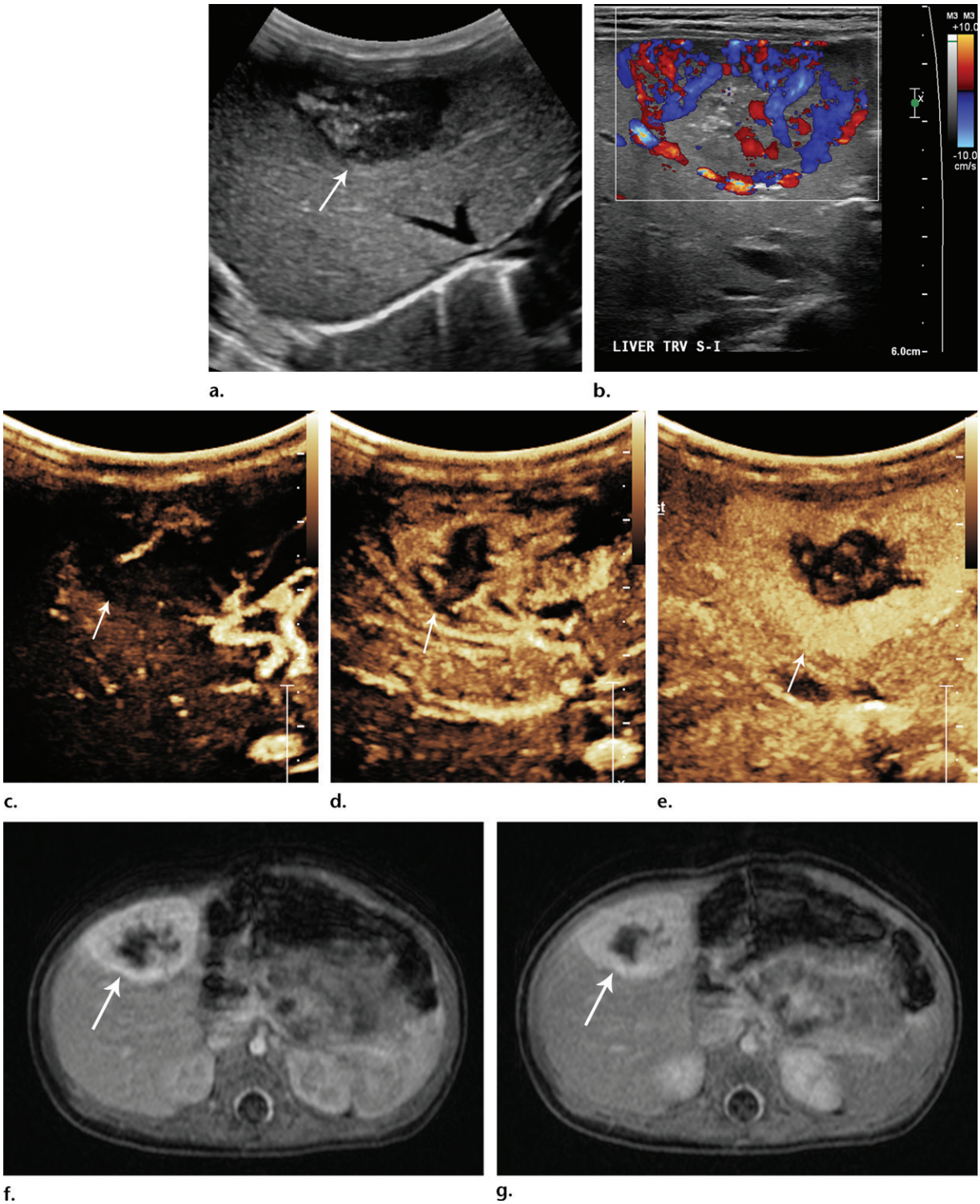
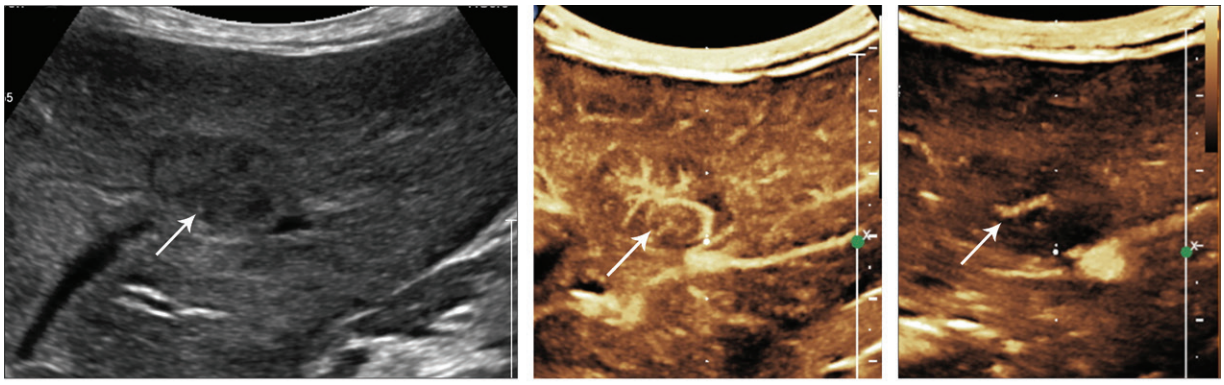


Figure 2. Rapidly involuting congenital hemangioma in a 39-day-old boy in the intensive care unit. This lesion was an incidental finding at pyloric US performed to determine the cause of vomiting. **(a, b)** Transverse gray-scale **(a)** and color Doppler **(b)** US images show a partially calcified focal mass (arrow in **a**) in the right liver lobe, with increased, predominantly peripheral vascular flow on the color Doppler image. **(c–e)** Transverse CEUS images obtained during the arterial **(c)**, portal venous **(d)**, and late venous **(e)** phases of enhancement show progressive centripetal enhancement of the lesion (arrow). **(f, g)** Similar to the CEUS images, the follow-up axial contrast-enhanced arterial **(f)** and portal venous **(g)** phase MR images show a peripherally enhancing lesion (arrow). CEUS revealed the classic enhancement pattern of infantile hepatic hemangioma and was comparable to conventional dynamic contrast-enhanced MR imaging in the evaluation of this lesion, without the need for sedation. MR imaging was performed to further assess this lesion, as intravenous CEUS was in the incipient stage of use. Performing CEUS at this critically ill patient's bedside in the intensive care unit obviated transport to the radiology department.



a. b. c.

Figure 3. FNH detected incidentally in a 4-year-old boy. **(a)** Sagittal gray-scale US image shows a hypoechoic focal lesion (arrow) in the right liver lobe. **(b)** Sagittal CEUS image obtained during the arterial phase shows early arterial enhancement in a spoke-wheel pattern (arrow) in the center of the lesion. **(c)** Sagittal CEUS image obtained during the late venous phase shows a central scar (arrow) with late enhancement. The spoke-wheel enhancement and central vascular scar are typical features of FNH seen at CEUS, CT, and MR imaging. CEUS scrutiny of the rest of the liver revealed no additional lesions. Follow-up was performed with CEUS; thus, sedation, gadolinium exposure, and the higher cost of MR imaging were avoided.

(Fig 1). The centrifugal enhancement occurs more commonly when lesions are smaller than 3.1 cm (57). During the late venous phase, more than half of these lesions are hyperenhancing compared with the liver parenchyma, and the remaining lesions are isoenhancing (Fig 1) (56). FNH lesions also demonstrate spoke-wheel arteries during the arterial phase, with an early feeding artery just adjacent to the lesion (53,55) (Figs 1, 3). There may be hypoenhancement of the central scar during the late venous phase (49,53) (Figs 1, 3). CEUS can be used to follow up these lesions for short intervals to establish stability.

Focal Fat

Focal fat is commonly found near the gallbladder, liver hilum, or portal bifurcation and has a geographic or polygonal shape (49,58). On gray-scale US images, it is variable in size and appearance and either hypoechoic or hyperechoic. Focal fat tends to be hyperechoic (Fig 4), whereas focal fatty sparing is a hypoechoic area surrounded by a more hyperechoic fatty liver (49). At intravenous CEUS, focal fat exhibits enhancement similar to that of the adjacent normal liver parenchyma during all contrast enhancement phases (58) (Figs 1, 4). These geographic areas are essentially normal tissue, and they do not contain abnormal vessels or exhibit a mass effect on adjacent structures (58). These are benign lesions for which neither CEUS follow-up nor additional imaging is required.

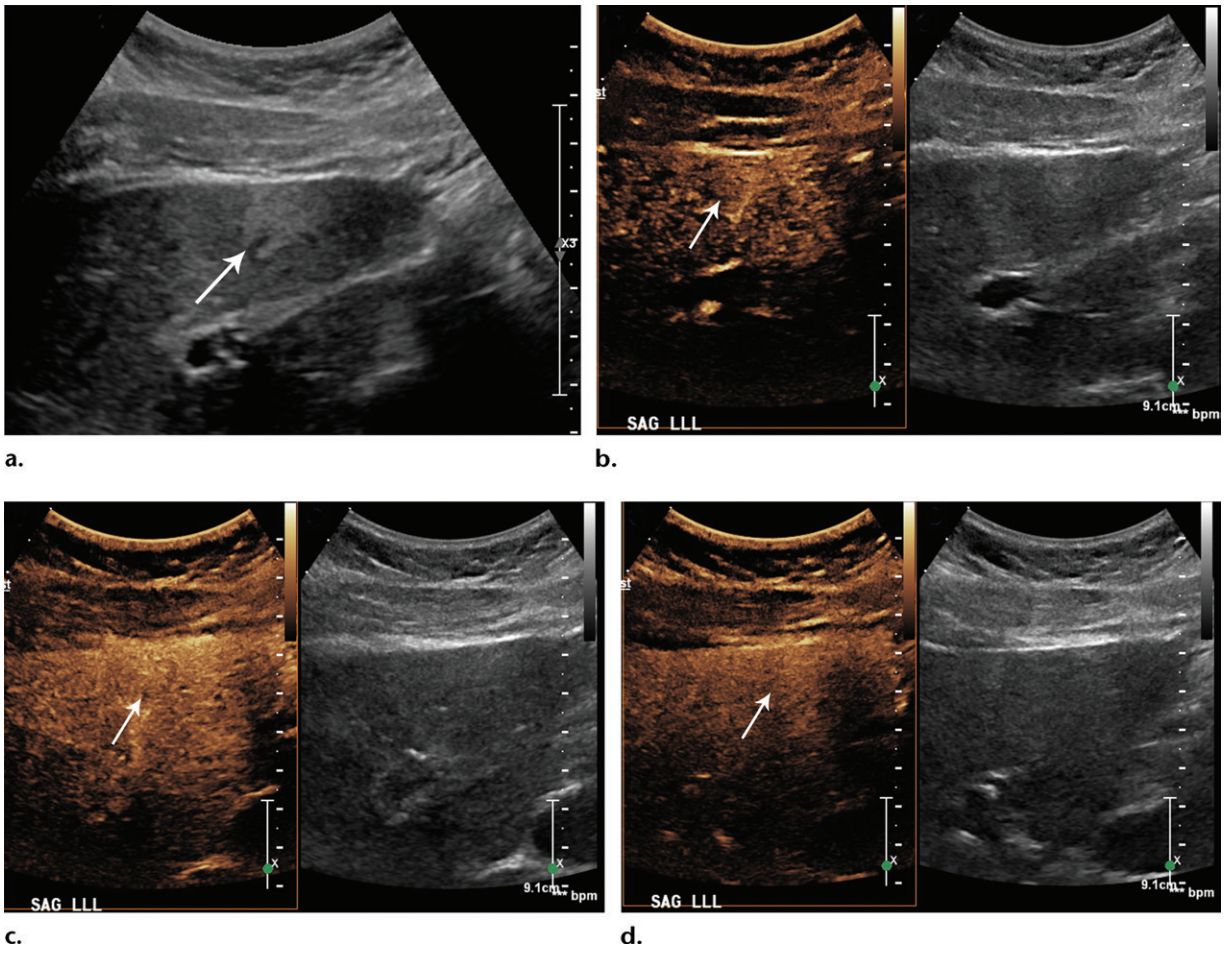
Hepatic Adenoma

Hepatic adenomas are benign lesions associated with the use of steroids (eg, oral contraceptives in young female individuals), and they can contain fat and hemorrhage. These lesions often mimic other benign and malignant lesions owing to their vascular pattern and propensity to bleed and thus may pose a diagnostic dilemma (2). A few pediatric conditions associated with a higher incidence of these lesions are Fanconi anemia, types I and III glycogen storage disease, familial diabetes, galactosemia, and tyrosinemia (2). There are four described classes of hepatic adenomas, with one form having malignancy potential (59). On gray-scale US images, these adenomas are encapsulated and have a variable appearance based on their composition. They may appear hyperechoic (when they contain fat) or iso- or hypoechoic (when they are within a fatty liver) (2). On CT and MR images, hepatic adenomas demonstrate early arterial enhancement and become isoattenuating (at CT) or isointense (at MR imaging) during the portal venous phase (2).

Our experience with hepatic adenomas depicted at CEUS is very limited, as these lesions are rare in children. However, at CEUS, they typically show rapid arterial enhancement in a centripetal fashion and become isoechoic to slightly hyperechoic during the portal and venous phases (Fig 1) (49). Unlike FNH, hepatic adenoma does not have a spoke-wheel arterial vascular pattern or central vascular scar. In a study conducted by Dietrich et al (54) involving eight hepatocellular adenomas, the hepatic adenomas did not enhance during the portal venous phase, and this lack of enhancement helped to distinguish them from FNH. However, this was a limited sample size, and these findings have not been validated in larger studies. These neoplasms can be readily followed up with CEUS for evaluation of lesion growth and potential bleeding.

Regenerative Nodule

Regenerative hepatic nodules, also referred to as nodular regenerative hyperplasias, develop as a



a. b. c. d.

Figure 4. Focal fat discovered incidentally in a 14-year-old girl at US performed to determine the cause of abdominal pain of 2 months' duration. **(a)** Sagittal gray-scale US image shows a focal echogenic lesion (arrow) in the left liver lobe. **(b–d)** Dual-screen sagittal CEUS (left) and gray-scale US (right) images show the lesion (arrow) to be isoenhancing relative to the liver parenchyma during the arterial **(b)**, portal venous **(c)**, and late venous **(d)** phases. MR imaging was not needed to confirm the diagnosis. Focal fat is a benign entity with enhancement similar to that of the adjacent liver parenchyma.

result of nodular transformation of the hepatic parenchyma and are believed to be a hyperplastic response to ischemia or small vessel disease. These nodules are variable in size, measuring only a few millimeters to a few centimeters (2,45). Regenerative hepatic nodules may be idiopathic, but they are associated with several disorders, including myeloproliferative and lymphoproliferative syndromes, congenital heart disease, and lupus erythematosis, and the use of steroids and antineoplastic medications (47).

The US findings depend on the size of the nodules and often have variable and nonspecific appearances (49). Small nodules might not be visualized. Larger nodules may be heterogeneous and distort the normal liver echotexture. However, these lesions can also be echogenic or both echogenic and hypoechoic centrally, probably owing to prior hemorrhage (2,47).

At CEUS, most regenerative nodules are isoenhancing relative to the liver parenchyma during all enhancement phases (Figs 1, 5). However, some nodules may show transient hypoenhancement relative to the liver parenchyma during the arterial phase (40,41). Because the arterial and portal venous blood supplies to these nodules may be inconsistent, hepatocellular carcinoma should still be suspected when a new nodule develops within a cirrhotic liver (41). Small regenerative nodules may not be readily seen on T2-weighted MR images, and in such cases, intravenous CEUS can be used as a problem-solving tool (Fig 5).

Malignancy

Malignant lesions have similar CEUS features, regardless of whether they are primary or metastatic. At gray-scale US, malignant tumors tend to be hypoechoic, but they can have a variable appearance, with features that overlap with those of benign lesions (2,4,58). Although nonenhanced US alone cannot be used to reliably identify a lesion as malignant, intravenous CEUS can facilitate additional characteriza-

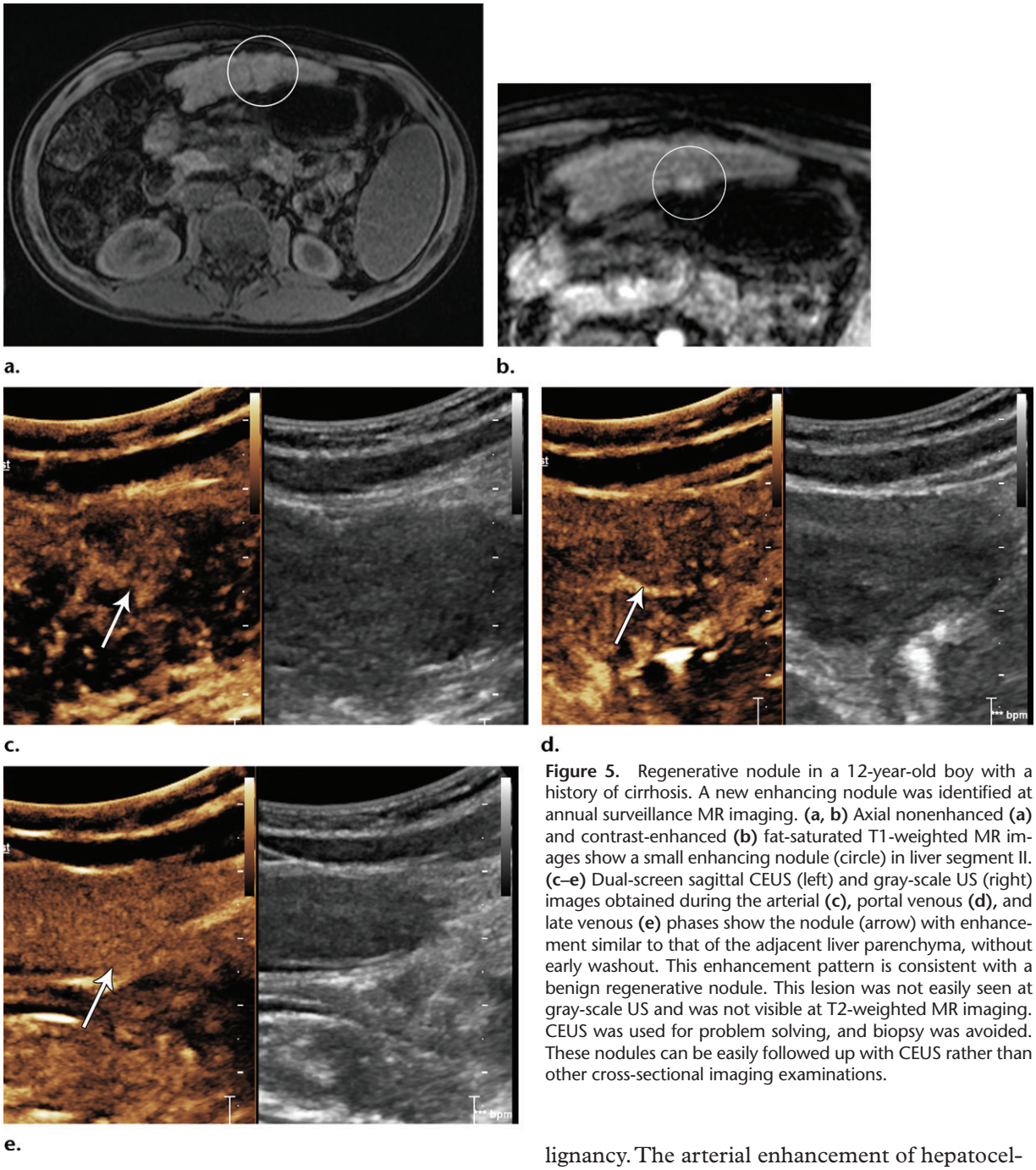


Figure 5. Regenerative nodule in a 12-year-old boy with a history of cirrhosis. A new enhancing nodule was identified at annual surveillance MR imaging. **(a, b)** Axial nonenhanced **(a)** and contrast-enhanced **(b)** fat-saturated T1-weighted MR images show a small enhancing nodule (circle) in liver segment II. **(c–e)** Dual-screen sagittal CEUS (left) and gray-scale US (right) images obtained during the arterial **(c)**, portal venous **(d)**, and late venous **(e)** phases show the nodule (arrow) with enhancement similar to that of the adjacent liver parenchyma, without early washout. This enhancement pattern is consistent with a benign regenerative nodule. This lesion was not easily seen at gray-scale US and was not visible at T2-weighted MR imaging. CEUS was used for problem solving, and biopsy was avoided. These nodules can be easily followed up with CEUS rather than other cross-sectional imaging examinations.

tion that may influence clinical decisions (56). Therefore, further imaging with CT or MR imaging is not always necessary.

The reference-standard finding of malignant lesions at intravenous CEUS is early intense arterial enhancement (ie, hypervascularity), which sometimes manifests with visible abnormal vessels feeding the mass and early contrast agent washout during the portal venous phase (4,42,49) (Figs 1, 6; Movie 2). Investigators in a recent pediatric study (42) reported that the hypoenhancement of focal liver lesions during the portal venous phase was highly specific for malignancy. The arterial enhancement of hepatocellular carcinoma at CEUS has been described as diffuse or heterogeneous, whereas rimlike peripheral arterial enhancement is seen with metastases (Fig 1) (4,56). Some metastases can appear hypoenhancing during the arterial phase (49). With malignant lesions, washout during the portal venous and late venous phases of CEUS is variable, occurring as soon as 60 seconds after the contrast agent injection in some cases and more than 90 seconds after the injection in other cases (58). Hence, it is important to obtain cinematic clips during CEUS and acquire images for at least 3–5 minutes. Another advantage of performing intravenous CEUS to evaluate potentially malignant lesions is that enhancing viable tissue, rather than

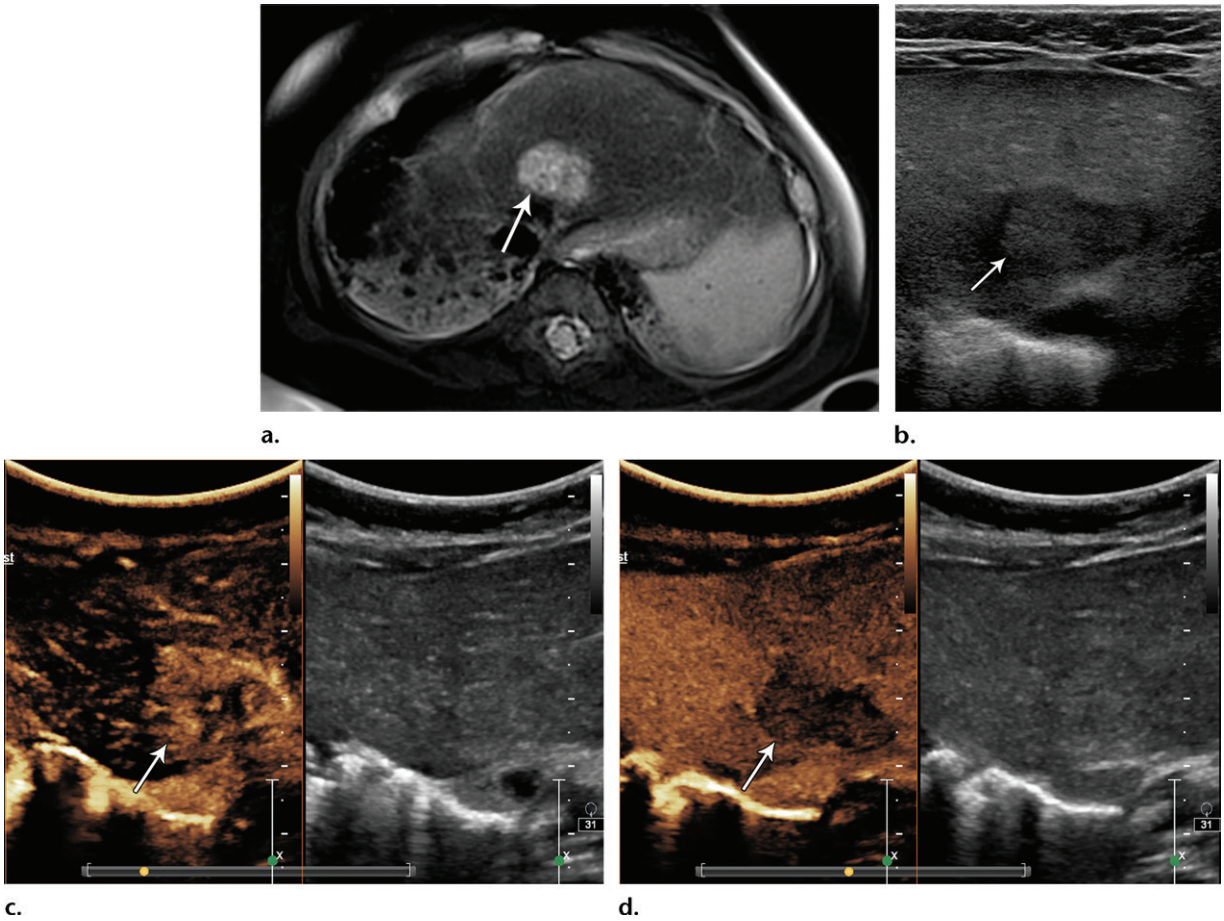


Figure 6. Hepatoblastoma in a 6-month-old girl, who initially underwent MR imaging for assessment of possible precocious puberty owing to an enlarged ovary that was seen at conventional US. **(a)** Axial T2-weighted abdominopelvic MR image shows a hyperintense liver lesion (arrow) that was incompletely assessed at the MR imaging examination, which was tailored for evaluation of precocious puberty. **(b)** Transverse gray-scale US image shows a heterogeneously echogenic liver lesion (arrow) that corresponds to the findings in **a. (c, d)** Transverse CEUS (left) and gray-scale US (right) images show early peripheral enhancement of the lesion (arrow) during the arterial phase **(c)** and brisk contrast agent washout (arrow) during the late venous phase **(d)**. Washout from a lesion during the portal venous phase at CEUS highly correlates with malignancy. α-Fetoprotein levels were elevated. The patient underwent biopsy, and histopathologic findings confirmed the diagnosis of hepatoblastoma. Subsequent MR imaging was not indicated, as no additional lesions were identified at CEUS. Performing CEUS enabled the patient to avoid additional sedation and gadolinium exposure.

nonenhancing necrosis, can be targeted during biopsy for maximal sample yield (58).

Hepatic Trauma

Abdominal injuries occur in 10%–15% of pediatric trauma cases. They more commonly result from falls and recreational activity accidents rather than from motor vehicle collisions, which are the primary cause of these injuries in adults (60). Contrast material administration improves the US detection of trauma-related liver injuries and rivals the detection of these lesions with contrast-enhanced CT in children (60–63). Parenchymal bleeding and trauma-related pseudoaneursyms also can be diagnosed with CEUS (61,64). Similar to solid-organ trauma assessed at CT, liver injuries are scored by using the American Association for the Surgery of Trauma organ injury scale (65).

The US appearance of hepatic trauma is based on whether a contusion, laceration, or hematoma is present, as well as the age of the injury. Hematomas and localized lacerations are initially hyperechoic at gray-scale US and become progressively smaller and hypoechoic with healing and hemolysis (66,67). The borders may be ill defined or well defined (61,68). Following US contrast agent administration, hematomas and lacerations are markedly hypoenhancing compared with the normal parenchyma and are best seen during a delayed phase, when there is diffuse enhancement of the parenchyma (61,62) (Fig 7, Movie 3). The lesions are geographic, and lacerations are often linear and well defined. The extent of injury can be underestimated at gray-scale US and appears larger following contrast agent administration (69). Injured regions that contain contrast material may reflect contusion rather than hematoma or

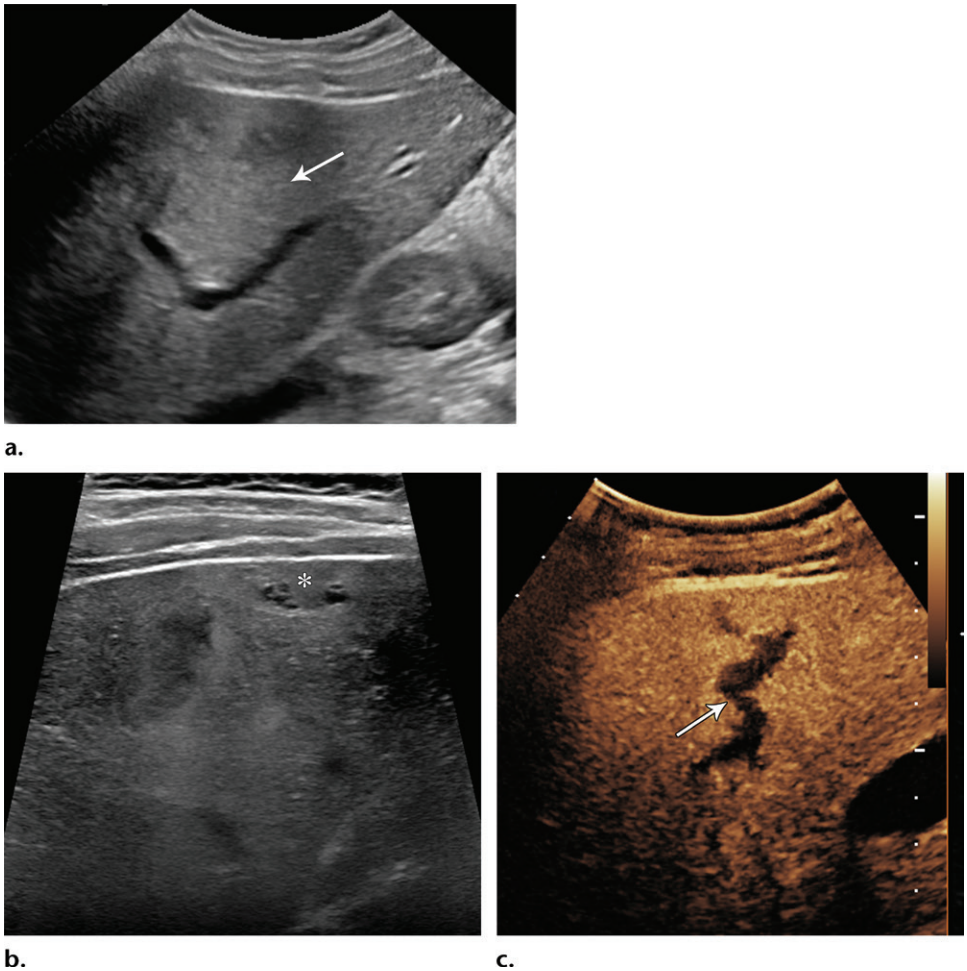


Figure 7. Liver laceration in a 7-year-old girl who fell while playing laser tag. **(a, b)** Sagittal **(a)** and transverse **(b)** gray-scale US images of an area of the liver with increased echogenicity (arrow in **a**) and a subcapsular collection of blood products (* in **b**) show no laceration. **(c)** Sagittal CEUS image shows a serpiginous hypoechoic defect (arrow), consistent with a grade 3 liver laceration (according to the American Association for the Surgery of Trauma scoring system), that is easily differentiated from the normal enhancing liver parenchyma. Performing CEUS in this hemodynamically stable child with a low-energy blunt trauma lesion obviated CT, enabling her to avoid ionizing radiation exposure and iodinated contrast material administration.

laceration (70). CEUS can also be used to follow up these lesions to resolution, and this application has been shown to be successful in adults and children (71).

CEUS cannot replace CT for the examination of patients who are hemodynamically unstable and/or have sustained a polytrauma. Rather, it is useful for screening children who have sustained a low-energy impact isolated to the abdomen and are hemodynamically stable, evaluating solid-organ injuries, and monitoring lesions that are being managed conservatively—and thus for reducing the radiation exposure from CT (3,62).

Conclusion

US is the first imaging examination to be used to evaluate focal liver lesions in children. With the advent of CEUS, these liver lesions can now be better characterized in a safe, well-tolerated, reproducible manner without ionizing radiation, sedation, or exposure to contrast agents that are associated with higher risks for adverse reactions. In addition, CEUS can reveal valuable real-time information about lesion vascularity. Recognition of the various enhancement patterns seen at CEUS of the pediatric focal liver lesions described herein can aid in making definitive diagnoses to help triage those who require intervention rather than conservative management.

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