Practical Contrast Enhanced Liver Ultrasound

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KEYWORDS

• Contrast-enhanced ultrasound • Liver lesion • Adult • Child

KEY POINTS

- Ultrasound contrast agents (UCAs) used for contrast-enhanced ultrasound (CEUS) are exceedingly safe.
- Lesions with contrast retention (no washout) in the delayed phase are overwhelmingly benign.
- Lesions with contrast washout in the delayed phase are concerning for malignancy.
- The American College of Radiology CEUS Liver Imaging, Reporting, and Data System can be used to categorize liver observations, including HCC, in certain at-risk patients.

Abbreviations

MRI	magnetic resonance imaging
GLUT-1	glucose transporter 1
CT	computed tomography
HNF-1α	hepatocyte nuclear factor - 1 alpha

INTRODUCTION

Contrast-enhanced ultrasound (CEUS) use is increasing worldwide, including in the United States, for multiple applications in patients of all ages. CEUS is most performed for focal liver lesion evaluation in adults and children because of its high safety profile and capability to yield a definitive diagnosis.[1] This often obviates multiphase CT or MRI for lesion characterization, which requires the use of ionizing radiation and potentially sedation or general anesthesia, respectively, particularly important in the pediatric population. CEUS leverages the inherent benefits of ultrasound, including portability and accessibility, using specific ultrasound contrast agents (UCAs) that are exceedingly safe, without the risk of renal or liver toxicity.[2] UCAs are cleared rapidly from the body, allowing for multiple injections during a single examination, and have no potential for deposition in the patient.[1]

The purpose of this review is to highlight the applications and technical considerations for performing CEUS for liver lesion evaluation, and to illustrate the imaging appearance of the most common liver lesions encountered in children and adults, emphasizing clinical relevance and current nomenclature.

CONTRAST-ENHANCED ULTRASOUND REQUIREMENTS

An UCA is necessary for CEUS. Current generation UCAs are composed of microbubbles of an inert insoluble fluorocarbon gas stabilized by a lipid

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and/or protein shell, with several formulations available for clinical use. Venous access is needed, and although a peripheral intravenous line or central venous catheter may be used, intravenous contrast material injection is often a new workflow for many ultrasound departments. Additionally, 2 team members are generally needed during a CEUS examination: one to inject the UCA and another to obtain images.

Ultrasound system contrast-specific software is also necessary to perform CEUS. The contrast software automatically decreases power output and other settings to decrease mechanical index and minimize bubble destruction. Other techniques including harmonic imaging with pulse inversion are used to distinguish the bubble-specific signal, and subtract background signal from tissue, allowing for a "contrast-only" image.[3] The contrast software of most vendors' ultrasound systems uses a split-screen display, providing a grayscale image and a contrast-only image simultaneously. The grayscale image enables visualization of the soft tissues for localization. The contrast-only image provides real-time soft tissue subtraction so signal from microbubbles is relatively enhanced, and typically only very echogenic interfaces (eg, organ and vessel walls, calcifications, and bowel gas) from the grayscale image are seen.

CONTRAST-ENHANCED ULTRASOUND LIMITATIONS

Contrast-enhanced CT and/or MRI should be considered rather than CEUS for liver observation evaluation in patients with multiple different appearing liver observations, such as patients with Fontan-associated liver disease, who are at increased risk for both benign and malignant lesions. Contrast-enhanced MRI allows for characterization of the liver and all lesions simultaneously, so is preferred.[4] Portions of the liver poorly seen at grayscale ultrasound will similarly be challenging to visualize at CEUS, such as lesions near the dome of the diaphragm or in the deep right hepatic lobe in large patients or patients with hepatic steatosis. Finally, contrast-enhanced CT and/or MRI should be considered rather than CEUS for masses with high likelihood of requiring complete imaging staging, which cannot be performed at CEUS alone.[4]

CONTRAST-ENHANCED ULTRASOUND TECHNIQUE

A grayscale ultrasound examination preceding CEUS allows for a thorough survey of the hepatic parenchyma, biliary system, and vasculature, and identification of findings of hepatocellular disease and/or portal hypertension, which may influence the differential diagnosis of focal findings in the liver. The liver lesion in question can then be precisely localized, and in a few scenarios, a definitive diagnosis can be made with grayscale ultrasound alone. These include simple hepatic cysts, classic focal fatty infiltration or sparing, and infantile hemangiomas with classic clinical features.[4] More commonly, however, the ultrasound appearance of a liver lesion is nonspecific, as many different liver lesions can seem similar at ultrasound. In addition, classic imaging findings are less commonly seen in hepatic steatosis, which is increasing in incidence.

When it is determined that CEUS may assist in making a confident diagnosis, first, an appropriate transducer should be selected. In adults, a curved array low-frequency transducer is typically ideal to best capture microbubble resonance. However, in infants and small children, a linear high-frequency transducer may allow for optimal lesion visualization, although bubble resonance (and thus perceived enhancement) may be less, and microbubble destruction rate is higher.

Second, an appropriate acoustic window should be chosen to ensure optimized and consist visualization of the observation, with the transducer placed as close as possible to the lesion. This may require placing the patient in the decubitus position, similar to routine ultrasound image optimization. An intercostal approach may be needed, with the patient's arm raised overhead to maximize the space between ribs. It is best if the lesion can be kept in the field of view during the entire respiratory cycle, so the lesion can be seen throughout the complete duration of UCA wash-in during normal respiration. The wash-in, or arterial phase, typically lasts for up to 45 seconds following UCA administration. The portal venous phase typically lasts from 30 to 120 seconds after UCA injection, which notably is earlier than CT and MRI where the portal venous phase typically begins around 45 seconds after contrast administration. The late phase lasts from 120 seconds to 4 to 6 minutes after UCA injection until clearance of the UCA.[5] Intermittent scanning should be performed during portal venous and late phases to decrease UCA destruction that can occur with continuous imaging. Artifacts at CEUS are well described and are important to minimize and consider in both performing and interpreting CEUS.[3,6,7]

BASIC INTERPRETATION PRINCIPLES

In general, CEUS interpretation predominantly relies on the appearance of the lesion in the delayed phase, with 2 possibilities: contrast material washout (hypoenhancement) or contrast material

retention (no washout; isoenhancement to hyperenhancement). Lesions without washout are overwhelmingly benign, and the specific pattern of arterial phase enhancement is important for definitive diagnosis.[1] Conversely, lesions that show washout, or become hypoenhancing compared with the background liver parenchyma, are much more likely to be malignant.[1] The remainder of this review details specific types of lesions, emphasizing the clinical significance and CEUS appearance. **Table 1** provides a summary of the appearance of different lesions during CEUS.

BENIGN LESIONS

Vascular Tumors

Vascular tumors in the liver are categorized using the 2018 International Society for the Study of Vascular Anomalies classification.[8] In infants and young children, the 2 most common vascular malformations are tumors: congenital hemangioma (also called solitary hemangioma) and infantile hemangiomas (also called multifocal or diffuse hemangiomas). Conversely, vascular malformations such as slow or fast flow malformations (previously called "hemangiomas" and still ubiquitously called this in most adult literature) are most common after the first decade of life through adulthood.

Congenital hepatic hemangioma

A congenital hemangioma is a fast flow vascular tumor that develops in utero and is present and typically largest at birth. These generally solitary vascular tumors are typically diagnosed within 6 months of life and are commonly incidental lesions without clinical significance. However,

Table 1
Enhancement appearance of various liver lesions at contrast-enhanced ultrasound

	Arterial Phase 10–45 s	Portal Venous Phase 30–120 s	Late Phase 120 s–6 min
Congenital hemangioma	Heterogeneous peripheral centripetal complete or incomplete fill-in	No washout of enhancing areas	No washout of enhancing areas
Infantile hemangioma	Peripheral hyperenhancement with rapid centripetal fill-in	No washout	• Hyperenhancment • Isoenhancement • Mild late washout
Hemangioma	Peripheral discontinuous nodular enhancement	Centripetal complete or partial fill-in	No washout of enhancing areas
Mesenchymal hamartoma	• Nonenhancement of cystic components • Gradual enhancement of septa and solid components	No washout of enhancing areas	No washout of enhancing areas
FNH	• Spoke-wheel, stellate centripetal enhancement • Possible enhancing central vessel	• No washout • Possible nonenhancing central scar	• No washout • Possible nonenhancing central scar
HNF-1α-inactivated adenoma	Heterogeneous hyperenhancement	No washout	No washout
Hepatoblastoma	Variable	Mild to marked washout[a]	Marked washout
HCC	Nonrim hyperenhancement	Sustained enhancement	Mild late washout
Cholangiocarcinoma	Rim hyperenhancement	Early and/or marked washout[a]	Marked washout
Metastasis	Variable	Early and/or marked washout[a]	Marked washout

[a] Early washout occurs less than 60 s. Marked washout seems nearly devoid of enhancement (punched out appearance) within 2 min.

patients with larger lesions may present with high-output congestive heart failure from vascular shunting. Most congenital hemangioma rapidly and spontaneously involute over the first year of life, termed rapidly involuting congenital hemangioma.[9] Occasionally, embolization may be necessary in infants to help cease intratumoral shunting, with resection considered when possible. No medical therapy is currently available to treat congenital hemangioma.

At ultrasound, congenital hemangioma is usually solitary and heterogeneous in echogenicity, with large vessels visible.[10] Calcifications may be seen.[11] At dynamic postcontrast imaging, there will be heterogeneous somewhat peripheral, often discontinuous and nodular enhancement that becomes more confluent at the lesion periphery over time (**Fig. 1**).[10] There may be complete fill-in with contrast material, although central portions of the tumor may not enhance, especially larger tumors, likely related to intratumoral hemorrhage, fibrosis, and/or necrosis.[9] Portions of the tumor that enhance in the arterial phase will typically remain isoenhancing to hyperenhancing in later phases without washout.[12]

Infantile hepatic hemangiomas

Infantile hepatic hemangiomas are multiple or innumerable/diffuse. These tumors develop in the first weeks or months of life and are generally not present at birth, unlike congenital hemangioma. Infantile hepatic hemangiomas are associated with cutaneous infantile hemangiomas, which are histologically identical tumors with GLUT-1 positivity. Infantile hemangiomas characteristically have rapid growth within the first year of life, followed by gradual involution during the first year of life, with small residual fibrofatty tissue. In addition to potential vascular shunting complications such as high-output heart failure, these tumors express type 3-iodothyronine deiodinase so patients may have hypothyroidism.[9] If treatment is necessary, the mainstay is propranolol.[9]

CEUS may not be necessary for diagnosis when multiple or innumerable liver lesions are encountered at grayscale ultrasound in a patient with multiple cutaneous infantile hemangiomas. At CEUS, infantile hemangiomas typically have peripheral discontinuous and nodular enhancement with very rapid homogeneous fill-in. Infantile hemangiomas are typically more homogeneous than congenital hemangiomas (**Fig. 2**).[9] There is usually sustained enhancement in the portal venous phase with hyperenhancement, isoenhancement, and mild washout all possible in the late phase.[10]

Vascular Malformations

Hemangioma

Hemangioma is a term used ubiquitously in the adult literature but is a distinct, nonneoplastic

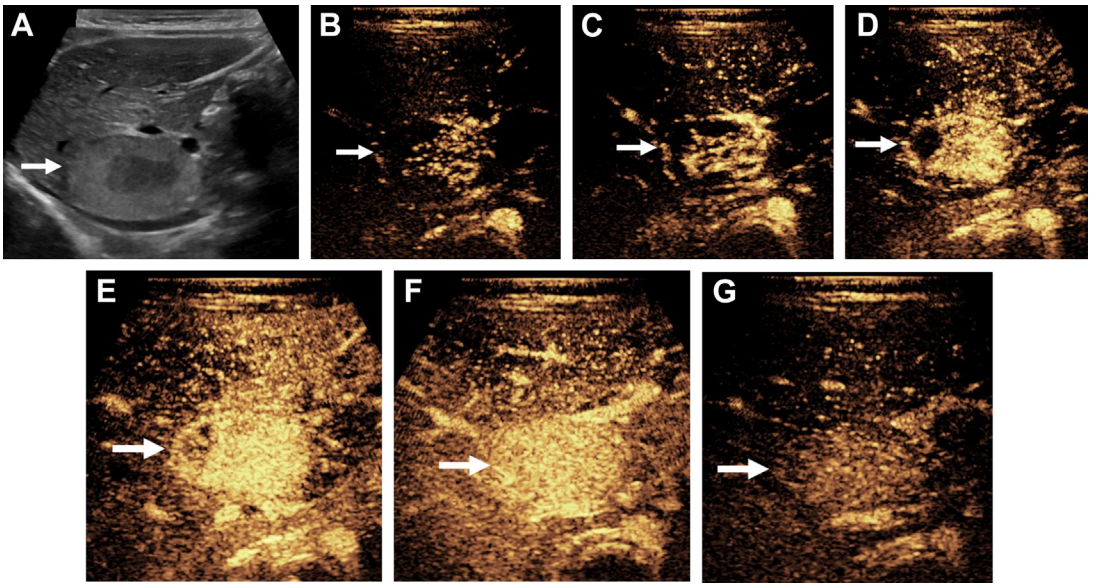

Fig. 1. A 4-month-old boy with congenital hemangioma incidentally discovered at renal ultrasound. (*A*) Transverse grayscale image demonstrates a circumscribed heterogeneous mass (*arrow*) in the inferior aspect of the right hepatic lobe. CEUS images in the transverse plane in the arterial phase at 4 (*B*), 5 (*C*), 6 (*D*), 8 (*E*), and 12 seconds (*F*) following sulfur hexafluoride lipid-type A microspheres contrast injection demonstrate heterogeneous, somewhat peripheral centripetal complete enhancement of the mass. In the late phase at 2 minutes 5 seconds following contrast injection (*G*), there is sustained enhancement of the mass without washout.

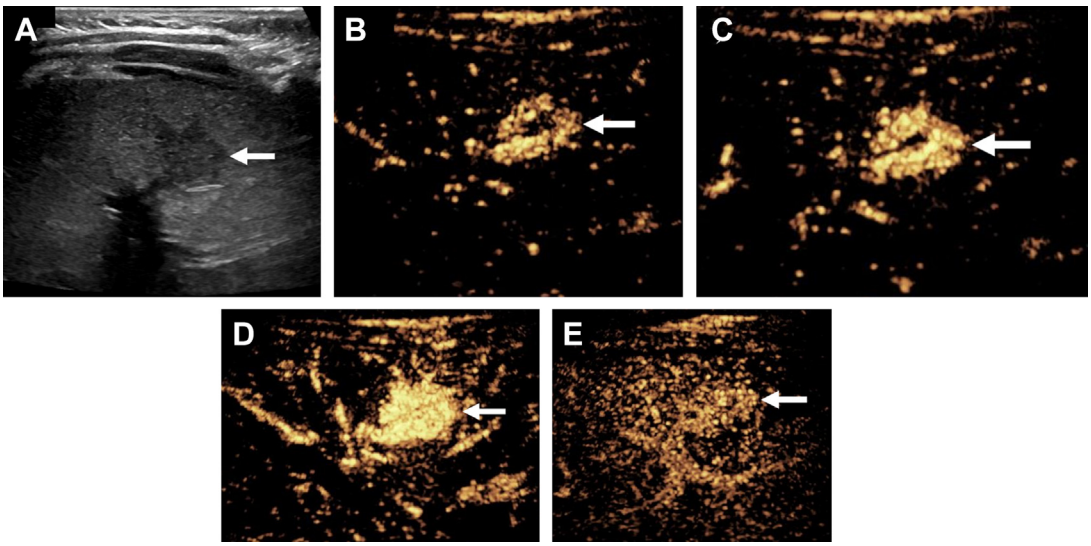

Fig. 2. A 20-month-old girl with multiple infantile hepatic hemangiomas. (*A*) Grayscale ultrasound image in the transverse plane shows a representative irregularly shaped hypoechoic lesion in the left hepatic lobe (*arrow*), with other hemangiomas not shown. CEUS images in the transverse plane in the arterial phase at 8 (*B*), 9 (*C*), and 10 seconds (*D*) after sulfur hexafluoride lipid-type A microspheres contrast injection show rapid peripheral discontinuous nodular enhancement with centripetal fill-in of the lesion. In the late phase, 2 minutes 10 seconds following contrast injection (*E*), there is sustained enhancement without washout.

lesion that is different from congenital and infantile hemangiomas. In adolescents and adults, these lesions are more appropriately called slow flow or fast flow malformations because they are not true hemangiomas.[8] Similar to their appearance at multiphase CT and MRI, at CEUS, these vascular malformations demonstrate peripheral discontinuous nodular enhancement with expanding puddles of contrast material that fill centripetally (outward to inward; **Fig. 3**). Fill-in can be complete or partial, potentially due to central clot or fibrosis. There is classically no washout, although mild late washout has been reported in some hemangiomas, which should not be a confusing finding if the characteristic arterial phase enhancement pattern is present.[6]

Mesenchymal Hamartoma

Hepatic mesenchymal hamartoma is a benign congenital lesion of uncoordinated primitive mesenchyme proliferation with pseudocysts in the periportal tracts, and no connection to bile ducts.[13,14] This lesion is usually diagnosed by 2 years of age, although patients may present prenatally.[14] Large lesions may cause abdominal distention and difficulty breathing.[14] Treatment is complete surgical resection. There is potential for local recurrence, and malignant transformation to undifferentiated embryonal sarcoma has been reported.[13,14]

Mesenchymal hamartoma is typically large (>10 cm) and unifocal, although multifocal cases have been reported.[12] At ultrasound, these lesions are typically almost completely cystic with variable amounts of internal fibrotic septations. At CEUS, the cystic components will not enhance, whereas enhancement of linear septations and any solid portions will be seen (**Fig. 4**).

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is a benign tumor composed of hepatocytes, Kupffer cells, malformed blood vessels, and immature bile ducts with a vascular central scar and is thought to occur due to a congenital or acquired vascular insult.[11,13,15] FNH classically occurs in young women with normal background liver parenchyma. In patients with diffuse liver disease, such as prior chemotherapy or Fontan-associated liver disease, these are called "FNH-like" lesions although they are similar to true FNH.[11,16] FNH can slowly enlarge over time, although spontaneously resolution has been reported.[15] No treatment is necessary unless there are symptoms related to mass effect when excision may be considered.[16]

At ultrasound, spoke-wheel internal vascularity is diagnostic. At CEUS, FNH is hypervascular, with stellate, spoke-wheel centrifugal (in to out) arterial phase hyperenhancement (APHE; **Fig. 5**). A central

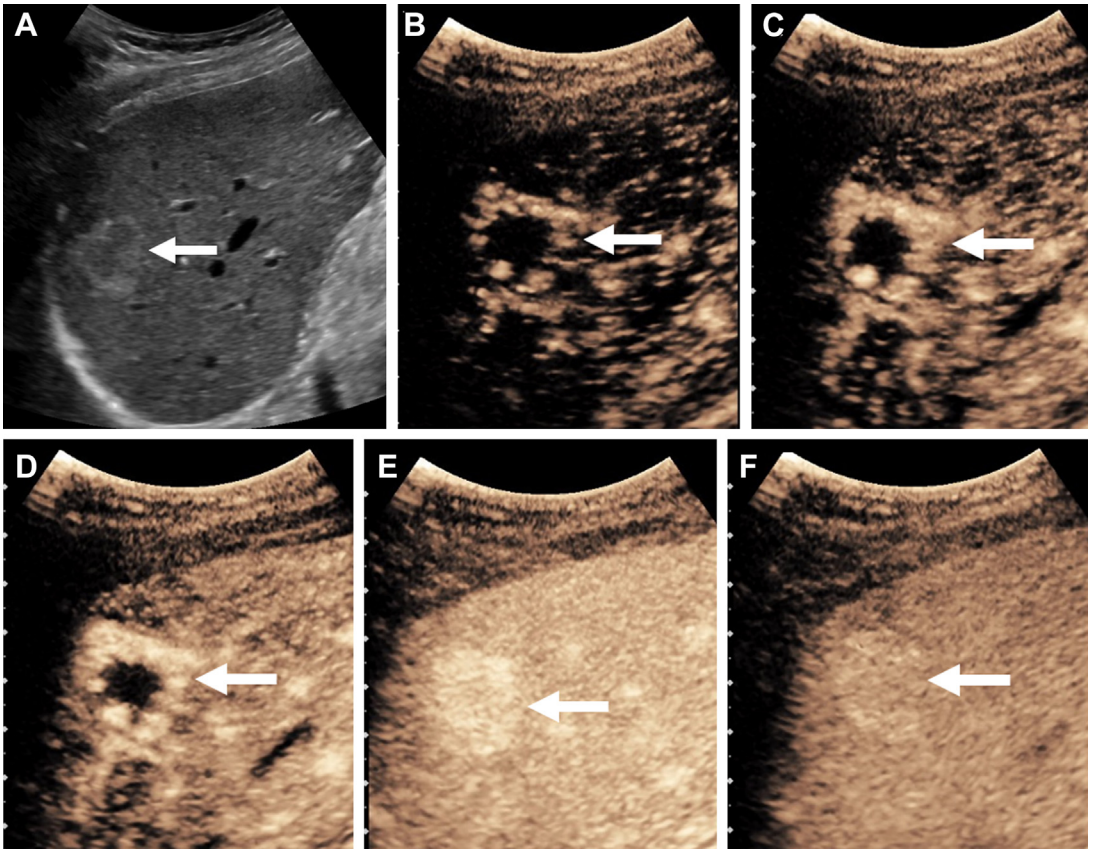

Fig. 3. A 55-year-old woman with hemangioma incidentally seen on CT (not shown) performed for abdominal pain. Grayscale ultrasound (*A*) shows an irregularly shaped mass (*arrow*) near the dome of the right lobe with echogenic rim and central hypoechogenicity. Following the intravenous administration of sulfur hexafluoride lipid-type A microspheres, at 11 seconds (*B*), peripheral discontinuous nodular enhancement is shown, with progressive puddling of contrast and centripetal enhancement at 13 seconds (*C*) and 14 seconds (*D*), with complete fill in by 48 seconds (*E*). No washout was seen at 2 minutes (*F*).

feeding vessel may be seen. Complete contrast fill-in is typical, although washout from a small central scar may be seen, as with other imaging modalities. FNH-like lesions are more commonly multiple, are usually smaller, and are less likely to have a central scar compared with FNH.[12] In the delayed phase, sustained enhancement occurs in about 90% of cases. Importantly, in cancer survivors, the lack of portal venous and late phase washout helps differentiate multiple FNH-like lesions from metastases, which typically show marked contrast agent washout by 2 minutes.[17]

Hepatocellular Adenoma

Hepatocellular adenoma is a benign hepatic neoplasm that predominantly occurs in women. Given increasing molecular and genetic information, our understanding of these lesions continues to evolve. Adenomas are now categorized into 7 distinct subtypes: inflammatory, HNF-1α-inactivated, β-catenin-activated (also called β-catenin mutated, caused by a mutation of exon 3), weak β-catenin-activated (caused by a mutation of exon 7/8), sonic hedgehog pathway activated, unclassified hepatocellular adenoma, as well as 2 subtypes with overlapping features of the inflammatory and β-catenin-activated subtypes.[11,18] The subtypes with currently best-described appearance at CEUS are further detailed below.

Inflammatory hepatocellular adenoma

Inflammatory hepatocellular adenoma (previously called telangiectatic adenoma or telangiectatic FNH) is the most common subtype and is associated with estrogen exposure, including oral contraceptive use or obesity.[16,19] Patients may present with fever, anemia, leukocytosis, and elevated serum C-reactive protein on laboratory analysis.[16] Risk of spontaneous rupture and

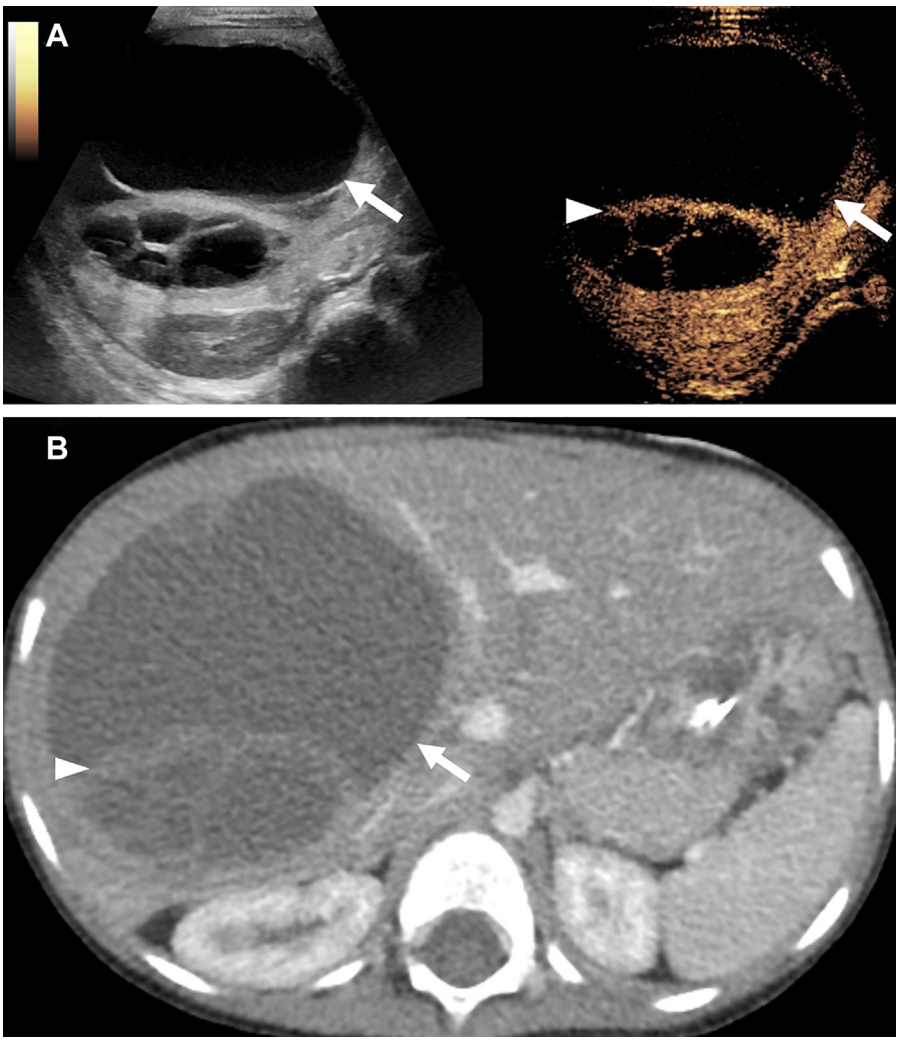

Fig. 4. A 3-year-old boy with mesenchymal hamartoma who presented with abdominal distention. At CEUS using sulfur hexafluoride lipid-type A microspheres, transverse split-screen image (*A*) with grayscale (left panel), and contrast (right panel) demonstrates a large mostly cystic mass (*arrow*) with nonenhancement of cystic areas and enhancement of internal septa and solid portions (*arrowhead*). Contrast-enhanced axial CT (*B*) at a similar level demonstrates a similar appearance with predominant cystic component (*arrow*) and a few internal enhancing components (*arrowhead*).

hemorrhage are greatest with this subtype, particularly when tumor diameter exceeds 5 cm.[11,19,20]

Background liver steatosis may make lesion visualization challenging. At CEUS in the arterial phase, inflammatory hepatocellular adenomas are hypervascular with subcapsular hyperenhancing arteries and a centripetal or heterogeneous filling pattern. Inflammatory hepatocellular adenomas will most commonly show mild washout in the portal venous phase or late phases,[20,21] with sustained enhancement less common.[21,22] Central, irregularly shaped areas of hypoenhancement are seen by the late arterial phase in up to one-third of inflammatory hepatocellular adenomas.[20] An enhancing rim may also be seen in the late phase.[21] Given overlap in appearance with HCC, biopsy may be necessary for diagnosis.

HNF-1α-inactivated hepatocellular adenoma

HNF-1α-inactivated hepatocellular adenomas (previously called steatotic adenomas) account for 35% to 50% of adenomas and are usually seen in women with oral contraceptive use[16] as well as patients with autosomal dominant maturity onset diabetes of the young type 3 (MODY3).[19] The clinical course for this subtype is typically uncomplicated, and treatment may entail simply discontinuing oral contraceptive use.[11,16] Potential

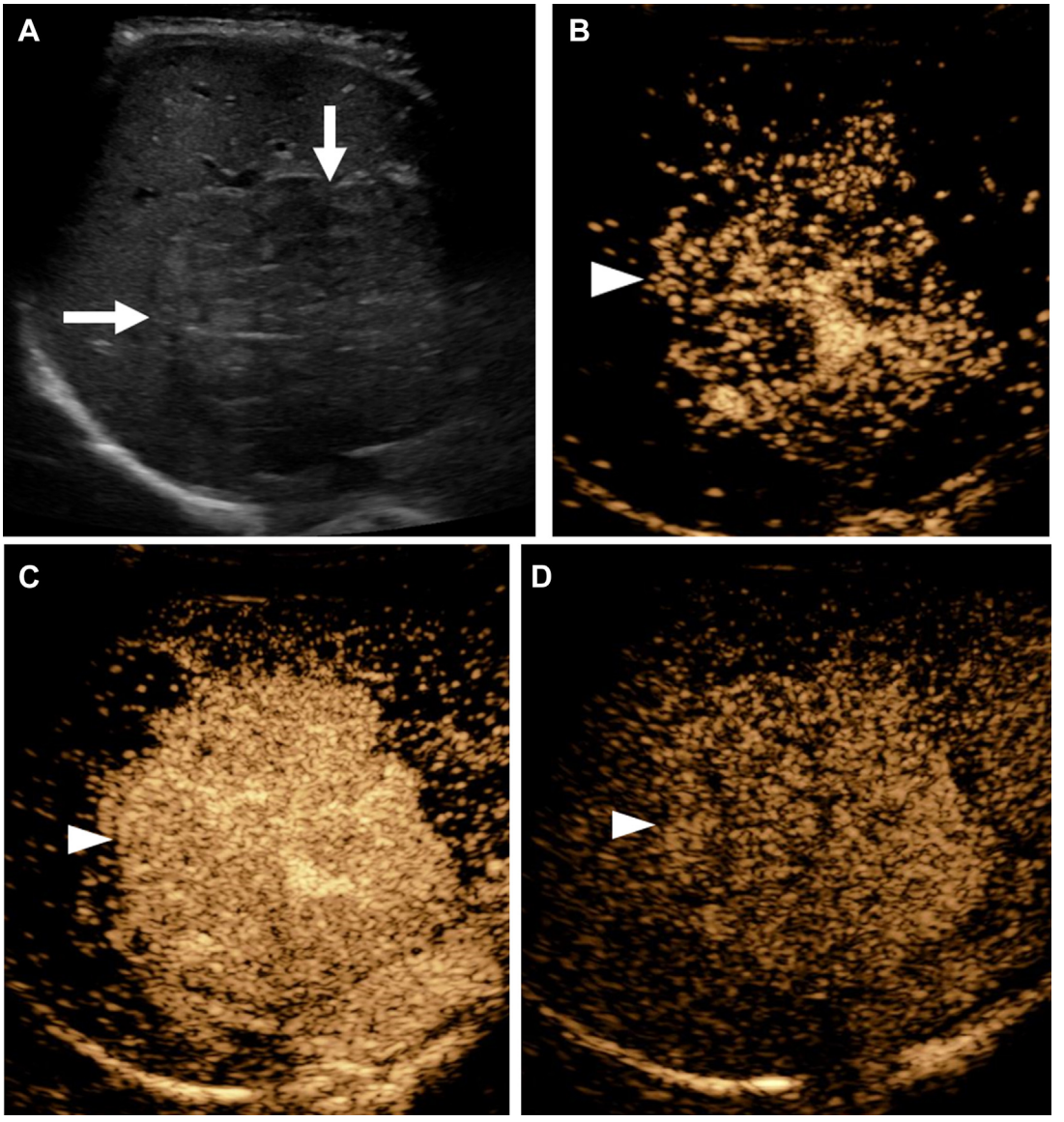

Fig. 5. A 16-year-old boy with FNH who presented with vague abdominal pain. (*A*) Transverse grayscale ultrasound demonstrates a heterogeneous somewhat circumscribed predominantly isoechoic mass (*arrows*) in the right hepatic lobe. Transverse CEUS images in the arterial phase at 26 seconds (*B*) and 32 seconds (*C*) following sulfur hexafluoride lipid-type A microspheres contrast injection demonstrate spoke-wheel centrifugal hyperenhancement of the mass (*arrowhead*) with an early enhancing central vessel. In the late phase at 6 minutes following contrast injection (*D*), there is overall contrast retention of the mass compared with the surrounding liver parenchyma (no washout).

for bleeding is lowest in this subtype, and there is also the lowest risk of malignant transformation.[18]

At CEUS, HNF-1α-inactivated hepatocellular adenomas show homogeneous hyperenhancement in the arterial phase (**Fig. 6**). Lesions show hyperenhancement or isoenhancement in the portal venous and late phases, with washout seen less commonly.[20–22] Sustained enhancement of HNF-1α-inactivated hepatocellular adenomas helps distinguish from the other adenoma subtypes and HCC, which often have mild late washout.

β-Catenin-activated hepatocellular adenoma

β-Catenin-activated hepatocellular adenomas account for 10% to 18% of adenomas. This subtype is the most frequent found in men, and there is an association with exogeneous androgen exposure,

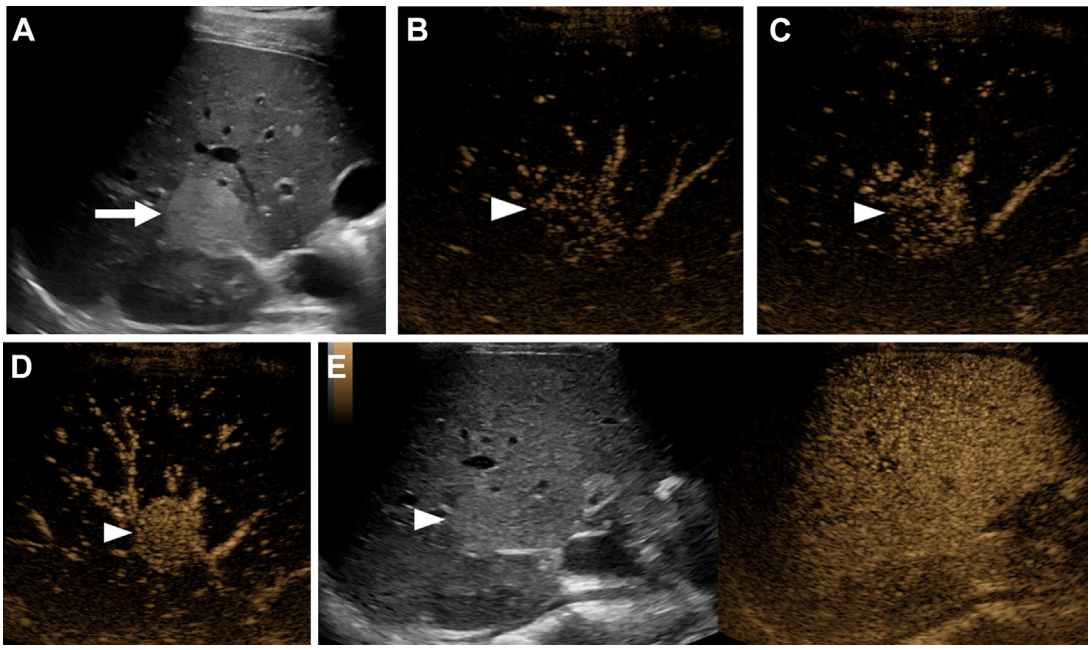

Fig. 6. A 14-year-old girl with MODY3 and HNF-1α-inactivated hepatocellular adenoma who presented with abdominal pain. Sagittal grayscale ultrasound image (*A*) demonstrates an echogenic mass in the posterior right hepatic lobe (*arrow*). Transverse CEUS images in the arterial phase at 14 seconds (*B*), 15 seconds (*C*), and 16 seconds (*D*) after sulfur hexafluoride lipid-type A microspheres contrast injection, there is heterogeneous early enhancement of the mass (*arrowhead*) with complete fill-in of contrast material. Split-screen CEUS image with grayscale (left panel) and contrast (right panel) in the late phase at 8 minutes 49 seconds after contrast injection (*E*) shows sustained enhancement of the mass (*arrowhead*), without washout.

such as for treatment of Fanconi anemia or for bodybuilding, as well as familial adenomatous polyposis and glycogen storage diseases.[11,16,19] Importantly, this subtype has the highest rate of malignant transformation at up to 50%; therefore, some authors suggest excision of any hepatic adenoma in a male patient.[11,19]

At CEUS, APHE is typically diffuse and homogeneous, with either portal venous or late phase washout in almost 90% of lesions.[20] Given overlap in appearance with HCC, biopsy may be necessary for diagnosis.

MALIGNANT LESIONS

Hepatoblastoma

Hepatoblastoma is the most common primary pediatric hepatic malignancy and 95% of cases are discovered by age 4 years.[23] Patients may present with abdominal distension or weight loss,[12] and serum alpha-fetoprotein level is elevated in 90% of patients.[11] The appearance of hepatoblastoma at CEUS has not been well studied, although a few published cases have demonstrated washout in the late phase, as expected for a primary hepatic malignancy (**Fig. 7**).[1] Hepatoblastoma staging uses PRE-Treatment EXTent of tumor,[24] which cannot be completed with CEUS alone; contrast-enhanced MRI and/or CT are mandatory for adequate hepatoblastoma staging.

Hepatocellular Carcinoma

In adults, HCC is the most common primary liver malignancy and the fourth most common cause of cancer-related death worldwide.[25] The American College of Radiology Liver Imaging, Reporting, and Data System (LI-RADS) published CEUS LI-RADS for the diagnosis of liver observations suspicious for HCC in at-risk patients.[5,26,27] Similar to the CT/MRI LI-RADS diagnostic algorithm, CEUS LI-RADS provides the technique, interpretation, and recommended management for untreated observations in patients at-risk for HCC. The various categories convey the increasing likelihood of HCC, ranging from LR-1 (definitely benign) to LR-5 (definitely HCC), similar to the CT/MRI LI-RADS diagnostic system. Additional categories, LR-NC (not characterizable due to image omission or degradation), LR-TIV (tumor-in-vein), and LR-M (probably malignant but not HCC specific) are also included.

Major CEUS LI-RADS criteria include: 1) lesion size, 2) presence or absence of APHE (nonrim; nondiscontinuous peripheral nodular, which would

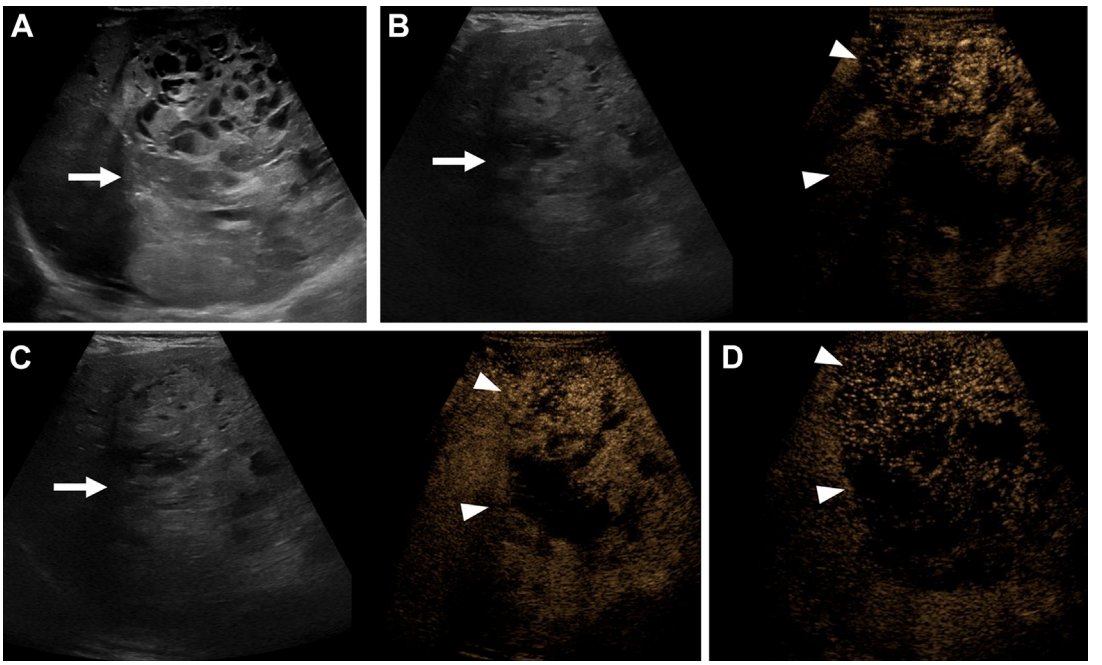

Fig. 7. A 7-month-old boy with hepatoblastoma who presented with abdominal distention. Sagittal grayscale ultrasound (*A*) demonstrates a large heterogeneous liver mass (*arrow*). Split-screen sagittal CEUS image with grayscale image (left panel) and contrast image (right panel) shows the heterogeneous mass (*arrow*), which has very heterogeneous arterial phase enhancement (*arrowheads*) at 14 seconds following sulfur hexafluoride lipid-type A microspheres contrast injection (*B*), with some fill-in of contrast material at 18 seconds (*C*). Washout of the mass (*arrowheads*) is seen at 2 minutes 9 seconds after contrast injection (*D*). In this child, CEUS was performed to better evaluate vascular involvement of the hepatoblastoma following CT and MRI.

indicate hemangioma), and 3) presence or absence of washout. Unique to CEUS LI-RADS, washout is characterized by its timing (early or late; <60 sec, or $\geq$ 60 sec, respectively) as well as by its degree (mild or marked). Marked washout is defined as a "punched out" appearance, nearly devoid of enhancement, within 2 minutes after contrast injection. Unlike CT/MRI LI-RADS, capsule is not a feature in CEUS. HCC classically shows nonrim APHE and mild, late washout. (**Fig. 8**) LR-M features include rim-APHE, early washout (<60 sec) or marked washout (punched out within 2 minute). As with LR-M observations in CT/MRI, biopsy is often needed.

Ancillary features favoring malignancy include definite growth, defined as 50% or greater size increase in 6 months or less, and those favoring HCC in particular include nodule-in-nodule architecture and mosaic architecture. Ancillary features favoring benignity include size stability in 2 years or greater and size reduction in absence of treatment.

Multiple recent publications in adult populations have shown that CEUS is highly specific for the diagnosis of HCC. For LR-5, positive predictive values of 97% to 98.5%, and specificity of 96%, have been reported, equivalent to CT/MRI LI-RADS.[28–30] It has been noted that approximately 50% to 75% of LR-M observations are HCC, and there may be a higher incidence of HCC among CEUS LR-3 observations relative to CT/MRI LR-3.

The latest American Association for the Study of Liver Disease guidance document includes CEUS as a potential modality for the characterization of liver observations in at-risk patients.[31] However, at this time, the Organ Procurement and Transplant Network does not recognize CEUS for transplant consideration; however, it may be used in select patients as a trouble-shooting tool when CT or MRI is contraindicated or inconclusive. CEUS has shown promise in the assessment of response to treatment of HCC; however, this is not yet included in the LI-RADS system.

Cholangiocarcinoma

The most common subtype to be encountered and diagnosed by CEUS is the peripheral, mass-forming intrahepatic cholangiocarcinoma. Classic iCC may seem as a circumscribed or ill-defined heterogeneous mass, or may be indistinct and infiltrative in appearance. At CEUS, iCC classically

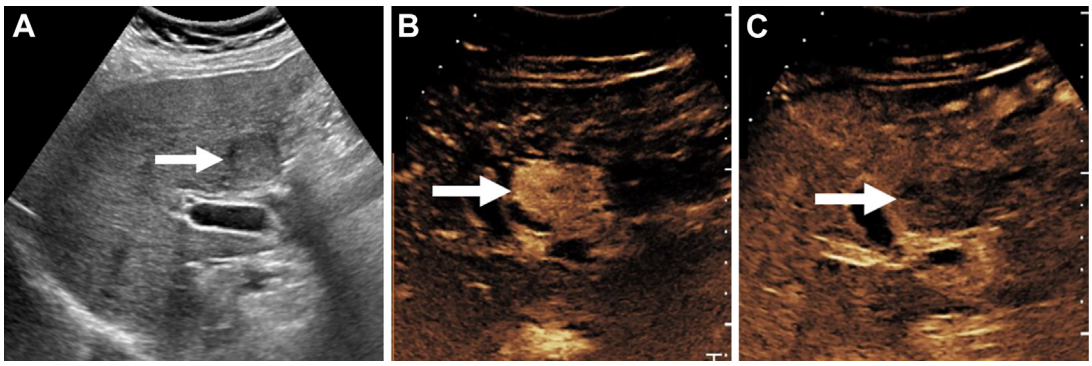

Fig. 8. A 76-year-old woman with chronic hepatitis B and a 3.6 cm hypoechoic well-differentiated HCC identified at surveillance ultrasound. Subsequent MRI was nondiagnostic due to severe motion degradation (not shown). Grayscale sagittal ultrasound image (*A*) shows a round, iso-to-hypoechoic nodule (*arrow*) in the posterior medial segment of left hepatic lobe. At CEUS using perflutren lipid microspheres, the lesion shows brisk, diffuse APHE at 17 seconds (*B*) with mild washout at 75 seconds (*C*) after contrast injection (CEUS LR-5, definitely HCC).

shows heterogeneous peripheral arterial phase hyperenhancement (rim-APHE) with washout that is rapid (<60 sec) and/or marked ("punched out" within 2 minutes) (iCC; **Fig. 9**).[32] The washout seen in iCC is discrepant from findings in CT and MRI, where delayed enhancement is generally seen. This discrepancy highlights one of the key differences of UCA, which are pure blood pool agents given the size of the individual microbubbles, unlike the relatively small iodinated and gadolinium-containing molecules that demonstrate an extravascular, interstitial phase allowing for delayed enhancement of otherwise nonenhancing or minimally enhancing tissue such as fibrosis/scar.

In patients at risk for HCC, rim-APHE, early and/or marked washout are features of LR-M (probably malignant but not HCC specific), helping distinguish these masses from HCC.[33] Biopsy is generally recommended.

Metastases

In adults, there are many different types of primary malignancies that can be associated with liver metastases, although colorectal carcinoma is one of the most common.[34] The most common primary pediatric tumors with liver metastasis are neuroblastoma and Wilms tumor.[11] Identification of a primary tumor or knowledge of malignancy history is important. At CEUS, metastases are usually multiple although can be solitary. Although the arterial phase appearance is variable, metastases will nearly always demonstrate portal venous

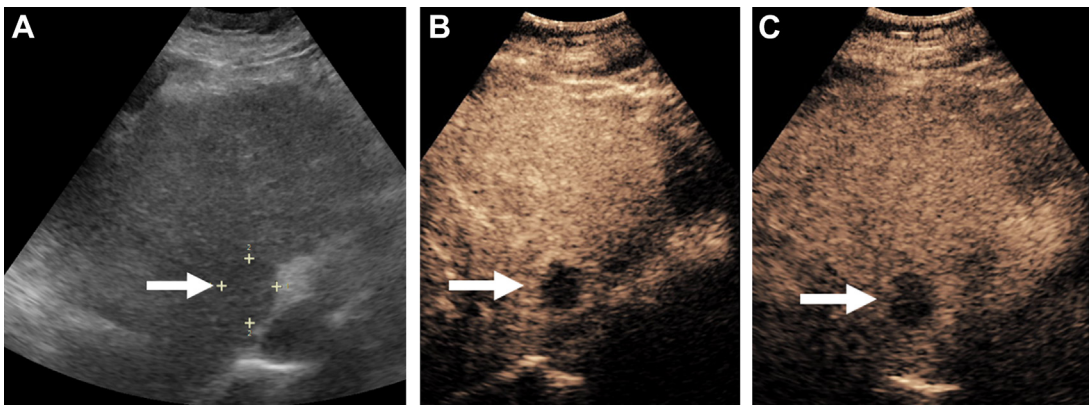

Fig. 9. A 66-year-old man with decompensated cirrhosis likely due to iron overload and alcohol abuse, presenting for transplant evaluation, was found to have a poorly differentiated adenocarcinoma at biopsy, consistent with a pancreaticobiliary primary tumor, likely representing cholangiocarcinoma. Grayscale ultrasound image (*A*) shows a rounded, iso-to-hypoechoic 3.3 cm nodule (*arrow*) high in the medial segment near the hepatic venous confluence. At CEUS performed with sulfur hexafluoride lipid-type A microspheres, the lesion demonstrates rim APHE at 20 seconds after contrast injection (*B*), with marked washout around 2 minutes (*C*).

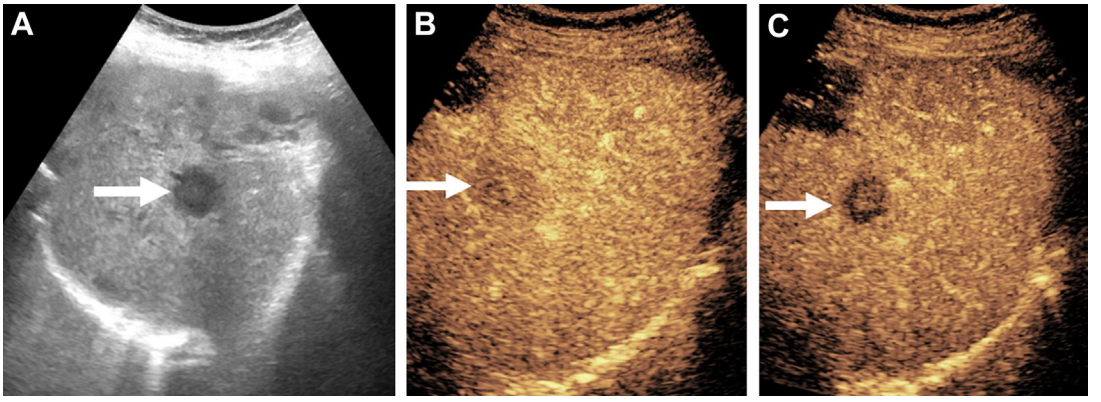

Fig. 10. A 82-year-old woman with liver metastasis due to breast cancer. Sagittal grayscale ultrasound image (*A*) demonstrates a hypoechoic nodule (*arrow*) in the right hepatic lobe. At CEUS using sulfur hexafluoride lipid-type A microspheres, there is hypoenhancement of the nodule in the arterial phase at 17 seconds following contrast injection (*B*), with early and marked washout at 42 seconds (*C*).

phase washout, typically within 1 to 2 minutes after UCA administration (**Fig. 10**)..[32,34]

INTERVENTION

Facilitated by the high safety profile of UCAs and the ability to inject multiple doses during a single encounter, CEUS has many potential uses in liver intervention.[35] CEUS may be used to improve visualization of a target lesion during biopsy or percutaneous ablation.[36–38] Microbubble contrast also helps distinguish viable (enhancing) from nonviable (nonenhancing) components of masses to help improve diagnostic yield of biopsies.[39] If multiple lesions are present, CEUS may help identify the most suspicious or accessible mass and exclude a benign cause.

CEUS is also becoming an important tool in posttreatment assessment of liver masses, particularly following transarterial chemoembolization and percutaneous ablation (radiofrequency or microwave).[40,41] The use of intraprocedural UCA immediately following an ablation procedure may help identify residual viable disease, allowing for repeat treatment during the same procedure, a benefit that has shown to improve patient outcomes.[42,43]

SUMMARY

Accurate liver lesion characterization is possible using CEUS in children and adults. UCA are safe and CEUS can eliminate the need for multiphase CT and MRI in many cases, which is particularly advantageous in children who are more susceptible to potential deleterious effects of ionizing radiation, and who may require sedation or general anesthesia to undergo diagnostic MRI.

CLINICS CARE POINTS

- Benign lesions have no washout and may have specific patterns of arterial phase enhancement that allow for definitive diagnosis.
- Hepatocellular carcinoma (HCC) demonstrate late (less than or equal to 60 seconds after contrast injection) and mild washout.
- Metastases typically demonstrate early washout (<60 seconds after contrast injection) or marked washout (nearly devoid of contrast within 2 minutes).

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