Journal of Radiology Nursing 38 (2019) 231–236

Contents lists available at ScienceDirect

Journal of Radiology Nursing

journal homepage: www.sciencedirect.com/journal/journal-of-radiology-nursing

Contrast-Enhanced Ultrasound During Percutaneous Hepatosplenic Biopsy and Liver Ablation: Practical Applications, Pharmaceutical Principles, Administration Technique, and Complications

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Keywords:
Contrast
Ultrasound
CEUS
Percutaneous
Liver
Spleen
Biopsy
Ablation

A B S T R A C T

Ultrasound guidance during percutaneous biopsy or thermal ablation of hepatosplenic tumors provides distinct benefits over computed tomography guidance; however, not all lesions are well demarcated by ultrasound. Lesions that are isoechoic to the surrounding normal parenchyma can be occult and procedural outcome by ultrasound guidance may be compromised. Ultrasound contrast administration has been advanced as a method to improve lesion delineation in these cases. In addition, ultrasound contrast can be used to evaluate therapeutic effect after thermal ablation. This manuscript reviews the pharmaceutical principles, technical considerations, and potential complications of ultrasound contrast agents to ensure safe and effective administration during percutaneous hepatosplenic biopsy and liver ablation.

Introduction

Ultrasound (US) guidance is a preferred method for the placement of procedural needles during percutaneous procedures to diagnose and treat hepatic and splenic tumors. Multielement transducers display images with high contrast ratio to allow visualization of most hepatosplenic tumors, which appear either hyperechoic or hypoechoic to the surrounding normal parenchyma due to differences in tumor cell composition and density. Another inherent advantage to the use of US guidance is real-time imaging capability that facilitates safe needle guidance. Finally, US does not expose the patient to ionizing radiation.

Despite these inherent advantages, not all hepatosplenic lesions are well demarcated by US imaging. Poor visualization may result in inadequate percutaneous biopsy sampling or incomplete assessment of liver ablation margins. The main limitations to the use of US guidance for needle placement include the following: lesions less than 1 cm in size, isoechogenicity to the surrounding normal parenchyma, depth of lesion that surpasses the capabilities of US penetrance, and locoregional structures that obscure the lesion such as the lung, gallbladder, or bowel (Sparchez et al., 2011).

Multidetector computed tomography (CT) is the main alternative means to image guidance for percutaneous hepatosplenic procedures. This cross-sectional imaging modality allows for improved anatomical detail and greater depth penetration. While hepatosplenic tumor boundaries are not always apparent on CT, intravenous (IV) contrast may be administered during the procedure to improve lesion identification.

Unfortunately, CT guidance for hepatosplenic directed percutaneous procedures is not without limitations. The CT equipment exposes patients to ionizing radiation and is expensive, incurring greater health care cost (Sparchez et al., 2011). Furthermore, CT does not allow real-time needle guidance without using a high-dose CT-fluoroscopy technique. In addition, if IV iodinated contrast is required for tumor visualization, the rapid passage of IV iodinated contrast medium through the visceral organs often limits the time to target the hepatosplenic lesion. Finally, iodinated contrast is restricted for patients with renal impairment or severe contrast allergies.

Given the technical advantages to US guidance, contrast-enhanced ultrasound (CEUS) has been successfully applied to several diagnostic and therapeutic applications to overcome the aforementioned limitations and provide an alternative to CT

Conflict of interest: No conflict of interest has been declared by the authors.

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https://doi.org/10.1016/j.jradnu.2019.07.008
1546-0843/$36.00/

guidance. Diagnostic radiologists have recently applied CEUS to improve diagnostic sensitivity for liver, breast, and renal lesions in patients who are not able to receive IV contrast owing to renal impairment or allergies (Guvener et al., 2017).

This review article will focus on the application of CEUS to improve imaging of hepatic and splenic lesions during percutaneous biopsy and thermal ablation procedures. The basic pharmaceutical and imaging properties will be reviewed. Several indications for appropriate use will be described, along with technical considerations and potential complications. Finally, several illustrative examples of US contrast use will be detailed.

CEUS Administration

Ultrasound contrast is an injectable medium that is administered through a peripherally inserted venous catheter. The agent is supplied as a white powder that is mixed with a predetermined amount of 0.9% sodium chloride immediately before injection (see Figure 1). After prolonged agitation, the isotonic suspension appears as a milky white, homogeneous solution. This solution comprises millions of microbubbles per milliliter suspended evenly in the saline. Microspheres are viable for up to 3 hours when kept within the vial (Bracco Diagnostics, 2016); however, manufacturer's recommendations are for injection through a peripherally inserted venous access immediately after reconstitution. Peripheral venous access is recommended to be via a needle or catheter measuring 20 gauge or larger. If agent is not used immediately, resuspension by vigorous agitation for several seconds is recommended before administration.

CEUS Imaging Physics

All intravenously injected contrast enhances soft tissues owing to differences in perfusion between tissues. The visualization of US contrast in the liver and spleen follows the same pattern seen in multiphase CT examinations after iodinated contrast administration (see Figure 2). For example, hepatosplenic tumors with increased vascularity will have a higher density of US contrast and increased rate of passage compared to the surrounding tissue.

Upon injection through the peripheral venous access, the bolus of microbubbles circulates through the cardiovascular system along with the red blood cells. As the microbubbles are of the same size or smaller (approximately 1-8 nm) compared to normal red blood cells (approximately 6-8 nm), the microbubbles also pass through the capillaries (Paefgen, Doleschel, & Keissling, 2015). During the application of CEUS in the liver or spleen, the passage of microbubbles follows a similar pattern to iodinated intravenous contrast. The microbubbles are first seen in the arterial phase approximately 20-60 seconds after peripheral injection, then in the portal venous phase after approximately 2 minutes, and finally in a parenchymal late phase after approximately 6 minutes (Ferraioli & Meloni, 2017). During the course of circulation, the microbubbles are disrupted and degraded. The microbubble shells are metabolized in the liver and the gases are removed during normal alveolar gas exchange (Piscaglia et al., 2010).

The passage of US contrast is identifiable on US owing to the interaction between the US waves and microbubble structure. As ultrasound waves are emitted from the US probe propagate, the pressure alterations result in subtle expansion and contraction of the flexible microbubble shells, which is uniquely different from the surrounding tissues (Piscaglia et al., 2010). The reflected US echoes return to the US detector and are registered as increased echogenicity compared to normal tissue.

Discussion

Although ultrasound contrast is novel to many radiology practices in the United States, the principle behind the current commercial products was first developed in the 1960s, well before the advent of CT contrast. The first microbubbles were created by manually agitating saline and autologous blood. Although this rudimentary form of ultrasound contrast was found to delineate vascular flow changes under careful US observation, the microbubbles were unstable and quickly dissolved in circulation (Paefgen, Doleschel, & Kiessling, 2015).

By the late 1980s, a stable product was approved by the FDA and made commercially available. This contrast agent was composed of an air-filled microsphere coated with albumin. Since then, US contrast agents have further improved in stability and biocompatibility and are available in several different compositions (Paefgen et al., 2015). For echocardiograms, FDA-approved contrast agents are composed of either perflutren lipid microspheres filled with octafluoropropane gas (Definity®, Lantheus Medical Imaging, Billerica, MA) or perflutren protein-type A microspheres that contain albumin (Optison™, GE Healthcare, Marlborough, MA). The recently approved agent for hepatic and urinary tract ultrasonography is a sulfur hexafluoride lipid-type A microsphere, with a core of sulfur hexafluoride gas contained by a shell composed of a phospholipid monolayer (Lumason®, Bracco Imaging, Monroe Township, New Jersey). Each microsphere is approximately 1.5-2.5

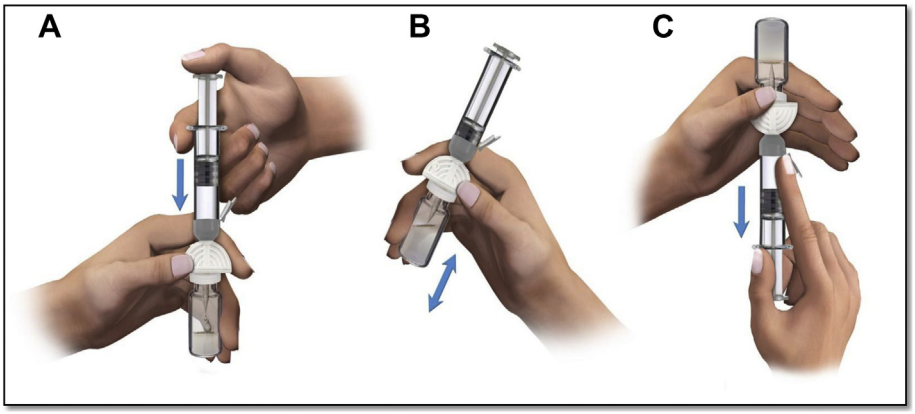

Figure 1. Preparation and administration of US contrast. The sulfur hexafluoride lipid-type A microsphere solution is provided in powder format (A), which is reconstituted in 5 mL 0.9% sodium chloride (B). This mixture is vigorously agitated for 20-30 seconds to create a homogenous solution (C). The milky white homogenous solution is aspirated and injected via a peripherally inserted venous catheter. US, ultrasound.

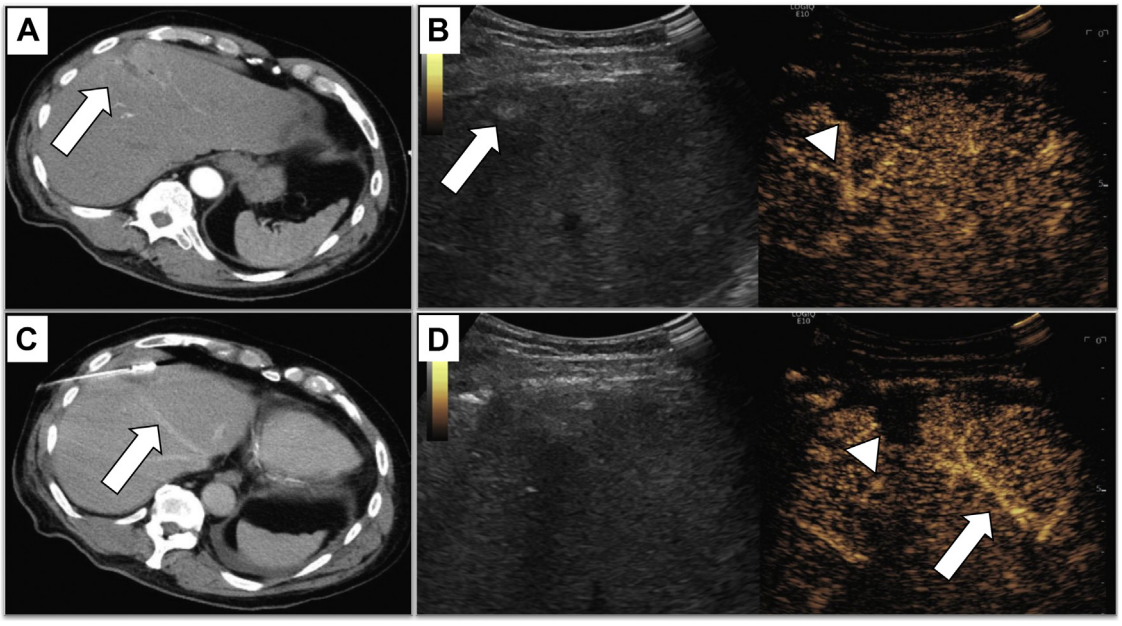

Figure 2. Matched CT and US contrast images to demonstrate appearance of liver lesion during microwave ablation procedure. Contrast-enhanced CT in the arterial phase with poorly delineated right liver lesion (A, arrow). Corresponding gray scale B-mode and matched CEUS images in the arterial phase with poorly visualized lesion on the gray scale B-mode image (B, arrow) and well-delineated lesion on the CEUS image (B, arrowhead). Contrast-enhanced CT in the venous phase during microwave ablation, which demonstrates middle hepatic vein (C, arrow). Corresponding CEUS that does not demonstrate lesion or vein on conventional gray scale B-mode but does demonstrate the lesion (D, arrowhead) and middle vein (D, arrow) on the matched CEUS images. CEUS, contrast-enhanced ultrasound; CT, computed tomography; US, ultrasound.

microns in diameter with pH ranging from 4.5 to 7.5 (Bracco Diagnostics, 2016).

Similar to IV iodinated contrast used for CT, US contrast can be used for diagnosis of hepatic and splenic tumors based on lesion flow dynamics. According to Piscaglia et al., different liver lesions will have varied presentations depending on their structure and the presence of liver cirrhosis (Piscaglia et al., 2010). Hepatocellular carcinomas in the setting of liver cirrhosis typically demonstrate diffuse hyperechogenicity in the arterial phase and slight hypoechogenicity in the late and portal phases when visualized with CEUS. Conversely, malignant lesions in the noncirrhotic liver may be markedly hypoechoic in the late phase, while benign tumors will typically be isoechoic or slightly hypoechoic in the late phase, and simple cysts and abscesses with have no enhancement. Omar and Freeman (2016) described the imaging appearance of splenic lesions. Benign splenic lesions typically will not enhance in any phase or demonstrate rapid enhancement with persistent late-phase enhancement, while malignant splenic lesions will have arterial enhancement with late-phase washout (Omar & Freeman 2016).

Beyond the diagnostic potential of CEUS, these microbubble agents have also been applied for the US-guided percutaneous biopsy of liver lesions. In a retrospective study by Partovi et al. (2017), 88.5% of patients with poorly visualized or invisible lesions on B-mode US were successfully biopsied using contrast enhancement instead of being rescheduled with CT. The use of US contrast increases the detection rate of poorly visible lesions (see Figure 3), aids in the identification of viable and nonnecrotic tumor (see Figure 4), and ultimately decreases the number of biopsy samples required for diagnosis (Partovi et al., 2017). A study by Cao et al. of 76 patients with poorly visible liver tumors on B-mode US reported successful biopsy with the application of contrast enhancement. No major complications were reported with the sensitivity, specificity, accuracy, false-positive rate, and false-negative rate reported as 92.8%, 100%, 93.4%, 0%, and 7.2%, respectively (Cao et al., 2019). The same principles can be applied for necrotic hepatic masses (see Figure 4). To the authors' knowledge, no case series has similarly examined the statistical utility of CEUS during splenic biopsy, possibly because of the relatively lower frequency of splenic biopsies; however, the same principles apply (see Figure 5).

For percutaneous liver ablation, US contrast can be useful not only during needle placement but also to assess ablation margins (see Figure 6). According to Ferraioli and Meloni (2017), successfully ablated tumor will not enhance, whereas a partially ablated tumor or new growth will enhance. A retrospective study by Lekht et al. (2016) compared the use of CEUS to contrast-enhanced CT in the follow-up management of liver thermal ablations and found no difference in outcome. Lekht et al. (2016) concluded that the use of CEUS in lieu of contrast-enhanced CT for the immediate post-ablation follow-up imaging can decrease the patient's cumulative dose of iodinated contrast and ionizing radiation (Lekht et al., 2016). It is important to note that in both CEUS and contrast-enhanced CT, an inflammatory reaction can be seen within the first post-procedure week that can appear as a 1-cm-thick hyperenhancing rim around the ablation zone during all vascular phases (Ferraioli & Meloni, 2017). This inflammatory reaction can be differentiated from viable tumor, as viable tumor will present with washout in the late phase (Ferraioli & Meloni, 2017).

Complications of US contrast are few and minor. The most common adverse reactions are headache, nausea, dysgeusia (parageusia), and injection site pain (Bracco Diagnostics, 2016). In a retrospective study by Piscaglia and Bolondi (2006), the rate of all adverse effects was reported at 0.125%, with 0.0086% major complications and no fatalities. Ultrasound contrast is not nephrotoxic and therefore is safe to use in patients with impaired renal function (Kim et al., 2017).

According to Guvener et al. (2017), future developments in US contrast agents may significantly impact diagnosis and therapeutic options through the expansion of microbubble, nanobubble, and nanodroplet function. For example, the microbubble surface could

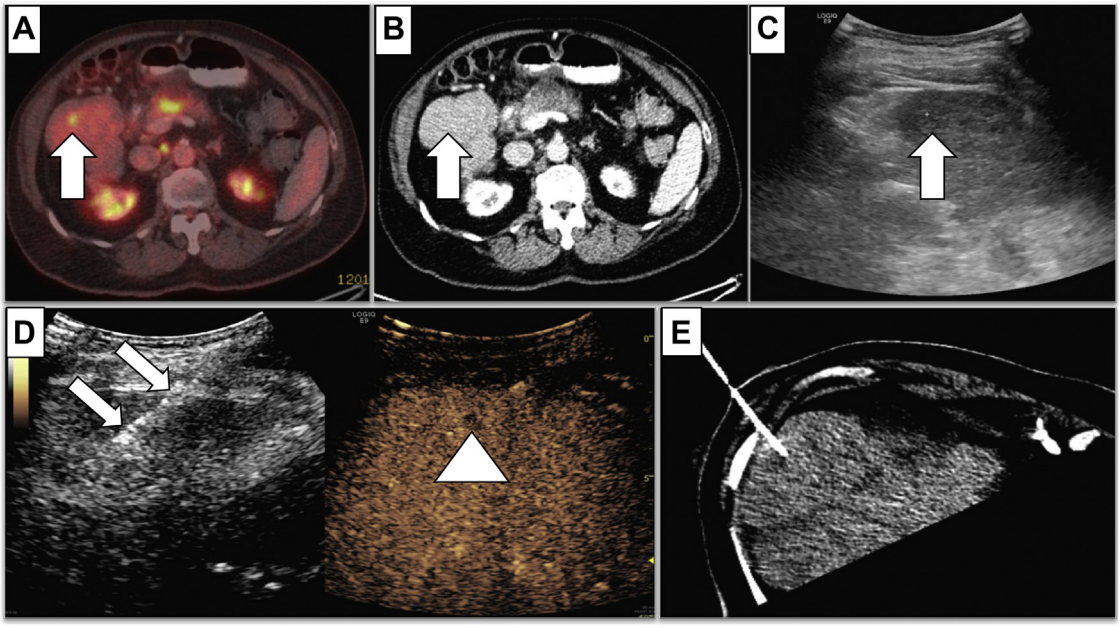

Figure 3. Percutaneous liver biopsy for a 76-year-old woman with a prior history of metastatic pancreatic cancer (FDG-avid lesion shown in A, arrow). The liver lesion was small in size and difficult to visualize on CT (B, arrow) or B-mode US (C, arrow). A single dose of US contrast (Lumason®, Bracco Imaging) improved visualization due to the discrepancy in vascularity between the lesion and the surrounding normal liver parenchyma (D, arrowhead), which allowed successful real-time needle biopsy (D, arrows). The needle location was further confirmed with noncontrast CT (E). Ultrasound-guided biopsy of the nodule confirmed results consistent with metastasis from the patient's known pancreatic primary. CT, computed tomography; US, ultrasound.

be altered with imbedded ligands that can be loaded with pharmaceutical agents for both direct and indirect drug delivery to specific cells or tumors. Another advanced application would amplify the energy emitted when a focused burst US wave strikes the microbubbles to ultimately result in focal destruction of the immediately adjacent capillary walls. This application would allow targeted extravasation of coadministered drugs at the exact location under the ultrasound beam. In a similar fashion, US is also

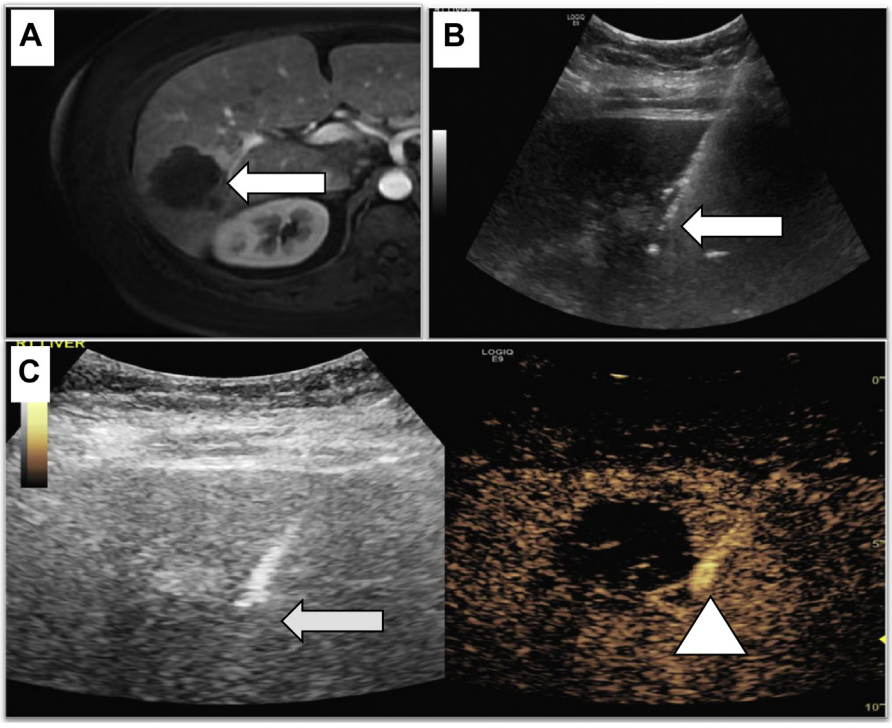

Figure 4. Percutaneous liver biopsy in a 59-year-old woman with thyroid cancer and an enlarging right liver mass with central necrosis (A, arrow). An initial biopsy attempt was unsuccessful due to the necrotic nature of the lesion (B, arrows). Ultrasound contrast was administered on the second biopsy attempt, which differentiated the hypoechoic necrotic tumor from the enhancing viable tumor (C, arrowhead) thus facilitating successful needle biopsy of the viable region (C, arrow).

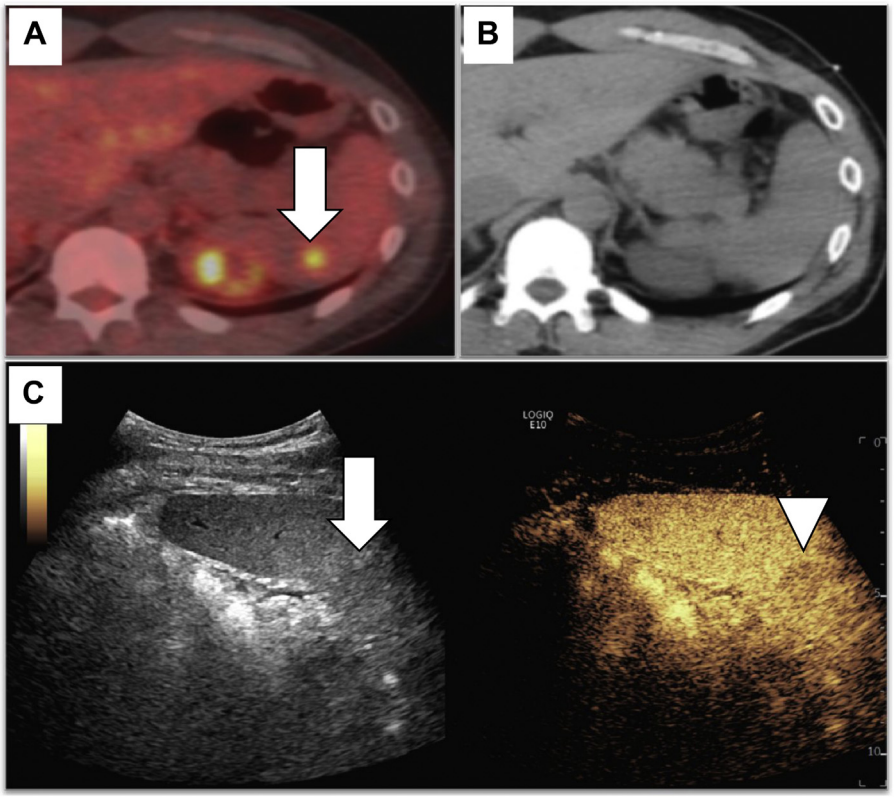

Figure 5. Percutaneous splenic biopsy in a 38-year-old man with a prior history of diffuse large B-cell lymphoma, who now presents with new splenic lesions on noncontrast PET/CT (A, arrow). As the lesions were small and difficult to visualize by noncontrast CT (B), the percutaneous biopsy was performed under US guidance. Although the small lesions proved isoechoic on gray-scale B-mode US (C, arrow), the application of CEUS enabled visualization (C, arrowhead).

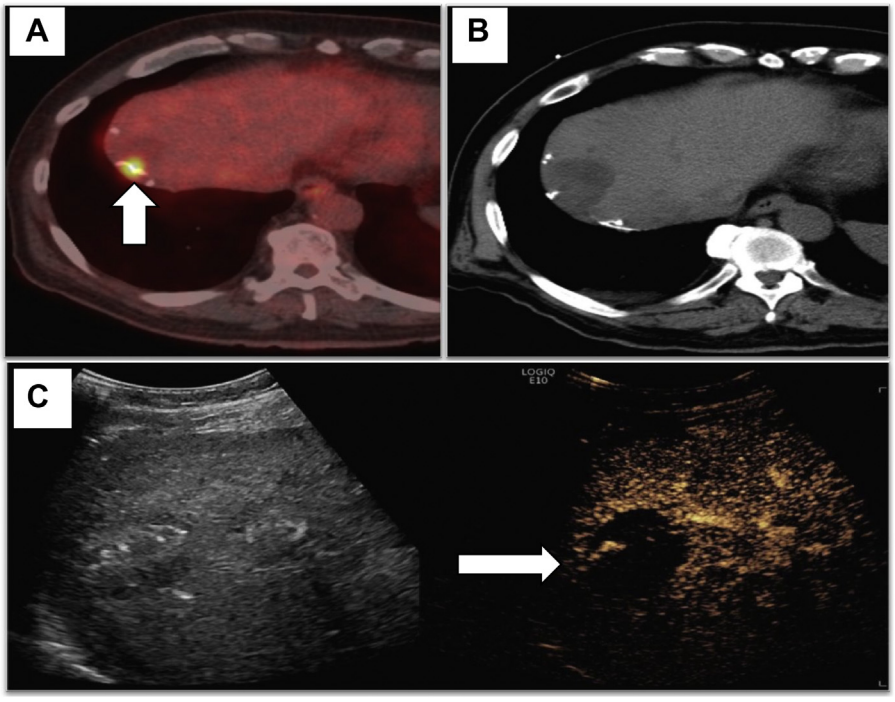

Figure 6. Percutaneous liver ablation in a 69-year-old man with a history of metastatic gastrointestinal stromal tumor, who now presents with recurrent tumor on PET-CT imaging in the region of prior percutaneous ablation. Recurrence is seen as FDG-avidity in the periphery of prior ablation zone (A, arrow), which is indistinguishable from necrotic tissue on noncontrast CT (B). Intravenous iodinated CT contrast was contraindicated owing to the patient's poor renal function. To ensure complete local control, US contrast was injected to localize small viable tissue (C, arrow) and to assess for complete ablation margins after completion of second ablation.

being used to disrupt the blood-brain barrier to enhance drug delivery to the brain (Guvener et al., 2017).

Conclusion

Ultrasound contrast is a valuable pharmaceutical agent during US-guided procedures in the liver and spleen. CEUS can improve visualization of tumors and evaluate for viable tumor postablation. Administration is straightforward and complication rates are low.

Acknowledgments

The authors acknowledge Kelly Kage, M.F.A., C.M.I. for the artistic contributions and medical graphics in this article.

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