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PERSPECTIVE

Contrast-Enhanced Ultrasonography and Its Application in Liver Interventions

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ABSTRACT

Ultrasound (US) guidance has been a fundamental tool for interventionalists to perform percutaneous procedures. A limitation to US guidance is poor lesion visibility on conventional B-mode (brightness mode) US. Contrast-enhanced US (CEUS) is an adjunct technique that facilitates the visualisation and localisation of lesions. We review the use of CEUS and its application in liver interventions and describe the experience in our institution in using CEUS in these procedures.

Key Words: *Contrast media; Radiology, interventional; Ultrasonography, interventional*

中文摘要

超聲造影檢查及其在肝臟介入中的應用綜述

何卓謙、王先民、黃皓廉、蕭志偉、余俊鴻、陳積聖、劉顯宇、陳崇文、王耀忠

超聲引導一直是介入醫生開展經皮手術的基本工具，它的其中一個局限性是傳統B模式（亮度模式）超聲對於病變的可見性欠佳。對比增強超聲這種輔助技術可幫助病變的檢出和定位。本文檢視對比增強超聲的使用及其在肝臟介入中的應用，並描述本院在有關操作中使用對比增強超聲的實踐。

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INTRODUCTION

Ultrasound (US) guidance has been a fundamental tool for interventionalists for various percutaneous procedures. It has the advantages of real-time imaging, lack of ionising radiation, and wide availability. However, the role of US guidance is greatly limited if the lesion has a poor visibility on conventional B-mode (brightness mode) US.

To overcome this limitation, contrast-enhanced ultrasound (CEUS) is an adjunct technique to facilitate the localisation of lesions.[1] In this article, we review the background information of US contrast agents and techniques for performing CEUS. We also describe the application of CEUS in liver interventions and our experience with this technique in our institution.

ULTRASOUND CONTRAST AGENTS

US contrast agents consist of gaseous microbubbles enclosed within shells.[2] They are injected intravenously. The size of microbubbles ranges from 1 to 10 μm.[3] Microbubbles respond differently under different acoustic energies. When microbubbles are subjected to low acoustic energy (mechanical index [MI] = 0.1-0.3), they oscillate and produce non-linear harmonic resonances.[2,3] Separation of the non-linear resonances from microbubbles and linear resonances from background soft tissue forms the basis of CEUS. These two signals can be separated using one of several soft tissue cancellation techniques, such as pulse inversion, frequency, and amplitude modulation.[2,4] Microbubbles are vulnerable to higher acoustic energies (MI > 0.3-0.6), which can cause cavitation and fragmentation.[2]

US contrast agents are classified into first and second generations, depending on the solubility of the gaseous content.[3,5] The first-generation US contrast agents, which consisted mostly of air, are largely obsolete due to their instability (as they will burst easily) and high solubility in blood. Most of the currently used second-generation contrast agents are composed of encapsulated inert gases with high stability and low solubility (e.g., perfluorobutane, perfluoropropane, and sulphur hexafluoride).[5] Currently, there are four agents that are available internationally for use in liver imaging, including sulphur hexafluoride within a phospholipid shell (SonoVue; Bracco Suisse SA, Switzerland), octafluoropropane within a bilayer phospholipid shell (Luminity; Lantheus Medical Imaging, Inc, North Billerica [MA], United States), perfluorobutane gas coated with a chicken egg–derived surfactant hydrogenated egg phosphatidylserine sodium [Optison; GE HealthCare, United Kingdom], and perflubutane enclosed in a phospholipid shell, which has immediate blood pool and delayed Kupffer cell uptake in the liver, which can last up to a few hours (Sonazoid[6-8]; GE HealthCare, Norway). In Asian countries, SonoVue and Sonazoid are more commonly used.[7]

SonoVue is taken up by the blood pool. It is the only registered US contrast agent in Hong Kong.[9] It is currently registered in 44 countries[10] and is available in Japan, Korea, Norway, Singapore and China, etc.[7] It is currently an unregistered drug in Hong Kong, and the relevant legal requirement needs to be observed before use.[8] Details can be obtained from the Drug Office of the Department of Health.[11]

Intravenous use of US contrast agents has a very safe profile. They are excreted via the lungs. The outer shells are biodegradable in general owing to the fact that they will be engulfed by macrophages in the reticuloendothelial system.[2] They are not nephrotoxic, and therefore can be administered in patients with renal failure.[5,6] It also has no effect on thyroid function as it does not contain iodine.[5] US contrast agents have a very low rate of anaphylactic reactions (1 in 7000 patients or 0.014%) compared to iodinated contrast agents or gadolinium-based contrast agents.[5,6]

Contraindications vary among different US contrast agents. For SonoVue, contraindications include, but are not limited to, hypersensitivity to the active substance or to any of the excipients (including polyethylene glycol), known right-to-left shunts, severe pulmonary hypertension, uncontrolled systemic hypertension, and adult respiratory distress syndrome.[12] For Sonazoid, contraindications include hypersensitivity to the active substances (including perfluorobutane gas and hydrogenated egg phosphatidylserine sodium) or to any of the excipients. Sonazoid is derived from egg. For patients with egg or egg products allergy, Sonazoid should only be used if the benefit clearly outweighs the potential hazard.[7] Care should be taken in patients with right-to-left shunts, unstable heart conditions, serious coronary arterial diseases or serious pulmonary diseases.[13] Readers are advised to read the relevant product information and package insert carefully before use.

TECHNIQUE OF CONTRAST-ENHANCED ULTRASOUND

One of the unique features of CEUS is that real-time imaging of contrast enhancement is enabled. The arterial phase usually occurs from 10-20 seconds to 30-45 seconds after injection. The portal venous phase ensues 30-45 seconds to 2 minutes post-injection and is followed by late phase, which ends when there is clearance of microbubbles from the circulation which is about 4-6 minutes.[4] For Sonazoid, the Kupffer cell uptake (post-vascular) phase usually starts 10 minutes post-injection and can persist up to a few hours.[7,10]

MI is the measure of acoustic power of an US beam. To minimise the disruption of the microbubbles, CEUS imaging is performed at low acoustic pressures with MI ranging from 0.05 to 0.3.[4] Different contrast agents may require different machine settings for optimal signals; for example, SonoVue can be used with a lower MI (<0.1) due to its softer shell, while a higher MI is needed for Sonazoid due to its stiffer outer shell.[9,14] Optimal MI settings may vary from machine to machine.

The dose of US contrast agent varies with different brands. The current recommended dose is 2.4 mL for SonoVue (peripheral vascular use), and 0.015 mL/kg body weight for Sonazoid.[12,13] Both SonoVue and Sonazoid need to be reconstituted before administration and readers are referred to the relevant package insert for detail information. A reminder on reconstituting Sonazoid from our experience is although an ampoule of 10 mL sterile water is provided in the package, only 2 mL is required for reconstitution. Using a 20G or larger catheter for contrast injection is recommended to minimise microbubble destruction. Slow hand injection of contrast agent over 2 to 3 seconds followed by a 5- to 10-mL saline flush is suggested.[4] Repeated contrast injection of the recommended dose can be considered if necessary.[15]

Dual-screen display with low MI B-mode and contrast-mode images side-by-side is commonly used during CEUS. A timer is also displayed to record the time after contrast injection (Figure 1). Depth of penetration of CEUS is usually less than that seen with conventional B-mode imaging due to low MI settings. The focal zone should be placed just deep to the target lesion.[4,15] It is important to avoid excessive or continuous scanning in a single plane in order to prevent microbubble destruction, which causes loss of contrast signal.[15] Again, repeated contrast injection can be considered to characterise a washed-out region for any arterial phase enhancement.[15]

Key features of hepatocellular carcinoma with SonoVue are arterial phase hyperenhancement followed by late and mild washout (Figure 2). Similarly for Sonazoid, hepatocellular carcinoma typically shows arterial phase hyperenhancement and a defect in the Kupffer cell phase.

There are many guidelines and publications describing the use of CEUS in characterising focal liver lesions. A complete description of lesion enhancement patterns

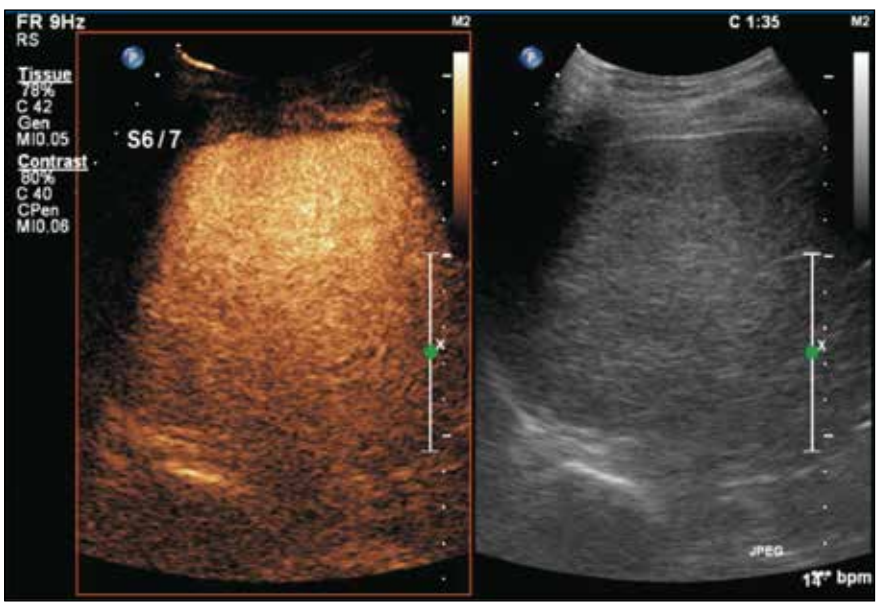

Figure 1. Dual-screen display with contrast-mode image on the left and low mechanical index B-mode (brightness mode) ultrasound image on the right side-by-side when performing contrast-enhanced ultrasound. A scanner timer is also displayed at the upper right corner of the screen.

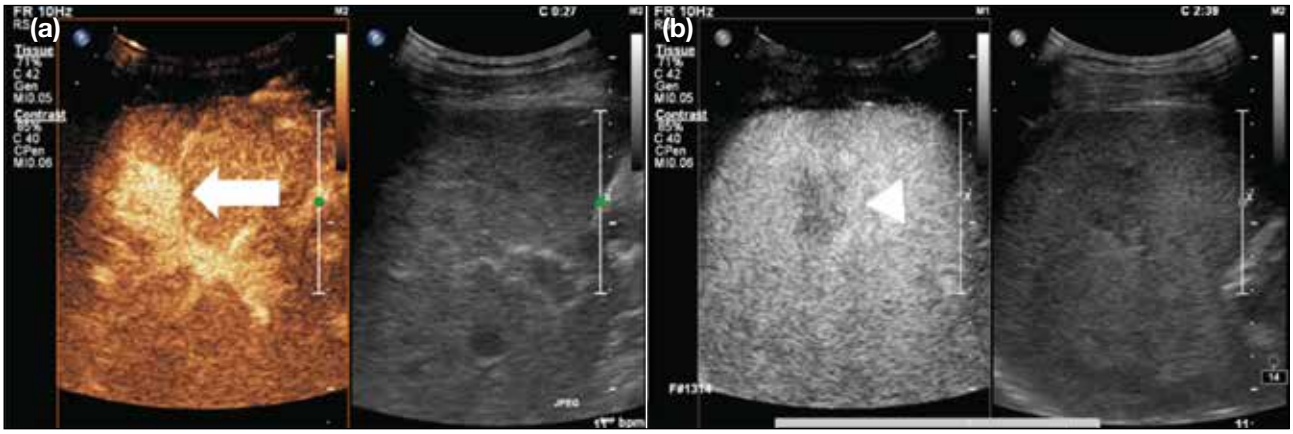

Figure 2. Case of typical hepatocellular carcinoma. (a) Contrast-enhanced ultrasound (CEUS) with SonoVue showed non-rim arterial phase hyperenhancement of the target lesion in segment V of liver (white arrow). The lesion measured 2.8 cm in maximal diameter (not shown). (b) In the late phase, this lesion demonstrated mild contrast washout (white arrowhead). This lesion was classified as CEUS LR-5 lesion (i.e., definitely hepatocellular carcinoma) according to the CEUS Liver Imaging Reporting and Data System version 2017.

and a lexicon are beyond the scope of this article. Readers are referred to the Guidelines and Good Clinical Practice Recommendations for CEUS in the Liver from WFUMB (World Federation for Ultrasound in Medicine and Biology), and CEUS of the liver: technical and lexicon recommendations from the American College of Radiology CEUS Liver Imaging Reporting and Data System working group for further information.[4,6] The current American College of Radiology CEUS Liver Imaging Reporting and Data System (LI-RADS) version 2017 only described the use of pure blood pool agents, and the use of Sonazoid will be addressed in the next version.[4]

APPLICATION OF CONTRAST-ENHANCED ULTRASOUND IN LIVER INTERVENTIONS

CEUS can enhance lesion conspicuity for percutaneous interventions, especially when they are not well depicted on conventional B-mode US.[16] Common uses of CEUS in liver interventions include guiding percutaneous biopsy and tumour ablation.

For indeterminate lesions on computed tomography (CT) or magnetic resonance (MR) imaging, CEUS may provide further diagnostic information to characterise the lesions. For example, indeterminate lesions showing absence of arterial hyperenhancement on CT or MR may be due to mistiming of the arterial phase imaging. Using CEUS can eliminate this problem since it is real-time continuous imaging.[4,6,7,17] Therefore, CEUS can be a problem-solving tool and may obviate the need for biopsy for indeterminate lesions on CT or MR.

CEUS is often employed in guiding percutaneous biopsy of focal liver lesions. It is helpful in both increasing lesion conspicuity and evaluating the viable vascularised portion of the lesion. In the recent guidelines issued by WFUMB, CEUS guidance for focal liver lesion biopsy should be attempted when the lesions are invisible or inconspicuous on conventional B-mode imaging and should be considered in lesions with potential necrotic areas or if previous biopsy resulted in necrotic material.[6] A two-dose procedure is recommended. The first dose of US contrast is used for characterising the target lesion and planning the needle path, and the second dose is used for the real-time CEUS guidance during interventions.[6] The safety and feasibility of using CEUS with SonoVue and Sonazoid in focal liver lesion biopsy have been reported in multiple studies.[16,18,19] With the use of CEUS, the need to abort the procedure and convert to CT guidance is potentially reduced. It also helps to confirm the target lesion in cases of advanced cirrhosis where multiple background cirrhosis-related nodules are common or of concurrent benign liver lesions (e.g., haemangioma), and therefore minimises mistargeting. Vascular complications after biopsy, such as pseudoaneurysm formation, can be detected by CEUS, avoiding the need for contrast-enhanced CT.[20]

CEUS is also valuable in guiding liver tumour ablation. Similar to guiding percutaneous biopsy of focal liver lesions, CEUS can increase lesion conspicuity, allow real-time needle guidance to the lesion during the procedure, and minimise mistargeting to other lesions. In a randomised controlled trial reported by Minami et al,[21] there was a significantly higher complete ablation rate

(94.7% vs. 65.0%) and a smaller number of treatment sessions when using CEUS guidance with Levovist in liver tumour ablation for lesions poorly depicted on conventional B-mode US. After ablation, gas clouds form in the treatment bed; they are markedly echogenic and obscure the ablation zone, but usually resolve after 10 to 15 minutes, and CEUS can then be performed post-ablation to evaluate for residual disease around the ablation zone.[22-25] Re-intervention can be performed in the same setting if indicated. Performing immediate

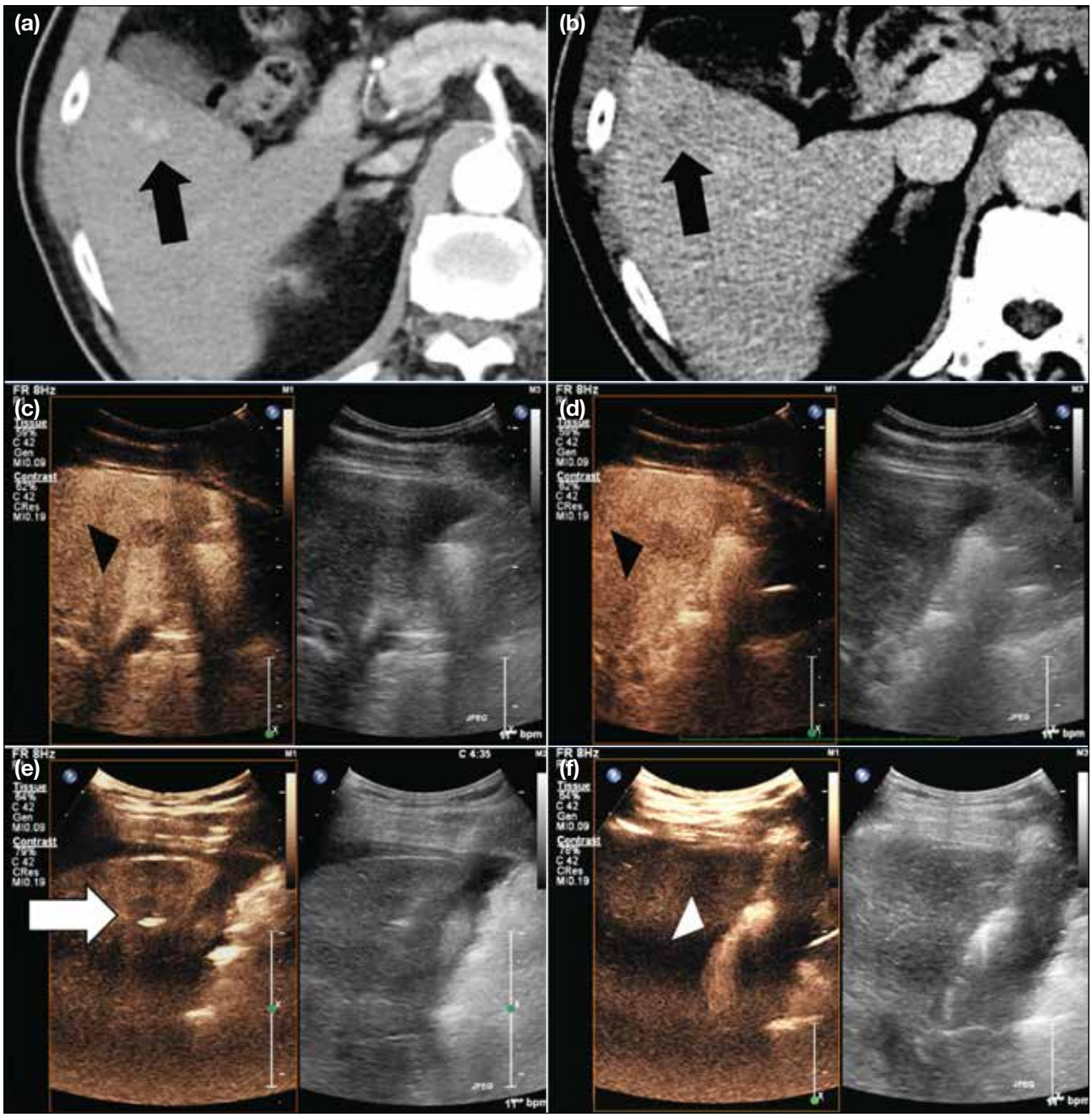

Figure 3. This patient had chronic hepatitis B viral infection and cirrhosis. (a and b) Axial contrast computed tomography (CT) liver showed two small arterial enhancing lesions in segment V of the liver with contrast washout in the delayed phase suspicious for hepatocellular carcinoma (black arrows). (c and d) The patient was referred to our team for percutaneous ablation of the lesions. On conventional B-mode (brightness mode) ultrasound, both of the lesions could not be well visualised (image not captured). Contrast-enhanced ultrasound (CEUS) with Sonazoid was then performed, with two nodular parenchymal defects in segment V of liver closely abutting each other during the Kupffer phase corresponding to the CT-detected lesions (black arrowheads). (e and f) Subsequent percutaneous ablation was performed under CEUS with Sonazoid during the Kupffer phase. The lesions were first targeted with a 22G spinal needle (white arrow) and then a microwave antenna was inserted with parallel technique under CEUS guidance (white arrowhead).

postprocedural CEUS with Definity can significantly reduce the incidence of residual tumour (0% vs. 16.7%) shown in a retrospective study by Lekht et al.[24] Mauri et al[25] also reported using CEUS with Sonovue after liver tumour ablation, detecting residual tumour in 29.0% of the ablations. They were able to repeat ablation immediately, with later CT showing 96.6% success. Nishigaki et al[23] reported the successful use of Sonazoid in detecting residual tumour and securing minimal ablative margins immediately after ablation. These show the effectiveness of immediate post-ablation CEUS in determining the adequacy of the ablation, which can potentially improve patient survival and clinical outcome.

SonoVue is the only registered US contrast agent in Hong Kong.[9] It can be used in guiding different liver interventions as described. However, its short enhancement period may not be ideal for liver interventions, especially in liver tumour ablation where the procedural time is usually long. Sonazoid provides a unique advantage with the prolonged Kupffer cell phase, which can last up to a few hours, providing a longer time window for real-time CEUS guidance.

We have recently introduced CEUS with Sonazoid in our institution. For patients referred to us for percutaneous liver tumour ablation, we would carry out a consultation in our interventional radiology clinic. During the consultation, we routinely perform a US of the index lesion for preprocedural planning. CEUS can be considered at the same juncture if the lesion cannot be clearly visualised on conventional B-mode US. If the lesion becomes more conspicuous after contrast administration and the time window of visibility appears technically feasible for percutaneous ablation, then CEUS-guided percutaneous ablation is scheduled. In our experience, the early Kupffer phase (10-30 minutes post-injection) provides a good intervention window. Avoiding unnecessary continuous scanning is important to minimise microbubble destruction. A second dose of contrast injection is also helpful if contrast signal loss occurs. CEUS with Sonazoid during interventional radiology clinic consultation can be safely performed in outpatient setting. In our institution, patients would be discharged following a 10- to 15-minute observation after administration of Sonazoid.

In our experience, CEUS with Sonazoid improves the detection and conspicuity of liver lesions (Figure 3). It enables real-time US guidance for lesions that are not conspicuous on conventional B-mode US when performing percutaneous liver procedures, obviating the need for CT guidance. This reduces the radiation exposure to patients, and possibly decreases the procedural time and complexity. CEUS has also a role in percutaneous liver tumour ablation to detect any residual tumour immediate post-ablation (Figure 4),

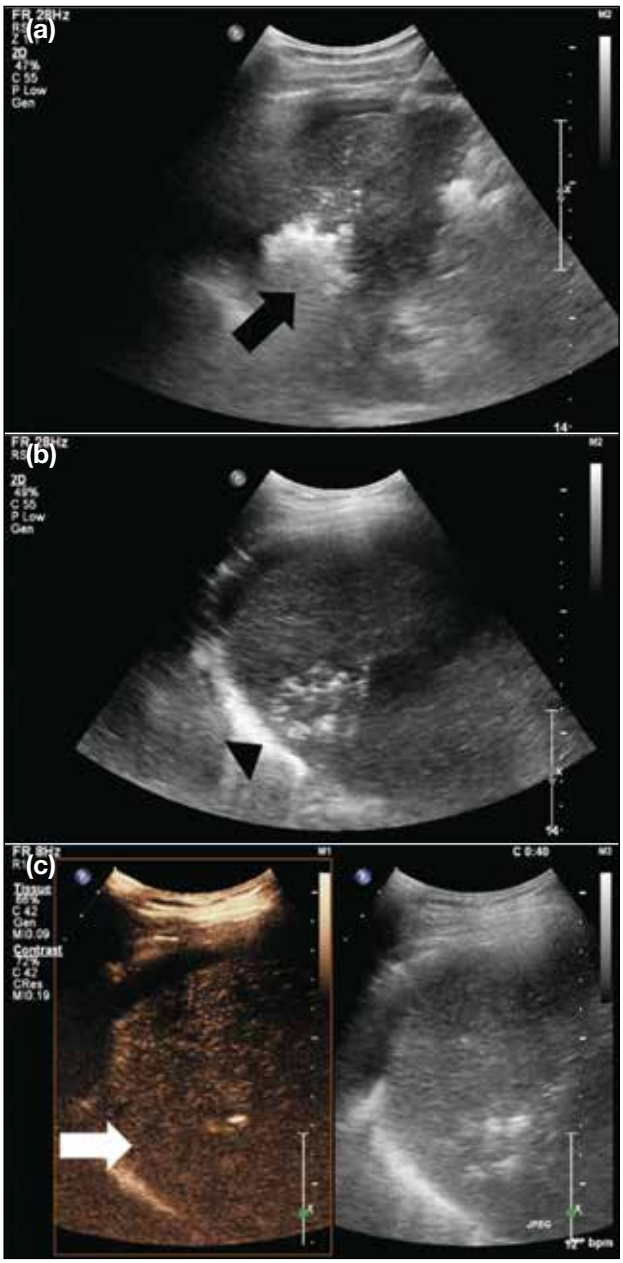

Figure 4. This patient had a hepatocellular carcinoma in segment VII of the liver. Percutaneous microwave ablation was performed. (a) Immediately after ablation, the ablation zone was largely obscured by a gas cloud (black arrow). (b) Twenty minutes after the ablation, the gas cloud had largely subsided and the ablation zone could be clearly demonstrated on ultrasound (black arrowhead). (c) Contrast-enhanced ultrasound performed with Sonazoid showed no marginal nodular enhancement adjacent to the ablation zone to suggest the presence of residual tumour (white arrow).

and re-intervention can be easily performed in the same setting if any residual tumour is detected. There are also no serious adverse reactions reported after intravenous administration of Sonazoid in our institution.

However, there are still some limitations of CEUS in guiding liver interventions from our experience. CEUS has a detection limit for deep lesions since the penetration may not be adequate with the presence of microbubbles and low MI settings. Similar to conventional B-mode US, there is also limitation for CEUS to detect lesions located at the liver dome.

CONCLUSION

CEUS is a safe and effective tool for liver interventions. It improves the visibility of lesions for needle guidance and is particularly useful when the lesions are small or not conspicuous on conventional B-mode US. The unique feature of Kupffer cell uptake of Sonazoid provides a longer time window for real-time guidance during liver interventions.

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