Contrast-enhanced ultrasound in the diagnosis of nodules in liver cirrhosis

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Core tip: Contrast-enhanced ultrasound is a relatively new imaging technique that can be effectively used in the diagnostic algorithms for liver nodules detected in hepatocellular carcinoma surveillance. There are several unique advantages of this technique that make this imaging technique very useful.

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Abstract

Contrast-enhanced ultrasound (CEUS) using microbubble contrast agents are useful for the diagnosis of the nodules in liver cirrhosis. CEUS can be used as a problem-solving method for indeterminate nodules on computed tomography (CT) or magnetic resonance imaging (MRI) or as an initial diagnostic test for small newly detected liver nodules. CEUS has unique advantages over CT and MRI including no renal excretion of contrast, real-time imaging capability, and purely intravascular contrast. Hepatocellular carcinoma (HCC) is characterized by arterial-phase hypervascularity and later washout (negative enhancement). Benign nodules such as regenerative nodules or dysplastic nodules are usually isoechoic or slightly hypoechoic in the arterial phase and isoechoic in the late phase. However, there are occasional HCC lesions with atypical enhancement including hypovascular HCC and hypervascular HCC without washout. Cholangiocarcinomas are infrequently detected during HCC surveillance and mostly show rim-like or diffuse hypervascularity followed by rapid washout. Hemangiomas are often found at HCC surveillance and are easily diagnosed by CEUS. CEUS can be effectively used in the diagnostic work-up of small nodules detected at HCC surveillance. CEUS is also useful to differentiate malignant and benign venous thrombosis and to guide and monitor the local ablation therapy for HCC.

INTRODUCTION

Ultrasound (US) is most commonly used for imaging surveillance for hepatocellular carcinoma (HCC) in high-risk patients[1]. Once a focal hepatic nodule is detected during HCC surveillance, a diagnostic imaging test is performed. The assessment of tumor vascularity is most important in the differential diagnosis of the nodules. Doppler US techniques have been used to detect vascularity in liver tumors; however, these techniques lack sensitivity to detect tumor vascularity. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) is most commonly used to characterize liver masses. Contrast-enhanced ultrasound (CEUS) using a microbubble contrast agent is a relatively new imaging technique and has been proved to be useful for characterizing liver tumors. CEUS enables a real-time demonstration of continuous hemodynamic changes of liver tumors after injection of the contrast material.
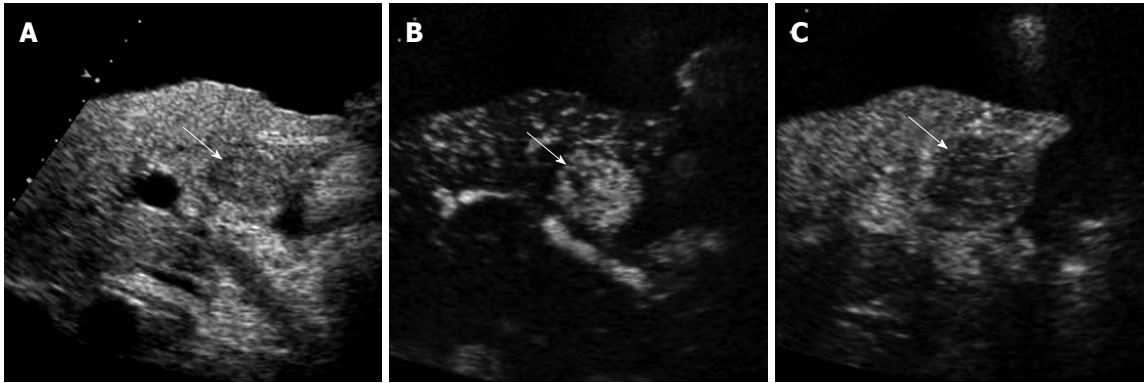
Figure 1 A 61-year-old man with hepatocellular carcinoma and renal failure. A: Gray-scale ultrasound shows a hypoechoic mass (arrow) within the cirrhotic liver. There is a large amount of ascites surrounding the liver. Contrast-enhanced computed tomography or magnetic resonance scan could not be performed because of renal failure; B: Contrast-enhanced ultrasound (CEUS) image in the arterial phase shows hypervascularity of the mass (arrow) relative to the liver; C: The mass (arrow) shows washout in the portal venous phase. The diagnosis of hepatocellular carcinoma was made based on imaging findings of CEUS without biopsy.

Recent practice guidelines for HCC provided recommendations for the diagnostic algorithm for newly detected nodules at HCC surveillance[1-3]. The application of the imaging test varies depending on the size of the nodules. For very small lesions (< 1 cm in size), follow-up with US scan is usually recommended in 3 mo as further imaging tests may not be reliable for the diagnosis. For lesions same or larger than 1 cm, the performance of multiphasic contrast-enhanced CT, MRI or CEUS is a reasonable next step. There has been a controversy on the use of CEUS because intrahepatic cholangiocarcinoma can be misdiagnosed as HCC and CEUS has been subsequently excluded from the diagnostic tests for HCC in updated AASLD practice guidelines[1]. However, it has been argued that intrahepatic cholangiocarcinoma is relatively rare in liver cirrhosis and CEUS can depict suggestive findings of cholangiocarcinoma[4]. As the imaging diagnosis of small nodules with 1-2 cm in size can be particularly challenging, a multi-modality approach is often needed. Biopsy is performed only when imaging findings are inconclusive.

In this article, we explain the technical aspects of CEUS and its differences from CT and MRI. Then CEUS imaging findings of HCC and other cirrhosis-related nodules and the role of CEUS in diagnosing tumor thrombosis and monitoring local ablation therapy for HCC are reviewed.

WHAT IS CEUS?

CEUS uses intravenous microbubble contrast agents that are small (3-5 μm) enough to pass through the pulmonary circulation. Microbubble contrast agents are approved for radiologic use in more than 50 countries and have excellent safety record with lower rate severe adverse reactions than CT contrast[5]. There are a few different types of microbubble contrast agents that are commercially available. Presently Definity (Lantheus Medical Imaging) and SonuVue (Bracco) are most widely used. These are purely intravascular contrast agents that show strong vascular enhancement after bolus injection and slowly diffuse into

the blood over about 5 min. Therefore, the contrast agent can be repeatedly injected with about 5-min intervals as needed. Sonazoid (Daiichi), which is most actively used in Japan, shows similar vascular enhancement and is taken up by Kupffer cells in the late phase.

CEUS requires a contrast specific imaging technique that is now widely available in most commercially available ultrasound systems. Low mechanical index (MI) contrast-specific mode is used to visualize the microbubbles continuously while suppressing signals from tissue. A dual-imaging mode, which enables simultaneous real-time display of gray-scale and contrast-specific mode, is essential for scanning small liver lesions. High MI frames can be used to disrupt microbubbles and the enhancement pattern of refilling the scanning plane can be evaluated. This is called disruption-replenishment technique and is useful to visualize vascular morphology within the tumor of enhancement pattern of rapidly-enhancing lesions, especially when it is used with maximum-intensity projection method[6].

WHY DO WE NEED CEUS?

CEUS has several advantages over CT or MRI. Firstly, microbubbles can be safely injected in patients with renal failure as there is no renal excretion of the contrast[5]. CEUS is therefore a useful problem-solving method for characterizing liver masses when CT or MRI is contraindicated due to renal failure (Figure 1). There is no need of blood test for renal function before contrast injection. Secondly, CEUS allows real-time assessment of arterial-phase enhancement, eliminating the issue of appropriate arterial-phase timing. CEUS often detects arterial-phase hypervascularity when CT or MRI fails to show it because of incorrect arterial-phase timing (Figure 2)[7]. Real-time evaluation also enables a detailed assessment of arterial-phase filling pattern and vascular morphology within the liver lesion which are often critical for differential diagnosis of rapidly enhancing hypervascular liver lesions[8]. Thirdly, washout phenomenon (negative enhancement of liver lesion relative to the liver in the late phase) in ma-
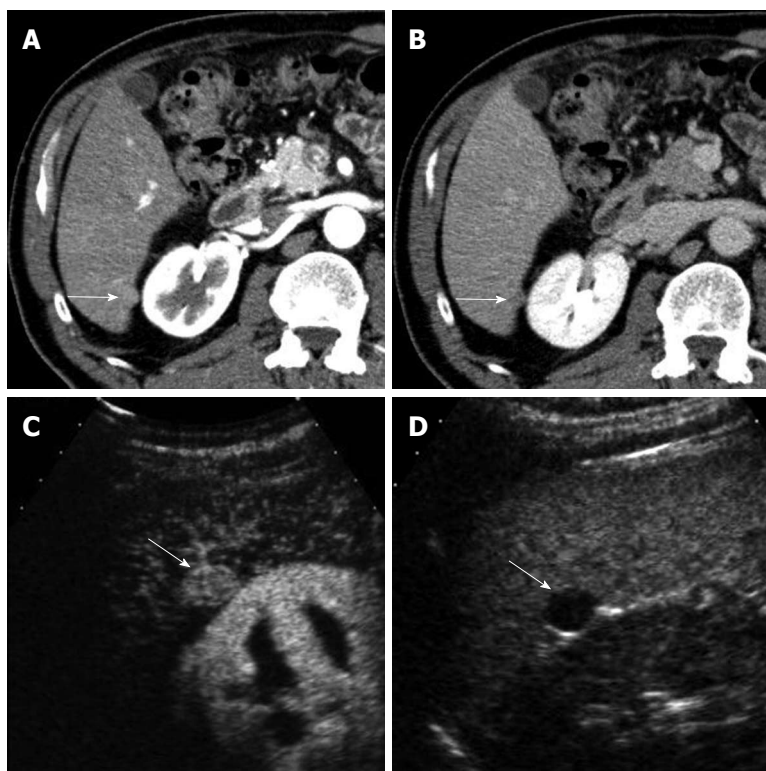
Figure 2 A 63-year-old man with moderately-differentiated hepatocellular carcinoma. A: Computed tomography scan in the arterial phase shows a small exophytic nodule (arrow) which shows similar attenuation to the liver; B: The nodule (arrow) is slightly hypoattenuating to the liver in the delayed phase; C: Contrast-enhanced ultrasound (CEUS) in the arterial phase clearly demonstrates hypervascularity of the nodule (arrow); D: CEUS in the portal venous phase shows washout of the nodule (arrow).

lignant liver lesions is more consistently seen on CEUS than CT/MRI. This is due to the different properties of the contrast material. Microbubbles in CEUS are purely intravascular and show washout in malignant tumors in the late phase; however, CT or MRI may not show washout in malignant tumors with high vascular permeability and large extracellular interstitial space because the contrast agent can leak into the interstitium[7,9]. Fourth, CEUS is relatively inexpensive and very well tolerated by the patients who are claustrophobic. CEUS can be easily repeated in short intervals if needed without the risk of ionizing radiation. Lastly, CEUS can be performed immediately when a new liver nodule is identified, allowing an immediate characterization of benign liver nodules such as hemangiomas and avoiding additional imaging tests[10].

On the other hand, CEUS is operator-dependent and requires extensive hands-on experience. There are sonographically difficult regions in the liver such as high right subphrenic area. CEUS is not an appropriate staging modality for HCC as it only images some part of the liver with each contrast injection. CT or MRI is always needed for proper tumor staging once HCC diagnosis is made. However, CEUS can be effectively used as a useful problem-solving method utilizing its unique advantages when CT or MRI is indeterminate or contraindicated (Figures 1 and 2)[10].

WHEN DO WE USE CEUS?

Image findings of liver nodules

HCC is characterized by arterial-phase hypervascularity and later washout on CEUS (Figures 1 and 2). The arterial-phase enhancement is often diffuse or heterogeneous. Peripheral rim-like enhancement is unusual in HCC and

is commonly seen in metastasis or intrahepatic cholangiocarcinoma[11]. Large HCCs often show non-enhancing areas due to necrosis or internal hemorrhage. Maximum intensity projection images can visualize vascular morphology in HCC which is typically very irregular and dysmorphic[6]. Washout in HCC tends to be late and often begins later than 90 s after injection whereas metastases or intrahepatic cholangiocarcinomas consistently show rapid washout (< 60 s)[9]. Most of small cholangiocarcinomas that are infrequently detected during HCC surveillance can be characterized by CEUS by demonstrating rim-like arterial phase enhancement and rapid washout in our experience (Figure 3). Biopsy should be performed when these unusual enhancement patterns for HCC are observed on CEUS.

Washout may not be seen in occasional cases of well-differentiated HCC. Washout timing is related to the pathologic differentiation of HCC: well-differentiated HCC tends to show later washout or no washout whereas poorly-differentiated HCC tends to show rapid washout[12]. It is important to understand that most new hypervascular nodules on CEUS detected during HCC surveillance are HCC regardless of washout if the nodules do not show the appearance of hemangioma[13]. However, a biopsy is needed to confirm HCC for hypervascular nodules without washout. CEUS is superior to CT or MRI for detecting hypervascularity of HCC because of real-time evaluation of arterial-phase enhancement[14-16]. Therefore, CEUS can be effectively used for characterizing non-hypervascular, indeterminate lesions on CT and MRI (Figure 2). There is a small subset of hypovascular HCC which is mostly of well-differentiated pathology. These lesions usually show a transient hypovascularity
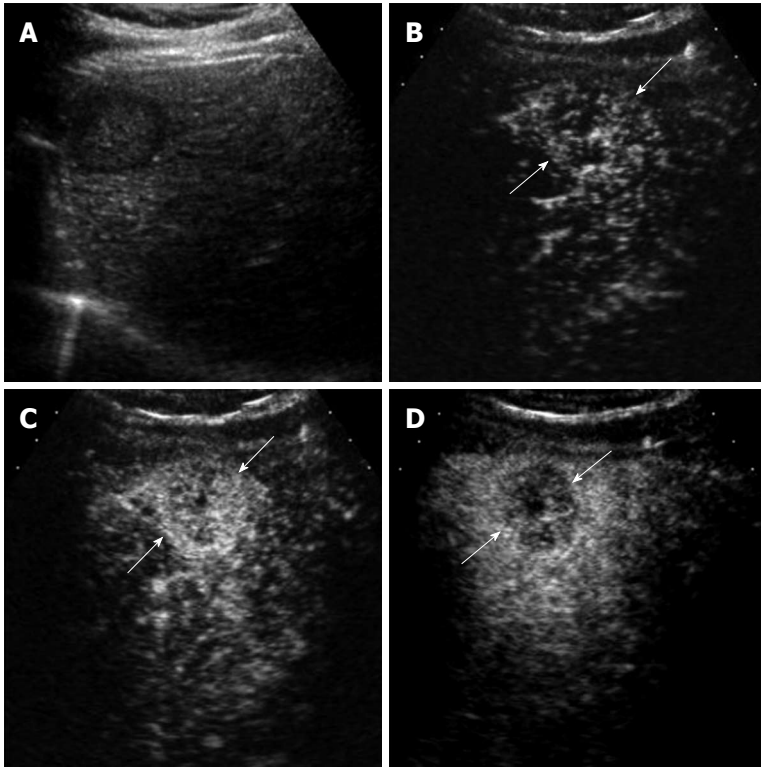
Figure 3 A 70-year-old man with intrahepatic cholangio-carcinoma detected during surveillance for hepatocellular carcinoma. A: Gray-scale ultrasound shows a hypoechoic mass in the liver; B: Contrast-enhanced ultrasound (CEUS) in the arterial phase obtained 14 s after contrast injection shows mild hypervascularity in the periphery of the mass (arrows); C: CEUS obtained at 19 s after contrast injection shows diffuse hypervascularity of the mass (arrows); D: The mass (arrows) shows rapid washout at 28 s after contrast injection. Biopsy revealed cholangiocarcinoma.
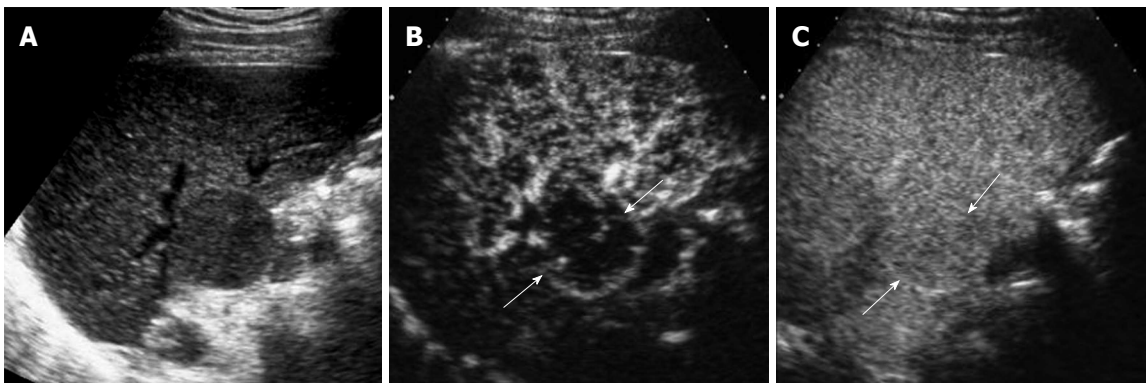

Figure 4 A 69-year-old man with well-differentiated hypovascular hepatocellular carcinoma. A: Gray-scale ultrasound shows an exophytic hypoechoic mass in the liver; B: The mass (arrows) is hypoechoic relative to the adjacent liver in the arterial phase of contrast-enhanced ultrasound; C: The mass (arrows) is isoechoic to the liver in the portal venous phase. Biopsy revealed well-differentiated hepatocellular carcinoma.

followed by gradual enhancement and the lesions become isoechoic relative to the normal in the portal venous phase and late phase (Figure 4).

Regenerative nodules or dysplastic nodules (DNs) are usually non-hypervascular. CEUS may show a transient hypoenhancement relative to the liver in the arterial phase, reflecting the step-wise changes of nodule perfusion during the hepatocarcinogenesis (Figure 5). Therefore, there is an overlap of imaging findings on CEUS between DNs and well-differentiated HCCs[17]. The differentiation is difficult not only on imaging but also on histological examination. Recent practice guidelines recommend a biopsy for all new liver nodules ≥ 1 cm that are indeterminate on imaging[18]; however, many of these nodules are borderline lesions, in which the differential diagnosis in small needle biopsy specimens is challenging

due to histological heterogeneity within the nodules. In the setting of a competing potentially fatal disease (*i.e.*, cirrhosis), the intensive identification, biopsy, and treatment of early HCCs has yet to be justified. Khalili *et al*[19], in their study of 93 indeterminate 1-2-cm nodules on dynamic CT, MRI, and CEUS, suggested a strategy of close imaging follow-up for most indeterminate 1-2-cm nodules, with selective application of biopsy for nodules with arterial hyperenhancement or in the presence of a synchronous typical HCC.

Hemangiomas are frequently detected during HCC surveillance. Gray-scale ultrasound findings, such as diffuse hyperechogenicity or hyperechoic peripheral rim, can help suggest the diagnosis of hemangioma. In fatty liver, hemangiomas are often hypoechoic relative to the echogenic liver parenchyma. In our recent study[20], 43/184
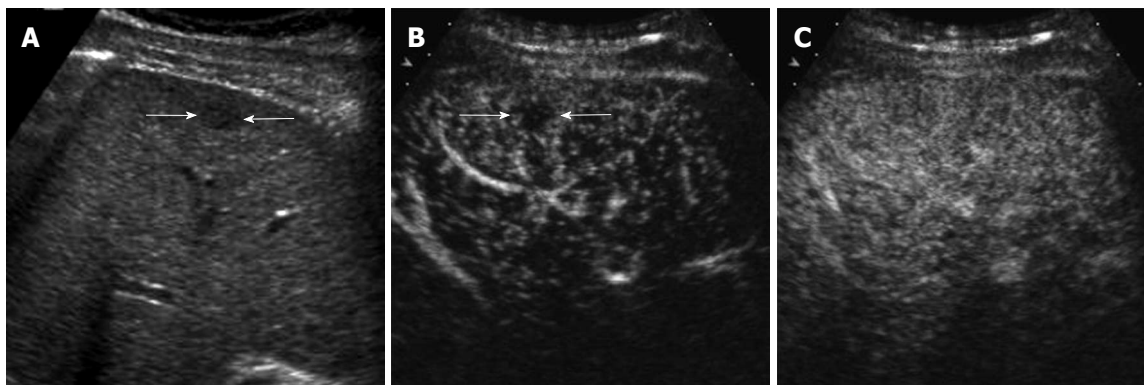
Figure 5 A 69-year-old man with dysplastic nodule. A: Gray-scale ultrasound shows a small hypoechoic nodule (arrows) in the subcapsular portion of the liver; B: The nodule (arrows) is hypoechoic to the liver in the arterial phase of contrast-enhanced ultrasound; C: The nodule is isoechoic to the liver in the portal venous phase. Biopsy revealed low-grade dysplastic nodule.
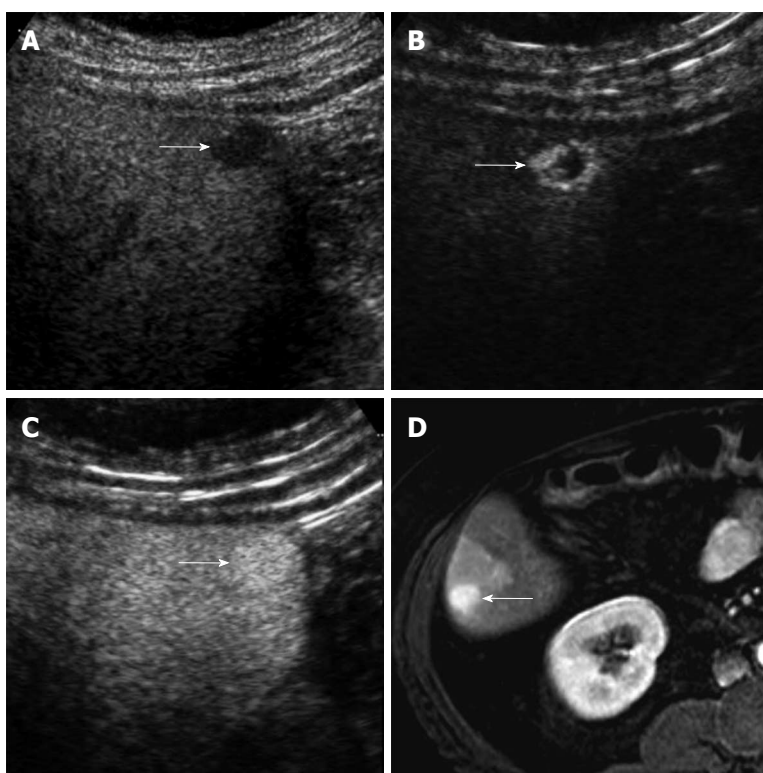

Figure 6 A 53-year-old woman with hemangioma. A: Gray-scale ultrasound shows a hypoechoic nodule (arrow) in the subcapsular portion of the liver; B: There is a peripheral strong hyperenhancement (arrows) in the arterial phase of contrast-enhanced ultrasound; C: The nodule (arrow) is homogeneously hyperechoic to the liver in the portal venous phase; D: The nodule (arrow) is homogeneously hyperintense to the liver without the appearance of peripheral enhancement in the arterial phase of contrast-enhanced T1-weighed magnetic resonance image.

(23%) of newly detected nodules at HCC surveillance were hemangiomas. Immediate performance of CEUS can achieve a confident diagnosis by demonstrating the characteristic enhancement pattern that includes peripheral nodular enhancement, gradual central fill-in, and sustained enhancement and avoid further imaging tests such as CT or MRI. CEUS is also useful to demonstrate the characteristic enhancement pattern in fast filling hemangioma which often shows homogeneous enhancement in the arterial phase of CT or MRI (Figure 6)[21].

Nontumorous arterioportal shunting is a common mimicker of malignancy in cirrhotic liver. It is typically wedge-shaped, peripherally located, and homogeneous hypervascular in the arterial phase. The lesion becomes isointense to the liver in the venous phase and never shows washout (Figure 7). Focal fat deposits or focal fat sparing areas with nodular appearance can mimic the appearance of focal liver masses. There lesions are mostly isoechoic to the liver in the arterial and late phases on CEUS. The presence of normal portal veins within the lesion can confirm the benign lesion[21].

CEUS as guidance or post-radiofrequency ablation monitoring for HCC

US is most commonly used for imaging guidance for radiofrequency ablation (RFA) of HCC because of its real-time imaging capability and no ionizing radiation. It is occasionally difficult to visualize the HCC lesion on US when the lesion is isoechoic to the liver or the underlying liver is severely cirrhotic with markedly heterogeneous echotexture. CEUS can help localize the lesion before RFA procedure by demonstrating a focal hypervascular
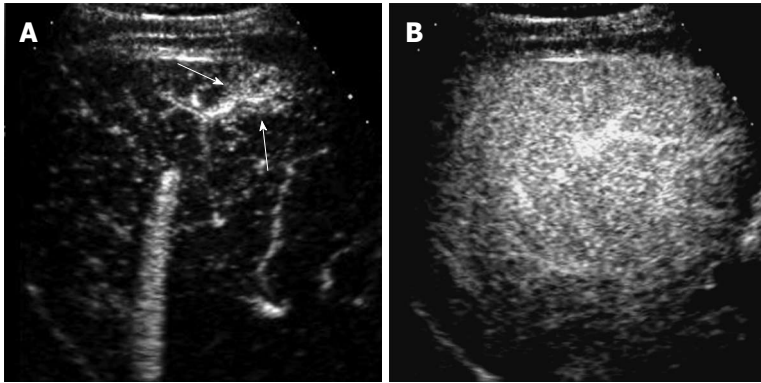
Figure 7 A 65-year-old man with nontumorous arterioportal shunt. A: Contrast-enhanced ultrasound in the arterial phase shows a wedge-shaped hypervascular lesion (arrows) in the subcapsular portion of the liver; B: The lesion is not visualized in the portal venous phase due to isoechogenicity to the liver.
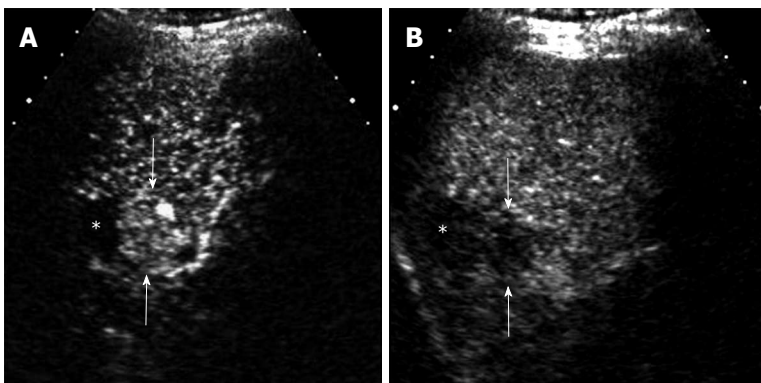

Figure 8 A 70-year-old man with recurrent hepatocellular carcinoma after radiofrequency ablation. A: There is a focal nodular hypervascular lesion (arrows) adjacent to an ablation zone (*) in the arterial phase of contrast-enhanced ultrasound; B: The lesion (arrows) shows washout in the portal venous phase.
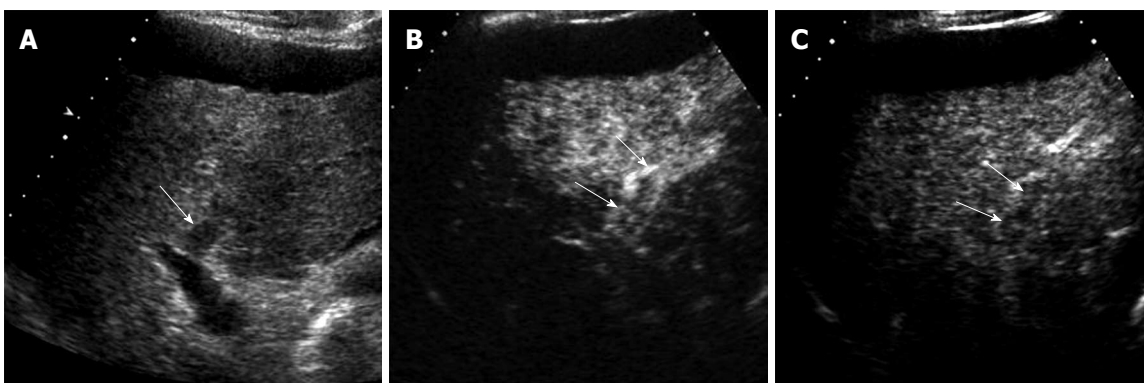

Figure 9 A 73-year-old man with malignant portal vein thrombosis associated with hepatocellular carcinoma. A: Gray-scale ultrasound shows a hypoechoic thrombus (arrow) within the anterior segmental branch of the right portal vein; B: The thrombus (arrows) is heterogeneously enhancing in the arterial phase of contrast-enhanced ultrasound; C: The thrombus (arrows) is hypoechoic relative to the liver in the portal venous phase.

lesion. Marginal recurrence adjacent to the ablation zone may not be easily located on gray-scale US because of the pre-existing abnormality. CEUS can easily identify the exact location of the recurrent HCC that can provide excellent guidance for RFA needle positioning (Figure 8)[22]. For post-RFA monitoring for HCC, CT or MRI is primarily used in our institution. CEUS is often performed when there is an indeterminate lesion on CT or MRI and often clarifies the abnormality with high confidence.

CEUS for determining malignant or benign venous thrombosis

Malignant thrombosis in the portal veins or hepatic veins is a critical determinant of HCC staging as it directly influences treatment strategy. CEUS is highly accurate to differentiate malignant and benign venous thrombosis. CEUS demonstrates enhancement within the malignant thrombosis in the arterial phase and subsequent washout similar to the parenchyma HCC masses (Figure 9)[23]. The presence of formed vessels within the thrombus is another useful feature to diagnose malignant thrombosis. However, care should be taken in assessing formed vessels within the thrombus on CEUS as recanalized portion within chronic benign thrombosis may mimic the appearance of formed vessels in malignant thrombus. Occlusive thrombosis and expansion of the venous lumen are more frequently seen in malignant than benign thrombosis, but these are not specific features of malignancy.

CONCLUSION

CEUS is an excellent imaging technique with several unique advantages over CT or MRI, including safe usage in renal failure patients, better detection of arterial-phase hypervascularity due to real-time imaging capability, consistent demonstration of washout in malignant lesions, and excellent patient's compliance. Therefore CEUS can be effectively used in the diagnostic algorithms of new liver nodules detected during HCC surveillance and pre- or post-RFA evaluation for HCC.

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