HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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The Role of Contrast-Enhanced Ultrasound in Hepatocellular Carcinoma Diagnosis

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G&H Currently, when is contrast-enhanced ultrasound typically used for diagnosis of hepatocellular carcinoma?

YK Contrast-enhanced ultrasound (CEUS) involves the administration of an intravenous contrast agent consisting of microbubbles with gas to better visualize organs and blood vessels. Currently, in my practice and in many others, CEUS tends to be used for hepatocellular carcinoma (HCC) diagnosis in patients who underwent computed tomography (CT) or magnetic resonance imaging (MRI) but have indeterminate findings (classified as Liver Imaging Reporting and Data System [LI-RADS] 3, 4, or M) or who have contraindications to CT or MRI. For example, patients with acute kidney injury or chronic kidney disease cannot use CT contrast safely, patients with cardiac leads or a pacemaker may not be able to undergo MRI, and some patients with claustrophobia may not tolerate MRI even with premedication. CEUS provides real-time imaging with high sensitivity to the contrast agents, and arterial-phase enhancement is a critical component in the diagnosis of HCC. If arterial-phase timing on CT or MRI is suboptimal—either too early or too late—arterial-phase hyperenhancement may not be detected. In such cases, CEUS can be performed to establish or clarify the diagnosis of HCC. The Organ Procurement & Transplantation Network and the United Network for Organ Sharing implemented a policy change in 2025 recognizing CEUS LI-RADS 5 as an accepted diagnostic category for HCC. Previously, only CT- or MRI-based LI-RADS 5 observations were eligible for liver transplant exception points. Thus, CEUS may be necessary in certain clinical scenarios because CT or MRI findings do not meet LI-RADS 5 criteria or because these modalities are contraindicated, as previously mentioned.

The evaluation of cholangiocarcinoma is another clinical scenario in which CEUS may be useful. In general, malignant liver lesions demonstrate washout, meaning that they become hypoenhancing relative to the surrounding liver in the later phases after contrast injection. However, owing to the desmoplastic stroma characteristic of cholangiocarcinoma, iodinated CT and gadolinium-based MRI contrast agents diffuse into the interstitium, resulting in progressive and persistent enhancement. This delayed enhancement pattern can sometimes resemble that of certain benign lesions, which may also demonstrate sustained enhancement in the later phases. In contrast, CEUS microbubbles remain strictly intravascular and do not leak into the interstitium. As a result, cholangiocarcinoma and other non-HCC malignancies typically demonstrate earlier and more marked washout on CEUS. This fundamental difference in contrast behavior between CEUS and CT/MRI can be diagnostically advantageous. I had a patient with a large biopsy-proven cholangiocarcinoma in the right lobe and a small enhancing lesion in the left lobe detected on MRI. Both lesions demonstrated a similar pattern of delayed enhancement on MRI, raising concern that the left-sided lesion could represent metastatic disease. CEUS, however, clearly differentiated the 2 lesions. The small left-lobe lesion demonstrated persistent enhancement without washout, consistent with a hemangioma, whereas the large cholangiocarcinoma showed early and marked washout. This case highlights the value of CEUS in distinguishing non-HCC malignancies from benign lesions when CT or MRI findings are inconclusive.

G&H How does CEUS compare with CT and MRI for HCC diagnosis in terms of specificity and sensitivity?

YK My colleagues and I conducted a multicenter international prospective validation study involving 11 sites across Europe and North America in collaboration with the CEUS LI-RADS working group, and the results were published in *Hepatology* in 2024. We found that CEUS achieved a specificity of 95.1% for LI-RADS 5 in the diagnosis of HCC, which is comparable with reported specificity rates of approximately 90% to 95% for CT and MRI. The sensitivity of LI-RADS 5 is intentionally not very high, as the diagnostic framework prioritizes minimizing false-positive results to ensure high diagnostic certainty. In our study, CEUS demonstrated a sensitivity of 62.9%, which is also comparable with reported sensitivities for CT and MRI, ranging from approximately 48% to 77%. Overall, these findings suggest that CEUS provides diagnostic accuracy comparable with CT and MRI for HCC characterization.

G&H What are the main limitations of using CEUS over CT or MRI?

YK CEUS is a targeted, lesion-focused examination. For example, when evaluating a hepatic nodule, the primary objective is to characterize that specific lesion rather than perform a comprehensive survey of the entire liver. CEUS is not intended to be used as a screening modality. Multiple contrast injections may be performed when assessing multiple lesions. In addition, late-phase imaging of the entire liver is recommended to detect any suspicious lesions demonstrating washout. However, systematic evaluation of the entire liver during the arterial phase is challenging, as the arterial phase typically lasts only 10 to 15 seconds. Furthermore, CEUS is limited in detecting extrahepatic disease or abnormal lymph nodes because it is not a cross-sectional imaging modality. In cases where baseline ultrasound visualization is poor—for example, when bowel gas obscures the liver—contrast administration may not substantially improve image quality.

G&H Could you discuss the cost and reimbursement of the contrast agent?

YK The contrast agent approved by the US Food and Drug Administration for liver imaging in the United States right now is comprised of sulfur hexafluoride lipid-type A microspheres (Lumason, Bracco Diagnostics). This is the same agent used in Europe under the name SonoVue. I believe the cost is approximately $94 per vial, which is cheaper than the cost of the contrast agent used in CT and MRI. Importantly, as of January 1, 2026, the reimbursement code for sulfur hexafluoride lipid-type A microspheres was reassigned from level 1 to level 2 imaging with contrast. This increased reimbursement from approximately $170 to $358, essentially doubling it. Now, reimbursement is comparable with that for CT and MRI.

G&H Are there any side effects or risks associated with the contrast agent?

YK I cannot say that there are none, but in comparison with CT and MRI, the contrast agent is much safer and is not associated with kidney toxicity or many side effects. The only issue is that a very small number of patients may have an allergic reaction to the contrast, estimated at 1 in 10,000 individuals (vs 1 in 140-500 for CT contrast and 1 in 1000-3000 for MRI contrast). Otherwise, I almost never see any side effects. It is also approved for the pediatric population.

G&H Is there a standardized examination protocol when using CEUS for HCC diagnosis?

YK Yes. A standardized protocol for CEUS has been established and is available through the American College of Radiology website. Imaging should be performed using contrast-specific mode with a low mechanical index (MI) to minimize microbubble destruction, which is standard practice in CEUS. Real-time imaging should begin at the time of contrast injection and continue through the arterial phase, typically up to 60 seconds after injection. Continuous real-time evaluation during the arterial phase is critical to accurately assess arterial enhancement. After the arterial phase, intermittent imaging is recommended rather than continuous scanning. This involves temporarily freezing the image and resuming scanning at defined intervals, usually every minute, until washout is observed. Although low-MI imaging reduces microbubble destruction, ongoing continuous insonation gradually depletes circulating microbubbles, resulting in fewer bubbles available during the late phase. This approach is particularly important in HCC, where washout may occur late—often at 3, 5, or even 7 minutes after contrast injection. Intermittent imaging helps preserve microbubble signal and optimizes detection of late washout. This protocol has been standardized and is widely accepted internationally.

G&H What factors might affect the performance of CEUS?

YK The main limiting factors relate to both patient characteristics and lesion features. As with ultrasound in

general, visualization of the liver may be suboptimal in obese patients, although the use of contrast can improve lesion conspicuity. Lesions located deep within the body—particularly those 15 to 20 cm from the transducer—can be difficult to visualize owing to signal attenuation. Detection is also more challenging for very small lesions.

In addition, equipment performance can influence image quality. Ultrasound systems vary in sensitivity and contrast-specific capabilities. Older-generation machines generally provide lower image quality compared with newer platforms, similar to the technological differences observed in CT, MRI, and other imaging modalities.

G&H How widespread has the adoption of CEUS been so far in the United States?

YK Despite its advantages, CEUS has not yet been widely adopted. Although many tertiary academic centers perform CEUS, availability remains limited in numerous practice settings. Efforts are ongoing to train providers and expand access; however, adoption has been gradual.

At present, CEUS is most commonly used for the evaluation of indeterminate lesions. Ideally, if broadly available, CEUS could be integrated more directly into surveillance workflows. For example, patients with cirrhosis or chronic hepatitis B virus infection undergo screening ultrasound every 6 months. If a nodule is detected on surveillance ultrasound, CEUS could be performed immediately during the same visit and may allow definitive characterization. A diagnosis of HCC could prompt direct progression to staging, whereas confirmation of a benign lesion would allow the patient to return to routine surveillance. A 2019 study evaluating CEUS across multiple applications reported that CEUS was performed on the same day as the initial examination in 78.4% of cases, and 66.7% of examinations were diagnostic, eliminating the need for further CT or MRI in most patients. In comparison, the average wait time was 52 days for CT and 124 days for MRI. This approach resulted in substantial cost savings, exceeding $100,000 in the study cohort. Because conventional ultrasound is already the primary surveillance tool, the ability to perform contrast enhancement immediately at the point of detection could facilitate earlier diagnosis, reduce delays in care, improve patient outcomes, and lower health care costs. Expanded access to CEUS, therefore, has important clinical and economic implications.

G&H What are the next steps in this area?

YK We are still trying to make CEUS LI-RADS HCC diagnosis better and are defining criteria. We are thinking of combining features such as CT and MRI with CEUS. There is much research going on in this area, for example, with quantification of blood flow using CEUS. Our group is also working on tumor response evaluation when patients are receiving, for example, systemic therapy such as chemotherapy or immunotherapy. These are very difficult to evaluate in the early stage, where the tumor size is not changing yet. We believe that by quantifying blood flow, not just looking, we may be able to do a better job. Additionally, there has always been interest and research in putting different ligands and/or antibodies in these microbubbles to target certain tissues and diseases. That could be used for diagnosis or for a therapeutic purpose if the microbubbles are targeted to a particular tissue; the bubbles could then be destroyed by sending a little higher ultrasound energy to facilitate drug delivery.

Disclosures

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Suggested Reading

Fraquelli M, Nadarevic T, Colli A, et al. Contrast-enhanced ultrasound for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. *Cochrane Database Syst Rev*. 2022;9(9):CD013483.

Hu J, Burrowes DP, Caine BA, et al. Nodules identified on surveillance ultrasound for HCC: CEUS or MRI as the initial test? *J Ultrasound Med*. 2023;42(6):1181-1190.

Kono Y, Piscaglia F, Wilson SR, et al; CEUS LI-RADS Trial Group. Clinical impact of CEUS on non-characterizable observations and observations with intermediate probability of malignancy on CT/MRI in patients at risk for HCC. *Abdom Radiol (NY)*. 2024;49(8):2639-2649.

Lyshchik A, Wessner CE, Bradigan K, et al; CEUS LI-RADS Trial Group. Contrast-enhanced ultrasound liver imaging reporting and data system: clinical validation in a prospective multinational study in North America and Europe. *Hepatology*. 2024;79(2):380-391.

Schellhaas B, Bernatik T, Dirks K, et al. Contrast-enhanced ultrasound patterns for the non-invasive diagnosis of hepatocellular carcinoma: a prospective multicenter study in histologically proven liver lesions in a real-life setting demonstrating the benefit of extended late phase observation. *Ultrasound Med Biol*. 2021;47(11):3170-3180.

Shin J, Lee S, Bae H, et al. Contrast-enhanced ultrasound liver imaging reporting and data system for diagnosing hepatocellular carcinoma: a meta-analysis. *Liver Int*. 2020;40(10):2345-2352.

Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922-1965.

Streb JW, Tchelepi H, Malhi H, Deurdulian C, Grant EG. Retrospective analysis of contrast-enhanced ultrasonography effectiveness in reducing time to diagnosis and imaging-related expenditures at a single large United States county hospital. *Ultrasound Q*. 2019;35(2):99-102.