Sonazoid contrast-enhanced ultrasonography (CEUS), since its first approval in 2007 in Japan, has been subsequently approved in 2012 in Korea, 2017 in Taiwan, and 2018 in China for the imaging of focal liver lesions. Following its approval and accumulation of evidence that reported increased sensitivity for the detection of hepatocellular carcinoma (HCC), CEUS is now incorporated into several practice guidelines as a second-line diagnostic test for HCC.1-4 In this issue of Journal of Liver Cancer, Jeong5 comprehensively reviewed Sonazoid CEUS from its development, characteristics, method of examination, standardization, imaging diagnosis of benign and malignant hepatic lesions, to introduction of current guidelines for HCC diagnosis using Sonazoid.

The advantages of CEUS compared to conventional b-mode ultrasound (US) are the improved detection of smaller HCCs, and reduction of false-referral rates.6,7 Also, one of the major advantage of CEUS is the increase in probability to differentiate HCCs from inconclusive nodules following computed tomography (CT) and magnetic resonance imaging (MRI) examination.6,8 In addition, unlike CT or MRI which uses static images, the real-time evaluation by CEUS minimizes misdiagnosis due to mistiming, especially in lesions that lack arterial phase hyperenhancement, or with late arterial wash-in appearances.9,10 Furthermore, as arterioporal shunts or vascular pseudolesions are seldom visible in CEUS, the combination of conventional grayscale US and CEUS has shown to effectively differentiate shunts or pseudolesions from true HCCs when MRI findings were inconclusive with a negligible number of false negatives.11 Moreover, for ill-defined nodules, defect reperfusion US imaging technique may be used to improve HCC diagnosis, which is based on an additional injection of Sonazoid at the Kupffer phase, and a fast wash-in of arterial flow in the Kupffer defect area confirms the diagnosis of HCC.12 In therapeutic perspectives, it has been shown that CEUS may increase the success rates of tumor ablation and biopsy.13 Another major advantage of CEUS is its safety, as most of the adverse events reported were minor.14 CEUS does not use any radiation, and it may be particularly useful in patients with renal function impairments as it does not involve the injection of potenially nephrotoxic contrast agents.

However, CEUS also has several limitations. First, the inherent limitations of US such as restricted sonic window in patients with obesity or advanced cirrhosis, and when the bowel gas is present, or the fatty tissue is abundant. Also, there may possibly be blind spots at the hepatic dome, caudate lobe, or the left lateral segment of the liver. Second, CEUS is operator-dependent and therefore diagnostic accuracy may largely depend on the skills and experience of the
operator which demands sufficient training and standardization of CEUS to maintain the required standards. Third, unlike CT or MRI, a single examination of CEUS may not be able to fully detect targeted lesions or the extent of the tumor which limits its use as a staging tool. Indeed, this is one of the main reasons why CEUS is not yet recommended as a first-line imaging study in major guidelines. Fourth, although Sonazoid CEUS may be a useful tool to monitor treatment response following locoregional therapies such as radiofrequency ablation or transarterial chemoembolization of a limited number of lesions, there is insufficient evidence for CEUS to be utilized as a monitoring tool during systemic therapy. Fifth, there is still controversy regarding the cost-effectiveness of CEUS for its use in HCC surveillance. Indeed, there are discrepancies between academic societies on the recommendation of CEUS for HCC surveillance, and therefore further studies are required to clarify its cost-effectiveness.

Despite all these considerations, this review has extended our knowledge and insight on the characteristics, efficacy, and important questions that need to be addressed regarding Sonazoid CEUS. It is without doubt a promising diagnostic tool with advantages of real-time diagnosis and enhanced safety. However, further studies are required to overcome the potential disadvantages of Sonazoid CEUS such as restricted sonic window, maintaining inter-observer diagnostic accuracy, shortcomings in monitoring treatment response especially in cases with extensive tumors and during systemic therapy, and partially validated cost-effectiveness as a surveillance tool for HCC.

**Conflict of Interest**

The authors have no conflict of interest to disclose.

**Ethics Statement**

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