INTRODUCTION

Grayscale ultrasonography (US) and Doppler US are widely used in the detection and differentiation of focal liver lesions (FLLs) relying on the differences in echogenicity and vascularity between the FLLs and surrounding liver tissues. However, grayscale US and Doppler US lack specificity in the characterization of FLLs. Contrast-enhanced US (CEUS) can achieve dynamic images of liver perfusion throughout the vascular phases. The later feature has led to dramatic improvement in the diagnostic accuracy of US for detection and characterization of FLLs as well as the guidance to therapeutic procedures and evaluation of response to treatment. This article describes the current consensus and guidelines for the use of UCAs for the FLLs that are commonly encountered in US. After a brief description of the bases of different CEUS techniques, contrast-enhancement patterns of different types of benign and malignant FLLs and other clinical applications are described and discussed on the basis of our experience and the literature data. (Clin Mol Hepatol 2013;19:1-16)

Keywords: Guidelines; Contrast enhanced Ultrasonography (CEUS); Focal liver lesions (FLLs)
throughout the vascular phases of the liver which lead to great advances in diagnostic accuracy of US. CEUS can be used routinely for lesions detected incidentally on conventional US, and used to clarify obscure lesions detected on computed tomography (CT) or magnetic resonance imaging (MRI). Real-time assessments of a FLL can be performed during at least 3-4 minutes using specific imaging methods based on contrast agents. The enhancement patterns depend on the microvascularization of the FLLs, and the characteristics of lesion scan be assessed based on three vascular phases: the arterial, portal venous (PV), and late phases.

There are two UCAs, Sonovue® and Sonazoid®, clinically used for liver images. Sonovue is strictly intravascular, whereas CT/MRI contrast agents also diffuse into the interstitial space. This is why there are a few differences during the arterial and PV phases in the behaviors of UCAs and CT/MRI contrast agents, which are otherwise very similar. Whereas, Sonazoid is cleared by Kupffer cells. Uptake of Sonazoid perfluorobutane microbubbles by the Kupper cells makes post vascular images (Kupffer phase images) similar to that of gadolinium ethoxybenzyl-diethylenetriamine-polyamine-DTPA-enhanced MRI. The recent introduction of UCA for Kupffer cell imaging has dramatically expanded the application of liver US.

CEUS is much more useful than CT/MRI in differentiating FLLs, and this cost-effective methodology also avoids the ionizing radiation used in CT® and has no severe adverse effects (the UCAs do not induce allergic reactions and are not excreted through the kidneys). The most important difference from CT/MRI is that CEUS allows real-time evaluation of liver nodules and immediate results to be obtained, and consequently CEUS provides a significant improvement in clinical practice with an accurate diagnosis, in contrast to the inconclusive results obtained in traditional US.

US is the most popular tool for diagnosing FLLs in Korea, especially in private clinics. Also, the expanding CEUS indications for FLLs make this technique an important tool in the assessment of vascularization, including evaluations for the detailed diagnosis of FLLs. The use of CEUS is already permitted by the Committee for New Health Technology Assessment in Korea, but appropriate guidelines have not yet been published. Consistent with the current situation of CEUS in Korea, the KASCU (Korean Association for the Study of Contrast Enhanced Ultrasonography) had final consensus meeting on 19 Jan 2013 in Daegu, Korea. We present current consensus and guidelines of CEUS for the Characterization of FLLs in this review.

### UCAs and safety issues

The use of UCAs was first described in the aorta during cardiac catheterization by Gramiak and Shah in 1968. Those UCAs were composed of bubbles without a shell and were large enough to be filtered by the lungs, so they disappeared within a few seconds after intravenous injection. There have been various attempts to overcome these shortcomings. Current UCAs are typically microbubbles encapsulated by a stabilizing shell such as albumin, polymer, or phospholipid. Microbubbles are miniature gas bubbles smaller than red blood cells (up to 7 μm in diameter) so that they easily pass through the capillary beds, thereby acting as blood-pool tracers based on using ultrasound signals back scattered from tissue to determine the US echogenicity.

The mid-1990s saw the development of Levovist® (Schering, Berlin, Germany) as a first-generation air-based UCA with galactose and palmitic acid as a surfactant, with a mean of 2-5 μm in microbubble diameter. After intravenous injection, the pharmacokinetic behavior of Levovist can be divided into a vascular phase and a delayed parenchymal phase. Its prolonged liver-specific phase is advantageous for distinguishing FLLs, but it is unsuitable for real-time applications, requiring a high mechanical index (MI) that destroys the microbubbles. Levovist production has ceased and it is no longer marketed.

In order to overcome the disadvantages of UCAs such as Levovist, second-generation UCAs were designed both to improve the US echogenicity and to last for longer periods in the bloodstream with low solubility. These features of microbubbles make stable nonlinear oscillations possible with a low MI, resulting in real-time harmonic signals. The UCAs for the liver currently available in Korea are SonoVue® (Bracco, Milan, Italy) and Sonazoid® (Daichi-Sankyo, GE Tokyo, Japan) (Table 1).

SonoVue has a phospholipid shell and a sulfur hexafluoride gas core and is available for liver studies in several countries. It has enabled real-time imaging using a nondestructive low MI, offering vascular-phase imaging (i.e., in the arterial, PV, and delayed phases) of the lesion for several minutes. Sonazoid is composed

| Table 1. Ultrasound contrast agents available for clinical use in Korea |
|----------------|----------------|-----------------|----------------|
| **Agent**     | **Diameter (µm)** | **Composition (shell/gas)** | **Company**               | **Imaging time (minutes)** |
| SonoVue®      | 2.5             | Phospholipid/sulfur hexafluoride | Bracco                  | 3-6                        |
| Sonazoid®     | 2.4-2.5         | Phospholipid/perfluorobutane    | GE Healthcare/Daiichi-Sankyo | 10-30                     |