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EDITORIAL

Understanding the differences between Japanese and U.S. guidelines on clinical practice for contrast-enhanced ultrasound of the liver

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Introduction

The first edition of the guidelines on medical ultrasound, "Ultrasonic Diagnostic Criteria for Hepatic Tumors", was published in 1988 by the Japan Society of Ultrasonics in Medicine. Subsequently, medical ultrasonic diagnostic equipment showed increased computing power and improved graphics performance, and then Doppler techniques such as color Doppler imaging and power Doppler imaging were incorporated. Starting in 2007, Sonazoid became available for clinical practice in Japan as a first in the world. Thus, the second edition of the guidelines published in 2012 reflected changes in the available contrast agents and new imaging developments for the liver [1].

The Liver Imaging Reporting and Data System (LI-RADS), which is supported and endorsed by the American College of Radiology (ACR), is both a set of standardized terminologies and a classification system for imaging findings in liver lesions. Upon its initial release in 2011, LI-RADS applied only to liver observations identified on computed tomography (CT) or magnetic resonance imaging (MRI). As contrast-enhanced ultrasound (CEUS) has been widely used in clinical practice, international experts convened to develop CEUS LI-RADS. After extensive discussions by the working group, the first edition of CEUS LI-RADS was published in 2016, and the current CEUS LI-RADS version 2017 is available at present [2].

Although CEUS LI-RADS shares fundamental concepts with the Japanese CEUS diagnostic criteria, there are some key differences in the medical concepts reflecting dissimilarities in the underlying methods of image acquisition and types of contrast material.

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Similarities between Japanese criteria and LI-RADS

Classic hepatocellular carcinoma (HCC) is usually diagnosed by "arterial enhancement with delayed washout" based on typical features on CT/MRI. Both in Japan and United States, arterial phase hyperenhancement (APHE) and the washout pattern are key elements of HCC diagnosis.

Japanese CEUS diagnostic criteria interpret and illustrate focal liver lesions for differential diagnosis of lesions such as HCC, liver metastasis, intrahepatic cholangiocarcinoma (ICC), hepatocellular adenoma, hepatic hemangioma, and focal nodular hyperplasia (FNH) [1]. According to CEUS LI-RADS, HCC, hepatic malignancies including ICC, hepatic hemangioma, cyst, and hepatic fat deposition/sparing can be classified [2].

Differences between Japanese criteria and LI-RADS

Surveillance

Patients with chronic hepatitis B/C or liver cirrhosis as a whole are recommended for HCC surveillance in Japan. Although the hepatitis C virus (HCV) carrier rate has decreased since 2000, HCV and hepatitis B virus (HBV) are still major causes of HCC in Japan. On the other hand, LI-RADS recommends screening for HBV infection or liver cirrhosis, not HCV infection. In the United States, surveillance is offered for patients with cirrhosis of varying etiologies when the risk of HCC is 1.5%/year or greater [3]. The estimated incidence of HCC in the absence of advanced fibrosis in patients with HCV infection is less than 1% a year. Therefore, HCV-infected patients without cirrhosis are excluded from the HCC surveillance algorithm in the United States.

In Japan, screening conducted every 3–4 months using US and serum tumor markers such as alpha-fetoprotein

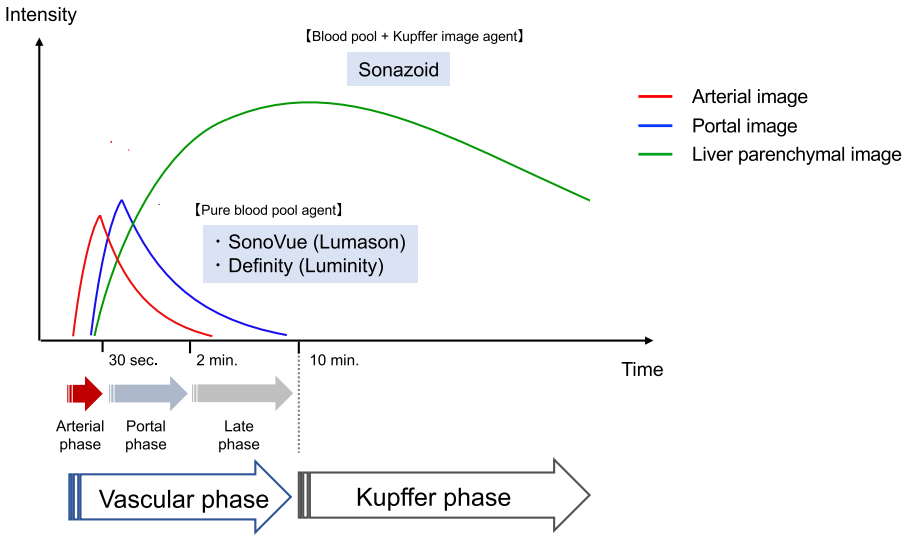

Fig. 1 Pharmacokinetic behaviors of US contrast agents. Vascular and Kupffer phase images can be obtained using Sonazoid, but not SonoVue (Lumason) or Definity (Luminity). Sonazoid microbubbles are taken up by Kupffer cells and show homogeneous enhancement in normally functioning liver parenchyma. Kupffer phase images are generally obtained 10 min after the injection of Sonazoid

(AFP), AFP-L3, and des-γ-carboxy prothrombin (DCP) is recommended in super high-risk groups (i.e., those with cirrhosis of HBV or HCV) [4, 5]. Additional investigations every 6 to 12 months with contrast-enhanced MRI or CT are considered optional. Meanwhile, the American Association for the Study of Liver Diseases (AASLD) recommends surveillance using US with or without serum AFP every 6 months [3].

Contrast medium

SonoVue is widely available in Europe and Asia and recently in North America under the trade name of Lumason. Sonazoid is available in Japan, South Korea, Norway, Taiwan, China, and Singapore. Although Sonazoid and SonoVue are classified as second-generation contrast agents, the behavior of each contrast agent in the liver is different: pure blood pool agents confined within the intravascular compartment (i.e., SonoVue), and agents taken up by Kupffer and/or reticuloendothelial cells (i.e., Sonazoid) [6]. The hemodynamic behavior of SonoVue enhancement during arterial (15–30 s), portal (30–120 s), and late (120–300 s) phases is evaluated. In addition, Sonazoid enhancement during the Kupffer phase (≥ 10 min) can be shown (Fig. 1). Therefore, APHE and washout are major features of HCC on SonoVue-enhanced US [2]. Meanwhile, APHE and Kupffer defects are major features of HCC on Sonazoid-enhanced US [1, 7, 8].

Diagnostic process and its background

In the Japanese CEUS diagnostic criteria, typical imaging features of lesions are described. The logic can be expressed as "Diagnosis → Typical imaging features" schematically. The LI-RADS diagnostic algorithm helps us categorize each liver observation from LR-1 to LR-5, reflecting the relative likelihood of having HCC. The logic can be expressed as "Typical imaging features → Diagnosis". As you can see, the two vectors are in opposite directions. The correlation similar to that correlation might be formed between civil and common laws.

In the United States, high specificity is required because patients with HCC receive curative treatment including liver transplant, and the LI-RADS diagnostic algorithm is designed to ensure high specificity and a positive predictive value for the diagnosis of HCC. Meanwhile, Japan has a universal medical care insurance system, and most people have easy access to medical care. Since people believe that the early detection of cancer helps to prevent cancer death, a highly sensitive test for detecting HCC may be preferable in clinical practice paradigms.

Conclusion

There are clear differences in etiology, cultural background, and healthcare insurance between Japan and the United States, with Sonazoid being used for HCC diagnosis in Japan, but not in the United States. Although the current version of CEUS LI-RADS does not support Sonazoid at present, CEUS LI-RADS has the potential to become a global standard in the event of the additional inclusion of Sonazoid. Meanwhile, our diagnostic criteria on CEUS are working well. Therefore, CEUS LI-RADS will not immediately become the Japanese gold standard. However, we Japanese do not stay loose if we do not need CEUS LI-RADS for the time being. We have to pay close attention to changes in CEUS LI-RADS to avoid being left behind regarding the global trend.

Declarations

Conflict of interest The author has no relationships relevant to the contents of this paper to disclose.

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