Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–8, 2017

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2017.06.014

● *Original Contribution*

HISTOLOGY-BASED ASSESSMENT OF SONAZOID-ENHANCED ULTRASONOGRAPHY FOR THE DIAGNOSIS OF LIVER METASTASIS

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(*Received* 27 *September* 2016; *revised* 10 *June* 2017; *in final form* 15 *June* 2017)

Abstract—This retrospective study aimed to assess the diagnostic performance of contrast-enhanced ultrasound with Sonazoid (S-CEUS) for liver metastasis. We enrolled in this study 98 patients with 148 histologically proven liver lesions, with 121 metastases and 27 non-metastases. The S-CEUS technique showed sensitivity in 95.0% (115 of 121), specificity in 44.4% (12 of 27) and accuracy in 85.8% (127 of 148) for the diagnosis of metastasis. Higher body mass index had a negative influence on the positive predictive value and accuracy, and a greater depth of the lesion had a negative influence on the accuracy. The management was changed in 8 patients (8.2%) because of S-CEUS findings. In conclusion, the addition of S-CEUS may offer a great benefit by improvement of the quality of diagnosis and management for patients with cancer who have a tentative diagnosis of liver metastasis by contrast-enhanced computed tomography. (E-mail: maru-cib@umin.ac.jp) **© 2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Contrast-enhanced ultrasound, Sonazoid, Liver metastasis, Diagnostic performance.**

INTRODUCTION

The management of patients with malignant disease is a critical issue in clinical practice. The selection and application of anti-cancer treatments depend on the clinical stages of the disease, which is determined by the presence or absence of metastatic lesion (Adams et al. 2013; Mehlen and Puisieux 2006). As the liver is one of the major target organs for investigating metastatic tumors, the detection and characterization of focal hepatic lesions by imaging modalities are important processes.

Ultrasound (US) likely is the most frequently used technique for the detection of focal hepatic lesions because of its simple, less-invasive nature and high temporal resolution with real-time imaging (Claudon et al. 2002). Additionally, the introduction of microbubble-based contrast agents has been added to the popularity of US (Lencioni et al. 2008; Quaia 2007; Rettenbacher 2007). Currently, contrast-enhanced US (CEUS) is considered a reliable imaging tool because of the improved detectability of blood flow with higher spatial resolution and the safety of microbubble contrast agents (D'Onofrio et al. 2015).

Sonazoid (GE Healthcare UK Ltd, Amersham, Buckinghamshire, England) is a second-generation contrast agent available in Japan, South Korea and Norway (Bouakaz and de Jong 2007; Sontum 2008). The characteristic feature of this agent is the accumulating property of the microbubble in the reticuloendothelial tissue such as the liver and spleen. Therefore, it provides a unique image in the post-vascular phase in addition to arterial phase enhancement (Claudon et al. 2013). The technique of CEUS with Sonazoid (S-CEUS) has various beneficial effects for the diagnosis and therapeutic support of focal hepatic lesions (Jang et al. 2015; Maruyama et al. 2016).

Although a number of studies have investigated the accuracy of CEUS in the diagnosis of metastatic liver tumor, most of them are based on clinical data and

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radiologic findings using computed tomography (CT) and magnetic resonance imaging (MRI) as a standard for metastatic liver tumor diagnosis but without using histologic results (Bernatik et al. 2001; Hoeffel et al. 2009; Mainenti et al. 2010; Mishima et al. 2016; Solbiati et al. 2001). Therefore, the present study examined the diagnostic performance of transabdominal S-CEUS for hepatic lesions suspected of being metastatic liver tumors by contrast-enhanced CT (CECT) with dynamic study, whose final diagnosis was confirmed histologically. The aim of the study was to verify the effectiveness of S-CEUS for detection, diagnosis and additional benefits in the management of patients with liver tumors suspected to be metastatic.

METHODS

Study outline

This retrospective study was approved by the ethics committee of Chiba University Hospital, Chuo-ku, Chiba, Japan. The inclusion criteria included (i) inpatients or outpatients (April 2011–October 2015) with primary cancer; (ii) those who were temporarily diagnosed as having metastatic liver tumor demonstrated by CECT; (iii) those who underwent S-CEUS for characterization of focal hepatic lesions; and (iv) those with histologic evidence for the diagnosis of hepatic lesions by biopsy or resected specimen. Patients with contraindications for the use of Sonazoid (*e.g.,* egg allergy, severe pulmonary disease or severe cardiac disease) were excluded. Written informed consent was obtained from all patients, and the investigation was carried out in accordance with the Declaration of Helsinki.

Ultrasound examination

The US machines used in the study were an SSA-770 A or 790 A US system (Toshiba, Tokyo, Japan) and a 3.75-MHz convex probe. All US examinations were conducted with the patient in the supine position or the left lateral-decubitus position. Patients were requested to breathe gently. The S-CEUS was performed using the harmonic mode with a low mechanical index level (0.17–0.27, median 0.19). The settings were as follows; the focal point at the deepest level of the lesion or the deepest level of the liver in the case of the patient having an undetectable hepatic lesion by B-mode US, the dynamic range of 40–50 dB, and optimal gain and image scaling (Kondo et al. 2015). Sonazoid was administered at a dose of 0.0075 mL/kg by manual bolus injection followed by a flush with 5.0 mL of normal saline solution *via* a peripheral vein, according to the literature (Kondo et al. 2015; Maruyama et al. 2016). The real-time observation for the target lesion or the surrounding parenchyma was performed from the time of agent injection for approximately 2 min. The observation then was suspended and restarted to observe the whole liver, including target lesions, at the 10-min phase. The phase was defined according to the literature, the arterial phase 10–45 s, the portal venous phase 45–120 s, the late phase after 120 s and the postvascular phase at the 10-min phase after agent injection (Claudon et al. 2013). The US examinations were performed by one of three hepatologists, who have much CEUS examination experience (H.M., more than 22 y; S.K., 5 y; or K.K., 3 y). The operator was masked to the subsequent histologic results.

Diagnosis of metastatic liver tumor by S-CEUS

The diagnosis of metastatic liver tumor by S-CEUS was based on the findings in the literature that summarized previous reports (Claudon et al. 2013). The criteria were the presence of contrast enhancement in the arterial phase, such as a rim or halo enhancement and early washout around the portal venous phase (45–120 s after the agent injection) showing hypo-enhancing lesions during the portal venous and late phases with punched out black foci.

The criteria for the diagnosis of hepatocellular carcinoma (HCC) are hyper-enhancement in the arterial phase, followed by washout in the late phase (120 s or later) (Claudon et al. 2013). Criteria for benign lesions, in contrast, are the presence of typical enhancement patterns for hemangioma or focal nodular hyperplasia (Claudon et al. 2013) or an enhancement appearance similar to surrounding non-tumor parenchyma. The final decision was made by 2 independent reviewers (H.M., S.K. or K.K.), and consensus decision making was implemented for inconsistent reading results.

CECT examination

CECT was performed using a 16-detector CT scanner (Light Speed Ultrafast 16, GE Healthcare, Wauwatosa, WI, USA; or Activion 16, Toshiba, Irvine, CA, USA), a 128-detector CT scanner (Aquilion CX, Toshiba) or a 320-detector CT scanner (Aquilion ONE, Toshiba). The contrast agent (iopamidol; Iopamiron 350, Nihon Schering, Osaka, Japan) was used at a dose of 100 mL and at an infusion rate of 3 mL/s by mechanical injection *via* a peripheral vein. Images were taken at three phases: the hepatic arterial phase, the portal venous phase and the equilibrium phase. Focal hepatic lesions with or without an enhancement were identified as metastatic liver tumors. However, lesions showing typical findings for cyst or hemangioma were excluded. All CECT images were assessed by radiologists in our hospital and by K.K.

Histologic examination

The liver samples were obtained by percutaneous/intra-operative biopsy using a biopsy needle (Monopty, Bard, Covington, GA, USA; Sonopsy C1, Hakko,