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● *Original Contribution*

# CLINICAL APPLICATION OF CONTRAST-ENHANCED ULTRASOUND USING HIGH-FREQUENCY LINEAR PROBE IN THE DETECTION OF SMALL COLORECTAL LIVER METASTASES

Si Qin, Yao Chen, Xiao-yin Liu, Wen-jie Cheng, Jun-li Yu, Wen-jing Zhang, Qing-ling Jiang, Yi-min Wang, Yan-ling Wen, and Guang-jian Liu

Department of Medical Ultrasonics, the Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China

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**Abstract—To compare the performance of contrast-enhanced ultrasound (CEUS) using high-frequency linear and convex probes in the detection of small colorectal liver metastases (CRLMs). A total of 85 patients with 143 small CRLMs were evaluated. High-frequency ultrasound (US) and CEUS detected significantly more superficial lesions within 60 mm below the skin than a convex probe ($p < 0.05$). The detection rate decreased in the chemotherapy group, especially when using a convex probe for US ($p < 0.05$). By combining convex and linear probes, detection rates of US and CEUS were significantly higher than that of a convex or a linear probe alone ($p < 0.05$). High-frequency US and CEUS helped to improve detection of small CRLMs and reduce the influence of chemotherapy. For patients with a high risk of CRLMs and those after chemotherapy, we recommend first scanning the liver by using a convex probe and subsequently screening the surface area of the liver and suspicious small lesions by using a linear probe. (E-mail: Liugj@mail.sysu.edu.cn; guangjian1977@gmail.com) © 2017 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

*Key Words:* **Contrast-enhanced ultrasound, High frequency, Colorectal cancer, Liver metastases, Detection.**

## INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant tumors, the third most common cancer and the fourth most frequent cause of cancer deaths worldwide (Torre et al. 2015). The incidence of colorectal cancer liver metastases (CRLMs) occurs as much as 50% during the process of the disease (Adam et al. 2012, Schima et al. 2005). Early detection of CRLMs is crucial for achieving cancer control in CRC patients (Larsen 2010). Trans-abdominal ultrasound (US) and contrast-enhanced ultrasound (CEUS) are safe and effective. They have been widely used for screening liver metastasis in clinical practice (Horie et al. 2013). CEUS has the advantages of real-time observation and it has shown high specificity for characterizing focal liver lesions (FLLs), comparable to contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMRI) (Claudon et al. 2013). However, routine liver US and CEUS examination are usually performed with a convex probe. The frequency of B-mode US is usually 2–5 MHz and the frequency of CEUS is usually 1.5–2.5 MHz for an abdominal scan (Ding et al. 2010; Kong et al. 2016). Relative lower frequency for CEUS imaging results in limited spatial resolution, and the near-field image quality is frequently unsatisfactory because of bubble destruction. Both drawbacks of CEUS restrain its performance in the detection and characterization of small CRLMs (≤10 mm) located in superficial position (Cantisani et al. 2014).

High-frequency US and CEUS have been successfully applied intra-operatively, which make intra-operative CEUS (IO-CEUS) the gold standard of the detection and characterization of CRLMs (Xu et al. 2011). The detection rate of intra-operative ultrasonography (IOUS) using a 5–7.5 MHz linear probe for lesions <2 cm is 95% (Arita et al. 2014; Zacherl et al. 2002). The sensitivity, specificity and accuracy of IO-CEUS are even higher than IOUS (Takahashi et al. 2012). Researchers have shown that a high-frequency linear probe is more advantageous for superficial and small lesions during surgery compared with a relatively low-frequency convex probe (Jung et al. 2010; Loss et al. 2012).

The clinical application of a high-frequency linear probe for trans-abdominal liver CEUS in CRC patients is

Address correspondence to: Guang-jian Liu, Department of Medical Ultrasonics, The Sixth Affiliated Hospital of Sun Yat-Sen University, Sun Yat-Sen University, NO. 26 Yuancunerheng Rd, Guangzhou 510655, China. E-mails: Liugj@mail.sysu.edu.cn; guangjian1977@gmail.com

rarely reported. In this study, we compared the performance of trans-abdominal CEUS using a high-frequency linear probe and a routine convex probe in the detection of CRLMs ≤10 mm in diameter.

## MATERIALS AND METHODS

*Patients*

This retrospective study was approved by the institutional ethics committee of the Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China. Informed written consent was signed by all patients who received CEUS examinations. From November 2013 to December 2015, 85 patients (49 men, 36 women; mean age, 55.2 ± 14.3 y SD) with a final diagnosis of CRLM were included in this study. The inclusion criteria were (i) CRC patients with newly detected FLLs shown by typical imaging findings of CRLMs and not greater than 10 mm in diameter on CECT/CEMRI (only CECT: n = 35; only CEMRI: n = 18; both CECT and CEMRI: n = 32) during regular follow-up (every 3–6 mo); and (ii) liver CEUS examination was performed within 1 wk after CECT/CEMRI. Patients with contraindications for CEUS were excluded. A total of 143 lesions were investigated, with mean size of 7.4 ± 1.9 mm in diameter (range, 3.0–10.0 mm, measured on CECT/MRI). A total of 54 patients (33 men, 21 women) declined chemotherapy, among them a total of 89 lesions were investigated with a mean size of 7.8 ± 2.0 mm in diameter (range, 4.0–10.0 mm). The other 31 patients (16 men, 15 women) accepted chemotherapy (FOLFOX n = 13, FOLFIRI n = 6, CapeOX n = 9, other chemotherapy n = 3); 54 lesions were studied with mean size of 8.4 ± 1.3 mm in diameter (range, 3.0–10.0 mm). No significant difference in the size of lesions was found between these 2 groups ($p = 0.648$, [95% CI, 0.899–1.436]).

*CEUS techniques*

Both US and CEUS examinations were performed using the same equipment (LOGIQ E9; GE Healthcare, Milwaukee, WI, USA), equipped with a convex probe C1-5 (–3 dB center frequency of 4 MHz and −3 dB bandwidth 2.8–5.0 MHz) and a linear probe 9 L (–3 dB center frequency of 6 MHz and −3 dB bandwidth 5.0–9.0 MHz) in the present study. All scans were performed by the same radiologist with more than 10 y of experience in liver CEUS. US and CEUS evaluation were performed after the radiologist reviewed the clinical history and the previous radiologic studies of each patient. B-mode US was first used to explore the whole liver. To avoid patient overdosage of ultrasound contrast agent (UCA) (SonoVue, Bracco, Italy), the lesion with the clearest appearance was selected as the target for the CEUS when multiple lesions were detected with similar B-mode signs in one patient.

Table 1. Imaging settings of CEUS

| | Parameters |
|---|---|
| Instrument | LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA) |
| Probe | C1-5, 9 L |
| CEUS mode | General |
| Transmit center frequency | C1-5: 2.5 MHz; 9 L: 4.5 MHz |
| MI | 0.09–0.16 |
| Number of focus | 1 |
| Position of focus | the bottom of the target lesion |
| Frame frequency | C1-5: 8 f/s; 9 L: 11 f/s |

CEUS = contrast-enhanced ultrasound.

A bolus injection of 2.0-mL UCA was administered intravenously for each CEUS procedure. General mode (transmit center frequency of convex probe: 2.5 MHz; transmit center frequency of linear probe: 4.5 MHz) of the CEUS presetting was used, with mechanical index ranging 0.09–0.16 and focus positioned at the bottom of the target lesion (Table 1). Coded phase inversion harmonic imaging technology was used in this study. The lesion was observed continuously for 2 min and then the whole liver was explored using CEUS until 5 min after injection of UCA. If we detected other suspicious lesions, UCA was reinjected for CEUS. Five min after the end of the CEUS examination with the convex probe, the liver was rescanned by linear probe for US and CEUS. Both still images and dynamic videos of US and CEUS were stored on the hard disk and were burned to DVD for subsequent analysis. The arterial, portal and late phases were defined as 10–30 s, 31–120 s and 121–360 s after injection of contrast agent, respectively (Claudon et al. 2013).

*CECT techniques*

CECT was performed using a 640-slice multi detector CT (Aquilion one, Toshiba Medical System, Tokyo, Japan). After an unenhanced helical sequence scan through the liver, 50–100 mL (1.5–2 mL/kg) of contrast agent (Ultravist370, Bayer AG, Leverkusen, Germany) was administered *via* the antecubital vein at a rate of 3 mL/s. The arterial phase sequence was initiated 8–12 s after starting the injection, followed by a portal venous phase sequence beginning at 70 s. The following CT acquisition parameters were used: 120 kV; 350–400 mA; collimation, 64 mm × 0.5 mm; slice thickness, 0.5 mm; slice increments, 3 mm; and pitch standard 53.

*CEMRI techniques*

CEMRI was performed using the 1.5 T MR System (Optima MR360, GE Healthcare). The protocol used in our hospital included standard T1- and T2-weighted sequences, DWI and 3-D LAVA-flex for dynamic enhanced imaging. A power injector was used for the intravenous administration of the contrast agent gadobenate