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Clinical Trials Study

Clinical value of contrast-enhanced ultrasound in early diagnosis of small hepatocellular carcinoma (≤2 cm) in patients with high risk factors

CEUS diagnosis small HCC

Qi Mei, Mei Yu, Qiong Chen

Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy.Contrast-enhanced ultrasound (CEUS) uses contrast microbubbles during ultrasound, allowing the detection and characterization of malignant focal liver lesions with much higher diagnostic accuracy, however, there are few reports focus on the pattern of enhancement of CEUS for the diagnosis of HCC smaller than 2cm.

AIM

This study aimed to investigate the clinical value of contrast-enhanced ultrasound (CEUS) in the early detection of small hepatocellular carcinoma (HCC) with high risk factors.

METHODS

A total of 395 patients with 632 nodules at high risk of HCC, who underwent regular follow-up at Xuhui Dahua Hospital from January 2007 to December 2021, were retrospectively examined. Conventional ultrasonography combined with CEUS was adopted to analyze the echo, size, location, and enhancement characteristics of benign and malignant nodules, as well as the enhancement methods for HCC with different diameters.

RESULTS

The follow-up rate was 92.15% (364/395) for 51.28 ± 45.09 mo. The conventional ultrasonography combined with CEUS revealed 65 (11.80%) nodules with a follow-up diagnosis of HCC, 19 (3.45%) dysplastic nodules, and 467 (84.75%) cirrhotic, benign, hyperplastic nodules. Among 65 cases of confirmed HCC, 40 (61.54%) were transformed from hypoechoic nodules, 9 cases (13.85%) from hyperechoic nodules, and the remaining 16 cases (24.62%) from isoechoic nodules. Significant differences in CEUS characteristics were found among cirrhotic nodules, dysplastic

nodules, and HCC nodules in each phase. Significant differences in the enhancement mode were observed between nodules ≤1 cm and those 1–2 cm. The smaller the HCC nodule, the later the contrast agent began to flush, and the longer the duration of contrast enhancement.

CONCLUSION
Conventional ultrasonography combined with CEUS could identify small HCCs and help monitor patients with early diagnosis of HCC. Significant differences in the enhancement mode were noted between nodules ≤1 cm and those 1–2 cm.

Key Words: Carcinoma; Hepatocellular; Contrast-enhanced Ultrasonography; Diagnostic imaging

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Core Tip: 1.Conventional ultrasonography plus CEUS was able to identify small HCC and help monitor patients with early diagnosis of HCC. 2.There were significant differences between the nodules ≤1 cm and those 1-2 cm in enhancement mode, the smaller the HCC nodule, the longer the duration of enhancement of contrast agent.

INTRODUCTION
Liver cancer is the sixth most common cancer worldwide, but the third most common cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) is the most common type of primary liver malignancy. Approximately 548,000 people are diagnosed with HCC every year, and almost as many people die as a result of it [2]. Developing countries have two to three times higher incidence of HCC compared with Western

countries[3]. It is estimated that the incidence of HCC will continue to increase until 2030 [4].

Imaging, involving multiphase computed tomography (CT) or magnetic resonance imaging (MRI), forms the basis of the diagnosis of HCC [5]. The development and progression of HCC are accompanied by a series of changes in hemodynamics in the lesion. During the transformation of a cirrhotic nodule to a dysplasia nodule and small hepatocellular carcinoma, the blood supply of the nutrient arteries in the nodule gradually increases, while that of the original portal vein gradually decreases. Ultrasound is a safe, commonly available, and cost-effective tool for screening patients with cirrhosis for HCC, but its diagnostic use is limited by its low specificity due to the variable appearances of HCC. The diagnostic accuracy of conventional ultrasonography for hepatic space-occupying lesions is only 53%–77% [6]. Contrast-enhanced ultrasound (CEUS) uses contrast microbubbles during ultrasound, allowing the detection and characterization of malignant focal liver lesions with much higher diagnostic accuracy [7]. The main advantage of CEUS is its ability to display microcirculatory blood perfusion of tissues in real time. The differences in the blood perfusion of benign and malignant tumors allows sonographers to make a qualitative and quantitative diagnosis [8]. It greatly increases the detection rate and diagnostic accuracy of early-stage tumors and satellite lesions of malignant tumors [9].

The diagnosis of small HCC relies solely on imaging because patients usually have no clinical signs [10]. However, these small nodules rarely display the radiological hallmarks of HCC [11]. Delaying diagnosis until the development of <2 cm nodules results in increased treatment failure or recurrence [12]. The use of CEUS to monitor and diagnose small HCC may improve patient outcomes.

We hypothesized that CEUS would be safe and effective in detecting small HCCs. Therefore, the present study was conducted to investigate the clinical value of CEUS in the early detection of small HCCs in patients at high risk of HCC. We analyzed the regular conventional color Doppler ultrasonography, follow-ups, and CEUS of the liver

performed in patients at high risk for HCC in our department followed up for more than 10 years.

MATERIALS AND METHODS

Participants

From January 2007 to December 2021, the clinical data of patients at high risk of HCC who underwent regular follow-up at Xuhui Dahua Hospital were prospectively collected. The inclusion criteria were as follows: (1) patients with chronic liver disease and those with cirrhosis diagnosed by clinical and related imaging examinations; (2) patients with cirrhosis complicated by intrahepatic space-occupying lesions, but undetermined nature of the lesions, or increase in one of the combined indicators of HCC (AFP or a new HCC marker Glypican-3), but imaging examination showing no space-occupying lesions; (3) family history of HCC; and (4) status post HCC surgery. The exclusion criteria were as follows: 1) hepatic tumor greater than 2 cm in diameter, or patients with advanced tumors complicated by a portal vein tumor thrombus; and (2) patients with metastatic liver cancer. This study was approved by the Dahua Hospital of Xuhui District Institutional Review Board (Approval No.201607). The patients gave consent for inclusion in the study.

Diagnostic criteria

The whole dynamic process of liver CEUS included arterial phase (15–30 s), portal phase (31–120 s), and delayed phase (121–360 s). A differential diagnosis was performed based on the hemodynamic characteristics of the intrahepatic nodules in dynamic CEUS. depending on the time of wash-in and wash-out. According to American College of Radiology (ACR) CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS), the CEUS features of HCC included homogeneous or inhomogeneous hyperechoic enhancement in the arterial phase and hypoechoic enhancement in the portal or delayed phases, which was called the "fast-in and fast-out" type and was a typical enhancement pattern of HCC [13,14]. Specifically, if CEUS showed rapid wash-in and no significant wash-out in the portal and delayed phases, namely a "fast-in and

isochronous-out" type, it was considered an atypical enhancement pattern of HCC (mostly manifestation patterns of small HCC). If CEUS showed that the lesion area had slower wash-in, and the portal and delayed phases showed isoechoic enhancement and wash-out isochronously as with the liver parenchyma, namely the "slow-in and isochronous-out" type, it suggested a dysplastic nodule. If CEUS showed isochronous enhancement for the intrahepatic lesion area and the peripheral liver parenchyma and the portal and delayed phases showed isoechoic enhancement and wash-out isochronously as with the liver parenchyma, it suggested a benign liver nodule.

All patients were clinically diagnosed with small HCC according to the hepatocellular carcinoma treatment guidelines issued by the European Association for the Study of the Liver (EASL). Common imaging tests included a four-phase multidetector CT, and dynamic contrast-enhanced MRI. Clinical diagnosis of small HCC was comprehensively based on the patient's history of chronic liver disease, AFP (>400µg/L for one month or >200µg/L for over two months), and typical HCC manifestations revealed by imaging examinations (hypervascular liver lesions in the arterial phase with washout in the portal veins or in the delayed phase) [15]. Patients with high suspicion of HCC were treated with puncture and then surgery.

Examination method

Color ultrasound instruments (Siemens Sequoia 512 and Siemens S2000, Siemens Ltd., Munich, Germany; Philips iU22, Royal Dutch Philips Electronics Ltd., Amsterdam, Netherlands, and LOGIQ E9, General Electric Co., Fairfield, Connecticut, USA) were used with an abdominal convex array probe, at a frequency of 1–5 MHz. The contrast agent was SonoVue containing 59 mg sulfur hexafluoride gas, and the microbubble suspension was prepared using 5 mL of 0.9% NaCl solution. According to the weight of each patient, a microbubble suspension of 2 mL/50 kg was taken for Siemens Sequoia 512 and S2000 ultrasound instruments, and 0.1 mL was added for each additional 5 kg. For Philips iU22 and GE GLOGIQ E9, 1 mL/50 kg of the suspension was used and 0.1 mL was added for each additional 5 kgg. The microbubble suspension was added via bolus injection through the peripheral vein, and 5 mL of 0.9% NaCl solution was

intravenously injected immediately. The CEUS information was stored in the form of real-time dynamic video, and qualitative and quantitative analyses of the contrast enhancement mode were conducted.

CEUS was performed by associate chief physicians and reviewed by physicians with the same qualification or superior physicians.

Statistical analysis

Statistical analyses were performed using SPSS software V. 22.0 (IBM Corp., Armonk, NY, USA). The categorical data were presented as n (%). The mean ± standard deviation (SD) was used for continuous data with normal distribution. The measurement data in the two groups were compared using a two-sample unpaired-sample t test. The categorical data were compared using the chi-square test. Simple logistic regression was used to analyze and weigh the various ultrasound indicators and overall scores in predicting the odds ratio of HCC. $P < 0.05$ indicated a statistically significant difference.

<u>RESULTS</u>

Baseline characteristics

A total of 395 patients were enrolled in the 14 years of follow-up, including 230 men and 165 women. Their age range was 11–85 years, with a mean of 54.67 ± 12.84 years. In these patients, 632 nodules were detected. The follow-up rate was 92.15% (364/395), and the rate of loss to follow-up was 7.85% (31/395); 14 died of decompensated cirrhosis or other cardiovascular diseases, and 17 withdrew from the chronic disease management group. A total of 551 nodules in 364 patients were selected for follow-up. During the regular follow-up every 3 mo, according to CEUS, 65 (11.80%) were diagnosed with HCC, 19 (3.45%) with dysplastic nodules, and 467 (84.75%) with cirrhotic benign hyperplastic nodules (**Figure 1** and **Table 1**). In 65 patients diagnosed with HCC based on CEUS, 55 cases (84.6%) were pathologically confirmed by further needle biopsy. Of the 93 patients who underwent surgery and needle biopsy, 1 had missed diagnosis (1 patient had 2 HCC nodules in the liver, but

only 1 was found by CEUS). This might be related to the scanning section selected by physicians or the blind area of the scanning section of the liver using CEUS. No significant error was found between the HCC nodule size in surgical results and that found using CEUS (error ≤ 5 mm).

Ultrasound combined with CEUS characteristics of the nodules

The ultrasound characteristics of the nodules classified into HCC and non-HCC groups are shown in **Table 2**. Significant differences were found between the groups, except for nodule location. A total of 40 nodules (61.54%) were transformed from hypoechoic nodules to HCC, 9 (13.85%) from hyperechoic nodules to HCC, and 16 (24.62%) from isoechoic nodules to HCC. A summary of the CEUS characteristics in different phases is shown in **Table 3**. Significant differences were observed between the cirrhotic nodules, dysplastic nodules, and HCC nodules in each phase.

Comparison of CEUS in different-sized HCC

As shown in **Table 4**, a comparison of CEUS findings according to the size of the HCC nodules revealed significant differences between the nodules ≤1 cm and those 1–2 cm in enhancement time and pattern ($P<0.05$). Figure 1 shows that the HCC nodule size negatively correlated with the start time of wash-out of the contrast agent, with a correlation coefficient $r = -0.386$. The smaller the HCC nodule, the later the contrast agent began to wash out (**Figure 3 and Figure 4**). The HCC nodule size negatively correlated with the duration of enhancement of the contrast agent, with a correlation coefficient $r = -0.349$. The smaller the HCC nodule, the longer the duration of enhancement of the contrast agent.

DISCUSSION

This study aimed to diagnose patients with chronic liver disease using convenient, safe, inexpensive, and real-time dynamic ultrasonic examinations. Conventional ultrasound and CEUS were used for screening, grouping, and monitoring of patients with chronic liver disease, so as to achieve the early diagnosis of small HCC. A total of 65 patients with HCC were diagnosed in early monitoring during the 11-year study

involving 395 patients with chronic liver disease in different stages. The confirmation rate was 99.6% (64/65), with one missed diagnosis because the patient had two HCC nodules on the liver and the second nodule was found on a preoperative MRI scan. The use of CEUS in this study allowed stratification of the small hepatic nodules into HCC and non-HCC groups to identify patients in need of comprehensive prevention and treatment.

In this study, early and regular evaluation with CEUS revealed hyperechoic enhancement in the arterial phase of the cirrhotic nodules. HCC could be confirmed regardless of whether it was a "fast-in and fast-out" or "fast-in and isochronous-out" pattern. A change in the contrast enhancement mode suggested pathological changes in the nodules. The development of the American College of Radiology (ACR) CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS) has been welcomed for its standardization of CEUS information, allowing for a more accurate diagnosis of hepatic nodules [16]. The LI-RADS uses the size of a lesion, the type and degree of arterial phase enhancement, the presence of wash-out, and the timing and degree of wash-out as the major features used for categorizing CEUS images [13]. These features were also significant in the present study in differentiating between cirrhotic nodules, dysplastic nodules, and HCC.

CEUS for small nodules is important for patients at risk of HCC because the diagnosis of a single small HCC comes with good prognosis and provides a potential for cure [17]. This study showed a high rate of diagnosis of small HCCs, which were all later confirmed to be HCCs. These results compared well with the findings of other studies that aimed to distinguish HCC from benign nodules when they were smaller than 2 cm. The use of gadoxetic acid–enhanced and diffusion-weighted MRI resulted in sensitivity and accuracy of 91% and 89%, respectively [18]. Another study using LI-RADS with CT achieved sensitivity and specificity of 72.7% and 90%, respectively [19]. However, one study used CEUS to identify hypervascularity in 190 nodules (95.5%) of 199 histologically confirmed HCC nodules [20]. The advantage of CEUS over other methods with similar results was that it was a modification of the standard ultrasound

screening. However, the technique did have some limitations. As shown by the missed diagnosis of one HCC in a patient who already had one HCC, the ultrasonic examination of the liver showed blind areas and interference by gas, or the ribs might result in a missed diagnosis. To address this, it was necessary to select different sections and change positions to observe various sections of the liver. CEUS is also a technique that requires experience, proficiency in section examinations, and understanding of nodules. Insufficient proficiency or understanding may lead to missed diagnosis or misdiagnosis.

Many studies have explored the CEUS images of HCC larger than 20 mm [15,20,21], but comparative studies on HCC nodules between the nodules ≤1 cm and those 1–2 cm are few. However, this study compared the enhancement mode of CEUS for small HCC nodules ≤2 cm of different sizes. The results showed that the smaller the HCC nodule, the longer the duration of enhancement of the contrast agent. This might be related to the differentiation of HCC and the blood supply of the hepatic artery and portal vein for HCC. The principle of why this enhancement mode is formed needs further exploration.

The study had some limitations. The patients were enrolled from one medical center, and hence the number of small HCC was less. A larger study from more centers would provide more evidence for these results. No direct comparison with alternative MRI or CT methods was found. So, we cannot directly infer that CEUS is superior to CT or MRI for the diagnosis of small HCC.

CONCLUSION

Conventional ultrasonography combined with CEUS could identify small HCCs and help monitor patients with early diagnosis of HCC. Significant differences were found in the enhancement of CN, DN, and HCC using CEUS, and also between the HCC nodules ≤1 cm and those 1–2 cm in the enhancement mode.

ARTICLE HIGHLIGHTS

Research background

Contrast-enhanced ultrasound (CEUS) is challenging in the diagnosis of small hepatocellular carcinoma (HCC) with a diameter of less than 2cm.

Research motivation

Many studies have explored the CEUS images of HCC larger than 20 mm, but comparative studies on HCC nodules between the nodules ≤1 cm and those 1–2 cm are few. However, this study compared the enhancement mode of CEUS for small HCC nodules ≤2 cm of different sizes.

Research objectives

To investigate the clinical value of contrast-enhanced ultrasound (CEUS) in the early detection of small hepatocellular carcinoma (HCC) with high risk factors.Especially to compared the enhancement mode of CEUS for small HCC nodules ≤2 cm of different sizes.

Research methods

Conventional ultrasonography combined with CEUS could identify small HCCs and help monitor patients with early diagnosis of HCC. Significant differences in the enhancement mode were noted between nodules ≤1 cm and those 1–2 cm.The smaller the HCC nodule, the later the contrast agent began to flush, and the longer the duration of contrast enhancement.

Research results

1.The conventional ultrasonography combined with CEUS revealed 65 (11.80%) nodules with a follow-up diagnosis of HCC, 19 (3.45%) dysplastic nodules, and 467 (84.75%) cirrhotic, benign, hyperplastic nodules.

2.There are 40 cases(61.54%) of HCC were transformed from hypoechoic nodules, 9 cases (13.85%) from hyperechoic nodules, and the remaining 16 cases (24.62%) from isoechoic nodules.

3.Significant differences in CEUS characteristics were found among cirrhotic nodules, dysplastic nodules, and HCC nodules in each phase.

4.Significant differences in the enhancement mode were observed between nodules ≤1 cm and those 1–2 cm.

Research conclusions

Conventional ultrasonography combined with CEUS could identify small HCCs and help monitor patients with early diagnosis of HCC. Significant differences in the enhancement mode were noted between nodules ≤1 cm and those between 1–2 cm. The smaller the HCC nodule, the later the contrast agent began to flush, and the longer the duration of contrast enhancement.

Research perspectives

Small HCC ultrasound imaging enhancement pattern compared with other medical imaging enhancement pattern is the research direction in the future.

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