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Quantitative analysis of contrast-enhanced ultrasonography: differentiating focal nodular hyperplasia from hepatocellular carcinoma

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Objective: To explore the potential of quantitative analysis of contrast-enhanced ultrasonography (CEUS) in differentiating focal nodular hyperplasia (FNH) from hepatocellular carcinoma (HCC).

Methods: 34 cases of FNH and 66 cases of HCC (all lesions <5cm) were studied using CEUS to evaluate enhancement patterns and using analytic software Sonoliver® (Image-Arena™ v.4.0, TomTec Imaging Systems, Munich, Germany) to obtain quantitative features of CEUS in the region of interest.

The quantitative features of maximum of intensity (IMAX), rise slope (RS), rise time (RT) and time to peak (TTP) were compared between the two groups and applied to further characterise both FNH and HCC with hypoenhancing patterns in the late phase on CEUS.

Results: The sensitivity and specificity of CEUS for diagnosis of FNH were 67.6% and 93.9%, respectively. For quantitative analysis, IMAX and RS in FNHs were significantly higher than those in HCCs ($p < 0.05$), while RT and

TTP in FNHs were significantly shorter ($p < 0.05$). Both the 11 FNHs and 62 HCCs with hypo-enhancing patterns in the late phase were further characterised with their quantitative features, and the sensitivity and specificity of IMAX for diagnosis of FNH were 90.9% and 43.5%, RS 81.8% and 80.6%, RT 90.9% and 71.0%, and TTP 90.9% and 71.0%, respectively.

Conclusion: The quantitative features of CEUS in FNH and HCC were significantly different, and they could further differentiate FNH from HCC following conventional CEUS.

Advances in knowledge: Our findings suggest that quantitative analysis of CEUS can improve the accuracy of differentiating FNH from HCC.

Dynamic contrast-enhanced ultrasonography (CEUS) has noticeably improved the detection and characterisation of focal liver lesions during the past decade [1]. The enhancement patterns of the lesion are evaluated in three vascular phases (the hepatic arterial, portal venous and late phases), where the hepatic arterial phase provides information on the degree and pattern of vascularity and the portal venous and late phases provide important information on the differentiation between benign and malignant liver lesions [1]. A previous study has shown that CEUS using SonoVue® (Bracco, Milan, Italy) and spiral-CT provides similar diagnostic accuracy in the characterisation of focal liver lesions [2].

The typical enhancement of focal nodular hyperplasia (FNH) on CEUS showed hyperenhancement in the three vascular phases with a stellate vascular and centrifugal enhancement in the arterial phase or a hypoenhancing central scar in the late phase [1, 3–5]. However, these features have not been observed in all cases of FNH, particularly in small lesions. A study on FNH showed that 3 out of 13 lesions (23.1%) were hypoenhancing in the late phase [6] and 3 out of 10 lesions <3 cm had spoke-wheel patterns and 2 had central scars [4]. There is also a broad variation of stellate vascular enhancement in FNHs with a range from 27.3% to 73.3% and of central scar with a range from 36.4% to 63.3% [3–5]. Thus, it can be difficult to differentiate atypical FNHs from other hypervascular malignant tumours, such as hepatocellular carcinoma (HCC), and hypervascular metastases [3]. Furthermore, a hypoenhancing central scar has been described in fibrolamellar HCC and sclerosing or scirrhous HCC [7, 8], and a central feeding artery with spoke-wheel sign has also been described in two scirrhous HCCs [8]. Hence, a comprehensive approach rather than simply estimating the haemodynamics could be beneficial for differential diagnosis.

The current low-mechanical-index techniques for CEUS are capable of real-time demonstration of continuous haemodynamic changes in both the liver and hepatocellular nodules, from which time-intensity curves can be obtained by means of analytic software and then a series of semi-quantitative perfusion measurements extracted and analysed [9–11]. This method has shown a possible benefit in diagnosing FNH by enabling analysis of the quantitative parametric curves of the five types of hypervascular liver lesions [9]. In the present study, CEUS was applied to evaluate enhancing patterns of FNH and HCC; quantitative features of CEUS in the two groups were generated with the analytic software Sonoliver® (TomTec Imaging Systems, Germany) and compared to explore their potential in the differential diagnosis. Furthermore, the quantitative analysis of CEUS was used to characterise both FNH and HCC with hypoenhancing patterns in the late phase on CEUS.

METHODS AND MATERIALS

Patients

This study was approved by the institutional ethics committee, and all subjects signed informed consent forms. Between April 2005 and July 2009, a total of 4000 patients at our hospital underwent CEUS. Retrospectively, the patients who met the criteria given below were enrolled in this study: (1) patients with hypervascular liver nodules confirmed by CEUS, (2) those with lesions confirmed as HCC by histology or confirmed as FNH by histology or clinical evidence, (3) those with maximum dimension of lesions <5 cm, and (4) those with lesions located in a good position for quantitative analysis; furthermore, only those patients without high respiratory motion were enrolled, as this would have led to the quality of fit between the log-compressed signal and the bolus perfusion model being below 80%. An optimum scanning nodule was focused for a patient with two or more nodules. Those patients with HCC who underwent chemotherapy, interventional therapy

or local treatment were excluded, as this might have affected the quantitative features. The final study group consisted of 100 cases (34 cases of FNH and 66 cases of HCC) and 100 optimum scanning nodules accordingly.

The cases of FNH included 14 males and 20 females [age range: 22–69 years; 38.38 ± 11.65 years (mean $\pm$ standard deviation)], in which 13 cases were confirmed pathologically as FNH; the other 21 patients with normal α -fetoprotein levels underwent MRI and, with no histology as a gold standard, were diagnosed by a radiologist (R-HZ) and a specialist in hepatobiliary (M-SC). The diagnostic criteria on MRI were as follows: (1) a prominent central scar, which was typically low intensity on T_1 weighted images, high intensity on T_2 weighted images and showed visible enhancement on delayed contrast-enhanced images; (2) predominantly high intensity with a spinning wheel appearance and pseudocapsule on fat-saturated T_2 weighted fast spin echo images; (3) no change on imaging during the follow-up from 12 to 24 months [3]. The maximum dimensions of the FNHs ranged from 1.00 to 4.90 cm (3.46 ± 0.99 cm, mean $\pm$ standard deviation).

The cases of HCC included 57 males and 9 females [age range: 28–78 years; 50.58 ± 10.73 years (mean $\pm$ standard deviation)]. They underwent hepatic resection based on the guidelines for diagnosis of and therapy for liver cancer produced by the Chinese Society of Liver Cancer. All cases were confirmed pathologically as HCC, their maximum dimension ranged from 1.00 cm to 5.00 cm (3.47 ± 0.95 cm, mean $\pm$ standard deviation).

Ultrasound protocol, contrast agent and injection technique

The patients were examined using a Sequoia® scanner (Siemens-Acuson, Mountain View, CA) with a curved 4C1 transducer (between 1.0 and 4.0 MHz) and cadence contrast pulse sequencing software. First, baseline ultrasound was performed to scan the whole liver and determine the optimum scanning section. Then, an intravenous bolus injection of 2.4 ml of SonoVue was administered, followed by a 5-ml saline flush. Real-time CEUS using a low mechanical index (between 0.17 and 0.19) was initiated as soon as the contrast agents were injected and was not terminated until clearance of the contrast agent from the hepatic parenchyma, up to approximately 4–6 min post

injection. A breath-hold was required during the arterial phase (10–40 s post injection) to avoid significant motion of the lesions. The probe was kept in place to maintain the lesion in the section of examination throughout the first 80 s post injection; the whole lesion was scanned intermittently every 15 s thereafter. Images and clips were stored in Digital Imaging and Communications in Medicine format (log-compressed signal) on a hard disk for offline analysis, which was performed on the compressed Windows Media (Microsoft Corporation, Redmond, WA) video files.

Image interpretation

Two radiologists (X-QP and L-ZL) with 6 years of experience each on CEUS were present for each examination. The radiologists were blinded to any of the clinical details of the patients, and the interpretation was made by consensus using the images and clips stored according to the guidelines [1]. The enhancement patterns were compared with the adjacent liver parenchyma during the hepatic arterial (10–40 s), portal venous (40–120 s) and late phases (>120 s, until bubble disappearance), which included hyperenhancement, isoenhancement and hypoenhancement. The features of complete hyperenhancement in the arterial phase, spoke-wheel arteries or centrifugal filling of the feeding artery in the arterial phase and hypoenhancing central scar in the portal venous phase or the late phase were analysed.

Sensitivity and specificity of CEUS for diagnosis of FNH

The sensitivity and specificity of CEUS for diagnosis of FNH were calculated using the screening test. The histological or clinical diagnosis was regarded as the gold standard. Any lesion showing hyper-/isoenhancement in the late phase and confirmed as FNH was true positive (TP) while that confirmed as HCC was false positive (FP). Any lesion showing hypoenhancement in the late phase and confirmed as FNH was false negative (FN) while that confirmed as HCC was true negative (TN). Sensitivity was defined as the number of TP/the number of FNH (TP+FN) and specificity as the number of TN/the number of HCC (TN+FP).

Quantitative analysis in CEUS

The analytic software Sonoliver was applied to derive the time–intensity curves of CEUS for different lesions. The software permitted the quantification of contrast

enhancement from a time sequence of perfusion frames and provided a modified lognormal distribution for best-fit optimisation, which was based on the indicator dilution theory after an intravenous bolus of contrast agents [12]. The region of interest (ROI) in the lesion was defined in the interior corresponding to >20% of the whole lesion, avoiding central large vessels, necroses and the edge of the lesion. The ROI in the reference was defined as the peripheral parenchyma near the same depth. Moreover, all the ROIs consisted of >100 pixels [11]. The echo-signal quantification was initiated as soon as the microbubbles were visualised by eliminating the baseline frames, after which the signals were smoothed with the bolus perfusion model. The respiratory motions were corrected by the automatic motion compensation feature of the software.

The estimated bolus arrival time was set to zero by truncating the data and resetting the value of time accordingly. Quantitative features were obtained including maximum of intensity (IMAX; the percentage ratio of intensity in the lesion as well as that in the reference at the highest point of the perfusion process), rise time (RT; time between 10% and 90% of IMAX), time to peak (TTP), rise slope (RS; IMAX divided by TTP) and the quality of fit between the log-compressed signal and the bolus perfusion model (Figure 1).

Histopathological analysis

Formalin-fixed, paraffin-embedded tissues (encompassing carcinoma and adjacent liver tissues) were sectioned

into 5- μ m thickness and processed with haematoxylin-eosin staining. HCCs were classified into three histological degrees: well differentiated, moderately and poorly differentiated according to the World Health Organization classification [13]. A liver pathologist (M-YC) performed the histopathological diagnosis.

Statistical analysis

Statistical analysis was performed using SPSS® 13.0 (SPSS Inc., Chicago, IL) and MedCalc® (Belgium) software. All data were described as mean $\pm$ standard deviation. The χ^2 test was used to compare the enhancing patterns of FNH and HCC on CEUS. The Mann-Whitney *U*-test was used to compare the quantitative features between FNH and HCC. The receiver operating characteristic (ROC) curve was produced to determine the cut-off scores of quantitative features in further characterising both FNH and HCC with hypoenhancing patterns in the late phase. The score closest to the point with both maximum sensitivity and specificity was selected as the cut-off score (MedCalc software). A value of $p < 0.05$ indicated statistical significance.

RESULTS

Histopathological diagnosis of HCC and FNH 66 HCCs and 13 FNHs were confirmed by histopathology. None of the patients with FNH had a medical history of chronic liver disease. The final pathological diagnosis of HCC was as follows: well-differentiated HCCs were observed in 10 lesions with diameters ranging from 3.0 to

Figure 1. Quantitative features of contrast-enhanced ultrasonography. Output time-intensity curves of the liver lesion (top curve) and reference (bottom curve), where thin curves correspond to the video signal intensity, and thick curves are smoothed with the bolus perfusion model. The estimated bolus arrival time is set to zero by truncating the data and resetting the values of time accordingly. IMAX, maximum of intensity (the percentage ratio of intensity in the lesion as well as that in the reference at the highest point of the perfusion process); RT, rise time (time between 10% and 90% of IMAX); TTP, time to peak.

5.0 cm (3.69 ± 0.74 cm), moderately differentiated HCCs were observed in 36 lesions with diameters ranging from 1.0 to 5.0 cm (3.43 ± 0.99 cm) and poorly differentiated HCCs were observed in 20 lesions with diameters ranging from 1.0 to 5.0 cm (3.47 ± 0.98 cm).

Enhancement of FNH and HCC on CEUS

Enhancing patterns of FNH and HCC have been summarised in Table 1. Both FNH and HCC groups showed hyperenhancement in the arterial phase. 28 and 23 out of 34 FNHs showed hyper-/isoenhancement in the portal venous and late phases, respectively, compared with 29 and 4 out of 66 HCCs in the portal venous and late phases. 6 and 11 out of 34 FNHs showed hypoenhancement in the portal venous and late phases, respectively, compared with 37 and 62 out of 66 HCCs in the portal venous and late phases. The proportions of enhancement patterns in the portal venous and late phases were significantly different between the two groups ($p < 0.001$, $p < 0.001$, respectively); the sensitivity and specificity of CEUS for diagnosis of FNH were 67.6% and 93.9%, respectively. In the arterial phase, 21 FNHs (61.8%) showed early complete hyperenhancement, 13 FNHs (38.2%) showed centrifugal enhancement with a spoke-wheel artery. Hypoenhancing central scars were present in four FNHs (11.8%) in the portal venous phase and/or in the late phase. Meanwhile, 54 HCCs (81.8%) showed complete homoenhancement in the arterial phase, and non-enhancing areas were observed in 12 HCCs (18.2%) in the arterial and portal venous phases. Centrifugal enhancement or hypoenhancing central scar was not present in any HCC.

Quantitative analysis of CEUS in FNH and HCC

The quality of fit values of the ROIs in all the lesions and references were $>80\%$ with satisfactory quality

of fit between the log-compressed signal and the bolus perfusion model. Typical enhancement curves obtained from the ROIs are presented for FNH and HCC (Figures 2 and 3). The measurement values extracted from FNHs and HCCs have been summarised in Table 2. A significant difference of IMAX, RS, RT and TTP was observed between FNH and HCC. IMAX and RS were significantly higher in FNHs than in HCCs ($p < 0.05$), while RT and TTP were significantly shorter in FNHs than in HCCs ($p < 0.05$).

ROC curves of quantitative features for further diagnosis of FNH with hypoenhancing patterns in the late phase

All the enhancement curves of 34 FNHs and 66 HCCs were analysed, and the sensitivity and specificity of IMAX for diagnosis of FNH were 88.2% and 47.7%, RS 79.4% and 60.6%, RT 76.5% and 63.6%, and TTP 76.5% and 68.2%, respectively, which were not satisfactory for differentiating FNH from HCC, relative to the visual characterisation of CEUS.

Then, the ROC curves were plotted to select cut-off scores of IMAX, RS and RT and TTP in further diagnosing FNH with hypoenhancing patterns in the late phase (Figure 4), and the corresponding statistical values from ROC curves have been summarised in Table 3. Both the 11 FNHs and 62 HCCs with hypoenhancing patterns in the late phase could be further characterised with their quantitative features. A lesion with a measurement above the cut-off score of IMAX or RS was considered as FNH, and below the cut-off score of RT or TTP it was also considered as FNH, and the sensitivity and specificity of IMAX for diagnosis of FNH were 90.9% and 43.5%, RS 81.8% and 80.6%, RT 90.9% and 71.0%, and TTP 90.9% and 71.0%, respectively.

Table 1. Enhancement patterns of focal nodular hyperplasia (FNH) and hepatocellular carcinoma (HCC) on contrast-enhanced ultrasonography

Groups	<i>n</i>	Diameter (cm)	Arterial phase	Portal venous phase ^a		Late phase	
			Hyperenhancing	Hyper-/isoenhancing	Hypoenhancing	Hyper-/isoenhancing	Hypoenhancing
FNH	34	3.46 ± 0.99	34 (100)	28 (82.4)	6 (17.6)	23 (67.6)	11 (32.4)
HCC	66	3.47 ± 0.95	66 (100)	29 (43.9)	37 (56.1)	4 (6.1)	62 (93.9)

Data are given as mean $\pm$ standard deviation or number (percentage) unless otherwise indicated.

^aThe proportions of enhancement patterns in the portal venous phase and in the late phase were significantly different between the two groups ($p < 0.001$).

Figure 2. A Sonoliver® (Image Arena™ v.4.0.; TomTec Imaging Systems, Munich, Germany) image of contrast-enhanced ultrasonography (CEUS) in the arterial phase and the time-intensity curves of focal nodular hyperplasia (FNH) in segment 4. (a) Native sequence of the CEUS image. Three regions of interest (ROI) are shown: a large polygon ROI delimiting the region where motion compensation is applied, a reference ROI (left) and an analysis ROI (right). (b) Output time-intensity curves of FNH (top curve) and the reference (bottom curve), measurements extracted from the FNH: maximum of intensity=165.61%, rise time=7.07 s, time to peak=7.29 s, rise slope=22.72.

(a)

(b)

DISCUSSION

FNH is the second most common benign focal liver lesion after haemangiomas, with an incidence of 3–5% in the population and a prevalence of 8% among all focal liver lesions [14]. It can be treated conservatively as a nodule composed of benign-appearing hepatocytes occurring in a liver. Therefore, there is a need to differentiate FNH from other hypervascular malignant lesions to avoid unnecessary surgical resection. Our current study has investigated the potential of quantitative analysis of CEUS in differentiating FNH from HCC. Our data show that overlapping enhancement patterns on CEUS were observed between FNH and HCC and could be differentiated using quantitative analysis of CEUS, suggesting that the current approach can be a beneficial tool for further differential diagnosis.

At present, CEUS is the only non-invasive approach to perform real-time imaging of perfusion in liver lesions without ionising radiation doses. Most malignant tumours show predominantly microbubble washout, while benign tumours show persistent microbubble uptake on CEUS with a low-mechanical-index mode and a sulphur hexafluoride-filled microbubble contrast agent [1, 2, 5]. Despite this, enhancement in the late phase provides important information about the nature of the lesion. Our findings show overlapping enhancement in the late phase between FNH and HCC in which approximately two-thirds of FNHs were hyper-/isoenhancing in the late phase compared with less than a tenth of HCCs and approximately a third of FNHs were hypoenhancing in the late phase compared with over nine-tenths of HCCs. The different enhancements of FNHs could be

Figure 3. A Sonoliver® (Image Arena™ v.4.0.; TomTec Imaging Systems, Munich, Germany) image of contrast-enhanced ultrasonography (CEUS) in the arterial phase and time-intensity curves of hepatocellular carcinoma in segment 5. (a) Native sequence of CEUS image. Three regions of interest (ROI) are shown: a large ROI delimiting the region where motion compensation is applied, a reference ROI (left) and an analysis ROI (right). (b) Output time-intensity curves of hepatocellular carcinoma (HCC) and the reference, measurements extracted from the HCC: maximum of intensity=106.60%, rise time=11.53 s, time to peak=11.98 s, rise slope=8.90.

(a)

(b)

because of the difference in the main drainage passages. It has been reported that the blood flow from FNHs drains into hepatic veins adjacent to the lesion via perinodular sinusoids or venous vessels [15], which might affect the enhancement of FNHs in the late phase. In the hypoenhancing cases of FNH in the late phase, the blood flow might drain directly into venous vessels, while in

the iso-enhancing cases, it might drain through perinodular sinusoids and then to venous vessels. On the other hand, the difference in iso- and hypoenhancement in the late phase of HCCs observed in our current study could be because of cellular differentiation, as two out of four iso-enhancing HCCs in the late phase were well differentiated, which is consistent with the

Table 2. Enhancement patterns of focal nodular hyperplasia (FNH) and hepatocellular carcinoma (HCC) on contrast-enhanced ultrasonography

ROI	IMAX (%)	RS	RT (s)	TTP (s)	QOF
FNH (<i>n</i> =34)	136.91 ($\pm$ 40.49)	14.94 ($\pm$ 7.88)	9.82 ($\pm$ 3.26)	10.43 ($\pm$ 3.56)	85.38 ($\pm$ 7.42)
HCC (<i>n</i> =66)	115.25 ($\pm$ 41.03)	9.79 ($\pm$ 5.26)	12.57 ($\pm$ 4.72)	13.37 ($\pm$ 5.10)	85.43 ($\pm$ 7.09)
<i>p</i> -value	0.014	0.000	0.003	0.003	0.973

Data are mean ($\pm$ standard deviation) unless otherwise indicated.

IMAX, maximum of intensity; QOF, quality of fit; ROI, region of interest; RS: rise slope; RT, rise time; TTP, time to peak.

Figure 4. Receiver operating characteristic (ROC) curves of quantitative features for diagnosis of focal nodular hyperplasia (FNH) with hypoenhancing patterns in the late phase. (a) ROC curves for maximum of intensity (IMAX) (area under the curve=0.680, cut-off score=103.55) and rise slope (RS) (area under the curve=0.839, cut-off score=12.94) in differentiating FNH with hypoenhancing patterns in the late phase from hepatocellular carcinoma (HCC). The ROC curves suggest that IMAX and RS have diagnostic significance with area under the curve >0.5 . The score closest to the point with both maximum sensitivity and specificity is selected as the cut-off score. Lesions with measurements above the cut-off score of IMAX or RS are considered as FNHs. (b) The ROC curves for rise time (RT) (area under the curve=0.838, cut-off score=9.88) and time to peak (TTP) (area under the curve=0.845, cut-off score=10.32) in differentiating FNH with hypoenhancing patterns in the late phase from HCC. The ROC curves suggest that RT and TTP have diagnostic significance with area under the curve >0.5 . Lesions with measurements below the cut-off score of RT or TTP are considered as FNHs.

observation that approximately half of the HCCs showing iso-enhancement in the late phase were well differentiated [16]. Several studies have suggested that typical features of FNH, a hypervascular mass with a stellate vascular and centrifugal enhancement in the arterial phase or with hypoenhancing central scar in the late phase, could be useful to distinguish FNH from other hypervascular lesions [1, 3–5]. However, in our current study, the typical features of centrifugal enhancement and spoke-wheel arteries were observed in only approximately one-third and central scars in one-tenth of FNHs, suggesting that the diagnosis of FNH for lesions <5 cm cannot solely depend on the enhancement of CEUS.

Measurements from the time–intensity curves can be helpful if a hypervascular lesion is difficult to characterise precisely on visual patterns of CEUS [17, 18]. Higher and more rapid enhancement has been observed in FNHs than in other lesions [8], although the absolute maximum intensity in the arterial phase cannot be used to differentiate benign from malignant lesions [18]. In the current study, we compared the quantitative features of CEUS in FNH and HCC using the software Sonoliver, which is modelled with an appropriate indicator dilution theory for microvascular networks [19]. Our findings show that IMAX and RS in FNH are significantly higher than those in HCC, and that RT and TTP are significantly shorter, suggesting that the quantitative features can be helpful to differentiate FNH from HCC. It is known that IMAX is proportional to the concentration of contrast agents, while RT and TTP are mainly affected by the blood flow rate [19], and IMAX, RT, TTP and RS have also been proved to correlate with neo-arterisation in HCC [11]. Thus, large arteries within the fibrous septa and the rich network of capillaries in the FNH, which provides arterial blood to the hepatocytes and sinusoids, could contribute to the highly hypervascular nature of most FNHs in imaging. The malformed microarteries in FNH could surpass the neovascularisation in HCC, which may explain the difference in quantitative features between FNH and HCC.

In our present study, the overlapping hypoenhancement in the late phase on CEUS between these two groups resulted in the low sensitivity of CEUS for diagnosis of FNH, and the quantitative analysis could not improve the sensitivity and specificity for differentiating

Table 3. Data from receiver operating characteristic curves of quantitative features in differentiating focal nodular hyperplasia with hypoenhancing patterns in the late phase from hepatocellular carcinoma

Statistical value	IMAX	RS	RT (s)	TTP (s)
Sensitivity (%)	90.9	81.8	90.9	90.9
Specificity (%)	43.5	80.6	71.0	71.0
Cut-off score	103.55	12.94	9.88	10.32
Area under the curve	0.680	0.839	0.838	0.845

IMAX, maximum of intensity; RS, rise slope; RT, rise time; TTP, time to peak.

FNH from HCC significantly relative to the visual characterisation of CEUS. Thus, we used quantitative analysis of CEUS to further characterise those FNHs and HCCs with hypoenhancing patterns in the late phase, and ROC curves to select and validate cut-off scores of the quantitative features. The ROC curves show the high sensitivities of IMAX, RT and TTP and the low specificity of IMAX, and that RS is the most useful measurement with both high sensitivity and specificity for diagnosis of those FNHs with hypoenhancing patterns. Our current findings suggest that quantitative analysis of CEUS can improve the accuracy to differentiate FNH from HCC following conventional CEUS.

There were some limitations in our present study. First, we applied quantitative analysis of CEUS to compare only between FNH and HCC, although other tumours (*e.g.* haemangiomas, adenomas and hypervascular

metastases) also frequently show hypervascular features. Second, the distorted perfusion measurements were obtained from the lognormal distribution function based on log-compressed non-linear signals, but should have been done with linear raw data [20]. More accurate evaluation of intratumoral blood perfusion could have been achieved if the kinetic data were recorded as linear raw data. Finally, the small number of FNHs with hypoenhancing patterns in the late phase could affect the accuracy of diagnostic assessment in the present study.

CONCLUSION

Quantitative features of CEUS in FNH and HCC were significantly different, and quantitative analysis could be a beneficial approach to improve the overall accuracy of diagnostic assessment in differentiating FNH from HCC.

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