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Original Paper

Contrast-Enhanced Ultrasound for the Characterization of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

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Key Words
Contrast-enhanced ultrasound · Differentiation · Hepatocellular carcinoma · Intrahepatic cholangiocarcinoma

Abstract
Purpose and methods: The ability of contrast-enhanced ultrasound (CEUS) to differentiate between hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) is still controversial. We reviewed the CEUS imaging of 819 patients (HCC=546, ICC=273) with an established pathological diagnosis. The enhancement patterns of lesions and the diagnostic performance of CEUS were analyzed. ***Results:*** Arterial hyperenhancement followed by washout was observed in 92.3% (504/546) of the HCC lesions and 85.7% (234/273) of the ICC lesions on CEUS ($p<0.05$). Additionally, the ICCs presented contrast washout much earlier than the HCCs, with an average time of 27.5 seconds after injecting the contrast agent compared with 70.1 seconds for the HCCs ($p<0.05$). Peripheral rim-like enhancement was observed in 68.5% (187/273) of the ICCs, which was significantly more common than that in the HCCs (2.0%, 11/546) ($p<0.05$). When using arterial hyperenhancement with a washout phase later than 43 seconds after injecting the contrast agent and with no peripheral rim-like enhancement as the diagnostic criteria for HCC ≤5 cm in diameter, the area under the curve was 0.808,

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with 64.1% sensitivity, 97.4% specificity and 73.6% accuracy. ***Conclusions:*** Although ICC may show the typical enhancement pattern of HCC on CEUS, peripheral rim-like enhancement and quick contrast washout show high efficiency in the differentiation of HCC from ICC.

Introduction

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) comprise the majority of primary liver cancers, with HCC overwhelmingly accounting for 85–90% of cases worldwide [1–5]. Although the incidence of ICC is relatively low, its rate has increased sharply in recent years [6, 7]. Because HCC and ICC have different biological behaviors, prognoses and treatment planning, differentiating between them is critically important for clinical management.

In patients with cirrhosis or chronic hepatitis, HCC can be noninvasively diagnosed by typical imaging findings of arterial uptake followed by washout on contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (CEMRI) [1–5]. In characterizing ICCs, CECT and CEMRI usually demonstrate progressive contrast uptake throughout the vascular phase, without contrast washout [8–11].

Contrast-enhanced ultrasound (CEUS), which is based on utilizing a microbubble contrast agent and real time contrast specific imaging (CSI) mode, has been performed and investigated in different fields over the past decade. The most successful application of CEUS has been the characterization of focal liver lesions (FLLs) because of significant improvements in its diagnostic ability compared with baseline gray scale and Doppler ultrasound (US) [12–16]. With regard to HCC, hyperenhancement during the arterial phase, with portal or late phase contrast washout, is the most typical finding on CEUS and is reported to be similar to the findings on CECT and CEMRI [17–19]. However, ICC also typically shows the same enhancement pattern on CEUS [8, 20, 21], which differs from that seen on CECT and CEMRI [9, 10, 22, 23] because of the different pharmacokinetics between the microbubble ultrasound contrast agent (UCA) and the contrast agents of CT or MRI [24]. Therefore, it may be difficult to differentiate between HCC and ICC using CEUS, and using this imaging modality as a noninvasive method to diagnose HCC may not be reliable. In the current study, 819 patients (HCC=546, ICC=273) with a pathological diagnosis were enrolled, and the enhancement features of both HCC and ICC on CEUS were evaluated to help differentiate between these two entities.

Materials and Methods

Patients

From May 2004 to July 2013, liver CEUS examinations were performed for 24,853 patients admitted to our hospital, including 10,928 for the characterization of FLLs and 5,788 to monitor local ablative treatments. Among the FLLs to be characterized, there were 6,150 malignant lesions suggested by CEUS, including 4,894 HCCs, 406 ICCs, 798 metastatic liver cancers and 106 rare malignant tumors. In the present study, we retrospectively analyzed the CEUS findings of all 273 ICC patients with pathological diagnoses (biopsy n=28; surgery n=245) for the last decade. To identify the differences between ICC and HCC, 546 HCC patients with final pathological diagnoses (biopsy n=45; surgery n=501) who underwent CEUS examinations during the same time period, were included for analysis at a 1:2 ratio with ICC, by assigning a random number to the qualified HCC patients and ranking the number to select the study group. According to the Edmondson grading system, there finally were 14 HCCs with grade I, seven with grade I-II, 344 with grade II, 105 with grade II-III, 71 with grade III, three with grade III-IV and two with

grade IV, respectively. For the study patients, the CEUS examination was performed before the lesions were treated. Patients with mixed hepatocellular cholangiocarcinoma were excluded from this study. The primary patient characteristics are listed in table 1. All patients provided signed informed consent before undergoing the CEUS examination. This study was approved by our hospital's institutional review board and was in accordance with the Helsinki Declaration.

Baseline US and CEUS Examinations

The US equipment and settings used in the present study are detailed in table 2. For each patient, a baseline US was performed at the beginning of the study and was immediately followed by the CEUS study. The FLLs (i.e., the number, location, size, shape, and echogenicity) and the liver disease history (i.e., cirrhosis, dilation and calculus of the bile duct) findings were scanned and recorded. In patients with multiple lesions, the largest lesion on baseline US was selected for the CEUS study. SonoVue® (Bracco, Italy), which is composed of phospholipid-stabilized microbubbles containing sulfur hexafluoride gas, was used as the UCA. The UCA was reconstituted by adding 5 ml of sterile saline before use. For each CEUS imaging session, 2.4 ml of the UCA was injected as a bolus into the antecubital vein, followed by a flush with 5 ml of 0.9% sodium chloride solution. The equipment was switched to CSI mode using a low mechanical index (MI) technique (MI <0.2). Upon completion of the UCA injection, the timer was started simultaneously. The target lesion and surrounding liver parenchyma were observed continuously for at least 5 minutes. From the time of the UCA injection, the arterial phase was defined as 10–30 seconds, the portal phase as 31–120 seconds, and the delayed phase as 121–360 seconds, according to the practice guidelines from the European Federation of Societies for Ultrasound in Medicine and Biology [12]. Dynamic imaging of the entire CEUS process, including the complete arterial phase and portal phase, as well as all or several sections of the delayed phase (depending on the storage abilities of the different scanners), was stored in the hard disk incorporated in the scanner and then transferred to the magnetic optical (MO) disk (between 2003 and 2005) or digital video disc (DVD) (between 2005 and 2007) or picture archiving and communication system (PACS) (ANNET, China) (from 2007 until the present). All procedures were performed in the same manner by four skilled investigators who each had least five years of experience in liver CEUS.

Image Analysis

The baseline US and CEUS images were retrospectively displayed from MO, DVD or PACS on a computer screen in a random order. The reviews were performed by consensus by two readers who each had at least five years of experience in liver CEUS; the readers were not involved in the imaging acquisition and they were blinded to the clinical histories, histopathologic results and other imaging findings. Compared with the surrounding liver parenchyma, the enhancement degree of the targeted lesion was categorized as nonenhancing, hypoenhancing, isoenhancing or hyperenhancing. Contrast washout was defined as the degree of change of enhancement from hyper- to hypoenhancement at the part of the lesion that showed contrast enhancement. When the lesion began to show hyperenhancement and washout, the times were recorded. The contrast distribution of the lesions in the arterial phase was described as follows: homogeneous enhancement (i.e., uniform contrast uptake by the whole lesion), heterogeneous enhancement (i.e., a combination of irregular contrast uptake areas and nonenhancing areas); and peripheral rim-like enhancement (i.e., a continuous ring of intense contrast uptake at the periphery of the lesion with an irregular inner edge and strip-like enhancement extending to the central portion of the tumor) [18, 19](fig 1). The diagnosis of cirrhosis was established by histology using a biopsy or surgical specimen or with a combination of consistent clinical, ultrasonographic or endoscopic findings.

Statistical Analysis

To analyze the correlation between the enhancement patterns and liver disease history, the patients were divided into two groups based on their liver history and then further divided into three subgroups to analyze the correlation between the enhancement patterns and tumor size (i.e., lesions measuring <2 cm, 2 to 5 cm and >5 cm in diameter). Differences in the quantitative data, such as age and tumor size between the subgroups, were compared with the student's *t*-test. Pearson's Chi-squared test was used to analyze the differences in the history of liver disease, tumor markers and enhancement patterns of the HCCs and ICCs within these subgroups. Receiver operating characteristic (ROC) curves were made based on the different HCC criteria for the diagnostic test, and the diagnostic performance was compared. A value of $p<0.05$ was considered to be statistically significant. The statistical analyses were performed using the SPSS® 16.0 software package (SPSS Inc., Chicago, Ill., USA).

Table 1. The main characteristics of HCC and ICC patients

Parameter	HCC (n=546)	ICC (n=273)	p
Age (years)			<0.05
Mean ± standard deviation	50.0 ± 11.0	55.0 ± 11.0	
Range	18–85	22–82	
Gender			<0.05
Male	492 (90.1)	160 (58.6)	
Female	54 (9.9)	113 (41.4)	
Hepatitis			<0.05
B virus	490 (89.7)	61 (22.4)	
C virus	0 (0)	0 (0)	
B+C virus	1 (0.2)	0 (0)	
Negative	25 (4.6)	189 (69.2)	
Missing data	30 (5.5)	23 (8.4)	
Cirrhosis			<0.05
Positive	446 (81.7)	52 (19.0)	
Negative	100 (18.3)	221 (81.0)	
Specimen for histology			
Percutaneous US guided biopsy	66 (12.1)	38 (13.9)	
Surgery	480 (87.9)	235 (86.1)	
Number of nodules/patients			
1	421 (77.1)	241 (88.3)	
>1	125 (22.9)	32 (11.7)	
Size of target nodule (cm)			<0.05
Mean ± standard deviation	7.3 ± 4.1	7.0 ± 3.0	
Range	1.0–20.5	1.2–20.0	
Size distribution of target nodule (cm)			<0.05
<2.0	33 (6.0)	3 (1.1)	
2.0–5.0	165 (30.2)	75 (27.5)	
>5.0	348 (63.7)	195 (71.4)	
Value of alpha-fetoprotein (ng/ml)			<0.05
>20	370 (67.8)	20 (7.3)	
≤20	173 (31.7)	228 (83.5)	
Missing data	3 (0.5)	25 (9.2)	
Value of CA 19–9 (U/ml)			<0.05
>35	36 (6.6)	175 (64.1)	
≤35	319 (58.4)	67 (24.5)	
Missing data	191 (35.0)	31 (13.4)	
Value of CA125 (U/ml)			<0.05
>35	90 (16.5)	81 (29.7)	
≤35	267 (48.9)	34 (12.5)	
Missing data	189 (34.6)	118 (43.2)	

Unless otherwise indicated, data are number of nodules, with percentages in parentheses.

Table 2. US Equipment and Contrast Specific Modes

US Equipment, Manufacturer	CSI Technique	Transducer	Mechanical Index
Acuson Sequoia 512®; Siemens, Mountain View, Calif.	Contrast Pulse Sequencing® (CPS)	Vector array® (model 4V1) , 1–4 MHz	0.07–0.19
Aloka SSD-Alpha 10®; Aloka, Japan	Contrast Harmonic Echo® (CHE)	Convex array® (model UST-9130), 2–6 MHz	0.06–0.10
Toshiba Aplio XV®; Toshiba, Japan	Contrast Harmonic Imaging® (CHI)	Convex array® (model PVT375BT), 3.5 MHz	0.07–0.12

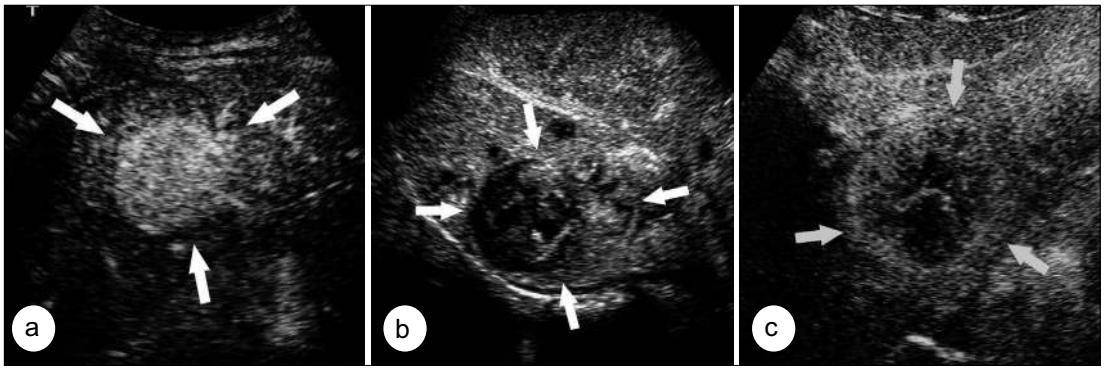

Fig. 1. Contrast distribution patterns of HCC and ICC on CEUS. **a** HCC in a 56-year-old man with cirrhosis showed homogeneous hyperenhancement in the arterial phase at 26 seconds. **b** HCC in a 42-year-old man with cirrhosis showed heterogeneous hyperenhancement in the arterial phase at 30 seconds. **c** ICC in a 63-year-old women without cirrhosis showed peripheral rim-like enhancement in the arterial phase at 21 seconds.

Results

Patient Characteristics

The clinical data showed that compared with ICC, HCC occurred mostly in younger predominantly male patients, and in those with chronic hepatitis infections and/or cirrhosis (all $p<0.05$). Regarding the tumor markers, elevated alpha-fetoprotein (AFP) was more common in the patients with HCC, whereas CA19-9 and CA125 were more common in the patients with ICC (all $p<0.05$). Elevated AFP levels (>20 ng/ml) were present in 67.8% (370/546) of the patients with HCC but only in 7.3% (20/273) of the patients with ICC, respectively (table 1).

HCC and ICC Enhancement Patterns

On CEUS, 92.3% (504/546) of the HCCs demonstrated arterial hyperenhancement with contrast washout in the portal and/or delayed phase, which was significantly more common than in the ICCs (85.7%, 234/273) ($p<0.05$). Among these lesions, the time when hyperenhancement and washout first appeared were significantly later in the HCCs than in the ICCs. The average time of the start of hyperenhancement was 15.4 seconds for HCCs and 13.9 seconds for ICCs; the time of the start of the contrast washout was 70.1 seconds for HCCs and 27.5 seconds for ICCs ($p<0.05$), respectively. Regarding the contrast distribution, homogenous and heterogeneous enhancement were the predominant findings for HCCs, whereas

Table 3. Enhancement patterns of HCC and ICC with different size

	HCC (n=546)				ICC (n=273)			
	<2 cm (n=33)	2-5 cm (n=165)	>5 cm (n=348)	p	<2 cm (n=3)	2-5 cm (n=75)	>5 cm (n=195)	p
Arterial phase								
Enhancement level				0.416				0.641
Hyperenhancement	32 (97.0)	157 (95.2)	336 (96.6)		3 (100)	61 (81.3)	170 (87.2)	
Isoenhancement	0 (0)	4 (2.4)	9 (2.6)		0 (0)	4 (5.3)	8 (4.1)	
Hypoenhancement	1 (3.0)	4 (2.4)	3 (0.9)		0 (0)	10 (13.3)	17 (8.7)	
Enhancement distribution				0.000				0.000
Homogeneous	29 (87.9)	121 (73.3)	103 (29.6)		3 (100)	17 (22.7)	7 (3.6)	
Heterogeneous	3 (9.1)	42 (25.5)	237 (68.1)		0 (0)	17 (22.7)	45 (23.1)	
Peripheral rim-like	1 (3.0)	2 (1.2)	8 (2.3)		0 (0)	41 (54.6)	143 (73.3)	
Portal phase				0.058				NA
Hyperenhancement	0 (0)	5 (3.0)	5 (1.4)		0 (0)	0 (0)	0 (0)	
Isoenhancement	8 (24.2)	36 (21.8)	48 (13.8)		0 (0)	0 (0)	0 (0)	
Hypoenhancement	25 (75.8)	124 (75.2)	295 (84.8)		3 (100)	75 (100)	195 (100)	
Delayed phase				0.000				NA
Hyperenhancement	0 (0)	2 (1.2)	1 (0.3)		0 (0)	0 (0)	0 (0)	
Isoenhancement	5 (15.2)	12 (7.3)	4 (1.1)		0 (0)	0 (0)	0 (0)	
Hypoenhancement	28 (84.8)	151 (91.5)	343 (98.6)		3 (100)	75 (100)	195 (100)	

Unless otherwise indicated, data are number of nodules, with percentages in parentheses.

peripheral rim-like enhancement (68.5%, 187/273) was the most common pattern for ICCs, occurring significantly more often than in HCCs (2.0%, 11/546) (p<0.05).

Enhancement Patterns With Different Lesion Sizes

The present study included 33 (6.0%) HCCs measuring <2 cm in diameter, 165 (30.3%) lesions measuring 2–5 cm and 348 (63.7%) lesions measuring >5 cm (table 3). The HCC lesions showing arterial hyperenhancement in the arterial phase and hypoenhancement in the portal and/or delayed phase accounted for 84.8% (28/33) of lesions <2 cm, 91.5% (151/165) of lesions of 2–5 cm, and 98.6% (343/348) of those >5 cm (p>0.05), respectively.

There were three (1.1%) ICCs <2 cm in diameter, 75 (27.5%) lesions of 2–5 cm and 195 (71.4%) lesions >5 cm. With regard to arterial hypervascularity, no significant difference was found between ICCs that were 2–5 cm in diameter (81.3%, 61/75) and those larger than 5 cm in diameter (87.2%, 170/195) (p>0.05), respectively.

Regarding the contrast distribution of HCCs, homogeneous enhancement was more common in HCCs measuring 2–5 cm in diameter (73.3%, 121/165), and heterogeneous enhancement was more common in HCCs measuring >5 cm (68.1%, 237/348) (p>0.05), respectively. Peripheral rim-like enhancement was significantly more common in ICCs measuring >5 cm in diameter (73.3%, 143/195) than in those measuring 2–5 cm (54.6%, 41/75) in diameter (p<0.05).

Enhancement Patterns Based On Liver Disease History

Regarding the history of liver disease, lesions in cirrhotic livers presenting with typical malignant CEUS features of arterial hypervascularity with portal and/or delayed phase contrast washout, had high numbers of both HCCs (91.2%, 382/419) and ICCs (88.5%, 46/52) ($p>0.05$), respectively (table 4). However, among these cirrhotic liver lesions, peripheral rim-like enhancement was also significantly higher in the ICCs (78.3%, 36/46) than in the HCCs (2.4%, 9/382) ($p<0.05$). Additionally, the washout of contrast enhancement was significantly shorter in the ICCs (27.8s) than in the HCCs (70.0s) ($p<0.05$) (fig 2).

Diagnostic Efficiency of CEUS Using Characteristic Features in HCCs and ICCs Less Than 5 cm in Diameter

According to the aforementioned results, peripheral rim-like enhancement and quick washout were considered to be the key points on the CEUS findings to differentiate ICCs from HCCs. We performed ROC analysis using different diagnostic criteria in all ICCs (n=78) and HCCs (n=198) with size ≤5 cm in diameter in the present study to evaluate the diagnostic performance of CEUS on HCC. When using arterial hyperenhancement with portal or late phase washout as the diagnostic criterion for HCC, the area under the curve (AUC) was 0.529, with 87.9% sensitivity, 17.9% specificity and 68.1% accuracy. When adding no peripheral rim-like enhancement to the diagnostic criteria for HCC, the AUC, sensitivity, specificity and accuracy was improved to 0.778, 86.4%, 69.2% and 81.5%, respectively. The ROC analysis showed that a cut-off value of 43 seconds for contrast washout may present the highest diagnostic performance to differentiate HCCs from ICCs. The AUC had its highest value of 0.808, and the specificity was further improved to 97.4%, when adding washout later than 43 seconds as a diagnostic criterion (table 5).

Discussion

At present, the CEUS findings of HCCs reported in the literature show some variance among different institutions, with arterial hyperenhancement varying from 61% to 97% and contrast washout ranging from 42% to 97% [25–28]. In the current study enrolling 546 pathologically proven HCC patients, 92% of the lesions showed typical features of arterial hyperenhancement with contrast washout. With respect to ICC, the similar enhancement pattern ranged from 56% to 100% [8, 11, 20–23]. In the present study, we summarized the CEUS findings from 273 pathologically proven ICC lesions, which may be the largest group of ICCs ever reported, with 86% of such lesions showing arterial uptake followed by washout.

Vilana et al. [8] reported the imaging features of 21 ICCs in the cirrhotic liver and found that all cases showed contrast enhancement (homogeneous in 10 cases and rim-like in 11 cases) in the arterial phase followed by washout during the venous phase. Therefore, 10 nodules (47.6%) corresponded to the specific pattern of HCC, according to the American Association for the Study of Liver Diseases criteria. Similar results were reported in an Italian multicenter study and a Chinese study. Galassi et al. [11] summarized the imaging features of 25 ICCs in cirrhotic livers and found that CEUS had a significantly higher rate of the misdiagnosis of ICC as HCC compared with CT (52% vs. 4.2%, $p=0.009$) and MRI (52% vs. 9.1%, $p=0.02$). Additionally, Li et al. [29] analyzed 54 CEUS images of histologically proven ICC and found that the typical HCC enhancement patterns were present even more often in ICC patients with chronic hepatitis (11 of 15, 73.3%) or with cirrhosis (11 of 16, 68.8%) compared with normal liver (8 of 23, 34.8%). Therefore, the differentiation of HCC from ICC is difficult according to the

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Table 4. Enhancement patterns of HCC and ICC in different liver background

	HCC (n=546)									ICC (n=273)								
	No cirrhosis (n=127)				Cirrhosis (n=419)				p	No cirrhosis (n=221)				Cirrhosis (n=52)				p
	<2 cm	2-5 cm	>5 cm	Total	<2 cm	2-5 cm	>5 cm	Total		<2 cm	2-5 cm	>5 cm	Total	<2 cm	2-5 cm	>5 cm	Total	
Arterial phase																		
Enhancement level									0.920									0.940
Hyperenhancement	5	25	93	123 (96.8)	27	132	243	402 (95.9)		2	48	138	188 (85.1)	1	13	32	46 (88.5)	
Isoenhancement	0	1	2	3 (2.4)	0	3	7	10 (2.4)		0	2	8	10 (4.5)	0	2	0	2 (3.8)	
Hypoenhancement	0	1	0	1 (0.8)	1	3	3	7 (1.7)		0	8	15	23 (10.4)	0	2	2	4 (7.7)	
Enhancement distribution									0.412									0.285
Homogeneous	5	24	24	53 (41.7)	24	97	79	200 (47.7)		2	11	5	17 (7.7)	0	5	2	7 (13.5)	
Heterogeneous	0	3	69	72 (56.7)	3	39	168	210 (50.1)		0	13	40	53 (24.0)	0	4	5	9 (17.3)	
Peripheral rim-like	0	0	2	2 (1.6)	1	2	6	9 (2.1)		0	34	116	151 (68.3)	1	8	27	36 (69.2)	
Portal phase									0.560									NA
Hyperenhancement	0	0	1	1 (0.8)	0	5	4	9 (2.1)		0	0	0	0 (0)	0	0	0	0 (0)	
Isoenhancement	3	3	13	19 (15.0)	5	33	35	73 (17.4)		0	0	0	0 (0)	0	0	0	0 (0)	
Hypoenhancement	2	24	81	107 (84.2)	23	100	214	337 (80.5)		2	58	161	221 (100)	1	17	34	52 (100)	
Delayed phase									0.077									NA
Hyperenhancement	0	0	0	0 (0)	0	2	1	3 (0.7)		0	0	0	0 (0)	0	0	0	0 (0)	
Isoenhancement	0	0	1	1 (0.8)	5	12	3	20 (4.8)		0	0	0	0 (0)	0	0	0	0 (0)	
Hypoenhancement	5	27	94	126 (99.2)	23	124	249	396 (94.5)		2	58	161	221 (100)	1	17	34	52 (100)	

Unless otherwise indicated, data are number of nodules, with percentages in parentheses.
p value showed the difference between cirrhosis and no cirrhosis group.

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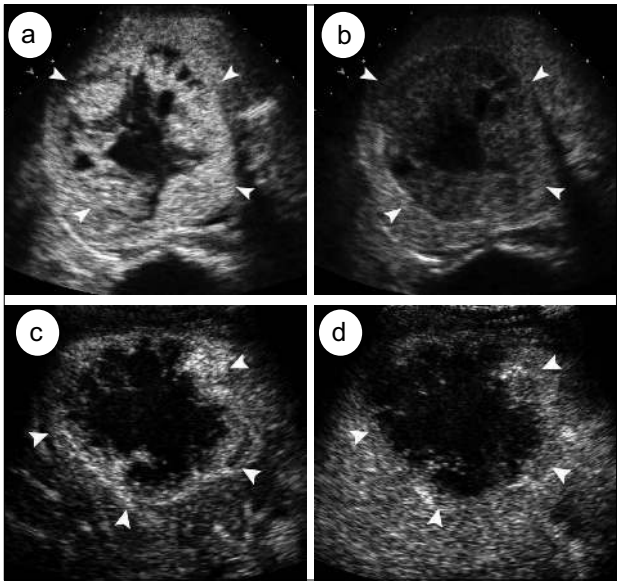

Fig. 2. 1. HCC of 7.9 cm in diameter in a 42-year-old man who presented was a typical CEUS pattern. **a** Arterial phase image taken at 24 seconds after UCA injection: The lesion presented heterogeneous hyperenhancement with center necrosis and irregular intra-nodular vessels. **b** Portal phase image at 86 seconds: The lesion showed hypoenhancement with a clear margin. The enhancement duration lasted for 49 seconds. From 11 seconds it began to show hyperenhancement and at 60 seconds it began to show contrast washout. 2. ICC of 6.8 cm in diameter in a 58-year-old man who presented with a typical CEUS pattern. **c** Arterial phase image taken at 16 seconds after UCA injection: The lesion presented a characteristic peripheral rim-like hyperenhancement. **d** Portal phase image at 42 seconds: The irregular rim-like enhancement showed clear contrast washout. The enhancement duration lasted for 27 seconds. From 12 seconds it began to show hyperenhancement and at 39 seconds it began to show contrast washout.

Table 5. Diagnostic performance of CEUS in characterization of HCC ≤5 cm using differentiation criteria

	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)
Criteria 1	0.529	87.9	17.9	68.1
Criteria 2	0.778	86.4	69.2	81.5
Criteria 3	0.808	64.1	97.4	73.6

Criteria 1: Arterial hyperenhancement with portal or late phase contrast washout.
Criteria 2: Criteria 1 together with no peripheral rim-like enhancement.
Criteria 3: Criteria 2 together with washout later than 43 seconds
Criteria 1 vs Criteria 2: $p<0.001$
Criteria 1 vs Criteria 3: $p<0.001$
Criteria 2 vs Criteria 3: $p=0.263$
AUC=Area Under Curve

enhancement pattern, particularly in the cirrhotic liver. Identifying those CEUS findings exclusive to ICCs is critically important for the differentiation of HCC.

In 2006, we first reported our initial experience of the CEUS findings of ICC and found that 44% (8/18) of the nodules showed irregular peripheral rim-like enhancement during the arterial phase [20]. Peripheral rim-like enhancement has been accepted as the most char-

acteristic finding of ICCs and it has been reported to range from 8 to 59%, although different definitions of this imaging finding are in use [8, 11, 20–22, 29, 30]. In another retrospective study from our group, peripheral rim-like hyperenhancement was found in 50% of ICCs, which was significantly less common in HCCs (4%) [21]. This specific enhancement distribution of ICCs was not only observed during imaging analysis, but also proven by quantitative analysis using time intensity curves in which the intensities of the peripheral portion were significantly greater than those of the central portion [21]. We further compared the CEUS findings with pathological findings in 32 mass-forming ICCs using semi-quantitative analysis and found hyperenhancing areas in the tumor always indicated an increased density of malignant cells [30]. Note that the peripheral rim-like enhancement pattern is due to a high degree of malignant cell proliferation in the peripheral regions and sclerotic, hypocellular or necrotic tissue in the central region of the tumor on pathological examination [30].

In the present study, peripheral rim-like enhancement was defined as a continuous ring of intense contrast uptake at the periphery of the lesion, with an irregular inner edge and strip-like enhancement extending to the central portion of the tumor [20, 21], in which regular thin-rim enhancement of the lesion capsule, such as in HCC, and thick-rim enhancement with regular central necrosis, such as in metastatic liver cancer, were excluded. In the present study, we found that this type of peripheral rim-like enhancement was the major difference, which was much more frequently present in ICCs (68.5%) than in HCCs (2%).

Quick contrast washout is another difference between the CEUS features of HCCs and ICCs. In the present study, we recorded the commencement time of hyperenhancement and washout for both entities and found that the ICCs presented significantly faster arterial hyperenhancement and contrast washout than the HCCs. The average time of contrast washout for ICCs was 27 seconds after the contrast injection, which was within the late arterial phase. The percentage of ICCs with arterial hyperenhancement presenting contrast washout at 27 seconds, 40 seconds and 60 seconds after the contrast injection were approximately 43%, 87% and 98%, respectively. There were only four ICCs showing contrast washout after 60 seconds. Small ICCs, particularly those measuring <2 cm in diameter and those in cirrhotic livers, usually present homogeneous hyperenhancement on CEUS, which may be easily misdiagnosed as HCC [8, 11]. However, it is well known that small HCCs are well differentiated pathologically and may present slow contrast washout on CEUS [26, 31, 32]. Therefore, we believe this feature is extremely useful for the differentiation of small HCCs from ICCs, particularly for tumors in the cirrhotic liver.

In the present study, we performed ROC analysis to evaluate the diagnostic performance of CEUS in the characterization of HCC with size ≤5 cm in diameter. Limiting the diagnostic criteria to arterial hypervascularity followed by washout resulted in a poor diagnostic performance with an AUC of only 0.529, 87.9% sensitivity, 17.9% specificity and 68.1% accuracy. However, the highest AUC (0.808) and specificity (97.4%) were achieved when using a washout of later than 43 seconds combined with no peripheral rim-like enhancement as additional diagnostic criteria for HCC. The patient groups used for the diagnostic test were not limited to those with liver disease background. In the current study the percentage of patients with hepatitis was 90% in HCC versus 22% in ICC; and those with cirrhosis was 82% in HCC versus 19% in ICC. Because patients with liver disease background is a precondition for noninvasive diagnosis of HCC, the CEUS criteria presented in the current study would have better specificity when adding the factor of liver disease background as one of the diagnostic criteria.

Because the radiological diagnosis of HCC is crucial, it is important to properly perform imaging analysis [1]. Proper performance is particularly important for CEUS. Studies should be performed at expert centers because CEUS is highly affected by operator skill and experience, patient-related factors, such as body habitus and cooperativeness, and tumor-related

factors, such as nodule location. Thus, CEUS should be carefully selected in the diagnostic algorithm by the specialist to ensure its effectiveness during clinical practice [12].

Conclusion

In summary, the majority of HCCs and ICCs may show typical patterns of arterial hyperenhancement, with portal or late phase contrast washout on CEUS. The differentiation between these two entities is difficult, but peripheral rim-like enhancement and quick contrast washout may be useful features in this regard. CEUS should have a proper position in the noninvasive diagnostic algorithm of HCC, with the benefits of safety, absence of radiation, good tolerability, cost effectiveness and high efficiency.

Disclosure Statement

The authors declare no conflict of interest.

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