Performance of contrast-enhanced sonography versus MRI with a liver-specific contrast agent for diagnosis of hepatocellular adenoma and focal nodular hyperplasia

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ABSTRACT

OBJECTIVE. The purpose of this article is to compare contrast-enhanced sonography (CEUS) with sulfur hexafluoride with MRI with the liver-specific contrast agent gadobenate dimeglumine in the diagnosis of hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) in a cohort of consecutive patients.

MATERIALS AND METHODS. Patients referred to a tertiary center for hepatobiliary disease who had suspected HCA or FNH on MRI performed with an extracellular gadolinium-based contrast agent underwent a prospective workup including CEUS and MRI with a liver-specific contrast agent. Diagnosis was definite when the findings of CEUS and MRI with a liver-specific contrast agent were concordant; histopathologic examination (HPE) was performed for cases with discordant findings. Descriptive statistics and the association between categoric variables were presented as numbers and percentages and were assessed using the Fisher exact test. The primary analysis was patient based. Sensitivity, specificity, and AUC and predictive values for the diagnosis of HCA and FNH were calculated separately for CEUS and MRI with a liver-specific contrast agent.

RESULTS. A total of 181 patients were selected for the first analysis. Findings from CEUS and MRI with a liver-specific contrast agent were concordant for 132 patients (73%) and discordant for 49 (27%). HPE was performed for 26 of the 49 patients with discordant findings (53%), with findings indeterminate for two of these patients, the findings of MRI with a liver-specific contrast agent correct for 21 of the remaining 24 patients (87.5%), and the findings of CEUS correct for three of these 24 patients (12.5%) ($p < 0.05$). For further analysis, 156 patients with concordant findings or HPE-proven cases were included. For CEUS, the sensitivity and specificity for the diagnosis of HCA and FNH were 85% and 87%, respectively; the ROC AUC value was 0.856; and the positive predictive value and negative predictive value were 79% and 90%, respectively. For MRI with a liver-specific contrast agent, the sensitivity and specificity were 95% each, the ROC AUC value was 0.949, and the positive predictive value and negative predictive value were 92% and 97%, respectively, for the diagnosis of HCA and FNH.

CONCLUSION. The findings of CEUS and MRI with a liver-specific contrast agent showed fair agreement for the diagnosis of HCA and FNH. MRI with a liver-specific contrast agent is diagnostically correct significantly more often than CEUS in cases with discordant findings that are HPE proven.

INTRODUCTION

Hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) are benign solid liver lesions that are mostly found in young women. Although both entities are benign and often asymptomatic, their pathogenesis and clinical management are different. For some patients with HCA, surgical resection may be considered, whereas patients with typical cases of FNH do not need further follow-up. Therefore, accurate diagnosis is important [1-3]. Contrast-enhanced sonography (CEUS) and MRI with a liver-specific contrast agent are imaging modalities with specific imaging features reported for both HCA and FNH, which may lead to confident diagnosis [3-10]. At present, both CEUS and MRI with a liver-specific contrast agent are regarded as the best complementary techniques for workup-based diagnosis of HCA and FNH, and final diagnosis can be considered definitive when the findings of both CEUS and MRI with a liver-specific contrast agent are concordant [3]. In uncertain or atypical cases, biopsy and histopathologic examination (HPE) are recommended [3] [11]. In addition, a few studies have reported MRI with a liver-specific contrast agent to be highly accurate for the diagnosis of HCA and FNH and can be considered a reference standard in cases with unequivocal lesiontypical findings [1] [6] [12-14]. However, MRI with a liver-specific contrast agent is costly, whereas CEUS has the potential to provide diagnosis of target lesions at a lower cost [15-18].

The purpose of the present study was to compare the diagnostic performance of CEUS with that of MRI with a liver-specific contrast agent in the differentiation of HCA and FNH in a large cohort of consecutive patients.

MATERIALS AND METHODS

Study Population

The ethics committee (institutional review board) at Erasmus University Medical Center approved this retrospective study, and informed consent was waived.

Patients were selected from prospectively collected databases from the departments of radiology and gastroenterology. Patients who met the inclusion criteria were those with a final diagnosis of HCA or FNH who had undergone liver imaging with both CEUS and MRI with a liver-specific contrast agent between May 2008 and December 2016. Exclusion criteria included a final diagnosis other than HCA or FNH, a history of cancer or known chronic liver disease, and the presence of multiple concurrent lesions of both HCA and FNH in the same patient.

Standard Workup Procedure

Patients referred to our institution with suspected HCA or FNH on an initial liver MRI examination performed with an extracellular gadolinium-based contrast agent (gadolinium-enhanced MRI) underwent standard liver workup with CEUS and MRI with a liver-specific contrast agent. CEUS was performed by a hepatogastroenterologist with 21 years of experience in ultrasound of the liver, including 5 years of experience in CEUS. MRI with a liverspecific contrast agent was subsequently performed within 4 weeks of the CEUS examination, and findings were evaluated and reported by one of three abdominal radiologists with expertise in liver imaging (8, 10, and 11 years of experience) who were blinded to the CEUS findings. Those cases for which diagnosis was uncertain at initial evaluation with MRI with a liver-specific contrast agent were discussed by two or three radiologists, and a consensus was reached regarding the final diagnosis.

Contrast-Enhanced Sonography

CEUS was performed using two ultrasound platforms (the Hitachi 900 and Preirus systems, Hitachi Medical Systems) with real-time grayscale, contrast-tuned imaging and a 2.5-5.0–MHz probe. The contrast agent that was used, sulfur hexafluoride (SonoVue, Bracco), was administered at a dose of 2.4 mL and flushed with isotonic saline. Examinations were executed in a standardized fashion. Patients first underwent unenhanced abdominal and hepatic sonography using conventional color Doppler or power Doppler imaging techniques, with the location, number, size, and sonographic features of the focal liver lesions recorded. Contrast agent was subsequently administered, and CEUS was performed. When multiple similar lesions of HCA or FNH were present, only the largest lesion was selected and evaluated with CEUS. Because of the unique network formed by the hepatic artery and the portal vein, three phases can be observed with CEUS [4-5]. Images were acquired in the hepatic arterial phase (10–40 seconds after injection), the portal venous phase (40–120 seconds after injection), and the late parenchymal phase (> 120 seconds after bubble disappearance). The vascularity and enhancement pattern of the lesion were evaluated for up to 5 minutes after injection of the contrast agent. Still images and digital cine loops were saved and were reviewed later for final assessment and report.

Criteria for the diagnosis of HCA and FNH were based on the European Federation of Societies for Ultrasound in Medicine and Biology protocol and guidelines [16] [19-22]. Central arteries were defined by the presence of enhancing central arteries with a spoke-wheel appearance. A central scar was defined as a central stellate hypoechoic area without contrast enhancement in the portal venous phase. Previous intralesional hemorrhage was defined as an irregular heterogeneous area without the presence of contrast filling. Late contrast enhancement (contrast agent reten-

tion) was defined as the presence of hyperechoic contrast filling compared with adjacent liver parenchyma in the portal phase. HCAs usually show homogeneous arterial contrast filling centripetally from the periphery to the center of the lesion. In the portal and late phases, the lesion becomes isoechogenic, sometimes with areas of previous intralesional hemorrhage. Alternatively, FNHs show a centrifugal spoke-wheel filling pattern in the arterial phase, followed by sustained homogeneous enhancement during the portal venous and late phases. A cinematic loop is recommended to check frame by frame for assessment of the filling pattern [23].

MRI

MRI was performed using a 1.5-T system (Signa, General Electrics) with a four-channel, phased-array body coil. The MRI protocol was identical for all patients: a single-shot fast spinecho sequence (slice thickness, 7 mm; TR/TE, 832/80–120; and flip angle, 90°), a fat-suppressed T2-weighted fast spin-echo sequence (slice thickness, 5–8 mm; TR/TE, 6315/90–93; and flip angle, 90°), and T1-weighted in-phase and opposed phase gradient-recalled echo sequences (slice thickness, 7 mm; TE, 4.6 ms [in phase] and 2.3 ms [opposed phase]; flip angle, 80°). Fat-suppressed, dynamic contrast-enhanced T1-weighted gradient-recalled echo imaging (slice thickness, 4–5 mm; TR/TE, 2.7–3.5/1.2; and flip angle, 12°) was performed in at least four phases (unenhanced, arterial, portal, and delayed phases) after administration of an IV bolus (2–2.5 mL/s) of gadobenate dimeglumine (MultiHance, Bracco) at a dose of 0.05 mmol per kilogram of body weight. The optimal arterial phase was based on bolus tracking. Finally, the same scan was repeated during a late hepatobiliary excretory phase 1–1.5 hours after injection.

For HCAs, typical MRI findings include signs of internal bleeding, atoll sign, small cystic areas, and diffuse homogeneous steatosis of the lesion. FNHs typically show the presence of a T2-weighted hyperintense central scar (spoke-wheel appearance). Both lesions show arterial phase hyperenhancement with a tendency toward isointensity in the portal venous phase. In addition, HCA is hypointense and FNH is hyper- or isointense on the hepatobiliary excretory phase image compared with surrounding liver parenchyma.

Reference Standard

Diagnosis was considered definitive in cases for which the findings of CEUS and MRI with a liver-specific contrast agent were concordant. When findings of CEUS and MRI with a liver-specific contrast agent were discordant, HPE of the lesion was performed after percutaneous image-guided biopsy of the target lesion. When CEUS was inconclusive or biopsy was contraindicated or undesirable, MRI with a liver-specific contrast agent was considered the reference standard for final clinical diagnosis in

cases with unequivocal lesion-typical findings. Furthermore, for patients with HCA, repeat MRI examination was performed every 6 months to monitor lesion regression after patient cessation of oral contraceptive use and pursuit of weight loss measures for obesity. For these patients, MRI with a liver-specific contrast agent was evaluated by all three abdominal radiologists, with a unanimous decision reached regarding MRI diagnosis. In addition, these patients were clinically observed for at least 1 year after imaging diagnosis. Final diagnosis and clinical management were discussed and assessed by the multidisciplinary hepatobiliary tumor board, which consisted of dedicated and experienced radiologists, surgeons, hepatogastroenterologists, and oncologists.

Case Evaluation

Patient age and sex, previous imaging reports, CEUS reports, reports from MRI with a liver-specific contrast agent, decisions of the multidisciplinary hepatobiliary tumor board, pathologic reports, final diagnoses, and clinical follow-up information were registered using a standardized and anonymized clinical reporting form in the online clinical software program OpenClinica (version 3.1.3.1, OpenClinica). From the imaging reports, the level of diagnostic confidence with CEUS and MRI with a liver-specific contrast agent was graded on a 5-point scale, with a grade of 5 representing a definite or confident diagnosis; 4, a probable or preferred diagnosis; 3, a relatively uncertain diagnosis; 2, an uncertain diagnosis; and 1, no diagnosis. For final analysis, grades of 5 or 4 were regarded as conclusive outcomes, and grades 3, 2, or 1 were regarded as inconclusive outcomes.

Data Analysis and Statistical Methods

The primary analysis was patient based. Descriptive statistics were used to describe the study population and the outcomes of both imaging modalities. The association between categoric variables was presented as numbers and percentages and was tested using the Fisher exact test. The conclusiveness of CEUS and MRI with a liver-specific contrast agent was presented as numbers and percentages. The sensitivity, specificity, ROC AUC value, positive predictive value (PPV), and negative predictive value (NPV) of CEUS were calculated using SPSS software (version 21, IBM). All tests were regarded as statistically significant when $p < 0.05$.

RESULTS

Study Population and Final Diagnosis

From a database of 196 patients who underwent both CEUS and MRI with a liver-specific contrast agent during the study, we identified 181 patients who fulfilled the inclusion criteria. These 181 patients (154 female patients and 17 male patients) were selected for first analysis. The findings of CEUS and MRI with a liver-specific contrast agent were concordant for 132 patients (73%) and discordant for 49 (27%). HPE was performed for 26 patients with discordant findings (53%); two of these patients had findings indeterminate for FNH or HCA. Patients with concordant findings and HPE proven cases (a total of 156 patients) were included for further analysis (Fig. 1). The mean patient age was 38 years (range, 17– 76 years). Patients had either a single lesion (63 patients; 40%) or multiple lesions (93 patients; 60%). Lesion size ranged from 1.6 to 14 cm. The final diagnosis was FNH for 98 patients (63%) and HCA for 58 patients (37%). Women were significantly overrepresented compared with men ($p < 0.001$), with no significant difference in sex ($p = 0.664$) or age ($p = 0.258$) found between patients with FNH and HCA.

Contrast-Enhanced Sonography and MRI

With a Liver-Specific Contrast Agent for Histopathologically Confirmed Cases

Diagnosis was definite (i.e., findings from CEUS and MRI with a liver-specific contrast agent were concordant) for 132 of 156 patients (85%) (Figs. 2 and 3), and diagnostic findings were discordant for the remaining 24 patients (15%). For both CEUS and MRI with a liver-specific contrast agent, all cases had conclusive findings (confidence level, 4 or 5). Further HPE was performed for 26 of 49 patients with discordant findings (53%) (Figs. 4 and 5). For two of the 26 patients who underwent HPE, findings could not clearly differentiate between HCA and FNH. For the remaining 24 patients (10 with HCA and 14 with FNH), the findings of MRI with a liver-specific contrast agent were correct for 21 of 24 patients (87.5%) and those for CEUS were correct for three of 24 patients (12.5%). This difference was statistically significant ($p < 0.05$). The remaining 23 of 49 patients with discordant findings (47%) included 14 patients with inconclusive CEUS findings (confidence level, 1, 2, or 3). MRI with a liver-specific contrast agent was considered the reference standard for clinical decision making and management for these 23 patients. These 23 patients were classified as having HCA (four patients) or FNH (19 patients) with a follow-up of 1–6 years. FNH lesions were unchanged at 1 year of follow-up and were dismissed from further follow-up. HCA lesions showed a gradual decrease in size with cessation of oral contraceptive use and pursuit of weight loss measures.

Conclusiveness of Contrast-Enhanced Sonography and MRI

With a Liver-Specific Contrast Agent

For CEUS, results were conclusive for 167 of 181 patients (92%) and inconclusive for the remaining 14 patients (8%). The results of MRI with a liver-specific contrast agent were conclusive for 180 of 181 patients (99%), with only one initial inconclusive diagnosis (1%) with an uncertain differentiation between HCA and FNH. At repeat MRI examination, the findings for this patient were considered conclusive.

Diagnostic Performance of Contrast-Enhanced Sonography Versus MRI With a Liver-Specific Contrast Agent

For further analysis, only patients with concordant findings (132 patients) and those with HPE-proven cases (24 patients) were considered, for a total of 156 patients. For CEUS, sensitivity and specificity were 85% (49 of 58 cases [49 cases with concordant findings plus nine that were HPE proven]) and 87% (85 of 98 cases [85 cases with concordant findings plus 13 that were HPE proven]), respectively, for the diagnosis of HCA and FNH, with an ROC AUC value of 0.856. The positive predictive value was 79% (49 of 62 cases [cases with concordant findings plus 13 that were HPE proven]), and the negative predictive value was 90% (85 of 94 cases [85 cases with concordant findings plus nine that were HPE proven]).

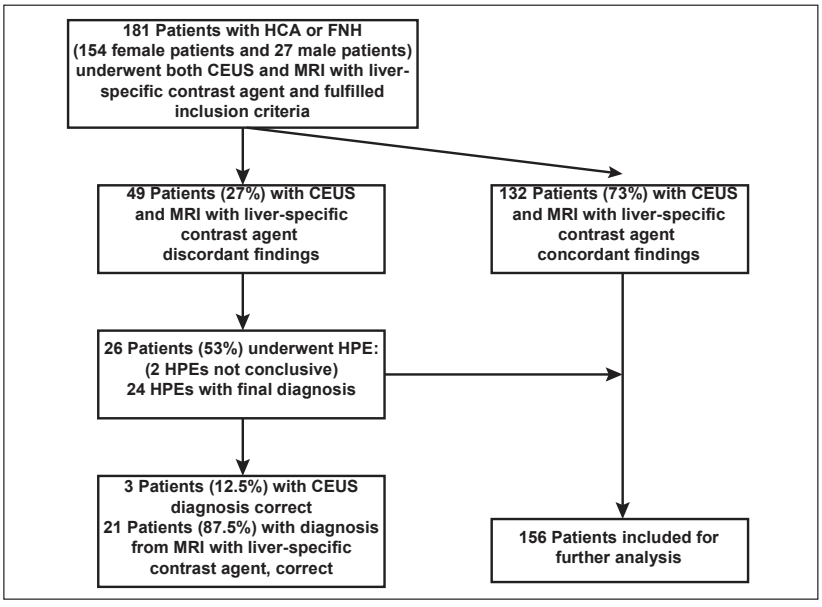

Fig. 1 — Flow diagram summarizing patient sampling and results. HCA = hepatocellular adenoma, FNH = focal nodular hyperplasia, CEUS = contrast-enhanced sonography, HPE = histopathologic examination.

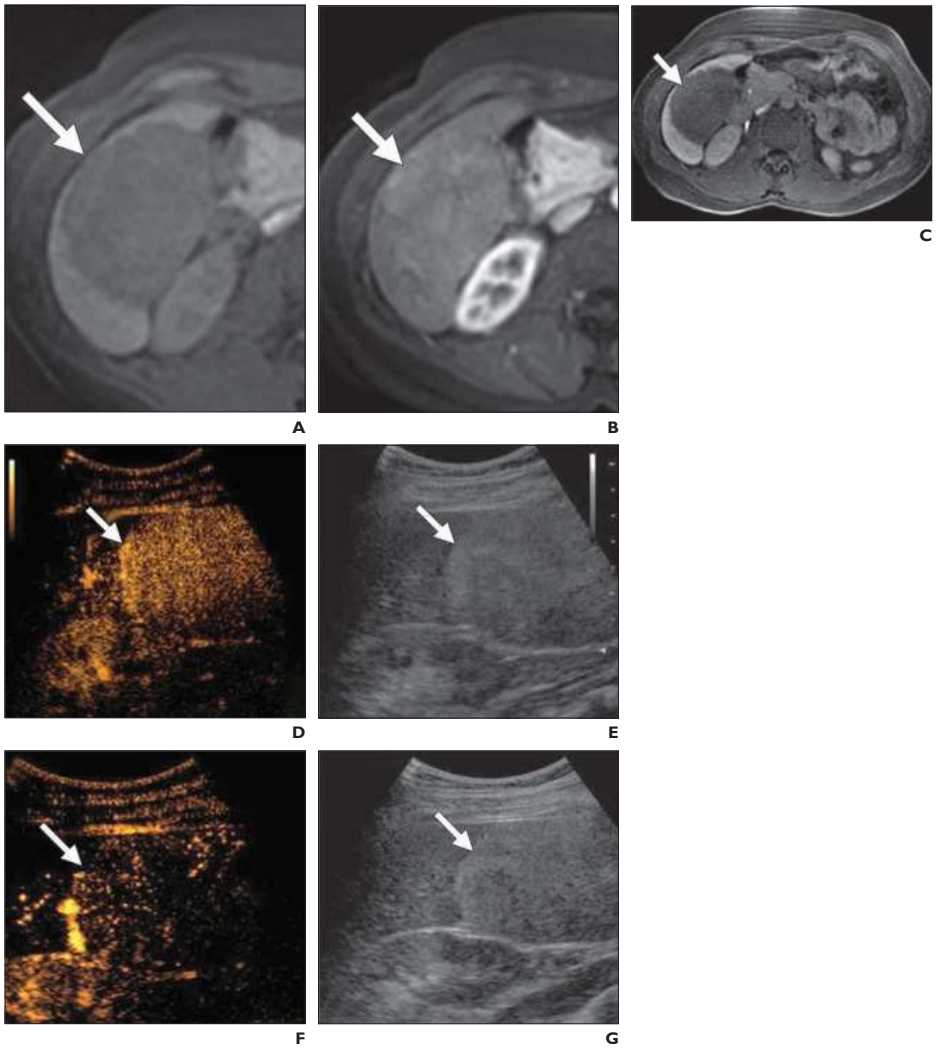

Fig. 2 — 41-year-old-woman with focal liver lesion who underwent contrast-enhanced sonography and MRI with liver-specific contrast agent; findings were concordant for hepatocellular adenoma. **A–C,** Images from MRI with liver-specific contrast agent show solitary lesion in liver segments V and VI (*arrow,* **A–C**). Lesion is hypointense on T1-weighted fat-saturated image (diffuse fatty content of lesion) (**A**), shows enhancement on arterial phase image obtained after IV contrast administration (**B**), and shows marked signal hypointensity on delayed hepatobiliary excretory phase image (**C**). Findings suggest adenoma of hepatocyte nuclear factor 1α– mutated subtype. **D–G,** Contrast-enhanced sonography images show hyperechoic homogeneous lesion with centripetal contrast enhancement (*arrow*, **D** and **F**) and with no washout and no retainment of contrast agent (*arrow*, **E** and **G**). Findings are concordant with MRI findings, resulting in confident diagnosis of adenoma.

For MRI with a liver-specific contrast agent, sensitivity and specificity were 95% (55 of 58 cases [55 cases with concordant findings plus three that were HPE proven]) and 95% (93 of 98 cases [93 cases with concordant findings plus five that were HPE proven]) for the diagnosis of HCA and FNH, respectively, with an ROC AUC value of 0.949. The positive predictive value was 92% (55 of 60 cases [55 cases with concordant findings plus five that were HPE proven]), and the negative predictive value was 97% (93 of 96 cases [93 cases with concordant findings plus three that were HPE proven]).

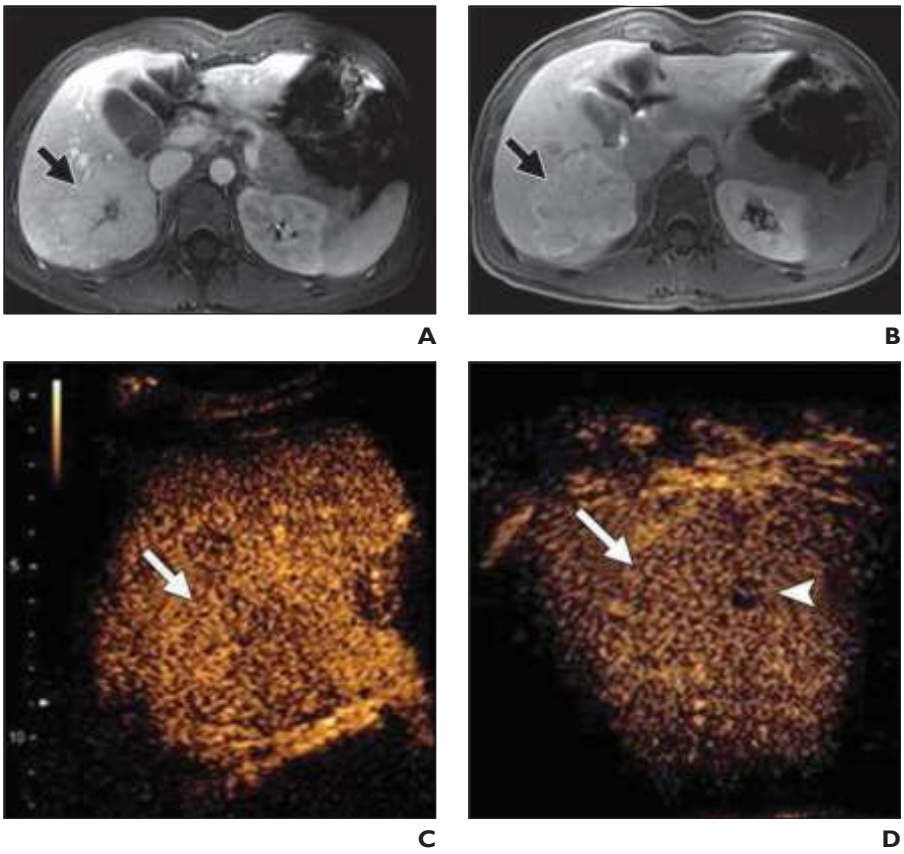

Fig. 3 — 25-year-old woman with focal liver lesion who underwent contrast-enhanced sonography and MRI with liver-specific contrast agent; findings were concordant for focal nodular hyperplasia. **A** and **B,** Images from MRI with liver-specific contrast agent show lesion (*arrow*, **A** and **B**) on right lobe of liver (in liver segments V–VIII) with features typical of focal nodular hyperplasia, including progressive enhancement of central scar (**A**) and hyperintensity on delayed hepatobiliary excretory phase (**B**). **C** and **D,** Contrast-enhanced sonography images show lesion (*arrow*, **C** and **D**) is isodense and heterogeneous compared with surrounding parenchyma. Image obtained after IV contrast administration shows centrifugal filling and retainment of contrast in lesion (**C**), with central scar evident on late phase image (*arrowhead*, **D**).

DISCUSSION

For the diagnosis of FNH and HCA, we found 85% agreement between CEUS and MRI with a liver-specific contrast agent. In addition, for 24 patients with discordant findings that were subsequently pathologically confirmed, MRI with a liver-specific contrast agent provided a correct diagnosis for significantly more patients than did CEUS (21 versus three patients). Another interesting finding is that CEUS resulted in a conclusive diagnosis for 92% of the patients, whereas the diagnosis resulting from MRI with a liver-specific contrast agent was initially conclusive for all but one patient (99%).

To our knowledge, only one other study, performed by Tselikas et al. [24] and involving 54 patients, has compared the added value of MRI performed using a liver-specific contrast agent (i.e., gadobenate dimeglumine) and CEUS with that of inconclusive extracellular gadolinium-based contrast-enhanced MRI (gadolinium-enhanced MRI) for the characterization of FNH and HCA. The authors found that the sensitivity and specificity of these modalities were not statistically different in the diagnosis of HCA and FNH. For lesions larger than 35 mm, although specificities were similar, sensitivity was higher for MRI with a liver-specific contrast agent. Our study was designed to directly compare CEUS with MRI with a liver-specific contrast agent, regardless of the outcome of previous gadolinium-enhanced MRI examination and lesion size. MRI with a liver-specific contrast agent is known to accurately diagnose FNH and HCA, irrespective of lesion size. To achieve a fair comparison, only patients with lesions that were exclusively FNH or HCA were included. Therefore, uncertainty regarding lesion identification in a one-on-one comparison was overcome in cases where patients had multiple different (HCA and FNH) lesions. In addition, in the present study, CEUS and MRI with a liver-specific contrast agent were performed and evaluated by separate readers, so previous personal impressions on lesion interpretation could not influence comparison of the imaging modalities.

The advantage of MRI with a liver-specific contrast agent in comparison with CEUS can be explained by the lack of hepatobiliary excretory properties of the ultrasound contrast medium. Although typical morphologic characteristics, including vascular contrast enhancement patterns, can be assessed by both imaging modalities, the decisive feature in terms of diagnosis with MRI with a liver-specific contrast agent is the ability to differentiate HCA from FNH in the delayed hepatobiliary excretory phase. Previous studies have shown that 20% of FNH lesions lack typical morphologic features, including a central scar, on imaging [13-14]. In addition, a subgroup of HCA (the β-catenin–positive subgroup) may show scarlike features on MRI with gadolinium chelates [25-26]. These cases may pose problems for confident diagnosis with CEUS. On the other hand, few studies have indicated that the inflammatory

subtype of HCA may show isointense or slightly hyperintense signal on delayed phase MRI with a liver-specific contrast agent [9] [27]. One of the three cases missed by MRI with a liver-specific contrast agent in our study was indeed HCA of an inflammatory subtype that was misinterpreted as FNH. Previous reports stated that CEUS is especially valuable in characterizing FNH lesions smaller than 3.5 cm. These small FNH lesions tend to present with classic imaging features more often than do larger lesions [28-29].

By use of MRI with a liver-specific contrast agent, we can combine the functional information (i.e., the hepatobiliary excretion properties) of the lesion with the morphologic information, leading to better diagnosis of FNH and HCA. The use of liver-specific contrast agents in MRI has become standard practice in liver imaging centers around the world. Currently, the two most frequently used agents are gadoxetate disodium (Eovist, Bayer HealthCare [in the United States]]) or gadoxetic acid (Primovist, Bayer Schering Pharma [in Europe]) and gadobenate dimeglumine (MultiHance, Bracco); these agents have extracellular properties but also an affinity for hepatocytes because contrast agent uptake is mediated by OATP1B3 transporters. Furthermore, gadobenate dimeglumine seems to have an advantage over gadoxetate disodium in enhancing visualization of the tumor during vascular phases [12], with no difference observed in the delayed hepatobiliary phase [30]. In a recently published study, gadoxetate disodium proved to have better hepatobiliary excretory properties than did gadobenate dimeglumine, which may result in a better ratio of lesion-to-parenchyma contrast and a more confident reading by the radiologist [31].

The European Medicines Agency approved the use of gadoxetate disodium and gadobenate dimeglumine after a scientific review of gadolinium deposition in the brain and other tissues [32].

Furthermore, the recent approval by the U.S. Food and Drug Administration of the use of microbubbles with the inert gas sulfur hexafluoride and a palmitic acid shell (SonoVue, Bracco) for diagnostic imaging of liver tumors in adults and children represents a potential for CEUS application in liver imaging [33]. We believe that our study may contribute to better and proper application of both imaging modalities in liver imaging performed for the diagnosis of HCA and FNH.

On the basis of our results, we believe that CEUS is less suitable as a stand-alone imaging modality for final diagnosis of FNH and HCA. It may be valuable as an adjunct tool for diagnosis in typical or suggestive cases identified by multiphase CT or gadolinium-enhanced MRI and for follow-up of lesions that have been confirmed as HCA by MRI with a liver-specific contrast agent or HPE. In addition, MRI with a liver-specific contrast agent has the advantage of providing comprehensive evaluation of all lesions, not only for differentiating between HCA and FNH but also for showing features that may be indicative of transformation to HCC in cases of HCA

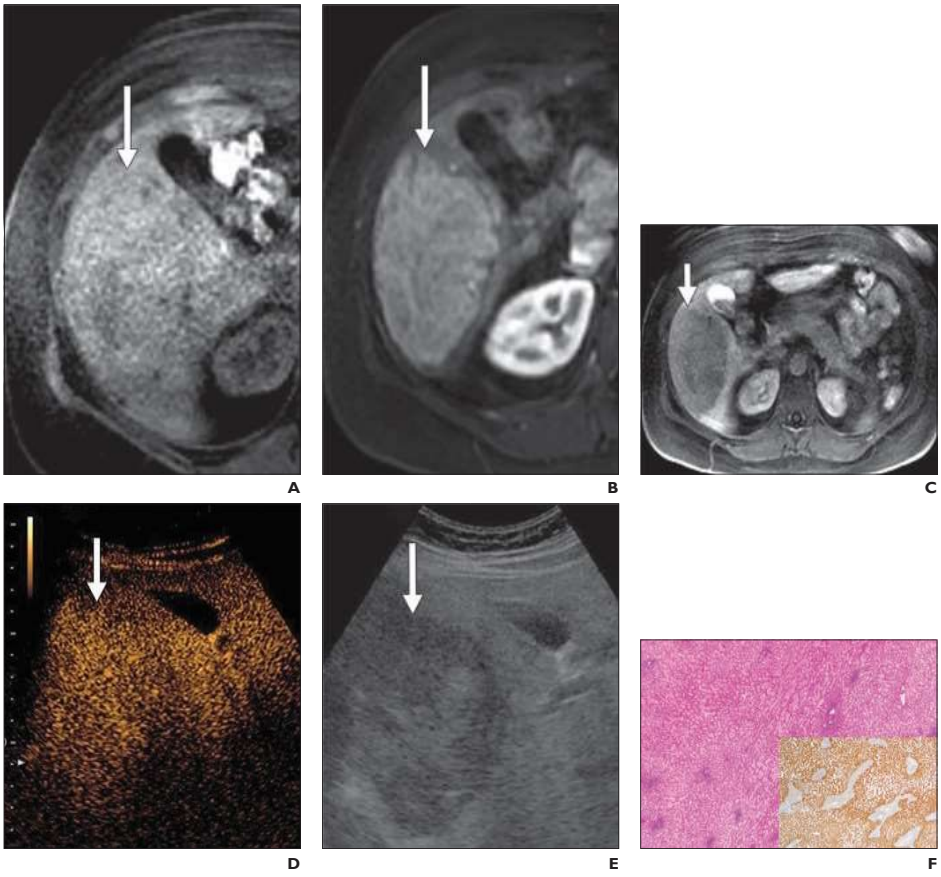

Fig. 4 — 32-year-old woman with large focal liver lesions who underwent contrast-enhanced sonography and MRI performed with liver-specific contrast agent; findings were discordant for hepatocellular adenoma.

A–C, Images from MRI with liver-specific contrast agent show large lesion in liver segments V and VI (*arrow*, **A–C**). Lesion was hypointense on T1-weighted gradient recalled echo sequence with fat saturation (**A**), showed enhancement on arterial phase image obtained after IV contrast administration (**B**), and showed marked hypointensity compatible with hepatocellular adenoma on delayed hepatobiliary excretory phase image (**C**).

D and **E,** Contrast-enhanced sonography images show that lesion (*arrow*, **D** and **E**) is hypoechoic in relation to surrounding parenchyma with suggestion of central scar (**D**) with centripetal contrast filling, homogeneity with retainment, and no washout (**E**). Lesion was interpreted as benign lesion that was probably focal nodular hyperplasia considering suggestive findings of central scar and contrast retainment.

F, Photomicrograph (H and E, ×25) from histopathologic examination of biopsy specimen of lesion proved adenoma of inflammatory subtype, with proliferation of benign hepatocytes, areas of sinusoidal dilatation, and inflammatory infiltrates. Photomicrograph (×100) (*inset*) shows C-reactive protein immunohistochemical staining with characteristic positivity for C-reactive protein.

on follow-up MRI. An increase in size or a change in enhancing properties of HCA on follow-up CEUS evaluation should warrant further evaluation by MRI.

The present study has some limitations, especially its retrospective analysis and the relatively limited number of pathologically confirmed diagnoses. Currently, dedicated MRI with a liver-specific contrast agent that results in a confident diagnosis is considered confirmative of FNH and HCA at centers with radiologists with expertise in liver imaging [6-7] [12-14]. Therefore, it would be impractical and possibly unethical to biopsy all lesions, despite a confident diagnosis provided by MRI with a liver-specific contrast agent. Another potential limitation might be selection bias. Because the analysis was performed retrospectively, patients were selected on the basis of final diagnoses of FNH or HCA. False-positive outcomes in the case of other diagnoses, such as liver hemangioma, were excluded, which may have culminated in an overestimated specificity for FNH or HCA. However, the purpose of the present study was to assess the value of CEUS compared with that of MRI with a liver-specific contrast agent, and we believe that our study design serves this purpose well.

In conclusion, CEUS has fair agreement with MRI with a liver-specific contrast agent for the diagnosis of HCA and FNH. In addition, MRI with a liver-specific contrast agent is superior to CEUS in cases with discordant findings with a pathologically confirmed final diagnosis.

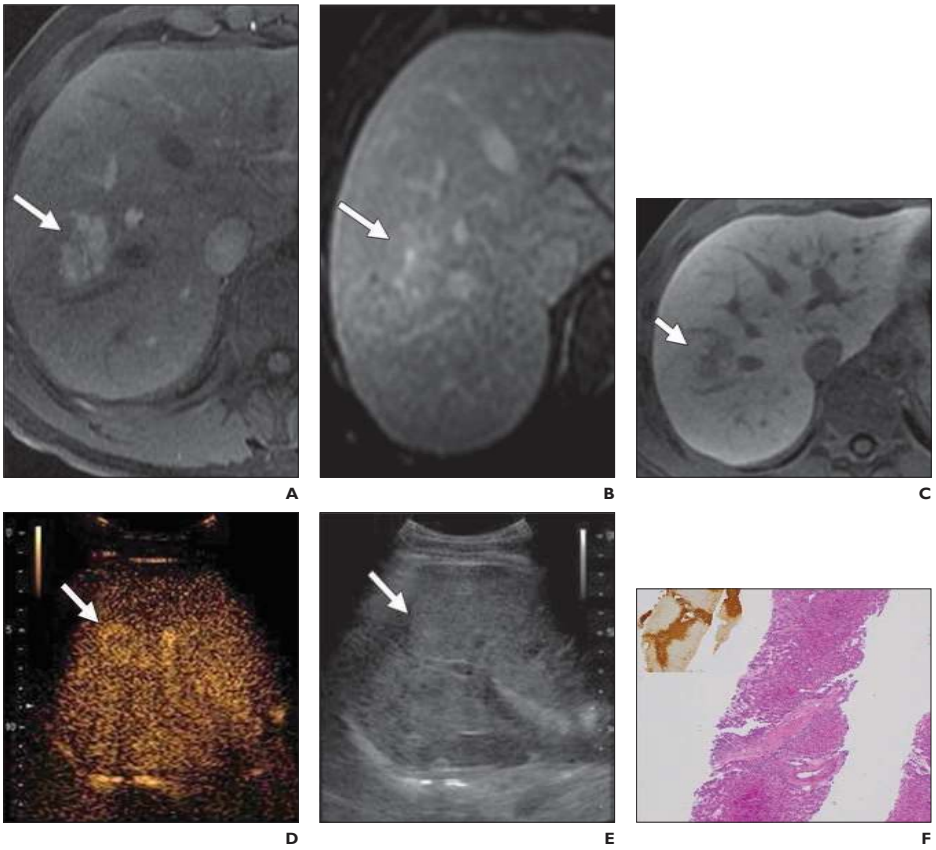

Fig. 5 — 24-year-old man with focal liver lesion who underwent contrast-enhanced sonography and MRI performed with liver-specific contrast agent; findings were discordant for focal nodular hyperplasia (FNH).

A–C, Images from MRI with liver-specific contrast agent show 4-cm large lesion found in right lobe (liver segments VII and VIII) (*arrows*). Lesion shows enhancement on arterial phase image (**A**) and late central scar enhancement on portal venous phase image (**B**). Lesion appears hypointense on hepatobiliary excretion phase image (**C**), and findings were therefore interpreted as hepatocellular adenoma.

D and **E,** Contrast-enhanced sonography images show isoechogenic lesion with central artery and scar (*arrows*), including centrifugal filling of contrast material on arterial phase image (**D**) and mildly hyperechogenic lesion on late phase image (**E**). Diagnostic confidence resulted in grading of lesion as FNH.

F, Photomicrograph (H and E, ×200) from histopathologic examination of biopsy specimen revealed typical features of FNH, such as large dystrophic arteries with thickened and narrowed lumens. Photomicrograph (×100) (*inset*) with glutamine synthetase immunostaining shows characteristic maplike pattern of glutamine synthetase. On retrospective review of MR images, lesion appears partly hypointense centrally on hepatobiliary excretion phase image shown in **C**; contrast excretion

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