

Central vascular structures as a characteristic finding of regenerative nodules using hepatobiliary phase gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced MRI and arterial dominant phase contrast-enhanced US

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Abstract

Objective We investigated the characteristic findings of regenerative nodules (RNs) for differentiating early hepatocellular carcinoma (HCC) from high-grade dysplastic nodules (HGDNs) using magnetic resonance imaging (MRI) with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA; EOB-MRI) and contrast-enhanced ultrasonography (CEUS) in patients with chronic liver disease.

Subjects and methods Pathologically confirmed lesions (100 early HCCs, 7 HGDNs, and 20 RNs with a maximum diameter of more than 1 cm and mean maximal diameters of 15.5, 15.1, and 14.8 mm, respectively) were enrolled in this retrospective study. The signal intensities of these lesions during the hepatobiliary phase of EOB-MRI were investigated, and findings characteristic of RNs using this modality were also evaluated using CEUS.

Results Ninety-eight of the 100 early HCCs that were hypo-intense ($n = 95$), iso-intense ($n = 2$), or hyper-intense ($n = 1$) and the seven HGDNs that were hypo-intense ($n = 6$) or hyper-intense ($n = 1$) during the hepatobiliary phase of EOB-MRI exhibited centripetal vessels during the arterial dominant phase of CEUS, although one early HCC that was hypo-intense exhibited both centrifugal and centripetal vessels. Eighteen of the 20 RNs and one early HCC that were hyper-intense with a small central hypo-intensity and the remaining two RNs that were hyper-intense on EOB-MRI exhibited centrifugal vessels during the arterial dominant phase of CEUS. The small central hypo-intense area corresponded to central vascular structures in the lesion, such as the hepatic artery and portal vein running from the center to the periphery, when viewed using CEUS.

Conclusion Central vascular structures may be a characteristic finding of RNs when observed during the hepatobiliary phase of EOB-MRI and the arterial dominant phase of CEUS.

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Keywords Magnetic resonance imaging with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid · Contrast-enhanced ultrasonography · Regenerative nodule · Early hepatocellular carcinoma · High-grade dysplastic nodule

Introduction

HCC develops in a multistep fashion consisting of regenerative nodules (RNs), low-grade dysplastic nodules (LGDNs), high-grade dysplastic nodules (HGDNs), early hepatocellular carcinoma (HCC), and finally progression to advanced HCC [1–3]. Early HCC and HGDNs should be regarded as malignant or premalignant lesions [4, 5], and

should therefore be treated. LGDNs are also considered to be premalignant; however, even using a resected specimen, the pathological diagnosis of a premalignant lesion can be difficult [4]. In contrast, RNs are not considered to be neoplastic lesions, but rather hyperplastic lesions with monoclonal proliferation of hepatocytes and no cell atypia [6], and only require follow-up care.

With the progression of cirrhosis, the echo signals in the liver parenchyma become heterogeneous, preventing the identification of these small hepatic lesions, including HCC, using conventional ultrasonography (US) [7]. Fusion imaging combining conventional US and hepatobiliary phase magnetic resonance imaging (MRI) with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA, Primovist; Bayer Schering Pharma AG, Berlin, Germany; EOB-MRI) as the reference standard can help to select targeted small hepatic lesions that appear as hypo-echoic or hyper-echoic lesions using conventional US [8]. Biopsies from these small hepatic lesions can be performed precisely under guidance using this fusion imaging [8].

It is important to discriminate benign hepatic lesions such as RNs from other malignant lesions so as to avoid unnecessary repeated tumor biopsies and for suggesting that only follow-up care is needed in patients with chronic liver disease. However, few reports have focused on the specific imaging of RNs using the hepatobiliary phase of EOB-MRI in patients with chronic liver disease [3, 9]. Recently, we reported that the tumor vessel patterns (centripetal or centrifugal vessels) observed during arterial dominant phase contrast-enhanced US (CEUS) using a perflubutane microbubble contrast agent (Sonazoid; Daiichi Sankyo, Tokyo, Japan) may be useful for differentiating RNs from early HCC or HGDNs. All (100 %) RNs showed centrifugal vessels; in contrast, most early HCCs (98 %) and HGDNs (100 %) showed centripetal vessels [10]. The presence of centrifugal vessels might correspond to the presence of the hepatic artery and the portal vein accompanied by the hepatic artery [10].

In the present study, we selected hepatic lesions with a maximum diameter of more than 1 cm and investigated the characteristic findings of RNs compared with those of early HCCs and HGDNs using the hepatobiliary phase of EOB-MRI and arterial dominant phase CEUS findings to evaluate the internal vascular structures of these hepatic lesions in patients with chronic liver disease.

Subjects and methods

Patients

Institutional review board approval and informed consent from all the patients were obtained for this retrospective

study. At our institution, 314 consecutive chronic liver disease patients with small hepatic nodules underwent conventional US, contrast-enhanced CT, EOB-MRI, fusion imaging combining conventional US with the hepatobiliary phase of EOB-MRI, and a tumor biopsy between January 2010 and November 2015. In cases with severe liver dysfunction, the uptake of Gd-EOB-DTPA in the normal hepatocytes was insufficient, making it difficult to detect hepatic lesions during the hepatobiliary phase of EOB-MRI. Therefore, we excluded patients with Child–Pugh grade C liver cirrhosis from the present study. Iso-echoic nodules on conventional US and hepatic lesions less than 1 cm in maximum diameter were also excluded because of the difficulty in achieving adequate fusion images to provide guidance for biopsies of the lesions and the biopsy itself because of a small target area. Lesions with a typical vascular pattern on contrast-enhanced CT were diagnosed as advanced HCC using the criteria recommended by the American Association for the Study of Liver Disease [11], and these lesions were excluded from the study because we targeted early HCCs, HGDNs, and RNs. Lesions without a typical vascular pattern on contrast-enhanced CT but that were pathologically diagnosed as advanced HCC were also excluded from the study because most of these lesions exhibited hypo-intensity during the hepatobiliary phase of EOB-MRI. We also excluded lesions for which a reliable pathological diagnosis could not be obtained because of a small biopsy specimen from the lesion or a “no-hit” result for the target lesion during a percutaneous biopsy. Finally, 101 patients with 127 hepatic lesions were diagnosed as having early HCCs, HGDNs, or RNs and were eligible for inclusion in the present study.

Table 1 shows the clinical characteristics of the patients with early HCC, HGDN, and RN lesions who were enrolled in this study. None of the patients had Budd–Chiari syndrome. The mean maximal diameters (mean \pm SD) of the early HCCs, HGDNs, and RNs were 15.5 ± 4.1 , 15.1 ± 5.4 , and 14.8 ± 4.9 mm, respectively. No significant differences were observed among the groups when examined using a Welch *t* test. The mean ages (mean \pm SD) of the patients with early HCCs, HGDNs, and RNs were 70.6 ± 8.3 , 66.9 ± 10.5 , and 68.5 ± 10.6 years, respectively. No significant differences were observed among the groups.

Pathological diagnosis

After confirming the location of the HCC lesions using fusion imaging combining conventional US and the hepatobiliary phase of EOB-MRI, at least two samples were obtained from each of the nodules using a 21-gauge fine-needle biopsy needle (SONOPSY; Hakko, Tokyo, Japan) or an 18-gauge biopsy needle (Biopsy-Cut; Bard,

Table 1 Clinical characteristics of enrolled patients with early HCC, HGDN, or RN lesions

Characteristics	Early HCC	HGDN	RN
No. of patients	81	7	13
Single lesion/two lesions/three lesions	63/14/3	7/0/0	8/3/2
Age (mean, range; in years)	70.6, 55–87	66.9, 51–81	68.5, 43–86
Sex			
Male/female	53/28	5/2	8/5
Etiology of HCC			
Hepatitis B/hepatitis C/hepatitis B and C/alcohol abuse/PBC	5/66/2/8/0	0/6/0/1/0	3/6/0/2/2
Child–Pugh classification			
Class A/B	76/5	6/1	11/2
Diameters of lesions (mean \pm SD, range; in mm)	15.5 \pm 4.1, 10–28 (<i>n</i> = 100)	15.1 \pm 5.4, 10–23 (<i>n</i> = 7)	14.8 \pm 4.9, 10–25 (<i>n</i> = 20)
B-mode imaging findings			
Echogenicity, hypo-echoic/hyper-echoic	60/40	6/1	17/3
Hypo-echoic rim, presence/absence	2/98	0/7	0/20
Mosaic pattern, presence/absence	0/100	0/7	0/20
Nodule in nodule, presence/absence	4/96	0/7	0/20

Early HCC early hepatocellular carcinoma, *HGDN* high-grade dysplastic nodule, *RN* regenerative nodule, *PBC* primary biliary cirrhosis

Covington, GA) under US guidance to ensure an accurate histological diagnosis [8]. A biopsy of the adjacent liver tissue was also performed to compare the histological findings between the hepatic nodules and the adjacent liver. The International Consensus Group for Hepatocellular Neoplasia (ICGHN) recently arrived at a consensus regarding the pathologic criteria for early HCCs [1, 12]. The ICGHN stated that the presence of stromal invasion or tumor cell invasion into the intratumoral portal tracts [13] should be recognized as the most important pathologic finding for the diagnosis of early HCCs. First, the presence of hyper-cellularity, characterized by an increased nuclear cytoplasmic ratio and cell atypia (such as deformity of the nuclei), was evaluated using hematoxylin-eosin staining, and architectural alterations in the thin trabecular structure and acinus were evaluated using silver impregnation. The diagnosis of stromal invasion is subjective and may require the assistance of Victoria blue staining [14] and immunohistochemical stains (cytokeratin 7) [14, 15] to differentiate it from pseudo-invasion. HGDNs exhibit cell atypia, but invasion of the portal space is not present [15]. In contrast, RNs appear as a benign monoclonal proliferation of hepatocytes without cell atypia [6], and an abnormal artery, as seen in focal nodular hyperplasia (FNH), is not present [16].

Eighty-one patients with 100 lesions were diagnosed as having early HCC, seven patients with seven lesions were diagnosed as having HGDN, and 13 patients with 20 lesions were diagnosed as having RN. Among the cases with RN lesions, the size and enhancement patterns

observed on the CEUS images or the hepatobiliary phase of the EOB-MRI images did not change during a follow-up period of at least 12 months.

Imaging methods

MR imaging

MR imaging was performed using a 1.5-T whole-body imager (Avant; Siemens Medical System, Erlangen, Germany). Simultaneously with the arrival of Gd-EOB-DTPA in the abdominal aorta at the level of the celiac artery, a power injector (Spectris Solaris EP; MEDRAD, Bayer Schering Pharma AG, Berlin, Germany) was used to inject 0.1 mmol/kg of Gd-EOB-DTPA at 1 mL/s through a catheter placed in the antecubital vein, followed by flushing with 20 mL of sterile saline solution at 2 mL/s. Arterial phase, portal phase, and late phase scanning were performed at 13, 70–85, and 180 s, respectively, after initiation of the contrast injection, and hepatobiliary phase scanning was performed at 20 min after initiation of contrast injection. The images were obtained using fat-suppressed volumetric interpolated breath-hold examination (FS VIBE) T1-weighted sequences (TR, 6.2 ms; TE, 3.15 ms; flip angle, 20°; bandwidth, 260 Hz/pix; matrix, 166 \times 320; acquisition time, 20 s). In addition, a fast low-angle shot (FLASH) T1-weighted sequence (TR, 115 ms; TE, 4.76 ms; flip angle, 70°; bandwidth, 260 Hz/pix; matrix, 192 \times 256; acquisition time, 20 s \times 3) was performed.

US imaging

Conventional US and CEUS procedures

First, we assessed the detection of HCC lesions using the LOGIQ E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) with native tissue harmonic gray-scale imaging using a convex probe with a frequency of 2–5 MHz or 1–6 MHz and a micro-convex probe with a frequency of 2–5 MHz (hereafter referred to as conventional US). As previously reported [10], a 0.2-mL dose of Sonazoid was injected into an antecubital vein at 0.2 mL/s via a 24-gauge cannula followed by 2 mL of 5 % glucose after the Sonazoid injection. CEUS images were acquired during three contrast phases, consisting of an arterial dominant phase (10–50 s after initiation of injection), a portal dominant phase (80–120 s after initiation of injection), and a post-vascular phase (10 min after initiation of injection).

Fusion imaging combining US and hepatobiliary phase of EOB-MRI

Fusion imaging was performed before CEUS and the biopsies. As mentioned in previous reports [8, 10], after successful registration of the conventional US and MR images obtained during the hepatobiliary phase of EOB-MRI, the results of real-time ultrasound scanning were then viewed simultaneously with the corresponding multiplanar reconstruction slice from the pre-acquired volumetric MR DICOM data. These procedures were also used to perform fusion imaging, in which color Doppler US or CEUS was combined with the hepatobiliary phase of EOB-MRI images.

Image analysis

Evaluation of intensity of hepatic lesions during hepatobiliary phase of EOB-MRI

The signal intensity of the lesions was recorded as hypo-intense, iso-intense, hyper-intense, or hyper-intense with a small central hypo-intense area, compared with the

surrounding liver parenchyma. In cases where mixed intensity was present, the intensity of the largest area was selected. For example, if the hypo-intense areas were larger than the hyper-intense or iso-intense areas, the signal intensity of the lesion was considered to be hypo-intense. However, when a small central hypo-intense area was definitely seen within a hyper-intense area, we considered the signal intensity of this lesion to be hyper-intense with a small central hypo-intense area.

Evaluation of intensity of hepatic lesions during T1-weighted sequence of unenhanced MRI

For all RNs and for HGDNs and early HCCs that exhibited hyper-intensity during the hepatobiliary phase of EOB-MRI, the signal intensities of the lesions were also evaluated during a T1-weighted sequence of unenhanced MRI.

Evaluation of tumor vessels and vascularity of hepatic lesions on arterial dominant phase CEUS

We evaluated images of the tumor vessels and classified the appearance of the tumor vessels during the arterial dominant phase into two patterns: centripetal vessels (running from the periphery to the center) and centrifugal vessels (running from the center to the periphery).

We also evaluated the images for the enhancement patterns during the arterial dominant phase and classified the patterns into five categories relative to the enhancement pattern in the surrounding liver parenchyma as follows: hypovascularity (the whole lesion), transient hypovascularity (the whole or a portion of the lesion) and subsequent isovascularity (the whole lesion), isovascularity (the whole lesion), partial hypervascularity (less than half of the lesion), and hypervascularity (the whole lesion or more than half of the lesion).

Evaluation of vascularity of post-vascular phase CEUS

The enhancement patterns of the lesion during the post-vascular phase were classified into three categories: iso-

Table 2 Hepatobiliary phase EOB-MRI findings for early HCC, HGDN, or RN lesions ($n = 127$)

Hepatobiliary phase EOB-MRI findings	No. of lesions (%)		
	Early HCC ($n = 100$)	HGDN ($n = 7$)	RN ($n = 20$)
Hypo-intense area	96 (96 %)	6 (86 %)	0 (0 %)
Iso-intense area	2 (2 %)	0 (0 %)	0 (0 %)
Hyper-intense area	1 (1 %)	1 (14 %)	2 (10 %)
Hyper-intense with small central hypo-intense area	1 (1 %)	0 (0 %)	18 (90 %)

EOB-MRI MRI with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid, *Early HCC* early hepatocellular carcinoma, *HGDN* high-grade dysplastic nodule, *RN* regenerative nodule

echoic (the whole lesion), partial hypo-echoic (hypo-echoic in less than half of the lesion and iso-echoic in the remaining area), and hypo-echoic (the whole lesion), compared with the surrounding liver parenchyma.

Image evaluation

The image evaluations were performed independently by two experienced radiologists who were blinded to the final diagnoses; both radiologists had at least 5 years of clinical experience performing sonography and MRI. The first and second radiologists reviewed all the sonographic images including the conventional US images and fusion imaging findings recorded on still images and cine clips. The third and fourth radiologists reviewed all the hepatobiliary phase of EOB-MRI images using a commercially available viewer system or a picture archiving and communication system (Synapse; Fujifilm Medical, Tokyo, Japan). Both groups of readers then met to arrive at a consensus regarding the image evaluation.

Statistical analysis

The Welch *t* test was used to compare the tumor size and patient age between each category of hepatic lesion (early HCC, HGDN, and RN). The sensitivity, specificity, and accuracy were calculated. A value of $P < 0.05$ was considered to indicate a statistically significant difference. The Ekuseru-Toukei 2012 software package (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for the statistical analysis.

Results

Hepatobiliary phase of EOB-MRI findings

Table 2 shows the hepatobiliary phase of EOB-MRI findings for early HCCs, HGDNs, and RNs. Ninety-six (96 %) of the 100 early HCCs were hypo-intense (Figs. 1a, 2a), two (2 %) were iso-intense, one (1 %) was

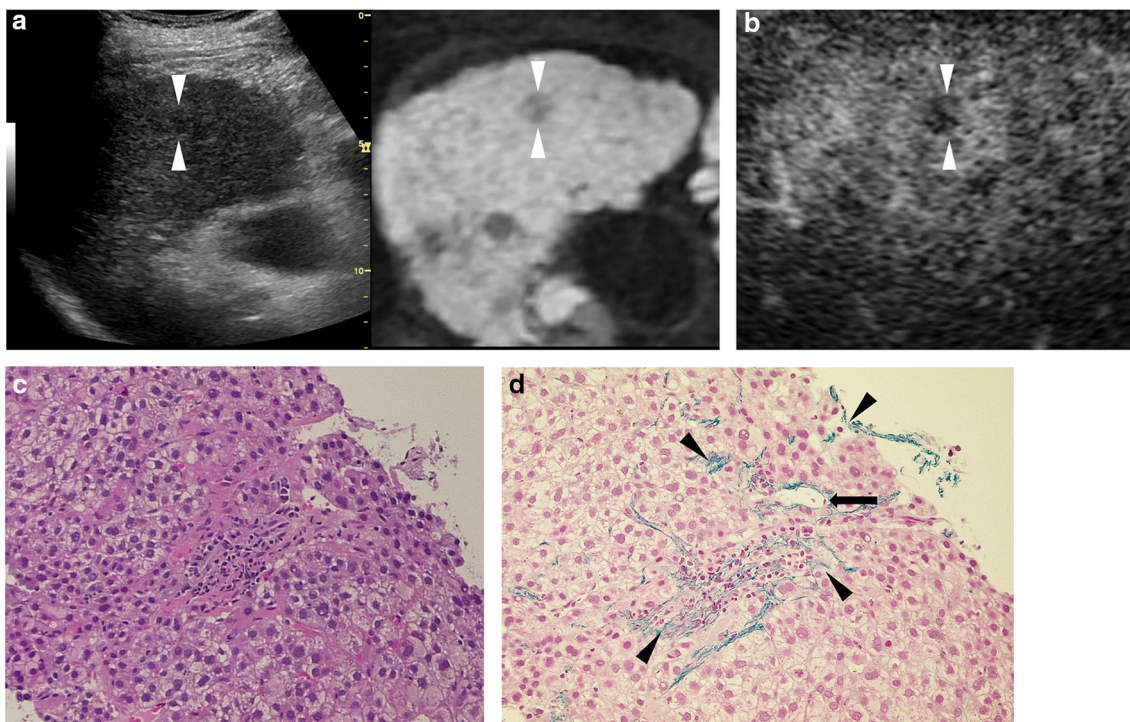


Fig. 1 A 75-year-old man with hepatitis C-related liver cirrhosis and an early HCC lesion (maximum diameter, 13 mm) in segment V. **a** Fusion images combining conventional US (left side) and the hepatobiliary phase of EOB-MRI as a reference (right side) on a single screen. The hepatobiliary phase of EOB-MRI shows a hypo-intense area in segment V (arrowheads). The fusion image shows the targeted early HCC lesion, which appears as an ill-defined hypo-echoic lesion on conventional US (arrowheads). **b** Arterial dominant phase CEUS image showing transient hypovascularity and centripetal

vessels. The arrowheads seen in **a**, **b** indicate the margin of the lesion. **c** Hematoxylin–eosin staining reveals slight hyper-cellularity with increased nuclear cytoplasmic ratio and deformed nuclei. However, stromal (portal tract) invasion is not seen clearly. **d** Victoria blue staining, showing elastic fibers surrounding the portal tract in blue, reveals stromal (portal tract) invasion compatible with a diagnosis of early HCC. The arrow indicates the portal vein, and the arrowheads indicate the portal tract; cancer cells are present within the portal tract

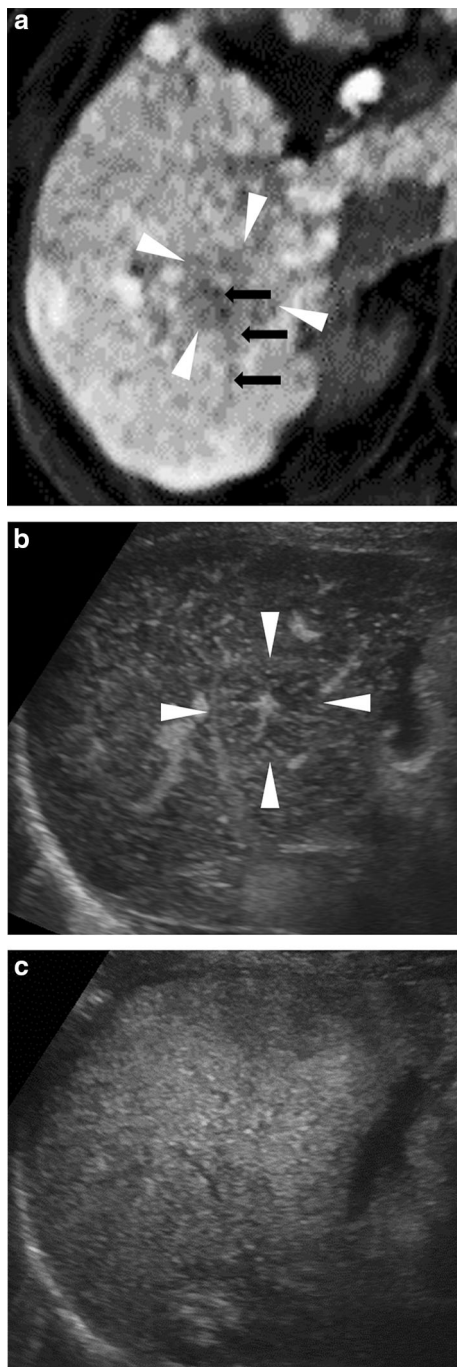


Fig. 2 A 70-year-old man with hepatitis C-related liver cirrhosis and an early HCC lesion (maximum diameter, 20 mm) in segment VI. **a** The hepatobiliary phase of EOB-MRI shows a hypo-intense area in segment VI. *Arrowheads* indicate the margin of the lesion, and the *arrows* indicate vascular structures such as the hepatic artery and portal vein penetrating the lesion. **b** An arterial dominant phase CEUS image shows isovascularity and both centrifugal and centripetal vessels. **c** A post-vascular phase CEUS image shows an iso-echoic area

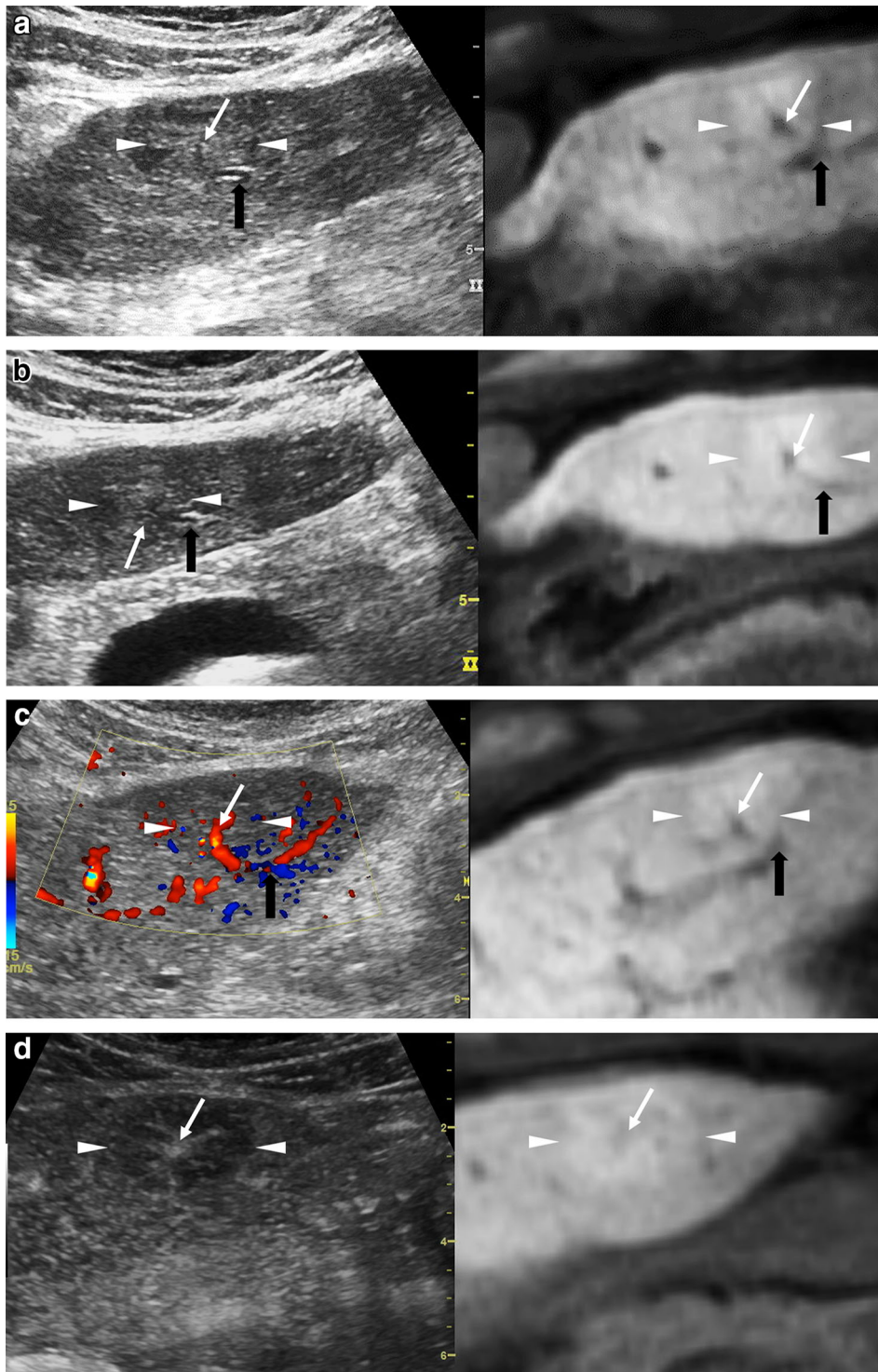
hyper-intense, and one (1 %) was hyper-intense with a small central hypo-intense area when viewed during the hepatobiliary phase of EOB-MRI (Table 2). Six (86 %) of

Fig. 3 A 70-year-old woman with hepatitis C-related liver cirrhosis and a RN (maximum diameter, 20 mm) in segment III. **a, b** Fusion images combining conventional US (*left side*) and the hepatobiliary phase of EOB-MRI as a reference (*right side*) on a single screen. The hepatobiliary phase of EOB-MRI shows a hyper-intense area with a very small central hypo-intense portion (*white arrow*) in segment III (*arrowheads*). The fusion image shows the targeted RN lesion, which appears as an ill-defined slightly hyper-echoic lesion with a very small central hypo-anechoic area (*white arrow*) on conventional US (*arrowheads*). Each very small central hypo-intense portion on the hepatobiliary phase of EOB-MRI and very small central hypo-anechoic area on conventional US is continuously connected with an adjacent portal vein (*black arrow*). **c** Fusion imaging combining a color Doppler US image (*left side*) and the hepatobiliary phase of EOB-MRI as a reference (*right side*) on a single screen. A small central hypo-intense portion (*white arrow*) on the hepatobiliary phase of EOB-MRI and central color flow (*white arrow*) on color Doppler US are connected to an adjacent portal vein (*black arrow*). **d** Fusion imaging combining an arterial dominant phase CEUS image (*left side*) and the hepatobiliary phase of EOB-MRI as a reference (*right side*) on a single screen. Arterial dominant phase CEUS images show transient hypovascularity of the lesion with a centrifugal hepatic artery running from the center to the periphery (spoke wheel pattern) (*arrow*) that corresponds to a hyper-intense area with a very small central hypo-intense portion on the hepatobiliary phase of EOB-MRI. **e–j** Arterial dominant phase CEUS images show a hepatic artery (*small arrowhead*) running from the periphery to the center (**e, f**), and a centrifugal hepatic artery running from the center to the periphery (centrifugal vessels) (*arrow*) (**f–j**). Subsequent arterial dominant phase CEUS images show both the hepatic artery and portal vein (*curved arrow*) (**g, h, j**) accompanying the hepatic artery and a centrifugal direction (**g–j**). This lesion appeared as transient hypovascularity; isovascularity was subsequently observed during the arterial dominant, portal dominant, and post-vascular phases (data not shown). The *arrowheads* seen in images **c–j** indicate the margin of the lesion. **k** Hematoxylin–eosin staining reveals hyperplasia of the parenchymal nodules, with no cell atypia, and slight proliferation of hepatocytes, which is consistent with a pathological diagnosis of RN. **l** Silver impregnation shows hyperplasia of the parenchyma with a normal reticulin fiber, which is consistent with a pathological diagnosis of RN. Neither the conventional US findings nor the EOB-MRI findings changed over a follow-up period of more than 3 years

the seven HGDNs were hypo-intense, and one (14 %) was hyper-intense (Table 2). Eighteen (90 %) of the 20 RNs were hyper-intense with small central hypo-intense areas (Fig. 3a–d), and two (10 %) were hyper-intense (Fig. 4a). In each of the two lesions, the maximum diameter was 10 mm (Table 2).

Evaluation of intensity during unenhanced T1-weighted sequences for hepatic lesions exhibiting hyper-intensity during hepatobiliary phase of EOB-MRI

Two early HCCs, one HGDN, and all 20 RNs exhibited hyper-intensity alone or hyper-intensity with a small central area of hypo-intensity during the hepatobiliary phase of EOB-MRI. These two early HCCs, one HGDN, and three



(15 %) of the 20 RNs showed hyper-intensity during the T1-weighted sequence before contrast enhancement, whereas the remaining 17 RNs were iso-intense.

In two early HCCs, one HGDN, and six of the 20 RNs, central vascular structures connected with the adjacent

portal vein were not detected during unenhanced T1-weighted sequences, whereas the remaining 14 RNs exhibited central vascular structures connected to the adjacent portal vein during unenhanced T1-weighted sequences.

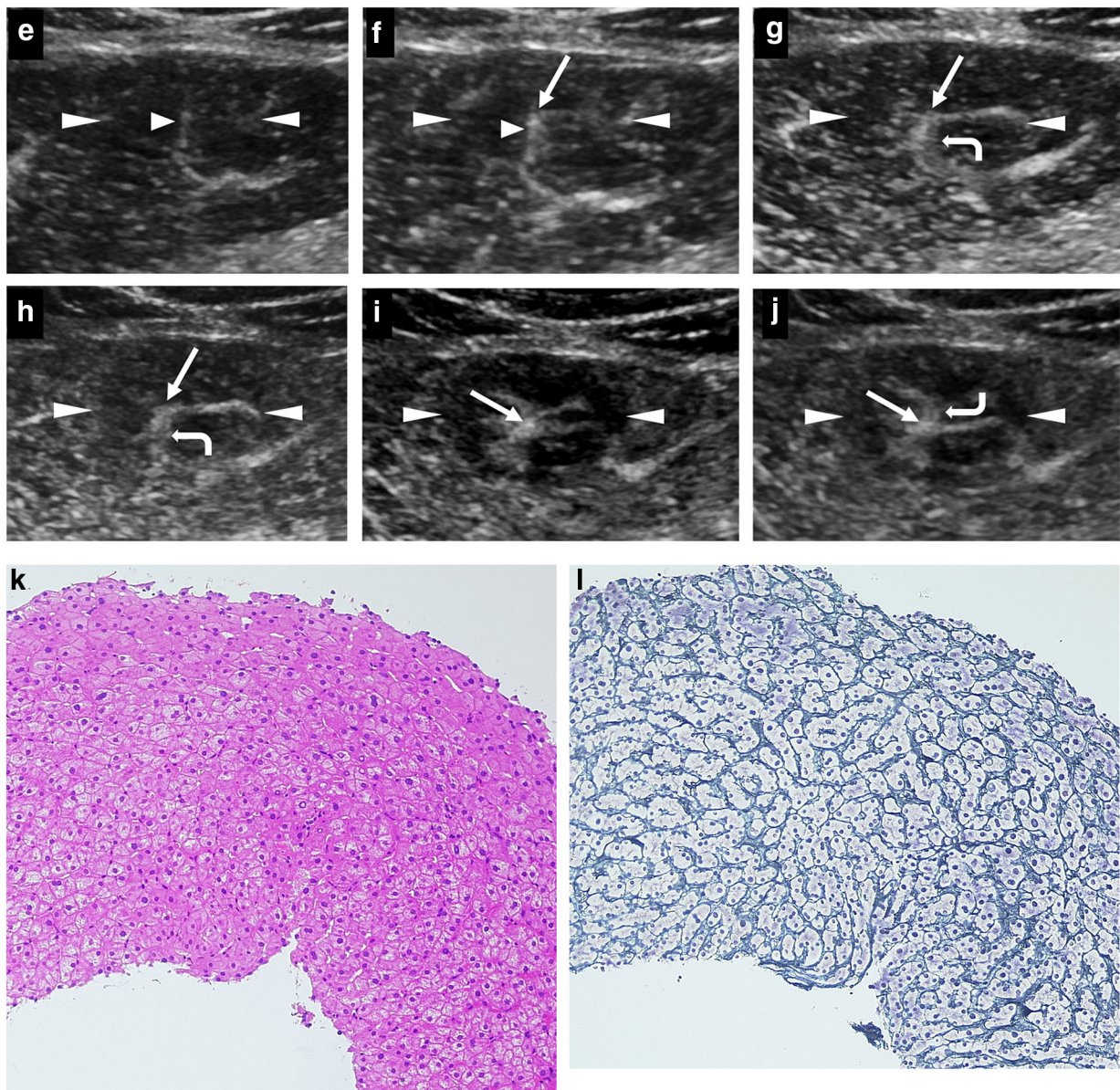


Fig. 3 continued

Findings of vessel patterns and vascularity during arterial dominant phase and echogenicity during post-vascular phase CEUS

Table 3 shows the arterial dominant phase CEUS findings for early HCCs, HGDNs, and RNs. Ninety-eight (98 %) of the 100 early HCCs exhibited centripetal vessels (running from the periphery to the center) (Fig. 1b) and were iso-echoic ($n = 87$), partially hypo-echoic ($n = 8$), or hypo-echoic ($n = 3$) during the post-vascular phase. One lesion exhibited both centrifugal (running from the center to the periphery) and centripetal vessels during the arterial dominant phase (Fig. 2b) and was iso-echoic during the post-vascular phase (Fig. 2c). The remaining one lesion

exhibited centrifugal vessels during the arterial dominant phase and was iso-echoic during the post-vascular phase. All (100 %) of the seven HGDNs exhibited centripetal vessels and were iso-echoic during the post-vascular phase. All (100 %) of the 20 RNs exhibited centrifugal vessels (Figs. 3d–j, 4b) and were iso-echoic during the post-vascular phase.

Findings for combined arterial dominant phase CEUS and hepatobiliary phase of EOB-MRI

Table 4 shows the hepatobiliary phase of EOB-MRI and the CEUS findings for early HCCs, HGDNs, and RNs. Ninety-eight of the 100 early HCCs that were hypo-intense

Table 3 Arterial dominant phase CEUS findings for early HCC, HGDN, or RN lesions ($n = 127$)

Arterial dominant phase CEUS findings	No. of lesions (%)		
	Early HCC ($n = 100$)	HGDN ($n = 7$)	RN ($n = 20$)
Centripetal vessels			
Hypovascular	1 (1 %)	0 (0 %)	0 (0 %)
Transient hypovascular	43 (43 %)	7 (100 %)	0 (0 %)
Isovascular	22 (22 %)	0 (0 %)	0 (0 %)
Partial hypervascular	29 (29 %)	0 (0 %)	0 (0 %)
Hypervascular	3 (3 %)	0 (0 %)	0 (0 %)
Total	98 (98 %)	7 (100 %)	0 (0 %)
Centripetal and centrifugal vessels			
Isovascular	1 (1 %)	0 (0 %)	0 (0 %)
Centrifugal vessels			
Transient hypovascular	1 (1 %)	0 (0 %)	19 (95 %)
Hypervascular	0 (0 %)	0 (0 %)	1 (5 %)
Total	1 (1 %)	0 (0 %)	20 (100 %)

CEUS contrast-enhanced US, *Early HCC* early hepatocellular carcinoma, *HGDN* high-grade dysplastic nodule, *RN* regenerative nodule

Hypovascular hypovascularity (the whole lesion) during the arterial dominant phase

Transient hypovascular transient hypovascularity (the whole or a portion of the lesion) with subsequent isovascularity (the whole lesion) during the arterial dominant phase

Isovascular isovascularity (the whole lesion) during the arterial dominant phase

Partial hypervascular partial hypervascularity (less than half of the lesion) during the arterial dominant phase

Hypervascular hypervascularity (the whole lesion or more than half of the lesion) during the arterial dominant phase

($n = 95$), iso-intense ($n = 2$), or hyper-intense ($n = 1$) and all the HGDNs that were hypo-intense ($n = 6$) or hyper-intense ($n = 1$) during the hepatobiliary phase of EOB-MRI exhibited centripetal vessels during the arterial dominant phase of CEUS (Fig. 1). One early HCC that was hypo-intense during the hepatobiliary phase of EOB-MRI exhibited both centrifugal and centripetal vessels during the arterial dominant phase of CEUS. In this case, the hepatobiliary phase of EOB-MRI also showed vascular structures, such as the hepatic artery and portal vein penetrating the lesion as unenhanced low signal intensity structures (Fig. 2a), and these structures corresponded to the centrifugal vessels (Fig. 2b). Eighteen RNs and one early HCC that were hyper-intense with a small central area of hypo-intensity during the hepatobiliary phase of EOB-MRI exhibited centrifugal vessels on the arterial dominant phase of CEUS, and the small central area corresponded to the hepatic artery and portal vein running from the center to the periphery (Fig. 3). The remaining two RNs only exhibited hyper-intensity during the hepatobiliary phase of EOB-MRI. However, the arterial dominant phase of CEUS revealed centrifugal vessels (Fig. 4).

When lesions exhibiting both an area of hyper-intensity with a small central area of hypo-intensity during the hepatobiliary phase of EOB-MRI and centrifugal vessels during the arterial dominant phase of CEUS were

diagnosed as RNs, the sensitivity, specificity, and accuracy were 90.0, 99.0, and 97.6 %, respectively.

Discussion

Advanced HCC, hepatic metastasis, hepatic adenoma, and hepatic hemangioma are known to exhibit centripetal vessels and various enhancement patterns during the arterial dominant phase [17, 18]. Centripetal vessels may correspond to subcapsular feeding arteries or the hepatic artery itself [18]. In contrast, typical FNH show centrifugal vessels and early enhancement during the arterial dominant phase of CEUS [19–21]. In the present study, 19 of the 20 RNs showed centrifugal vessels and transient hypovascularity during the arterial dominant phase. Centrifugal vessels might correspond to the hepatic artery (FNH case) [19–21] or both the hepatic artery and the portal vein (RN case) running through the portal tract within the lesion.

In the present study, 18 (90 %) of the 20 RNs appeared as hyper-intense with a small central area of hypo-intensity during the hepatobiliary phase of EOB-MRI, while only one of the 100 early HCCs exhibited the same finding during the hepatobiliary phase of EOB-MRI. All the cases exhibiting hyper-intensity with a small central area of

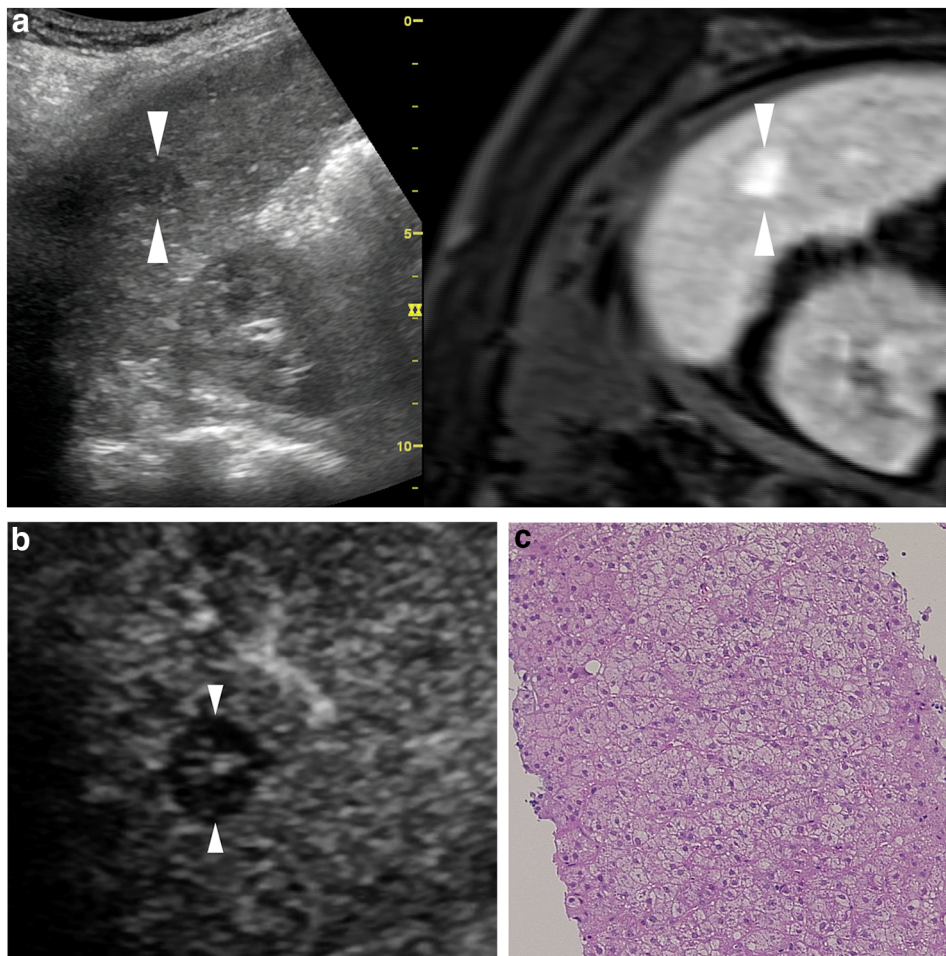


Fig. 4 A 74-year-old woman with hepatitis C-related liver cirrhosis and a RN (maximum diameter, 11 mm) in segment VI. **a** Fusion images combining conventional US (*left side*) and the hepatobiliary phase of EOB-MRI as a reference (*right side*) on a single screen. The hepatobiliary phase of EOB-MRI shows a hyper-intense area alone in segment VI (*arrowheads*). The fusion image shows the targeted RN lesion, which appears as an ill-defined slightly hypo-echoic lesion without a very small central hypo-anechoic area (*white arrow*) on conventional US (*arrowheads*). **b** Arterial dominant phase CEUS

images show transient hypovascularity of the lesion with a centrifugal hepatic artery running from the center to the periphery (spoke wheel pattern). **c** Hematoxylin–eosin staining reveals hyperplasia of the parenchymal nodules, with no cell atypia, and slight proliferation of hepatocytes, which is consistent with a pathological diagnosis of RN. Neither the conventional US findings nor the hepatobiliary phase of EOB-MRI findings changed over a follow-up period of more than 3 years

Table 4 Hepatobiliary phase EOB-MRI and arterial dominant phase CEUS findings for early HCC, HGDN, or RN lesions ($n = 127$)

Hepatobiliary phase EOB-MRI and arterial dominant phase CEUS findings	No. of lesions (%)		
	Early HCC ($n = 100$)	HGDN ($n = 7$)	RN ($n = 20$)
Hypo-intense area and centripetal vessels	95 (95 %)	6 (86 %)	0 (0 %)
Hypo-intense area and centripetal and centrifugal vessels	1 (1 %)	0 (0 %)	0 (0 %)
Iso-intense area and centripetal vessels	2 (2 %)	0 (0 %)	0 (0 %)
Hyper-intense area and centripetal vessels	1 (1 %)	1 (14 %)	0 (0 %)
Hyper-intense area and centrifugal vessels	0 (0 %)	0 (0 %)	2 (10 %)
Hyper-intense with small central hypo-intense area and centrifugal vessels	1 (1 %)	0 (0 %)	18 (90 %)

EOB-MRI MRI with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid, *CEUS* contrast-enhanced US, *Early HCC* early hepatocellular carcinoma, *HGDN* high-grade dysplastic nodule, *RN* regenerative nodule

hypo-intensity during the hepatobiliary phase of EOB-MRI exhibited centrifugal vessels during the arterial dominant phase of CEUS. This small central area of hypo-intensity during the hepatobiliary phase of EOB-MRI corresponded to central vascular structures, such as the hepatic artery and portal vein, running from the center to periphery when observed using CEUS. Therefore, this finding may be a common characteristic of RNs.

In general, an RN is a nodule observed in patients with liver cirrhosis; however, various non-typical lesions consisting of non-cirrhotic benign hepatocellular nodules are also grouped together as RNs according to the International Working Party classification [2]. Two cases with multiple RN lesions accompanied by Budd–Chiari syndrome [8, 22] and another case with multiple RNs accompanied by non-cirrhotic portal hypertension [23] exhibited hyper-intense areas with (relatively large lesions) or without (relatively small lesions) a small, central, hypo-enhanced area during the hepatobiliary phase of EOB-MRI. Despite the small sample size, we believe that our findings for the hepatobiliary phase of EOB-MRI are similar to those in these three previous reports [8, 22, 23]. In the present study, two relatively small RN lesions (both with a maximum diameter of 10 mm) showed areas of hyper-intensity alone during the hepatobiliary phase of EOB-MRI and a centrifugal vessel pattern during the arterial dominant phase of CEUS. Therefore, in cases with relatively small RN lesions, CEUS may be more sensitive than EOB-MRI for detecting small central vascular structures because of the high spatial and time resolution of CEUS.

In the present study, an unenhanced T1-weighted sequence revealed three of the 20 RNs to be hyper-intense and the other 17 RNs to be iso-intense. In contrast, all 20 RNs exhibited hyper-intensity alone or hyper-intensity with a small central area of hypo-intensity during hepatobiliary phase MRI with Gd-EOB-DTPA. Therefore, most of the RNs showed an increased uptake of Gd-EOB-DTPA, compared with the surrounding liver parenchyma. Meanwhile, two early HCCs and one HGDN that were hyper-intense during the hepatobiliary phase of EOB-MRI did not exhibit an increased uptake of Gd-EOB-DTPA because these lesions appeared as hyper-intense during an unenhanced T1-weighted sequence. The function of hepatocytes in early HCCs, HGDNs, and RNs on EOB-MRI may be an important finding when making the differential diagnosis, although further analysis is needed in the future.

Lim et al. [24] reported that RNs in cirrhotic liver, especially in cases with advanced macronodular liver cirrhosis, were visualized as enhanced nodules surrounded by thin septa with a lower attenuation on CT images obtained during arterial portography and as non-enhanced nodules surrounded by enhanced fibrous septa during CT hepatic arteriography (CTHA). According to imaging observations

of RNs, CT arterial portography showed very small dots with a higher attenuation in the center of the lesions, representing the portal veins, while CTHA showed small dots of enhancement within the lower-attenuation nodules, which probably represented the hepatic arterial branches within the lesions. In the present study, all 20 RNs exhibited centrifugal vessels, including the hepatic artery and portal vein, during the arterial dominant phase of CEUS. Therefore, we believe that imaging observations of a small central hypo-intense area within a hyper-intense area in an RN during the hepatobiliary phase of EOB-MRI may represent the presence of the portal tract, including the hepatic artery and portal vein, within the RN.

FNHs and RNs are benign hepatocellular nodules that might represent anomalies of the components of the portal tract [25]. Hyper-intensity or iso-intensity during the hepatobiliary phase of EOB-MRI is a characteristic and prevalent finding of FNHs [26–29]. According to figures seen in previous reports, a typical FNH with a central scar showed a hyper-intense area with a small hypo-intense area during the hepatobiliary phase of EOB-MRI [26–29]. We think that a small central hypo-intense area within a hyper-intense area in an RN during the hepatobiliary phase is similar in nature to the central scar within FNHs. The central scars of FNHs represent abnormal portal tracts that include an abnormal and relatively large hepatic artery and a thin portal vein [25]. In contrast, the center of RNs may consist of an almost normal portal vein and a hepatic artery that are divided from a normal portal vein and a normal hepatic artery accompanied by a portal vein.

Our study had several limitations. First, the pathological diagnosis of all the lesions, especially early HCCs, was based on criteria obtained using needle-biopsy specimens. Therefore, early HCCs with hyper-cellularity and architectural alterations with a thin trabecular structure and acinus, but no proof of stromal invasion despite the use of Victoria blue staining to clarify the presence of stromal invasion, were diagnosed as HGDNs, although biopsies of more than two samples were performed for each of the hepatic nodules. If specimens could have been obtained from other areas of the lesions, including the portal area, such lesions might have been diagnosed as early HCCs. These limitations could have resulted in an underestimation of the histological grades in cases with advanced HCC and early HCC lesions with internal histological heterogeneity. Second, the overall number of HGDN and RN cases included in this study was relatively small, because we tended to perform biopsies of hepatic nodules to identify HCC in high-risk patients who exhibited hypo-intense nodules in the liver when examined using EOB-MRI. Third, this study was conducted retrospectively, although we examined consecutive patients. A future prospective study utilizing a larger number of subjects is

recommended to confirm and extend our results seen in this smaller sample.

In conclusion, hyper-intensity with small central hypo-intensity during the hepatobiliary phase of EOB-MRI was a characteristic finding of RNs. This small central hypo-intense vascular structure on EOB-MRI corresponded to centrifugal vessels running from the center to the periphery of the lesion when examined during the arterial dominant phase of CEUS. This finding can be used to differentiate RNs from malignant or premalignant hepatic lesions, such as early HCCs or HGDNs, and also can be used to avoid unnecessary repeated tumor biopsies and indicate a need for follow-up care only in patients with chronic liver disease.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent was obtained from the patients for being included in this study.

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