Acta Med. Okayama, 2013
Vol. 67, No. 4, pp. 239–244

Acta Medica Okayama

http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

The Diagnosis of Hypovascular Hepatic Lesions Showing Hypo-intensity in the Hepatobiliary Phase of Gd-EOB-DTPA-enhanced MR Imaging in High-risk Patients for Hepatocellular Carcinoma

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The aim of this study was to evaluate the histologic diagnosis of hypovascular hepatic lesions showing hypointensity on hepatobiliary phase images of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI (EOB-MRI). In 38 patients with hepatocellular carcinoma (HCC) after curative treatments and 18 patients with liver cirrhosis, 105 hypovascular nodules that were hypointense at the hepatobiliary phase of EOB-MRI were biopsied and the clinical usefulness of these EOB-MRI findings for the diagnosis of HCC was examined. Of the 105 nodules (median diameter = 12 mm), 78 (74.3%), 11 (10.5%), and 16 (15.2%) were diagnosed as HCC, dysplastic, and non-neoplastic, respectively. The positive predictive value (PPV) of hypointensity at the hepatobiliary phase of EOB-MRI for the diagnosis of HCC increased to 77–90% when combined with the following factors: washout appearance on the delayed phase of triple-phase CT, hyperintensity in diffusion-weighted image of MRI, or the appearance of a hypoechoic part in ultrasonography. PPV increased to 100% when all 3 factors were positive. A relatively large proportion of hypovascular lesions that showed hypo-intensity in the hepatobiliary phase were confirmed to be HCC, and the accuracy of HCC increased when combined with other imaging findings.

Key words: hepatocellular carcinoma, hypovascular, diagnosis, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid, magnetic resonance imaging

Hepatocellular carcinoma (HCC) is the most frequent primary hepatic malignancy and is currently recognized as a major cause of death in cirrhotic patients. Epidemiological data have indicated that the incidence of HCC is increasing, and that HCC will be a worldwide health problem in the near future [1–3].

Progress in the imaging modalities for diagnosing HCC is remarkable. The development of the multidetector row CT, CT during hepatic arteriography (CTHA), or CT during arterial portography (CTAP) has made it possible to detect small hepatic nodules

Received August 6, 2012; accepted February 5, 2013.
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[4, 5]. Enhancement at the arterial phase and hypoattenuation at the portal phase detected by these contrast-enhanced imaging techniques is now regarded as a distinctive feature of HCC in cirrhosis. However, the definitive diagnosis of a hypovascular nodular lesion remains a critical challenge for clinicians [6]. The issue is particularly complicated for small nodules, because many of these may be preneoplastic lesions [7], such as low-grade dysplastic nodules or high-grade dysplastic nodules [8]. At present, a biopsy is necessary for the definitive diagnosis of these hypovascular nodules.

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) (Primovist, Bayer Schering Pharma AG, Berlin, Germany) is a new liver-specific contrast agent for magnetic resonance imaging (MRI) [9–11]. This contrast agent has unique characteristics. It is taken up into normally functioning hepatocytes and is excreted in the bile ducts in 10–20 minutes after injection. Consequently, lesions deficient in normally functioning hepatocytes can be visualized as hypointense regions in this hepatobiliary phase [9]. However, few studies have been conducted to determine whether these minutely imaged lesions in patients with cirrhosis are indeed HCC [11–15].

Therefore, we conducted a retrospective study to clarify the histologic diagnosis of hypovascular hepatic lesions showing hypointensity on hepatobiliary phase images of Gd-EOB-DTPA enhanced MRI.

Patients and Methods

Patients. Between April 2008 and May 2009, 33 patients with liver cirrhosis and 44 patients with HCC after curative treatment (11 surgical resection, 30 radiofrequency ablation, 1 microwave coagulation and 2 percutaneous ethanol injection) were examined with both Gd-EOB-DTPA-enhanced MRI (EOB-MRI) and ultrasonography (US) for the surveillance of HCC. A total of 138 hypointense liver lesions at the hepatobiliary phase of EOB-MRI were detected. Among them, 29 nodules that showed enhancement at the hepatic arterial phase in triple-phase CT or MR imaging were excluded. All of the remaining 109 hypovascular nodules were histologically diagnosed by biopsies. Three nodules were excluded because tissue specimens were too small to be diagnosed accurately, and one nodule of cholangiocellular carcinoma was also excluded. Thus, 105 nodules in 56 patients (18 patients with liver cirrhosis and 38 patients with HCC after curative treatment) were included in this study.

Methods. The patients with cirrhosis underwent US every 3 months and CT or MRI every year for the surveillance of HCC. The patients with HCC after curative treatment underwent US every 2 or 3 months and CT or MRI at least once a year.

MR imaging was performed on a 1.5-T MR system (Magnetom Avanto, Siemens, Erlangen, Germany) with a three-dimensional (3D) volumetric interpolated breathhold examination (VIBE). The technical parameters were: repetition time (TR, msec)/echo time (TE, msec), 4.04 msec/minimum; flip angle (FA), 15 degrees; field of view (FOV), 320 mm; thickness, 3.5 mm; partition, 52; matrix, 256 × 154; generalized autocalibrating partially parallel acquisition (GRAPPA) with an acceleration factor of 2 and a bandwidth of 340 Hz per pixel. All patients received a dose of 0.025 mmol/kg Gd-EOB-DTPA intravenously at a rate of 2 mL/s.

After the administration of the contrast material, triple-phase images (arterial phase, 35 sec after arterial phase, 70 sec after arterial phase) were obtained. The arterial phase was determined by the automatic triggering techniques that are commercially available as bolus detection software termed C.A.R.E (Combined Application Reduce Exposure) by Siemens. Dynamic imaging and hepatobiliary phase imaging (20 min after the administration of contrast material) were performed using the T1-weighted 3D-VIBE sequence with fat suppression. Single-shot echo-planner (EPI) diffusion-weighted images (DWIw) were acquired as follows: TR/TE, 1,300/85 msec; FOV, 320 × 240 mm; slice thickness, 7.0 mm; matrix, 128 × 90; EPI factor, 62; parallel imaging (GRAPPA with acceleration factor of 2); 3 separate b-values (0, 50, 1,000 s/mm^2; and acquisition, prospective acquisition correction [PACE]).

All patients were examined by a 64-MDCT system (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan). Precontrast and triple-phase (arterial, portal venous, and equilibrium phases) post-contrast scans of the liver were acquired. An automatic bolus-tracking program (Real Prep, Toshiba Medical Systems) was used to set the scanning timing for arterial phase after contrast injection. Arterial-phase scanning was started 16 sec after triggering. Portal venous and equilibrium-phase

scanning were started 60 and 240 sec after injection. Iohexol (Omnipaque, Daiichi-Sankyo, Tokyo, Japan) with an iodine concentration of 300 mgI/mL was administered, and we delivered 600 mgI/kg in 25 sec. The regions that showed hypoattenuation at the portal venous phase of triple-phase CT were defined as having a washout appearance.

Ultrasonographic examinations were performed using SSA-770A (Toshiba Medical Systems, Tokyo, Japan) or Prosound α10 (Aloka, Tokyo, Japan) by 2 board-certified hepatologists who are also board-certified fellows of the Japan Society of Ultrasonics in Medicine.

Each tumor-aimed biopsy was performed percutaneously under US guidance using a 21-gauge needle at least twice and put into a bottle filled with formalin to avoid sampling errors. All specimens were stained with hematoxylin-eosin and silver impregnation. Histological diagnosis was performed by 2 board-certified pathologists and 2 board-certified hepatologists according to the criteria outlined by an International Working Party.

All images were reviewed independently by 2 board-certified hepatologists, and compared with the histological findings. Disagreements about the interpretations were resolved by consensus.

The continuous data (*e.g.*, age, tumor size and values of tumor markers) were analyzed using Wilcoxon rank-sum test. Chi-squared tests or Fisher's exact test was used for categorical parameters. All statistical analyses were performed using JMP software, version 8.0.1 (SAS Institute, Inc., Cary, NC, USA). *P*-values smaller than 0.05 were considered significant.

Informed consent was obtained from all patients. The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki, and was approved by the ethical committee of the institute.

Results

Patient data were obtained and compared between groups with and without previous treatments of HCC (Table 1). The median age of the 56 patients was 70 years (range 53–83 years). The age, gender, cause of liver disease, tumor markers, and the median size of nodules did not differ significantly between the 2 groups. The positive ratio of HCC did not differ between patients with and without previous treatment for HCC (70.1% v.s. 81.6%, $p = 0.20$).

Of the 105 nodules, 78 nodules (74.3%) were histologically diagnosed as HCC (77 nodules, well differentiated HCC; 1 nodule, moderately differentiated HCC). Eleven (10.5%) and 16 nodules (15.2%) were diagnosed as dysplastic and non-neoplastic lesions, respectively.

Table 2 shows the imaging patterns of pathologi-

Table 1 Patient data and characteristics of nodules

	total	Previous treatment for HCC		*P* value
		yes	no	
Patient characteristics				
Number (%)	56	38 (67.9)	18 (32.1)	
Age (yr)	70 (53–83)	69 (53–83)	71 (57–83)	0.35
Gender (male/female)	41/15	29/9	12/6	0.52
Cause (HCV/HBV/HCV and HBV/other)	49/5/1/1	33/4/0/1	16/1/1/0	0.40
AFP (ng/mL)	12.0 (2.0–383.4)	11.2 (2.0–91.1)	20.2 (2.5–383.4)	0.40
AFP-L3 (%)	0.5 (0.0–27.0)	0.0 (0.0–27.0)	0.5 (0.0–0.5)	0.21
DCP (mAU/mL)	24 (10–166)	22 (10–81)	26 (13–166)	0.30
Nodule characteristics				
Number (%)	105	67 (63.8)	38 (36.2)	
Size (mm)	12 (6–20)	12 (6–20)	12 (6–19)	0.47
HCC (%)	78 (74.3)	47 (70.1)	31 (81.6)	0.20

All variables are indicated as median (range) unless otherwise noted.

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, alpha-fetoprotein; AFP-L3, lectin-bound alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

cally diagnosed nodules. Of the 78 HCCs, 62 nodules (79%) contained hypoechoic regions on conventional US B-mode, and 71 (91%) showed a washout appearance at the portal venous phase of triple-phase CT. In the meantime, 33 (42%), 28 (36%) and 26 (33%) nodules showed hyperintensity on T1, T2 and diffusion-weighted images, respectively.

As shown in Table 3, the positive predictive value (PPV) of hypointensity at the hepatobiliary phase of EOB-MRI (EOB-hypo) for the diagnosis of HCC was 74.3% (95% C.I., 65.2–81.7). It increased to 77.2% when the nodule showed a washout appearance on the delayed phase of triple-phase CT, 81.6% when the nodule contained hypoechoic regions in conventional US B-mode, and 83.9% when the nodule showed hyperintensity in DWI. In addition, PPV was increased to 85.9–91.3% when combined with 2 of these 3 factors. All of the 21 nodules that were positive for these 3 factors were diagnosed as HCC (Fig. 1).

Discussion

Gd-EOB-DTPA is a new type of contrast enhancement material for MRI, and the enhancement effect at the hepatobiliary phase is independent from the blood flow. Gd-EOB-DTPA is transported into hepatocytes via organic anion transporters (OATPs) and excreted into bile canaliculi via the multidrug resistance-associated protein MRP2. OATP1B3, which is expressed in the basolateral membrane of hepatocytes, is especially important for transport of Gd-EOB-DTPA [9, 16, 17]. Typically, accumulation of Gd-EOB-DTPA

Table 2 Imaging patterns and pathological characterization of nodules

	Number (%)	US appearance on B-mode	Signal intensity at delayed phase of dynamic study	Signal intensity of MRI		
				T1 W.I.	T2 W.I.	diffusion W.I.
		hyper-echoic / hyper- and hypo-echoic / hypo-echoic	iso / hypo	hyper / iso / hypo	hyper / iso / hypo	hyper / iso / no study
Hepatocellular carcinoma	78 (74.3)	16/20/42	7/71	33/34/11	28/40/10	26/50/2
Well differentiated	77 (73.3)	15/20/42	7/70	33/33/11	28/39/10	26/49/2
Mod. differentiated	1 (1.0)	1/0/0	0/1	0/1/0	0/1/0	0/1/0
Dysplastic nodules	11 (10.5)	4/3/4	1/10	6/4/1	5/4/2	3/8/0
Low-grade	8 (7.6)	2/3/3	1/7	4/3/1	2/4/2	2/6/0
High-grade	3 (2.9)	2/0/1	0/3	2/1/0	3/0/0	1/2/0
No malignancy	16 (15.2)	8/4/4	5/11	3/7/6	5/7/4	2/13/1

Table 3 Positive predictive value for the diagnosis of hypovascular HCC

	Number of nodules	HCC	PPV (95% C.I.)
Hypointense at the hepato-biliary phase of EOB-MRI	105	78	74.3 (65.2–81.7)
Combine with one factor			
Wash out at delayed phase (W/O)	92	71	77.2 (67.6–84.6)
Contains hypoechoic lesion on US (US)	76	62	81.6 (71.4–88.7)
Hyperintensity at diffusion weighted image (Diff)	31	26	83.9 (67.4–92.9)
Combine with two factors			
W/O + US	64	55	85.9 (75.4–92.4)
W/O + Diff	29	26	89.7 (73.6–96.4)
US + Diff	23	21	91.3 (73.2–97.6)
Combine with three factors			
W/O + US + Diff	21	21	100 (74.5–100)

HCC, hepatocellular carcinoma; PPV, positive predictive value; EOB-MRI, Gd-EOB-DTPA-enhanced magnetic resonance imaging.

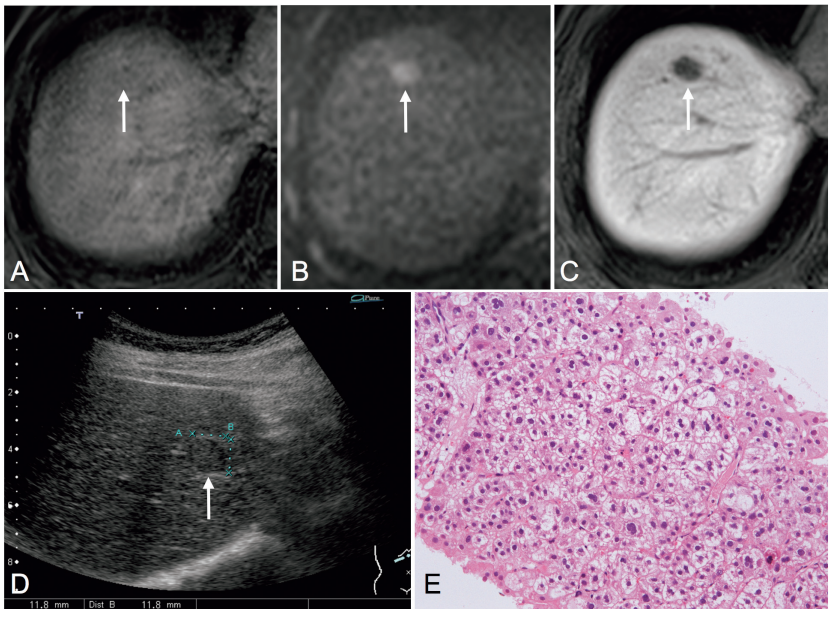

Fig. 1 Typical findings of hypovascular hepatocellular carcinoma (HCC). **A**, T1-weighted enhanced MRI (arterial phase); **B**, Abdominal MRI (diffusion weighted image, b = 1,000); **C**, Gd-EOB-DTPA-enhanced MRI (hepatobiliary phase); **D**, Abdominal ultrasonography; **E**, Histological finding of biopsied specimen (well-differetinated HCC).

is inhibited in malignant liver lesions, such that they appear hypointense at the hepatobiliary phase [9].

Because so-called "early HCCs" do not show a classical HCC pattern, which is enhancement at an early arterial phase and washout at a portal venous phase, it is very difficult to distinguish them from other nonmalignant liver nodules by traditional imaging modalities. In the present study, we found that 74.3% of hypovascular nodules that showed hypointensity at the hepatobiliary phase of EOB-MRI were HCCs. This PPV for the diagnosis of small hypovascular HCC is relatively high compared with other imaging modalities. Tajima *et al.* reported that only 9 of 19 (47%) liver nodules showing hypoattenuation on CTHA were diagnosed as well-differentiated HCC [18]. Also, Hayashi *et al.* reported that 1 of 9 (11%) liver nodules showing isoattenuation or hypoattenuation on CTHA and hypoattenuation on CTAP were diagnosed as well differentiated HCC [5].

Recently, other liver-specific contrast agents have been used, and those agents can also reveal hypovascular HCCs in some cases. Superparamagnetic iron oxide (SPIO) is a tissue-specific MR imaging contrast that is taken up by Kupffer cells in the liver; however, most of the well-differentiated HCCs had a similar number of Kupffer cells in the tumorous and nontumorous tissues. Therefore, it is difficult to distinguish dysplastic nodules from well-differentiated HCCs by SPIO-enhanced MR imaging alone [19]. Sonazoid is a lipid-stabilized suspension of perfluorobutane and is also taken up by the Kupffer cells. According to a recent report, only 3 of 13 (23.1%) well-differentiated HCCs showed a perfusion defect in the Kupffer phase so that the diagnosis of hypovascular HCC by this method is also limited [20].

In our study, PPV of EOB-MRI at the hepatobiliary phase was high (74.3%); however, the result is somewhat unsatisfactory because the false positive rate was 26%. To achieve a higher PPV, we combined it with 3 independent factors: washout appearance at the delayed phase on triple-phase CT, the existence of a hypoechoic region in conventional US B-mode, and hyperintensity in DWI. As shown in Table 3, the PPV was raised to about 80% when combined with one factor, and increased to almost 90% when combined with 2 factors. When all 3 factors were positive, PPV reached 100%. Liver biopsy for the diagnosis of HCC has several potential risks, such as intra-abdominal bleeding and the dissemination of tumor cells. The combination of examinations that we

presented in this study would be very helpful in cases in which hypovascular nodules are found in cirrhotic livers and physicians must decide whether to biopsy them or not.

The limitations of our study are as follows. First, there must be some sampling errors in US guided biopsies. Second, the pathologists and hepatologists were different in each case, although they were all board-certified doctors.

In conclusion, a relatively large proportion of hypovascular hepatic lesions that were hypo-intense in hepatobiliary phase images of Gd-EOB-DTPA-enhanced MRI were confirmed to be HCC, and the accuracy of the diagnosis of HCC increased when combined with other imaging findings.

Further large-scale studies are needed to verify more precisely the value of Gd-EOB-DTPA-enhanced MRI for the diagnosis of HCC and to integrate it into a diagnostic algorithm.

Acknowledgments. We thank Mr. Toshi Matsushita from Okayama Diagnostic Imaging Center and Dr. Hideo Gobara from Okayama University Hospital Department of Radiology for some technical advice and comments about CT and MR imaging.

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