Was Hypervascular Hepatocellular Carcinoma Visible on Previous Gadoxetic Acid-Enhanced Magnetic Resonance Images?

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Key Words
Carcinogenesis · Gadoxetic acid · Hepatocellular carcinoma · Magnetic resonance imaging (MRI)

Abstract

\textbf{Background:} During the follow-up of patients with chronic liver disease, hypervascular hepatocellular carcinomas (HCCs) can develop either from pre-existing high-risk nodules or by de novo hepatocarcinogenesis. The purpose of this study was to evaluate, by retrospective analysis, the detectability and signal intensity on previous hepatocyte-phase gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) of hypervascular HCC initially detected on current EOB-MRIs. \textbf{Methods:} We examined 50 initially detected hypervascular HCCs that showed typical enhancement features on EOB-MRI in 39 patients whose previous EOB-MRI images obtained 6–19 months earlier were available. The detectability of each hypervascular HCC on the hepatocyte phase images of previous EOB-MRIs was assessed. The imaging features on hepatocyte-phase images of previous EOB-MRIs at the locations where hypervascular HCCs were found on the current EOB-MRI images were classified as detectable or undetectable. The signal intensities of detectable nodules (defined as group A) on hepatocyte-phase images of previous EOB-MRIs were classified as hypointense, isointense, or hyperintense. Nodules undetectable on the hepatocyte-phase images of previous EOB-MRIs were assigned to group B. \textbf{Results:} Twenty-two (22/50, 44\%) hypervascular HCCs were detectable on the earlier hepatocyte phase images (group A).

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contrast, 28 (28/50, 56%) hypervascular HCCs were not detectable on the hepatocyte phase of earlier EOB-MRI images (group B). **Conclusion:** When the previous EOB-MRI images were used as the reference, more than half (28/50, 56%) of hypervascular HCCs initially appearing on the current EOB-MRI images were found not to have developed from nodules detectable on the previous MRIs through the traditionally accepted process of multistep carcinogenesis. Instead, they seemed to have developed via an “imaging-occult” process of carcinogenesis in patients with chronic liver diseases.

**Introduction**

In patients with chronic liver diseases, step-wise carcinogenesis of hepatocellular carcinoma (HCC) has been described as multistep hepatocarcinogenesis, although some hypervascular HCCs do develop via de novo carcinogenesis. During multistep hepatocarcinogenesis, gradual increases in size and cellular density are observed according to the following progression of hepatocellular nodules: hypovascular hepatocyte nodules including regenerative nodules, low-grade dysplastic nodules, high-grade dysplastic nodules, early HCC, and hypervascular progressed HCC that may be well, moderately, or poorly differentiated histologically [1–4]. Based on this theory of carcinogenesis, most hypervascular HCCs are thought to develop from hypovascular early HCC. Recent radiological investigations have revealed that early HCC can frequently be detected via its hypointensity on hepatocyte-phase images of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) [5, 6]. In addition, other recent studies have reported that some non-hypervascular nodules that show hypointensity on EOB-MRI hepatocyte-phase images can progress to hypervascular HCC [7–9]. Thus, EOB-MRI is useful in predicting the development of hypervascular HCC in patients with chronic liver diseases because it allows frequent detection of high-risk nodules with the possibility of progression to hypervascular HCC.

On the other hand, in certain cases, hypervascular HCCs can occur via de novo carcinogenesis [10, 11]. The mechanism of such a process remains unclear because of the rarity of de novo HCC. Nonetheless, it is important to document areas of the liver without premalignant lesions when following patients with chronic liver diseases to account for the possibility of de novo HCC. The frequency of de novo HCC development, despite being of clinical significance, is unknown.

The purpose of this study was, by retrospective analysis, to evaluate the detectability and signal intensity on the hepatocyte-phase images of previous EOB-MRIs of hypervascular HCCs initially detected on current EOB-MRIs.

**Materials and Methods**

**Patients**

This retrospective study was performed in accordance with the principles of the Declaration of Helsinki and was approved by our institutional review board. Between January 2008 and January 2014, 4,778 EOB-MRI examinations were performed on 1,778 patients at our institution. The study coordinator, a radiologist with 9 years of experience, searched the radiological database at our institution for reports of cases in which gadoxetic acid was used as a contrast material; the following search terms were also used: “hepatocellular carcinoma,” “HCC,” and “hepatoma.” The coordinator then identified radiological reports that suggested hypervascular HCC on EOB-MRI. Patients were further selected based on the availability of (i) a conclusive diagnosis of new-onset hypervascular HCC and (ii) EOB-MRI obtained prior to the initial diagnosis of hypervascular HCC (previous EOB-MRI). Hypervascular HCC was diagnosed.
based on pathological evidence or characteristic EOB-MRI findings according to the following modified imaging-based practical guidelines proposed by the American Association for the Study of Liver Diseases (AASLD) [12]: wash-in on hepatic arterial-dominant phase (HAP) images and wash-out on dynamic late-phase EOB-MRI images obtained 2 min after the administration of gadoxetic acid. Moreover, since conclusive EOB-MRI criteria have not been established, all hypervascular HCC cases confirmed by EOB-MRI were accompanied by typical computed tomography (CT) findings suggested by the AASLD imaging-based practical guidelines [12] for dynamic CT obtained within 3 months after the current EOB-MRI. Our institutional protocol on the follow-up of patients with chronic liver diseases indicates that EOB-MRI should be conducted every 6 months. Therefore, the previous EOB-MRI images used in this study were obtained at least 6 months before the initial diagnosis of hypervascular HCC by the current EOB-MRI for all patients.

Patients with a history of hypervascular HCC were excluded from this study to eliminate possible confounding by intrahepatic metastatic hypervascular HCC. Finally, 50 hypervascular HCCs (mean diameter 13.5 mm, range 6–44 mm) in 39 patients (22 men and 17 women; age range 51–88 years, mean age 70.5 years) were included in this study (fig. 1). The etiology of hepatitis was as follows: viral hepatitis type C (n=34), viral hepatitis type B (n=1), alcohol-related (n=2), schistosomiasis (n=1), and non-alcoholic steatohepatitis (NASH) (n=1). HCC diagnosis was confirmed by histopathology (n=21) or imaging-based practical guidelines (n=29). Six patients had multiple HCCs: three patients had two lesions (n=3; maximum diameter, 22 mm, 17 mm, and 14 mm), two had three lesions (n=2; maximum diameter, 25 mm and 11 mm), and one had five lesions (n=1; maximum diameter, 17 mm). Thirty-three patients had solitary HCC (33/39, 84.6%). The time interval between the previous and the current EOB-MRI was 183–574 days (mean 320.1 days).

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**Fig. 1.** Inclusion criteria for enrollment of study participants.

### Chart: Inclusion Criteria for Enrollment of Study Participants

| Between January 2008 and January 2014, 4778 EOB-MRI examinations for 1778 patients. |
|---|
| With hypervascular HCC? |
| Yes | Excluded |
| No | n=603 |
| With previous EOB-MRI? |
| Yes | n=288 |
| No | Excluded |
| With history of having hypervascular HCC? |
| Yes | Excluded |
| No | n=249 |

50 hypervascular HCCs in 39 patients
Magnetic Resonance Imaging
EOB-MRI was performed by using a superconducting magnet operating at 1.5 T (Signa EXCITE HD, GE Medical Systems, Waukesha, WI, USA) with an 8-channel phased-array coil or at 3 T (Discovery 750; GE Medical Systems) with a 32-channel phased-array coil. After the pre-contrast T1-weighted fast spoiled gradient-echo imaging, T2-weighted fast spin-echo images and diffusion-weighted single-shot spin-echo echo-planar images were obtained. Dynamic fat-suppressed gradient-echo T1-weighted images with a three-dimensional acquisition sequence (liver acquisition with volume acceleration) were obtained before (pre-contrast) and at 20–30 s (HAP), 1 min (portal venous phase), 2 min, 5, 10, and 20 min (hepatocyte-phase) after the administration of gadoxetic acid (EOB Primovist; Bayer HealthCare, Berlin, Germany). The contrast material (0.025 mmol/kg body weight) was administered intravenously as a bolus at a rate of 1 ml/s via a 22-gauge intravenous cubital line, which was flushed with 20 ml of saline using a power injector (Sonic Shot 50; Nemoto Kyorindo, Tokyo, Japan). HAP images were acquired using a fluoroscopic triggering technique. It is generally recognized that EOB-MRI contrast-enhanced images might not be identical to dynamic CT delayed-phase images because of the differences in hemodynamics of gadoxetic acid and the iodine contrast material used for CT. According to our EOB-MRI protocol, dynamic late-phase images were obtained 2 min after the administration of gadoxetic acid, and these approximately corresponded to the dynamic CT delayed-phase images. The images were acquired in the transverse plane. A section thickness of 5 mm with 2.5 mm overlap (i.e., no section gap) was applied. The sequence parameters are summarized in Table 1.

### Table 1. MR sequence parameters for EOB-MRI

| Parameter                      | 1.5-T system                      | 3-T system                      |
|-------------------------------|-----------------------------------|---------------------------------|
| Sequence                      | Three-dimensional gradient-echo T1-weighted imaging (LAVA) | Three-dimensional gradient-echo T1-weighted imaging (LAVA) |
| Repetition time (ms)           | 3.8                               | 3.0                             |
| Echo time (ms)                | 1.9                               | 1.4                             |
| Matrix                        | 320 × 192                         | 256 × 192                       |
| Field of view (cm)            | 35–42 × 40–45                     | 34 × 27.2                       |
| Section thickness/intersection gap (mm) | 5/–2.5                           | 5/–2.5                          |
| Number of signals acquired    | 1                                 | 1                               |
| Acquisition time of hepatocyte phase (s) | 18                                | 16                              |

LAVA = liver acceleration volume acquisition.

Image Analyses
The same radiologist who conducted patient selection performed imaging analysis. On the hepatocyte-phase images of the previous EOB-MRIs, imaging features were first classified into detectable or undetectable. In addition, the signal intensity of each detectable nodule was classified as hypo-, iso-, or hyperintense.

If a nodule was detectable by showing hypointensity or hyperintensity on the previous EOB-MRI hepatocyte-phase images, it was considered to have developed via multistep carcinogenesis (group A). “Imaging-occult” carcinogenesis was identified when no nodule was detected on the previous EOB-MRI hepatocyte-phase images at the location where hypervascular HCC was observed on the current EOB-MRI. These cases were classified as undetectable (group B) in the present study.

The time interval between the previous and current EOB-MRIs and the lesion size on the current EOB-MRI were compared between the two groups using the Wilcoxon test. A p-value of <0.05 was considered statistically significant. JMP software (Ver. 9; SAS Institute, Cary, NC, USA) was used for all statistical analyses.
Results

Of the 50 hypervascular HCC lesions confirmed by current EOB-MRIs, 22 (22/50, 44.0%) were classified as detectable (group A) on the previous EOB-MRI hepatocyte-phase images. Almost all of these lesions showed hypointensity (21/22, 95.5%, fig. 2) with only one lesion showing hyperintensity (1/22, 4.5%). The remaining 28 hypervascular HCC lesions (28/50, 56.0%) were classified as undetectable on previous EOB-MRI (group B). Of these, one nodule showed hyperintensity on pre-contrast fat-saturated T1 weighted images of the previous EOB-MRI, whereas the other 27 were undetectable on any images, including the hepatocyte-phase images of the previous EOB-MRI. There were no detectable nodules classified into the iso-intensity category (fig. 3, table 2).

No significant differences in the time intervals between previous and current EOB-MRIs were observed between group A (289.9 ± 82.5 days) and group B (339.3 ± 110.1 days) (p=0.1005). In addition, the lesion size of the hypervascular HCC nodules confirmed on the current EOB-MRIs did not differ significantly between group A (13.6 ± 4.6 mm) and group B (13.3 ± 6.9 mm) (p=0.5610, table 3).

Fig. 2. Imaging studies of a 64-year-old man with hypervascular HCC. a Current EOB-MRI hepatocyte-phase scan shows a hypointense nodule in S8 measuring 11 mm (arrow). b Current arterial-phase image shows hypervascularity (arrow). c The nodule could be detected in a previous study (238 days earlier) as a hypointense nodule in the hepatocyte phase measuring 5 mm (arrow). d An arterial-phase image in the previous study did not show hypervascularity (broken line arrow).
Discussion

Multistep carcinogenesis is traditionally thought to be the mainstream pathological mechanism of hypervascular HCC development in patients with chronic liver diseases, whereas de novo lesions are considered to occur less frequently. A number of hypovascular nodules have been found to show hypointensity on EOB-MRI hepatocyte-phase images [5, 13–15]. Although the exact histopathologic nature of hypovascular, hypointense nodules seen on EOB-MRI hepatocyte-phase images remains unclear, several useful studies attempting to establish the pathological diagnosis of such nodules have been conducted recently based on follow-up results. Motosugi et al. reported that the 1-year cumulative risk for hypervascularization of such nodules was 15.6%, which increased to 37.6% for nodules larger than 10 mm [7]. However, Kumada et al. reported that the 1-year cumulative risk of hypervascularization was as high as 77.3% for nodules measuring ≥15 mm, whereas the risk for nodules smaller than 15 mm was 16.9% [8]. Kim et al. and Hyodo et al. reported similar results, i.e., that 31–35% of such nodules (including those smaller than 5 mm) exhibited hypervascularization during a mean follow-up period of approximately 1 year [16, 17]. It might be difficult to compare the above-mentioned results in detail because of different follow-up times or nodule sizes. However, considering results indicating that a substantial proportion of hypovascular nodules showing hypointensity on EOB-MRI hepatocyte-phase images can progress to typical hypervascular HCC during a relatively short follow-up period, such nodules might usefully be treated as early HCC or close-to-early HCC in the clinical setting.
Although the exact histopathologic nature of these nodules remains to be clarified, the consensus report of the 4th International Forum for EOB-MRI [18] suggested that many of them might be early HCC or high-risk nodules with potential to progress to hypervascular HCC. Thus, EOB-MRI is useful in monitoring small early HCC or high-risk nodules for their hypervascular HCC progression via multistep carcinogenesis of the liver over a long period of time in patients with chronic liver diseases.

The present study, however, suggested that more than half of the hypervascular HCCs confirmed on current EOB-MRI images (28/50, 56%) were undetectable on the previous EOB-MRI hepatocyte-phase images. Thus, they were thought to arise via an "imaging-occult" carcinogenesis process. Here, it should be recognized that "imaging-occult" carcinogenesis defined in the present study differs from pathologic de novo carcinogenesis. For example, the nodules might have been present earlier but simply could not be detected due to their

### Table 2. Imaging features of HCC nodules on previous hepatocyte-phase EOB-MRI images

| Group A | Group B |
|---------|---------|
| Detectable on hepatocyte phase images | Undetectable on hepatocyte phase images |
| 22/50 nodules (44.0%) | 28/50 nodules (56.0%) |
| Hypointensity | Hyperintensity |
| 21/50 nodules (42.0%) | 1/50 nodules (2.0%) |
| Detectable on another sequence | Undetectable on any other sequences |
| 21/50 nodules (42.0%) | 1/50 nodules (2.0%) |

Group A, detectable nodules on hepatocyte-phase images of the previous EOB-MRI. Group B, undetectable nodules on the hepatocyte-phase images of the previous EOB-MRI.

### Table 3. Comparison of the two patient groups

|                        | All patients | Group A patients | Group B patients | p-value |
|------------------------|--------------|------------------|------------------|---------|
| Age (years)            | 70.5 ± 9.4   | 73.1 ± 7.7       | 68.0 ± 10.2      | 0.1637  |
| Gender (M:F)           | 22:17        | 9:10             | 13:7             | 0.2670  |
| Interval from the previous study (days) | 320.1 ± 102.0 | 289.9 ± 82.5 | 339.3 ± 110.1 | 0.1005  |
| Sizes of the HCCs (mm) | 13.5 ± 6.1   | 13.6 ± 4.6       | 13.3 ± 6.9       | 0.5610  |
| Etiology of hepatitis  |              |                  |                  |         |
| Viral hepatitis type C |              | Viral hepatitis type C | Viral hepatitis type C | 0.2896  |
| (n=34)                 |              | (n=17)           | (n=17)           |         |
| Viral hepatitis type B |              | Viral hepatitis type B | Viral hepatitis type B |         |
| (n=1)                  |              | (n=1)            | (n=1)            |         |
| Alcoholic              |              |                  |                  |         |
| (n=2)                  |              |                  |                  |         |
| Schistosomiasis        |              |                  |                  |         |
| (n=1)                  |              |                  |                  |         |
| NASH                   |              |                  |                  |         |
| (n=1)                  |              |                  |                  |         |

Data for age, interval from the previous study, and sizes of the HCCs are presented as mean ± standard deviation. NASH=non-alcoholic steatohepatitis. The Wilcoxon test was used for continuous variables, whereas the Chi-square test was used for categorical data.
small size or the relatively low resolution and/or quality of EOB-MRI. In this study, the section thickness of the previous EOB-MRI hepatocyte-phase images was 5 mm with a 2.5-mm overlap; thus, lesions smaller than 2.5 mm might potentially be undetectable. Alternatively, the nodules might also have been present but showing complete iso-intensity to the surrounding liver parenchyma due to gadoxetic acid uptake, making them undetectable on the previous EOB-MRI hepatocyte-phase images. Therefore, a hypervascular HCC lesion classified as having an “imaging-occult” carcinogenesis because it was undetectable on the previous EOB-MRI hepatocyte-phase image might not necessarily have arisen via a pathological de novo carcinogenesis process. As a result, not all hypervascular HCC nodules that developed via “imaging-occult” carcinogenesis in this study corresponded to pathological de novo lesions, and the frequency of HCC development via de novo carcinogenesis remains undetermined.

Nevertheless, the results of this study might be of clinical importance because “imaging-occult” and de novo carcinogenesis might overlap to a certain degree in HCC development, and this fact might help estimate the frequency of hypervascular HCC arising from de novo carcinogenesis.

The present study had several limitations. First, the study cohort was relatively small, and the main cause of hepatitis in our patients was hepatitis C virus infection. Thus, our findings might not be generalizable to patients with hepatitis B infection or other conditions. Second, there might be considerable selection bias in each patient group. However, such bias could be of limited importance because, although the time interval between the previous and current EOB-MRI tended to be shorter for group A patients, there were no statistically significant differences between the two groups in terms of age, sex ratio, time interval between EOB-MRIs, lesion size, or etiology of hepatitis. Finally, the retrospective study design was a limitation. For example, the final decision on the presence of a current hypervascular HCC and any pre-existing nodules for patient enrollment was made based on EOB-MRI data alone rather than in combination with ultrasonography and dynamic CT findings. A study method that combined these imaging modalities might be effective in minimizing the bias of different diagnostic performance by ultrasonography, dynamic CT, and EOB-MRI in detecting small HCC lesions and determining a nodule’s hypervascular nature, but such a method is clearly not practical in the clinical setting. If ultrasonography or dynamic CT, both of which are generally used worldwide for HCC screening in patients with chronic liver diseases, were employed for patient enrollment in this study, the results might be different from the present findings. Therefore, prospective cohort studies are needed to clarify the frequency of “imaging-occult” and multistep carcinogenesis among patients with chronic liver diseases.

Conclusions

The present study revealed that more than half of hypervascular HCCs (28/50, 56.0%) initially found in patients with chronic liver diseases did not develop from hypovascular nodules detectable on the hepatocyte-phase images of previous EOB-MRI but from “imaging-occult” nodules that were undetectable on previous EOB-MRI hepatocyte-phase images. Thus, radiologists and hepatologists should be aware that a considerable number of hypervascular HCCs may suddenly appear via “imaging-occult” carcinogenesis, rather than via the commonly accepted mechanism of multistep carcinogenesis, during the follow-up of patients with chronic liver diseases using EOB-MRI. The “imaging-occult” carcinogenesis process might partially overlap with pathological de novo carcinogenesis.
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