Effect of imaging timing on the hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance imaging in patients with severe liver cirrhosis

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Aims and objectives

Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) - enhanced MR imaging enables improved detection of hepatic lesions over gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA)-enhanced MR imaging [1]. After injection, rapid and specific hepatocyte uptake with biliary excretion occurs in approximately 50% of the injected dose. Since the normal hepatic parenchyma uptake Gd-EOB-DTPA, these areas exhibit T1 shortening and show hyperintensity on T1-WI. In contrast, since most of the focal liver lesions do not contain hepatocyte within the lesion and do not show uptake of Gd-EOB-DTPA, these lesions exhibit T1 shortening and show hypointensity on T1-WI. Therefore, Gd-EOB-DTPA can be useful for the detection and characterization of liver lesions.

Liver signal intensity is significantly lower in patients with chronic liver disease than in those with normal liver function [2]. The degree of liver enhancement in the hepatobiliary (HB) phase may reflect liver cell function. The measurement of liver signal intensity in the HB phase may be useful in predicting whole and regional hepatic functional reserves [2]. In other words, severe liver cirrhosis (LC) strongly damages the hepatocyte-specific uptake of Gd-EOB-DTPA. The decrease in the uptake of Gd-EOB-DTPA in the HB phase causes decrease of the contrast between liver lesions and the liver.

To improve diagnostic ability of hepatocellular carcinoma (HCC) in patients with severe LC, we attempted to perform super-delayed phase image acquisition, approximately 80 minutes after intravenous EOB injection. Part of the study was presented on ECR 2013 (SS 1801b: Parenchymal and vascular contrast improvement in super-delayed phase images of Gd-EOB-DTPA enhanced MRI of the liver. Kobayashi S, Matsui O, Gabata T, Koda W, Minami T, Kozaka K, Kitao A).

At the presentation, although hepatic parenchymal and vascular contrast improvement in super-delayed phase images of Gd-EOB-DTPA was stated, the improvement of lesion conspicuity was not revealed.

So our aim was to clarify the effect of imaging timing on lesion conspicuity in severe liver cirrhosis using the contrast values of "portal vein (PV)-to-liver" and "lesion-to-liver" in the hepatobiliary phase (HB phase) and super-delayed phase of Gd-EOB-enhanced MRI.
Methods and materials

Institutional ethics committee approval was obtained and written informed consent was waived for this retrospective study. This study comprised 28 patients (14 men and 14 women, mean age: 66.0 years) with severe LC (13 moderately differentiated HCCs) or normal liver function (15 benign lesions or hepatic metastases), all of whom underwent EOB-enhanced MRI for preoperative assessment.

Imaging

All individuals underwent MR imaging of the liver with a 1.5- or 3-Tesla MR system (SignaHDx; GE Healthcare, Milwaukee, WI, USA). For signal reception in all examinations, an 8-channel anteroposterior phased-array surface coil that covered the entire liver was placed around the patient. Imaging protocols included unenhanced sequences (coronal single-shot fast spin-echo [SSFSE], transaxial T2-weighted fast spin-echo [FSE], in- and out-of-phase gradientecho [(GRE)], dynamic GRE sequences in the arterial, portal-venous, late, HB, and super-delayed phases (30-35 s, 65-70 s, 3 min, 20 min, and >80 min respectively). Each patient received an intravenous bolus injection of Gd-EOB-DTPA (gadoxetic acid; Bayer Schering Pharma, Osaka, Japan) as a contrast agent at a dose of 25 mol/kg body weight and a flow rate of 2 mLs, followed by a 20-mL saline flush. Dynamic and delayed imaging was performed with a fat-suppressed 3D T1-weighted GRE sequence employing parallel imaging (LAVA-XV ASSET breathhold TR/TE = 3.1/1.4 ms; flip angle, 15 degree; field of view, 42 × 42 cm; matrix, 384 × 256, interpolated to 512 × 512; thickness, 4 mm; overlap 2 mm; ASSET acceleration, 2.0).

Image analysis

The signal intensities of the lesion (which are consisted of 13 moderately differentiated hepatocellular carcinoma in cirrhosis and 15 benign lesion and metastases on normal liver) and surrounding background liver as well as portal vein (PV) were measured by placing regions of interest (ROIs). The ROI of the lesion was determined as the maximum oval or adjacent area at the level of the largest diameter of the lesion. A similarly sized ROI was set over the adjacent liver parenchyma by avoiding the large vessels. ROIs were measured in the HB and super-delayed phases. The ROI of the PV was placed on main portal vein.

The contrast of PV-to-liver or lesion-to-liver was calculated according to the following formula:

\[
\text{Contrast} = \frac{(S_{IA}-S_{IB})}{(S_{IA} + S_{IB})} \ldots(1)
\]

where \(S_{IA}\) is the signal intensity of PV or lesion, \(S_{IB}\) is the signal intensity of the liver.
Statistical analysis

Statistical analysis was performed with commercial software (Prism 5; GraphPad Software, San Diego, CA, USA). Contrast of PV-to-liver in patients with normal liver function and patients with severe LC were compared by Mann-Whitney non-parametric test. In addition, the contrasts of PV-to-liver and lesion-to-liver in HB and super-delayed phases were compared by use of the Wilcoxon signed-rank test.
Results

Figure 1 shows liver MR images of Gd-EOB-DTPA-enhanced T1-weighted MRI of a 36-year-old female with liver hemangioma (normal liver function). Figure 2 shows liver MR images of Gd-EOB-DTPA-enhanced T1-weighted MRI of a 56-year-old female with moderately differentiated HCC (severe LC).

Compared to in the normal liver function case (Figure 1), in patients with severe LC (Figure 2), the degree of contrast media uptake in the liver were low and slow on HB phase image acquired on 20 min after EOB administration. However, the contrast of lesion-to-liver was improved in the super-delayed phase compared with the HB phase in severe LC case (Figure 2).

Figure 3 shows that the median of lesion-to-liver contrast value of normal liver function and severe cirrhosis cases in hepatobiliary phase of Gd-EOB-DTPA enhanced MRI.

The contrast in patients with normal liver function (0.39, IQR 0.32-0.48) was significantly higher than that in patients with severe LC (0.15, IQR 0.11-0.23) in HB phase of EOB-enhanced MRI (P<0.0001). Figure 4 shows the contrast of PV-to-liver contrast value of severe cirrhosis cases in hepatobiliary phase and super-delayed phase of Gd-EOB-DTPA enhanced MRI. In patients with severe LC, the contrast in super-delayed phase (0.27, IQR 0.23-0.42) was significantly higher than that in HB phase (0.15, IQR 0.11-0.23) (P<0.0001). Figure 5 shows the contrast of lesion-to-liver contrast value of severe cirrhosis cases in hepatobiliary phase and super-delayed phase of Gd-EOB-DTPA enhanced MRI. The contrast in super-delayed (0.10, IQR 0.06-0.13) phase was also significantly higher than that in HB phase (0.02, IQR 0.01-0.06) (P<0.0001).

After taken-up by hepatocytes, Gd-EOB-DTPA is eventually excreted via the biliary pathway without any change to its chemical structure [2]. Because of these characteristics, it has the potential to be used as a tracer for quantification of liver function [2]. In patients with chronic liver dysfunction, liver imaging at 30 minutes after the injection may be necessary to gain the maximal liver enhancement in the hepatobiliary phase [2].

In our study, poor lesion-to-liver contrast value of severe cirrhosis cases in hepatobiliary phase of Gd-EOB-DTPA enhanced MRI increased in super-delayed phase image. So, we suggest that it might be effective to examine the super-delayed phase liver imaging in liver dysfunction cases such as severe LC, to improve conspicuity of the focal liver lesions such as moderately differentiated HCC.
Images for this section:

**Fig. 1:** Liver MR images of Gd-EOB-DTPA-enhanced T1-weighted MRI of a 36-year-old female with liver hemangioma (normal liver function).

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**Fig. 2:** Liver MR images of Gd-EOB-DTPA-enhanced T1-weighted MRI of a 56-year-old female with moderately differentiated HCC (severe LC).

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Fig. 3: Lesion-to-liver contrast value of normal liver function and severe cirrhosis cases in hepatobiliary phase of Gd-EOB-DTPA enhanced MRI.

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**Fig. 4:** PV-to-liver contrast value of severe cirrhosis cases in hepatobiliary phase and super-delayed phase of Gd-EOB-DTPA enhanced MRI.

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Fig. 5: Lesion-to-liver contrast value of severe cirrhosis cases in hepatobiliary phase and super-delayed phase of Gd-EOB-DTPA enhanced MRI.

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Conclusion

Since lesion conspicuity was increased on super-delayed phase of Gd-EOB-enhanced MRI in comparison with routine hepatobiliary phase images, we argue that it might be effective to obtain MR images at the adequate imaging timing for diagnosis of HCCs in the patients with severe LC.
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References
