Visualization of liver uptake function using the uptake contrast-enhanced ratio in hepatobiliary phase imaging

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Aims and objectives

Background
Gadoxetic acid disodium is a liver-specific magnetic resonance (MR) contrast agent that is taken up into hepatocytes through passive transport using a receptor on the cell surface and then is excreted into the biliary tract (1-5). Approximately half of injected gadoxetic acid disodium is taken-up by hepatocytes. This uptake reaches a plateau after approximately 20 minutes and persists for approximately 2 hours (6,7). Recent reports suggest that gadoxetic acid disodium can also be used as a tracer for liver function testing (8,9). It is feasible to analyse the contrastagent accumulation in the hepatobiliary phase, as has been described by Motosugi et al. and Yamada et al., who used a semi-quantitative approach relating the liver SI to the splenic SI (9,10).

Evaluation of liver function is critical for the determination of whether a patient can safely undergo liver treatment. In addition to the Child-Pugh classification (11), many studies have described indices that can be used to measure and reflect the liver reserve, including the indocyanine green retention value (ICG-R15) (12), the ICG clearance test (ICG-K) (13) and 99mTc-galactosylhuman serum albumin (GSA) scintigraphy (14,15).

Purpose
The purpose of this study was to visualize liver uptake function using the uptake contrast-enhanced ratio in hepatobiliary phase (Uptake CERH) imaging performed with gadoxetic acid disodium.
**Fig. 1:** Design of this study

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Patients

• This retrospective study was approved by the institutional review committee of our institution, and all patients provided written informed consent prior to participation. • 37 patients (24 men, 13 women; age range, 37-84 years; mean age, 68 years) with hepatocellular carcinoma (HCC) and 23 (13 men, 10 women; age range, 33-76 years; mean age, 63 years) with metastatic liver tumors underwent gadoxetic acid disodium-enhanced MRI. • Clinical data on serum viral markers, chronic liver disease, and Child-Pugh class were assessed. • In total, 55 and 5 patients were found to have Child-Pugh class A and Child-Pugh class B disease, respectively. • A total of 23 patients underwent surgery for tumor excision. All were found to have Child-Pugh class A disease.

Methods - MRI Technique 1

• MR images were obtained on 3.0 T clinical scanner equipped with a Cardiac coil. • We adopted liver acquisition with volume acquisition pulse sequences to evaluate the Uptake CERH values. The liver acquisition with volume acceleration pulse sequences is standard sequences. • MRI parameters were as follows: repetition time = 3.1 msec, echo time = 1.4 msec, flip angle = 12, matrix size = 256 × 224 (512 zip), field of view = 38 cm, slice thickness = 3.8 mm (zip2), and location per slab = 54, Acceleration = 1.76.

Methods - MRI Technique 2

• Two sets of axial images were acquired in the liver plane: the liver acquisition with volume acceleration pre-contrast enhance and hepatobiliary phase images. Hepato-biliary phase images were imaged after an intravenous bolus injection of Gd-EOB-DTPA for 20 minutes. • The Gd-EOB-DTPA was administered intravenously as a bolus dose at a rate of 1 mL/sec through an intravenous cubital line that was flushed with 40 mL saline using a power injector.

Methods - Uptake CERH image 1

In this study, we assumed that contrast enhanced ratio in hepato-biliary phase (CERH) in the spleen was similar to contrast enhanced ratio in the extracellular matrix (CEREM). The CEREM and Uptake CERH value were defined as the percentage of signal gain between the pre-contrast images and hepatobiliary phase images as follows:

\[
\text{CERH} \, (\%) = 100 \times \left( \frac{\text{SI}_H}{\text{SI}_P} - 1 \right) \quad \ldots \ldots \, (1)
\]

\[
\text{CEREM} \, (\%) = 100 \times \left( \frac{\text{SI}_{H\text{ (spleen)}}}{\text{SI}_{P\text{ (spleen)}}} - 1 \right) \quad \ldots \ldots \, (2)
\]

\[
\text{Uptake CERH} \, (\%) = \text{CERH} - \text{CEREM} \quad \ldots \ldots \, (3)
\]

where \( \text{SI}_H \) and \( \text{SI}_P \) are the signal intensity in the hepato-biliary phase images and in the pre-contrast enhanced images, respectively.
SI_H (spleen) and SI_P (spleen) are SI_H and SI_P in the spleen.

Methods - Uptake CERH image 3

• The Uptake CERH values of whole liver parenchyma without HCC and metastatic tumor were measured in all patients. • The measurement of Uptake CERH value was performed by one radiologist and one PhD. Region of interest (ROI) acquisition was performed using OsiriX (Ver.3.9.4) medical imaging software. • Hepato-biliary phase were used to define ROIs for the spleen and the whole liver parenchyma without tumor. The defined ROIs were drawn in the Uptake CERH images for Uptake CERH value analysis.

Methods- Biochemical Liver function tests

• The medical records of 60 patients were reviewed for levels of serum albumin, serum total bilirubin level, prothrombin activity (PT%), platelet count, and ICG-R15 that were obtained within 1 week before or after MR imaging. Two patients with ICG-R15 intolerance were contained in this study. • The relationship between Uptake CERH value and biochemical liver function tests was investigated through correlational analysis.

Methods - cellular density in the liver parenchyma 1

• The number of cells per unit area (cellular density) was measured as background liver tissue cellularity on pathological specimens stained with hematoxylin and eosin. • A pathologist decided the most common location in the measurement area. The ROIs had a rectangular sampling area of 340 mm2 in the 400 microscope fields around which the apparently pathologic finding had been observed under lower magnification.

Methods- cellular density in the liver parenchyma 2

• Cell density was measured within 10 ROIs surrounding non-cancerous background liver tissue; the mean was assumed to be the cell density of each portion of the liver. • The number of cells was calculated using Win Roof ver. 5 (Mitani Corporation, Fukui, Japan), and the number of nuclei was obtained using a threshold setting for nuclear color extraction. In the present study, we assumed that the number of nuclei was similar to the number of cells.

Statistical analyses

• Statistical analyses were performed using statistical software. The Mann-Whitney test and Tukey’s multiple comparison test were used to evaluate differences in the Uptake CERH value according to the classified liver function. • The Pearson correlation coefficient was used to evaluate correlations between the Uptake CERH value and biochemical liver function tests, cellular density in the liver parenchyma. • Two-tailed P values of less than 0.05 were considered to indicate a significant difference.
Fig. 1: Design of this study

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Methods
- cellular density in the liver parenchyma 3-

Measurement data

Hepatocellular image
Uptake CERH image

ROI

Uptake CERH values

Microscopic examination
WinRoof

Hepatocellular density

Data Analysis
Relations of Uptake CERH values and hepatocellular density in the surrounding non-cancerous background liver tissue.

Fig. 2: Methods- cellular density in the liver parenchyma 3-

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Results

Results - Contrast enhanced ratio in hepato-biliary phase imaging

• Figure 1 shows the Uptake CERH images. As clinical liver damage worsens, the Uptake CERH images show lower Uptake CERH values (Uptake CERH images are shown transitioning from red to black). The ICG-R15 intolerance case shows a lowest Uptake CERH value, the Uptake CERH images are shown in purple (Uptake CERH = 0.3 ±3.0%). • Table 1 summarizes the clinical liver damage classification and the Uptake CERH values of parenchyma without HCC and metastatic tumor. Uptake CERH value was significantly higher with Child-Pugh classification A (92.4 ± 36.6%) than in classifications B (34.7 ± 24.9%) (p < 0.01). Uptake CERH value was significantly higher with metastatic liver tumor (105.0 ± 23.3%) than HCC (76.8 ± 43.1%) (p < 0.05). Uptake CERH value was significantly higher with non chronic liver disease group (117.9 ± 26.8%) than in hepatitis (78.8 ± 24.1%), cirrhosis (21.1 ± 20.1%) (p < 0.001).

Results - Biochemical liver function test

• Table 2 summarizes the correlation between Uptake CERH value, CERH value, CEREM and liver function tests. The Uptake CERH value, CERH value correlated with albumin, bilirubin, PT (%), ICG-R15, platelet count (p < 0.05). The CEREM value did not correlate with bilirubin, PT (%), ICG-R15, platelet count (p > 0.05). • Figure 3 shows the correlation between ICG-R15 and Uptake CERH value, CERH value. The Uptake CERH value and CERH value correlated with ICG-R15 (r = 0.61, 0.57, respectively).

Results - cellular density in the liver parenchyma

• The CERH value and hepatocellular density were lower with liver damage group than no liver damage group (Figure 4). • Figure 5 shows the correlation between hepatocellular density in the surrounding noncancerous background liver tissue and the CERH and Uptake CERH values. Cellular density was correlated with both the Uptake CERH and CERH values (r = 0.80, 0.75; p < 0.01, respectively).
Images for this section:

**Fig. 1 Uptake CERH images in Liver**

(a) No liver damage
Uptake CERH = 130.2 ±11.8%

(b) Chronic hepatitis
Uptake CERH = 111.6 ±8.4%

(c) Cirrhosis
Uptake CERH = 15.8 ±8.1%

(d) ICG-R15 intolerance
Uptake CERH = 0.3 ±3.0%

**Fig. 3:** Fig. 1 Uptake CERH images in Liver

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**Table 1.** Summarizes the clinical liver damage classifications and the Uptake CERH values of tumor-free parenchyma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Uptake CERH value(%)</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh</td>
<td></td>
<td></td>
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<tr>
<td>A (n = 55)</td>
<td>92.4 ± 36.6</td>
<td>Mann Whitney test p &lt; 0.01</td>
</tr>
<tr>
<td>B (n = 5)</td>
<td>34.7 ± 24.9</td>
<td></td>
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<tr>
<td>Tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC (n = 37)</td>
<td>76.8 ± 43.1</td>
<td>Mann Whitney test p &lt; 0.05</td>
</tr>
<tr>
<td>Metastasis (n = 23)</td>
<td>105.0 ± 23.3</td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no chronic liver disease(n = 20)</td>
<td>117.9 ± 26.8</td>
<td>Tukey's Multiple comparison p &lt; 0.001</td>
</tr>
<tr>
<td>Hepatitis (n = 33)</td>
<td>78.8 ± 24.1</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis (n = 15)</td>
<td>21.1 ± 20.1</td>
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</tbody>
</table>

**Fig. 4:** Table 1. Summarizes the clinical liver damage classifications and the Uptake CERH values of tumor-free parenchyma

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Table 2 Summarizes the correlations among the Uptake CERH values and the liver function test results

<table>
<thead>
<tr>
<th></th>
<th>ICG-R15 (%)</th>
<th>Alubmin (g/dl)</th>
<th>Bililubin (mg/dl)</th>
<th>PT (%)</th>
<th>Platelet (10^4/ul)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptake CERH (%)</td>
<td>-0.611 ( &lt; 0.01 )</td>
<td>0.472 ( &lt; 0.01 )</td>
<td>-0.356 ( &lt; 0.01 )</td>
<td>0.411 ( &lt; 0.01 )</td>
<td>0.426 ( &lt; 0.01 )</td>
</tr>
<tr>
<td>CERH (%)</td>
<td>-0.568 ( &lt; 0.01 )</td>
<td>0.388 ( &lt; 0.01 )</td>
<td>-0.366 ( &lt; 0.01 )</td>
<td>0.350 ( &lt; 0.01 )</td>
<td>0.401 ( &lt; 0.01 )</td>
</tr>
<tr>
<td>CEREM (%)</td>
<td>0.222 ( 0.09 )</td>
<td>-0.339 ( &lt; 0.01 )</td>
<td>-0.041 ( 0.75 )</td>
<td>-0.231 ( 0.08 )</td>
<td>-0.110 ( 0.40 )</td>
</tr>
</tbody>
</table>

Pearson r (p value)

Fig. 5: Table 2 Summarizes the correlations among the Uptake CERH values and the liver function test results

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Fig. 3 The correlation between ICG-R15 and Uptake CERH value, CERH value

(a) ICG-R15 and CERH values 
(r = 0.57, p< 0.01)

(b) ICG-R15 and Uptake CERH values 
(r = 0.61, p< 0.01)

Fig. 6: Fig. 3 The correlation between ICG-R15 and Uptake CERH value, CERH value

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Fig. 7: Fig. 4 Hepatocellular density and Uptake CERH value.

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Fig. 5 Correlation of hepatocellular density and CERH value, Uptake CERH value.

(a) Hepatocellular density and CERH value  
(r = 0.75, p< 0.01)

(b) Hepatocellular density and CERH value  
(r = 0.80, p< 0.01)

Fig. 8: Fig. 5 Correlation of hepatocellular density and CERH value, Uptake CERH value.

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Conclusion

Discussion

Uptake CERH images were used to visualize differences in liver uptake on the basis of the degree of clinical liver damage (Figure 1). Uptake CERH values progressively and significantly decreased with an increase in clinical liver damage (Table 1). The Uptake CERH value showed the best correlation with the biochemical liver function test results (Table 2). In patients with ICG-R15 intolerance, the Uptake CERH values were approximately 0% (Figure 1 (d)).

In addition, the Uptake CERH value showed a stronger correlation with ICG-R15 compared with the CERH value (Figure 3). Furthermore, the Uptake CERH value was better correlated with hepatocellular density compared with the CERH value (Figure 5). These results justify the assumption that CERH in the spleen is similar to CEREM.

ICG-R15 is the most important index for evaluating liver uptake function. However, ICG-R15 assumes that uptake is homogeneous throughout the liver. Even in tumor-free liver parenchyma, the detection of heterogeneous and partial liver uptake is possible because the Uptake CERH value of the whole liver parenchyma is measured directly. Uptake CERH imaging is therefore a useful technique for visualization of heterogeneous liver uptake.

limitations

• This study had several limitations. First, the study population included no cases of Child-Pugh class C. • Second, although a T1 map might be preferable for quantitative analysis of signal intensity of the liver parenchyma on gadoxetic acid disodium enhanced MRI, a T1 map was not constructed. • Because this study was performed in a clinical setting.

Conclusion

Uptake CERH images can be used to visualize heterogeneous and partial uptake of a contrast agent by the liver; therefore, Uptake CERH imaging is a potentially useful technique for the assessment of liver uptake function in patients with clinical liver damage.
References


