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Quantitative analysis of liver function using superparamagnetic iron oxide- and Gd-EOB-DTPA-enhanced MRI: Comparison with Technetium-99m galactosyl serum albumin scintigraphy

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ABSTRACT

Purpose: To examine whether or not the parameters regarding the signal intensity of the liver parenchyma on superparamagnetic iron oxide (SPIO)- and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI are correlated with the parameters of Technetium-99m galactosyl serum albumin (^{99m}Tc-GSA) scintigraphy.
Materials and methods: This retrospective study consisted of 55 and 33 patients who underwent SPIO- and Gd-EOB-DTPA-enhanced MRI in addition to ^{99m}Tc-GSA scintigraphy, respectively. For each patient, we calculated Pre *R2** and Pre *R2*, which are equivalent to *R2** (=1/*T2**) and *R2* (=1/*T2*) values of the liver parenchyma; $\Delta R2^*$ and $\Delta R2$, which represent differences in *R2** and *R2* values of the liver parenchyma before and after administration of SPIO; and the increase rates of both the liver-to-spleen signal intensity ratio (LSR) and the liver-to-major psoas muscle signal intensity ratio (LMR) on the hepatobiliary phase compared with the precontrast image. For ^{99m}Tc-GSA scintigraphy, the receptor index LHL15 and the blood clearance index HH15 were recorded.
Results: Regression analysis showed a moderate correlation between Pre *R2** and LHL15 ($P < 0.05$). Mild to moderate correlations were also obtained between any combination of $\Delta R2^*$ and $\Delta R2$ on the one hand, and LHL15 and HH15 on the other ($P < 0.05$). There were moderate correlations between any combination of increase rates of LSR and LMR on the one hand, and LHL15 and HH15 on the other ($P < 0.05$–0.001).
Conclusion: Pre *R2**, $\Delta R2^*$, $\Delta R2$ and the increase rates of LSR and LMR could be used as quantitative indicators of liver function.

1. Introduction

Liver function is usually evaluated using laboratory data obtained by blood sampling. However, different laboratory values are considered to reflect different aspects of liver function. For example, serum bilirubin and albumin levels represent biliary excretion and protein synthesis, respectively. Because it is difficult to evaluate liver function using a single parameter, a combination of multiple parameters, such as Child-Pugh classification, has been used as more reliable indicator of liver function until now. On the other hand, the indocyanine green (ICG) retention rate test may be related to several processes [1].

Technetium-99m galactosyl serum albumin (^{99m}Tc-GSA) scintigraphy is a representative imaging modality for predicting liver function [2]. This examination utilizes the fact that asialoglycoprotein (ASGP) receptor is present only in mammalian hepatocytes and binds specifically to the ASGP [2]. The uptake of ^{99m}Tc-GSA is an independent biochemical process that no other test can assess. A hyper-asialoglycoproteinemia is reported in patients with chronic liver disease and, the number of ASGP receptors is decreased in the cirrhotic liver [2]. ^{99m}Tc-GSA scintigraphy can give quantitative information on liver function and was recently recognized as the best method for evaluating liver functional reserve [3–5]. ^{99m}Tc-GSA scintigraphy is an accepted

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modality to assess liver function, and is routinely used for this purpose in Japan [2].

Now a liver-specific contrast agent, including superparamagnetic iron oxide (SPIO) and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), is widely used to improve the detectability of focal liver lesions and the characterization of liver tumors on magnetic resonance (MR) imaging [6–9]. SPIO is taken up by the reticuloendothelial system of Kupffer cells (KC), whereas Gd-EOB-DTPA is taken up specifically by hepatocytes. Therefore, the change in the MR signal of the liver parenchyma before and after administration of each contrast agent can reflect a "function" of the liver. Because there is no biological marker suggesting the uptake of these contrast agents in the liver, the radiological evaluation of liver "function" using these agents should be an independent and exclusive method. Furthermore, it is of added, clinical value if we can obtain quantitative information on liver function, as well as the diagnosis of liver tumors. However, only a handful of reports have discussed MR findings using a liver-specific contrast agent with liver function [1,10–13]. To the best of our knowledge, MR findings using a liver-specific contrast agent have not been compared with ^{99m}Tc-GSA scintigraphy yet.

In this study, we set up multiple parameters regarding the signal intensity of liver parenchyma on SPIO- and Gd-EOB-DTPA-enhanced MRI and examined whether or not they correlated with the parameters of ^{99m}Tc-GSA scintigraphy.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the institutional review board of our hospital. The requirements for informed consent were waived for the retrospective study.

Referring to the medical data recorded at our hospital, we enrolled 57 patients who had undergone SPIO-enhanced MRI in addition to ^{99m}Tc-GSA for the evaluation of liver tumor and function between January 2007 and October 2007. One patient with a recent history of blood transfusion and administration of iron was excluded, and another was excluded for poor image quality due to respiratory artifacts. The remaining 55 patients included 37 men and 18 women (age range: 17–82 years; mean age 64.5 years). The hepatitis B surface antigen was present in 13 cases and the hepatitis C virus antibody in 34 cases. Neither of these was seen in 11 cases. Four and 51 patients were clinically diagnosed to have normal liver and chronic hepatitis/liver cirrhosis, respectively. The grading of liver dysfunction was evaluated based on the Child-Pugh classification for the 51 patients with chronic hepatitis/liver cirrhosis, and 37, 13, and 1 patients were categorized into Grades A, B, and C, respectively.

We also enrolled 35 patients who had undergone Gd-EOB-DTPA-enhanced MRI in addition to ^{99m}Tc-GSA for the evaluation of liver tumor and function between June 2008 and January 2010. One patient with obstructive jaundice due to hilar cholangiocarcinoma was excluded, and another was excluded for poor image quality due to respiratory artifacts. The remaining 33 patients included 23 men and 10 women (age range: 36–86 years; mean age 69 years). The hepatitis B surface antigen was present in 5 cases and the hepatitis C virus antibody in 15 cases. Neither of these was seen in 13 cases. Five and 28 patients were clinically diagnosed to have normal liver and chronic hepatitis/liver cirrhosis, respectively. The grading of liver dysfunction was evaluated based on the Child-Pugh classification for the 28 patients with chronic hepatitis/liver cirrhosis, and 19, 8, and 1 patients were categorized into Grades A, B, and C, respectively.

The MR examination and scintigraphy were performed within 1 month for each patient, and no treatment was performed between these two examinations for any patients.

2.2. MR imaging and scintigraphy

MR imaging was performed on a whole-body 1.5 T scanner (Intera Achieva Nova Dual; Philips Medical Systems, Best, Netherlands). For SPIO-enhanced MRI, $T2^*$ and $T2$ maps were generated before and 10 min after intravenous injection of 0.016 mmol Fe/kg of ferucarbotran (Resovist; Bayer, Osaka, Japan). Dynamic scanning of each map was not performed. The detailed imaging parameters were as follows. (A) For the $T2^*$ map: 2D multi-slice multi-echo FFE, body coil, TR/mTE/FA = 256/26/28°, EPI factor = 29 (ΔTE 1.8 ms), FOV 40 cm, matrix 126 × 144, slice thickness/gap = 5/0 mm, 10 slices (5 slice × 2), scan time 48 s (24 s × 2), and breath-holding. (B) For the $T2$ map: 2D multi-slice multi-echo TSE, body coil, TR/1st TE/FA = 3000–4000 ms/10 ms/90°, TSE factor = 32, echo space = 10 ms, FOV 40 cm, matrix 256 × 176, slice thickness/gap = 5/0 mm, scan time 5 min, and breath-triggering. For generation of the $T2^*$ map, modulus, real, and imaginary data were acquired for each TE at each slice. ΔB_0 correction along the z-axis was made, and $T2^*$ decay was calculated for each pixel. For generation of the $T2$ map, data were acquired for each TE at each slice. $T2$ decay was calculated for each pixel.

For Gd-EOB-DTPA-enhanced MRI, multiphase dynamic study including arterial, portal and late phases was performed using axial 3D THRIVE (three-dimensional $T1$ high-resolution isotropic volume excitation). MR images scanned before and 20 min after intravenous injection of 0.1 mL/kg (total amount: 4.5–8 mL) of Primovist (Bayer) were evaluated in this study. The detailed imaging parameters were as follows: SENSE body coil, TR/TE/FA = 3 ms/1 ms/20°, matrix 224 × 116, FOV 36 cm, RFOV 75%, SENSE factor 1.3, slice thickness/gap = 4 mm/−2 mm, centric k-space ordering, SPIR, acquired 80 sections, scan time 18 s, and breath-holding.

^{99m}Tc-GSA (185 MBq) was injected intravenously, and dynamic images were recorded with the patient in the supine position using a STARCAM (GE Medical Systems, Milwaukee, WI, USA), which is a large-field-of-view gamma camera with a low-energy, general-purpose, collimator. Digital images (128 × 128 matrix) of an anterior abdominal view were acquired at a rate of 1 s/frame (60 frames) during the first minute after the bolus injection of ^{99m}Tc-GSA, followed by a rate of 1 min/frame (14 frames). Data acquisition was stopped 15 min later. Hepatic and cardiac counts on the image taken 15 min after intravenous injection (L15 and H15), and cardiac count on the image taken at 3 min after intravenous injection (H3) were measured by covering the entire accumulation in the liver and heart. The receptor index LHL15 (=L15/H15 + L15; normal range, 0.950 ± 0.015) and the blood clearance index HH15 (=H15/H3; normal range, 0.529 ± 0.044) were recorded for each patient [14]. As liver dysfunction advances, LHL15 decreases and HH15 increases.

2.3. Image analysis

The PRIDE $T2^*$fit tool (Philips Medical Systems) was applied to analyze the $T2^*$ map. First, two experienced radiologists together selected three slices without significant artifacts. They measured the $T2^*$ value by placing as large a region of interest (ROI) as possible on the liver parenchyma as avoiding vessels, tumors, and artifacts in consensus fashion (Fig. 1). For each slice, two rectangular ROIs were placed: one in the right lobe and the other in the left. The average of the six $T2^*$ values was taken as the "$T2^*$ value" of the patient. Finally, $R2^*$ (=1/$T2^*$) values before and after SPIO administration were recorded for each patient. The same size and shape of ROI was placed at the same position of the liver parenchyma for $T2^*$ maps before and after administration of SPIO. A $T2$ map was generated on