Abstract. The present study aimed to evaluate regional liver function impairment following transcatheter arterial chemoembolization (TACE), assessed by magnetic resonance imaging (MRI) enhanced by gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA). Additionally, this study evaluated the associations between signal intensity and various clinical factors. A prospective study was conducted between March 2012 and May 2013 with a total of 35 patients. Gd-EOB-DTPA-enhanced MRI was performed 3–5 days after TACE therapy. The signal to noise ratio (SNR) was subsequently calculated for healthy liver tissue regions and peritumoral regions, prior to and 20 min after Gd-EOB-DTPA administration. The correlation between clinical factors and relative SNR was assessed using Pearson's correlation coefficient or Spearman's rank correlation coefficient. Prior to Gd-EOB-DTPA administration, the SNR values showed no significant difference ($t=1.341$, $P=0.191$) in healthy liver tissue regions (50.53±15.99; range, 11.25-83.46) compared with peritumoral regions (49.81±15.85; range, 12.34-81.53). On measuring at 20 min following Gd-EOB-DTPA administration, the SNR in healthy liver tissue regions (82.55±33.33; range, 31.45-153.02) was significantly higher ($t=3.732$, $P<0.001$) compared with that in peritumoral regions (75.77±27.41; range, 31.42-144.49). The relative SNR in peritumoral regions correlated only with the quantity of iodized oil used during TACE therapy ($r=0.528$, $P=0.003$); the age, gender, diameter and blood supply of the tumor, or Child-Pugh class of the patient did not correlate with relative SNR. Gd-EOB-DTPA-enhanced MRI may be an effective way to evaluate regional liver function impairment following TACE therapy.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common types of liver cancer, with ~748,300 new liver cancer cases and 695,900 liver cancer-related mortalities occurring worldwide (1). The overall five-year survival rate of HCC is 3% in the USA (2). A population-based study conducted by Guiu et al reported that the one-year survival rate of HCC had increased to 32.8% and the five-year survival rate of HCC had risen to 10.0% over the past four decades (3). Surgical resection is the first option for HCC patients who meet the Milan Criteria (4): (i) one lesion <5 cm; (ii) ≤3 lesions <3 cm; (iii) no extrahepatic manifestations and (iv) no vascular invasion. However, it is not feasible when patients present at an advanced stage of the disease (5). Furthermore, conservative treatments, including chemotherapy, radiotherapy and biotherapy may not achieve satisfactory curative results (6). Transcatheter arterial chemoembolization (TACE) is the primary treatment option for patients with unresectable HCC (7). Approximately 16-55% patients can benefit from TACE therapy and achieve a low rate of tumor regression. Llovet et al reported that TACE resulted in objective responses that were sustained for $\geq 6$ months in 35% of cases, and was associated with a lower rate of portal-vein invasion compared with conservative treatment (8). Following TACE therapy, HCC tumor cells undergo ischemia and necrosis. Healthy liver tissue is inevitably damaged during the procedure, which may adversely affect the postoperative recovery of the patient (9). Magnetic resonance imaging (MRI) in combination with liver-specific contrast agents facilitates the detection of focal liver disease, and has been demonstrated to be superior to computed tomography (CT) for this purpose (10).
Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA; Primovist), is a liver-specific, paramagnetic contrast agent developed by Bayer-Schering Pharma (Berlin, Germany) with combined perfusion and hepatocyte-selective properties. A number of studies have demonstrated the reliability of Gd-EOB-DTPA as a non-invasive tool for estimating overall and regional liver cell function and viability, through measuring the cytomembrane transporter function (such organic anion transporting polypeptide 1 and MRP) (11-13). The present study aimed to investigate the potential utility of Gd-EOB-DTPA-enhanced MRI in the evaluation of regional liver function damage in peritumoral regions following TACE therapy.

Materials and methods

Ethics statement. Written, informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of The Second XiangYa Hospital of Central South University (Changsha, China).

Patients. A total of 35 HCC patients who underwent Gd-EOB-DTPA-enhanced MRI of the liver were enrolled in this prospective study between March 2012 and May 2013. Of the 35 patients, four were excluded from the study due to poor postoperative clinical status and two were excluded due to poor breath-holding during MRI examination. The final study population comprised 29 patients [18 males and 11 females; mean age ± standard deviation (SD), 49.86±11.05 years; age range, 28-76 years].

The diagnosis of HCC was determined on the basis of the following criteria: Typical lesions observed on at least one imaging modality (CT, MRI or ultrasound) with an elevated serum α-fetoprotein level (>400 ng/ml; n=23) or liver biopsy with pathological confirmation of HCC (n=12).

Inclusion criteria were as follows: Patients who could understand the study documents (which contained the study design, content, background, methods and possible treatment outcomes), had a single lesion with tumors <10 cm in size; were categorized as Child-Pugh class A or B prior to surgery and were receiving TACE therapy for the first time. Exclusion criteria were as follows: Severe motion artifacts due to poor breath-holding, profound liver cirrhosis, multiple lesions, tumors >10 cm in size, obstruction of main or first branch of portal vein, difficulty in locating the feeding artery during the procedure or hepatic artery to portal vein shunting. Exclusion criteria for the use of Gd-EOB-DTPA were as follows: Allergy to Primovist, severe cardiovascular disease or kidney insufficiency (glomerular filtration rate <60 ml/min/1.73 m²).

TACE protocol. TACE was performed via the femoral artery under GELCE 3100 (GE Healthcare, Fairfield, USA) bidirectional digital subtraction angiography. Using the Seldinger technique (14), a catheter sheath was inserted into the femoral artery with the aid of a guide wire. The Yashiro, RH catheter or Microcatheter (Terumo, Tokyo, Japan) was sent to the artery feeding the tumor. The Yashiro and RH catheters were the first option for TACE therapy; when these two catheters were not effective, the microcatheter was used, as it is smaller than the microcatheter was used, as it is smaller than

MRI protocol. MRI was performed 3-5 days after TACE therapy using a 3T superconducting MRI system (Philips, Amsterdam, Netherlands) with a phased array body coil (SENSE XL Torso; Philips) and the following imaging parameters: 7 mm section thickness and 3 mm intersection gap. Three-dimensional T1-weighted turbo field echo sequence with spectral saturation inversion recovery fat suppression [repetition time (TR), 3.0 ms; echo time (TE), 1.35 ms; field of view, 350x320 mm; matrix, 124x100; flip angle, 10˚] was utilized pre-contrast and post-contrast (15 s, 90 s, 3 min and 20 min after injection of Gd-EOB-DTPA). Respiratory-triggered T2-weighted fast spin echo sequence with short TI inversion recovery fat suppression (TR, 1,113 ms; TE, 70 ms; field of view, 350x320 mm; matrix, 268x200; flip angle, 90˚) was used prior to injection of the contrast agent. The contrast agent was used at a dose of 0.025 mmol/kg body weight and at an injection rate of 2 ml/s by 20 ml saline flush using an intravenous line (via the cubital vein).

Imaging analysis. In the evaluation of hepatocytic uptake of Gd-EOB-DTPA, signal intensity (SI) of the region of interest (ROI) of the liver was measured by one radiologist with 20 years experience of abdominal imaging, who was blinded to the clinical data and selection of ROIs. The ROIs were selected to be as large as possible, avoiding large vessels and biliary ducts, and the identical location was used prior to and following Gd-EOB-DTPA administration. Each ROI was circular or oval. Signal to noise ratio (SNR) was calculated for peritumoral and healthy liver tissue regions (Fig. 1), by dividing the SI of the tissue by the standard deviation of the image noise (background noise outside of the patient's body).

The relative SNR in the peritumoral regions was measured to assess the correlation between hepatocytic uptake of Gd-EOB-DTPA and potential clinical influencing factors (patients age, gender, diameter of the tumor, blood supply of the tumor, Child-Pugh class and quantity of Iodized oil used). Relative SNR = ([SNR_after - SNR_before]/SNR_before] x 100.

Statistics. The data are presented as the mean ± SD (range) and were analyzed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The correlation between clinical factors and relative SNR was analyzed using Pearson's correlation coefficient or Spearman's rank correlation coefficient. Pearson's correlation analysis was used to evaluate the association between the relative SNR of liver parenchyma and the age of the patient, the diameter of the tumor and the quantity of iodized oil used for TACE therapy. Spearman's rank correlation was used to evaluate the association between the relative SNR of liver parenchyma and clinical parameters including gender, blood supply of the tumor and Child-Pugh class. The quantitative parameter of healthy liver tissue regions vs. peritumoral regions was calculated using a paired t-test. P<0.05 was considered to indicate a statistically significant difference.
Assessment of clinical influencing factors. Of the 29 patients, 22 were categorized as Child-Pugh class A and seven as Child-Pugh class B. The quantity of iodized oil used for individual patients varied from 5-30 ml, with a mean quantity of 16.14±7.04 ml. A poor blood supply to the tumor was observed in nine patients, while a rich blood supply was observed in the remaining 20. The diameter of the tumor ranged from 3.1-9.9 cm, with a mean diameter of 6.94±2.15 cm. No correlation was observed between the blood supply and the diameter of the tumor (r=0.276, P=0.148). Detailed clinical information is listed in Table I.

Gd-EOB-DTPA uptake in different liver tissue regions. Prior to Gd-EOB-DTPA administration, no significant difference
was observed in the SNR values of healthy liver tissue regions (50.53±15.99; range, 11.25-83.46) compared with those of peritumoral regions (49.81±15.85; range, 12.34-81.53; t=1.341, P=0.191). When measured 20 min after the administration of Gd-EOB-DTPA, the SNR values of healthy liver tissue regions (82.55±33.33, range 31.45-153.02) were significantly higher compared with those of the peritumoral regions (75.77±27.41, range 31.42-144.49; t=3.732, P<0.001; Fig. 2). Further detail is shown in Table II. The SNR measured in healthy liver tissue regions was significantly increased at 20 min after the administration of Gd-EOB-DTPA compared with that prior to its administration (t=6.175, P<0.001). In peritumoral regions, the SNR also exhibited a significant increase when measured 20 min after Gd-EOB-DTPA administration (t=6.844, P<0.001) compared with that prior to administration. The absolute change in SNR for healthy liver tissue regions was significantly higher (t=3.005, P=0.006) compared with those of the peritumoral regions (Fig. 3).

Association between relative SNR and its potential influencing factors. The relative SNR did not correlate with the age (r=0.151, P=0.434), gender (r=−0.381, P=0.055) or Child-Pugh class (r=0.106, P=0.584) of the patient. Additionally, no correlation was observed between the SNR and the blood supply (r=0.241, P=0.209) or the diameter (r=0.226, P=0.238) of the tumor. Relative SNR, measured 20 min following Gd-EOB-DTPA administration, was observed to correlate only with the quantity of iodized oil used during TACE therapy (r=0.528, P=0.003; Fig. 4). Further detail is shown in Table III.

Discussion

As TACE therapy may damage normal liver tissue, patients with pre-existing liver dysfunction commonly experience hepatic failure following TACE therapy (15). A previous study conducted by Chen et al suggested that the liver function after TACE therapy was significantly decreased compared with the preoperative status (16). Injuries caused by TACE therapy may affect the selection of the surgical procedure for patients subsequently requiring tumor resection (17). Reliable estimation of regional liver function in the preoperative and postoperative periods is crucial, particularly for patients at high risk of hepatic failure. Shimizu et al (18) evaluated
In conclusion, the present data demonstrates an apparent decrease in Gd-EOB-DTPA uptake in peritumoral liver regions compared with healthy liver tissue regions 20 min after Gd-EOB-DTPA administration, indicating the existence of regional hepatocytic injury caused by TACE therapy. Gd-EOB-DTPA-enhanced MRI may therefore represent an effective, non-invasive tool for evaluating regional liver function impairment following TACE therapy. Furthermore, an association was observed between the relative SNR and the quantity of iodized oil used, indicating that the dosage of oil used may impact the subsequent level of functional liver impairment. Further study should be concerned with the timing of liver function recovery after TACE therapy using Gd-EOB-DTPA-enhanced MRI.

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