SPANDIDOS PUBLICATIONS

Role of diffusion-weighted imaging in evaluating therapeutic efficacy after transcatheter arterial chemoembolization for hepatocellular carcinoma

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Abstract. The decision to repeat transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) is based on correct evaluation of response to therapy. The purpose of this study was to investigate whether apparent diffusion coefficient (ADC), a quantitative parameter of diffusion-weighted imaging (DWI), can predict early HCC recurrence after TACE. Results obtained using this method were compared with those using iodized-oil computed tomography (CT). DWI was performed on 25 patients with 36 HCCs before and 5-7 days after TACE to calculate the ADC of HCC. Patients were also evaluated with iodized-oil CT immediately after TACE. Contrast-enhanced CT was performed 3 months after TACE to confirm early relapse of HCC lesion. After TACE, the percent change in ADC (%ADC) from before to after therapy was significantly increased in non-relapsed lesions (85.2±12.4%) compared to relapsed lesions (8.0±56.7%, p=0.0004). However, no difference in area under the curve was seen for receiver operating characteristic analysis to predict early relapse after TACE between %ADC from DWI (95% confidence interval, 0.743-1.026) and iodized-oil CT (95% confidence interval, 0.703-1.016). ADC from DWI can evaluate the efficacy of TACE for HCC as effectively as iodized-oil CT, and may help in deciding whether to repeat TACE.

Introduction

Hepatocellular carcinoma (HCC) is an aggressive tumor with a median survival following diagnosis of approximately 6-20 months (1). Although the mainstay of therapy is surgical resection, the majority of patients are ineligible due to tumor extension or underlying liver dysfunction. Transcatheter arterial chemoembolization (TACE) is one of the most common therapeutic options for large HCCs that are not amenable to other treatments, such as resection or radiofrequency ablation (2-4). Despite attempts at complete therapy, viable neoplastic tissue remains in some cases after TACE (2,3). After treatment, follow-up imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and sonography have been used to assess therapeutic efficacy. However, conventional imaging necessitates injection of contrast material and shows some limitations in the evaluation of therapeutic efficacy. Since the 1990s, diffusion-weighted imaging (DWI) has increasingly been used for the evaluation of extracranial sites such as the abdomen and pelvis (5-11). Effective anticancer treatment results in tumor lysis, loss of cell membrane integrity and increased extracellular space, allowing increased diffusion of water (12,13). The apparent diffusion coefficient (ADC) is calculated from DWI and correlates with water diffusion without any need for injection of contrast material. Median ADC before and after TACE is significantly increased among patients with HCC (8,9). Iodized-oil CT is widely used to confirm HCC response to TACE immediately after TACE (14-16). However, to the best of our knowledge, ADC has not been correlated to the degree of effectiveness of TACE against HCC as estimated by iodized-oil CT. The purpose of this study was to compare DWI and iodized-oil CT for predicting early HCC recurrence after TACE.

Materials and methods

Patients. Prospective subjects comprised 27 consecutive patients with 38 HCCs diagnosed between January and July 2009 according to characteristic imaging findings (early enhancement on dynamic contrast-enhanced CT) and positive results for serum antibody to viral hepatitis. Each patient was fully informed about the purposes and potential risks and benefits of the study and provided written consent prior to enrolment. This study was performed in accordance with the regulation of the local Ethics Committee using routine medical test. Evaluation with DWI was performed before TACE, then 36 HCCs (mean diameter, 2.0 cm; range, 0.8-5.2 cm) in 25 patients (21 men, 4 women; mean age, 72.0 years; range, 61-92 years) depicted with DWI before TACE were re-evaluated

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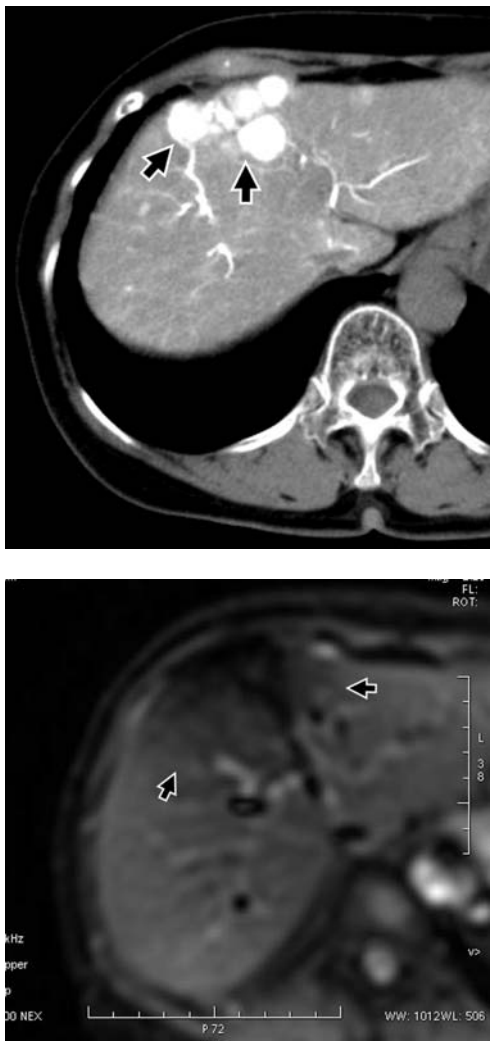

Figure 1. A 78-year-old woman with multiple HCCs in the left medial segment of the liver. (A) Contrast-enhanced CT through the intra-arterial catheter depicting multiple HCCs (arrow). (B) DWI before TACE with degraded quality due to artifact, resulting in missed tumors (arrow).

with DWI after TACE. However, two HCCs in two patients were not able to be depicted with DWI before TACE due to presumed MRI artifacts that degraded image quality (Fig. 1), and these patients were therefore excluded from the study.

MRI study. All patients were examined using a 1.5-T MRI unit (Signa HDx; GE Medical Systems, Milwaukee, WI, USA) with a 40 mT/m maximum gradient capability and built-in body coil. MRI was performed 1-2 days before and 5-7 days after TACE. DWI was obtained in 25-sec breath-hold periods using a transverse spin-echo echo-planar sequence (repetition time, 4125 ms; echo time, 56.7 ms; gradient strength, 40 mT/m; matrix size, 128x128; section thickness, 7 mm; interslice gap, 1.5 mm; three signals acquired; field of view, 360 mm). DWI and ADC maps were acquired using b-values of 0 and 500 mm^2/s applied in the z direction. Quantitative ADC maps were calculated using commercially available software and an imaging workstation (Functool and AW4.3; GE Medical Systems). ADC was measured by a radiologist (K.K.) with >20 years of experience in hepatobiliary radiology imaging and >10 years of experience with DWI. Circle-shaped regions of interest (ROIs) were placed on HCCs and surrounding non-tumorous hepatic parenchyma on the monitor of the Functool workstation to calculate ADC (Fig. 2B and C; Fig. 3B and C), based on the following formula:

$$ADC = [\ln(s0/s1)]/(b1-b0)$$

where ln is the natural log, b0=0 mm^2/s, b1=500 mm^2/s and s0 and s1 are the signal intensities of the lesion on images obtained at each b-value. Size of the ROI was set to cover the entire tumor on the slice depicting the tumor in maximum diameter. Mean ADC of four regions of interest placed at normal hepatic parenchyma, avoiding vessel structures, was also recorded before TACE (Figs. 2B and 3B). Changes in the ADC value 5-7 days after TACE were determined by calculating the percent change in ADC from baseline (before TACE), with each patient serving as his/her own control (Fig. 2B and C; Fig. 3B and C). The percent change in ADC (%ADC) from before to after TACE was calculated based on the following formula:

$$\%ADC = (ADC^a - ADC^b)/ADC^b$$

where ADC^b, ADC of HCC before TACE; and ADC^a, ADC of HCC after TACE.

Iodized-oil CT. All patients underwent non-enhanced CT immediately after the TACE procedure using an angio-CT system (Asteion; Toshiba Medical Systems, Tokyo, Japan). Helical CT images were obtained in a craniocaudal direction with 5-mm-thick sections at 120 KVp and 200 mA during a single breath-hold helical acquisition. CT scans were read by two radiologists (T.Y. and S.I.) with 8 and 19 years of experience, respectively, in abdominal and interventional radiological image interpretation. These investigators evaluated the success of the TACE procedure independently. Differences in assessment were resolved by consensus. As an evaluation criterion, iodized oil retention was defined as complete (≥90%; Fig. 2A) or incomplete (<90%; Fig. 3A).

TACE procedure. After inserting a catheter into the appropriate hepatic artery or distal branch, TACE was performed by injecting a chemotherapeutic drug emulsion, followed by gelatin sponge particles 1-2 mm in diameter (Gelpart; Nihon-Kayaku, Tokyo, Japan). The emulsion consisted of iodized oil (1-5 ml; Lipiodol Ultra Fluid; Terumo, Tokyo, Japan) and epirubicin hydrochloride (10-30 mg; Kyowa Hakko Kogyo, Tokyo, Japan), mixed by 10-20 passages through a three-way stopcock.

CT follow-up. For the evaluation of lesion relapse, all patients underwent follow-up CT at 3 months after TACE. Contrast-enhanced dynamic CT examinations were performed using helical scanners (Aquilion; Toshiba Medical Systems). A total of 100 ml of non-ionic contrast material (iopamidol 300 mgI/ml, Bayer HealthCare, Osaka, Japan) was administered through an intravenous catheter with an automatic injector at a rate of 3-4 ml/s. Images were obtained at 45-55 and 60-70s after initiating injection of contrast material, representing the hepatic arterial and portal venous phases,

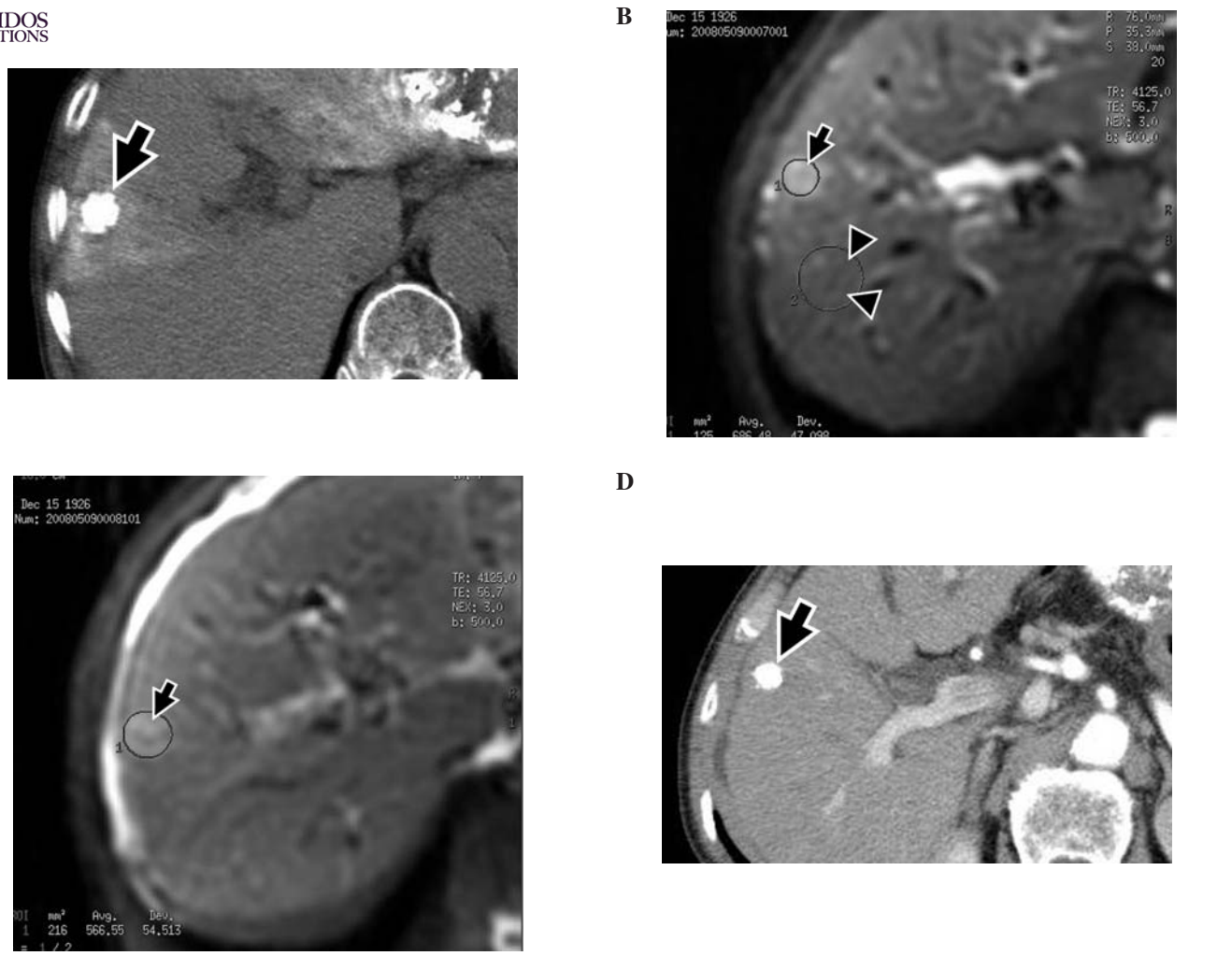

Figure 2. A 69-year-old man with a 1.1-cm HCC in the right hepatic lobe. (A) Iodized-oil CT shows complete iodized oil retention in the tumor (arrow). (B, C) DWI before (B) and after (C) TACE displayed on the Functool workstation monitor. Regions of interest were placed in the tumor (arrow) and surrounding hepatic parenchyma (arrowhead). DWI shows hyperintense signals in tumor both before and after TACE (arrow). ADC in HCC was higher after TACE ($3.45x10^{-3}$ mm^2/s) than before TACE ($1.15x10^{-3}$ mm^2/s) (%ADC, 200%). Mean ADC in surrounding hepatic parenchyma ($1.15x10^{-3}$ mm^2/s) resembled that of HCC before TACE ($1.15x10^{-3}$ mm^2/s). (D) Contrast-enhanced CT at 3 months after TACE depicted only complete iodized oil retention and no relapse of tumor (arrow).

respectively. We obtained images in a craniocaudal direction at a 5-mm slice thickness and a 5-mm interval. Parameters of multi-detector CT examinations were: slice thickness, 1.0 mm; and interval, 1.0 mm. Tumor relapse was defined as enhancing foci near the iodized oil of an embolized lesion on follow-up CT.

Statistical analysis. Statistical analysis was performed using SPSS version 10.0 software (SPSS Inc., Chicago, IL). Mean pretreatment ADC values were compared between relapsed and non-relapsed lesions using the unpaired t-test. The %ADC between relapsed and non-relapsed lesions and pretreatment ADC values between HCC lesions and surrounding hepatic parenchyma were compared using the Mann-Whitney U-test due to the unequal variance between groups. Receiver operating characteristic (ROC) analysis was performed to determine a threshold %ADC to differentiate relapse and non-relapse of HCC lesions. Two-sided tests were used, with values of $p<0.05$ indicating statistical significance.

Results

Of the 36 HCC lesions evaluated on follow-up contrast-enhanced dynamic CT, 13 lesions had relapsed and 23 lesions had not. Mean (± standard deviation) ADC in 36 HCCs from the 25 patients before TACE was $1.271\pm0.395 \times 10^{-3}$ mm^2/s, showing no significant difference from that in normal liver parenchyma ($1.286\pm0.234 \times 10^{-3}$ mm^2/s; p=0.901; Mann-Whitney U-test). ADC before TACE did not differ significantly between relapsed ($1.357\pm0.46 \times 10^{-3}$ mm^2/s) and non-relapsed lesions ($1.222\pm0.355 \times 10^{-3}$ mm^2/s, respectively; p=0.33; unpaired t-test). Non-relapsed lesions were found to show significantly larger %ADC than relapsed lesions (85.2±12.4% vs. 8.0±56.7%, respectively; p=0.0004; Mann-Whitney U-test).

Iodized-oil CT immediately after TACE demonstrated 26 complete lesions and 10 incomplete lesions. Correlations between iodized-oil CT and relapse are shown in Table I. ROC analysis for the prediction of relapse with iodized-oil

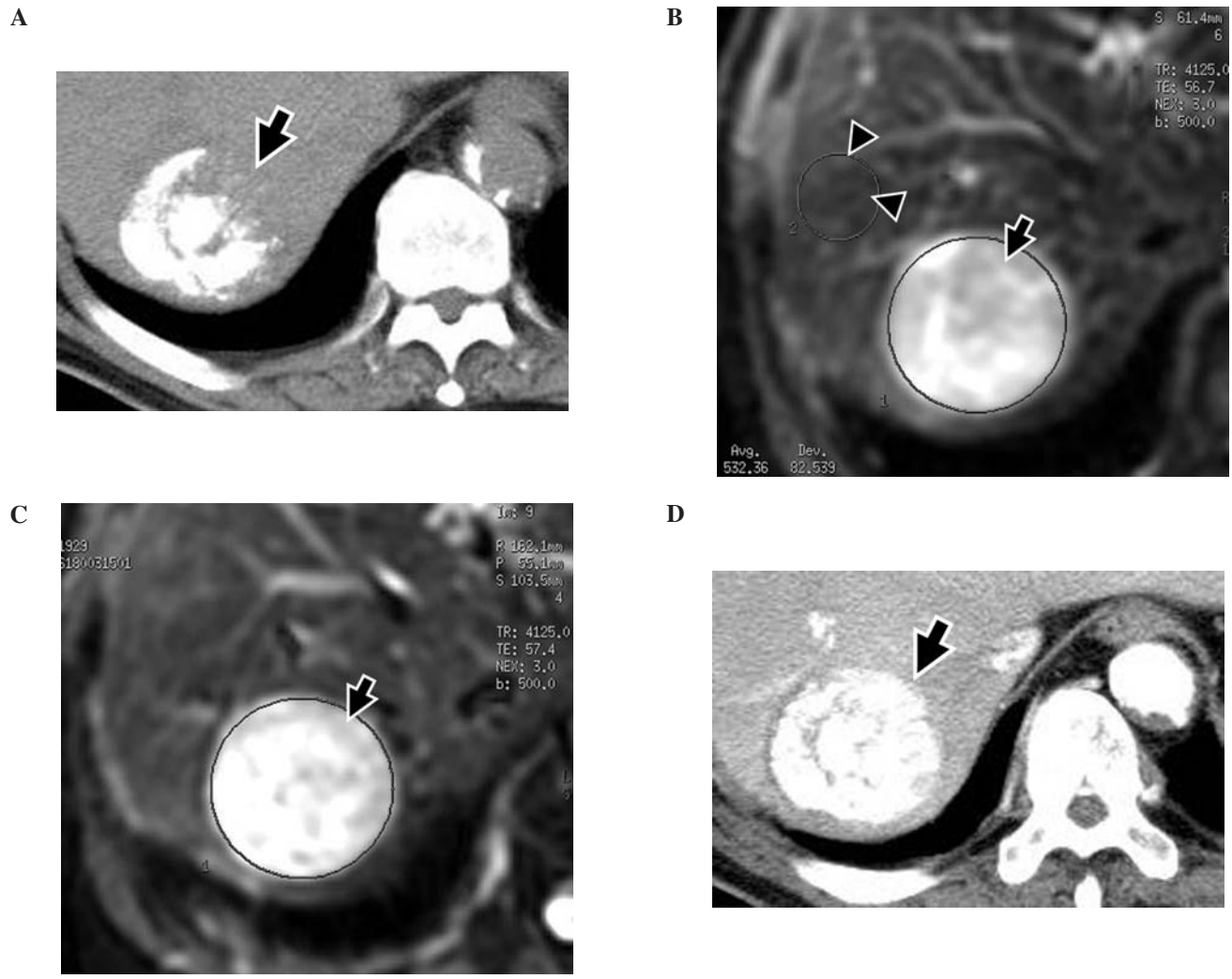

Figure 3. A 69-year-old man with a 4.8-cm HCC in the right hepatic lobe. (A) Iodized-oil CT shows incomplete retention of iodized oil in the tumor (arrow). (B, C) DWI before (B) and after (C) TACE displayed on the Functool workstation monitor. Regions of interest were placed in the tumor (arrow) and surrounding hepatic parenchyma (arrowhead). DWI shows hyperintense signals in tumor both before and after TACE (arrow). ADC in the tumor after TACE ($1.02x10^{-3}$ mm^2/s) was not elevated compared to that before TACE ($1.1x10^{-3}$ mm^2/s) (%ADC, -7.3%). Mean ADC in surrounding hepatic parenchyma ($1.21x10^{-3}$ mm^2/s) resembled that of HCC before TACE ($1.1x10^{-3}$ mm^2/s). (D) Contrast-enhanced CT at 3 months after TACE revealed tumor relapse close to iodized oil retention (arrow).

Table I. Correlation between iodized-oil CT findings and HCC lesion relapse.

	Relapse		
CT	+	-	Total
Complete lesions	3	23	26
Incomplete lesions	10	0	10
Total	13	23	36

CT and %ADC are shown in Fig. 4. The area under the curve for ROC analysis was 0.860 [95% confidence interval (CI), 0.703-1.016] for iodized-oil CT and 0.885 (95% CI, 0.743-1.026) for %ADC. Sensitivity, specificity and accuracy of iodized-oil CT and %ADC (threshold %ADC value set at 13.6%) are shown in Table II.

Discussion

HCC is a common cause of cancer death throughout the world. The majority of patients cannot undergo curative resection because of the advanced stage of the disease at the time of presentation or because of underlying cirrhosis. TACE is reportedly one of the most effective palliative measures for HCC. TACE with or without lipiodol is typically used in patients with large HCC (>3 cm) that is not amenable to other treatments. When TACE or transcatheter arterial embolization alone was compared with conservative treatment (treatment of symptoms and complications only), survival was significantly improved with the former treatments (4,17). However, despite widespread acceptance of this modality, two large randomized trials failed to demonstrate any survival advantage for TACE compared with a variety of other treatments or conservative management (18,19). Although randomized controlled trials have not been performed, repeat TACE based on tumor response offers favorable prognosis compared with planned periodic TACE

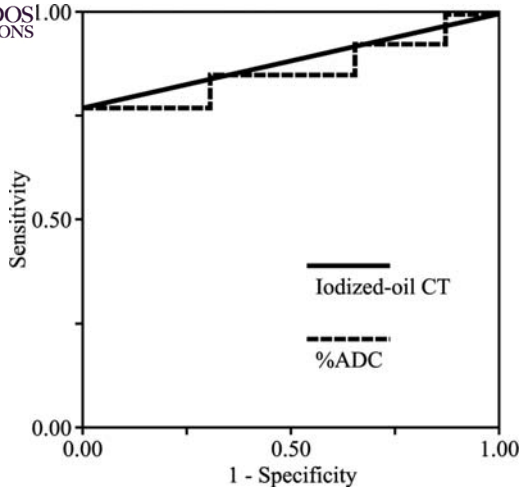

Figure 4. Results of receiver operating characteristic analyses for differentiation of relapsed and non-relapsed lesions with iodized-oil CT and %ADC.

Table II. Accuracy of iodized-oil CT findings and %ADC in relapsed and non-relapsed lesions.

	Sensitivity (%)	Specificity (%)	Accuracy (%)
CT	76.9	100	91.7
%ADC	76.9	100	91.7

The threshold %ADC value was set at 13.6%.

(20). TACE causes some degree of ischemic hepatic damage, which has the potential to lead to hepatic decompensation (21,22). The decision to repeat TACE or add percutaneous ethanol injection therapy should be based on the assessment of residual or recurrent tumor. Accordingly, correct evaluation of tumor response and recurrence after TACE is currently one of the most interesting issues for physicians. Although patterns and distributions of iodized oil in the tumor are useful for assessing the therapeutic effects of TACE (14-16), artifacts produced by iodized oil complicate the evaluation of recurrent tumor with contrast-enhanced CT (23). Contrast-enhanced MRI has been used to evaluate the efficacy of TACE (16,24), but high signals on pre-contrast imaging and the contrast-enhanced fibrous capsule of the tumor also interfere with the detection of recurrent tumors (16,25). Doppler or contrast-enhanced ultrasonography also shows limitations in the evaluation of HCC after TACE due to motion artifacts or ultrasound attenuation (16,26,27).

DWI is a new kind of functional imaging technology that can explore the random diffusion motion of water molecules *in vivo*. DWI has been found to be useful for lesion detection with higher accuracy compared with superparamagnetic iron oxide-enhanced MRI (7). Quantitative DWI analyses have also been used for tumor differentiation. Malignant hepatic tumors such as metastases and HCC show higher ADC values than benign lesions such as cysts and hemangiomas (5,6). Several researchers have used ADC measurement to evaluate tumor responses to treatment in cerebral gliomas (28), soft-tissue sarcoma (29) and colorectal hepatic metastases (11). Tumor lysis, loss of cell membrane integrity and an increased extracellular space are considered to contribute to increases in both water diffusion and ADC, which correlates with water diffusion (12,13). The usefulness of DWI in the evaluation of therapeutic efficacy after TACE for hepatic tumors has already been reported in some animal and human studies. Some researchers have reported that areas of dead cells in VX-2 tumors in rabbits display high ADC, while areas of viable cells show low ADC after TACE (30,31). ADC values also correlated with pathological percentage of necrosis after TACE in a human study (32). Kamel *et al* (9) and Chen *et al* (8) reported that the ADC value in human HCC increases after TACE. ADC was significantly higher in lesions that responded to TACE than in non-responding lesions (33). However, the percent change in ADC from baseline showed a similar area under the curve in ROC analysis for differentiation of relapsed and non-relapsed lesions with iodized-oil CT in the current study. DWI was not found to represent a reliable predictor of local HCC recurrence after TACE compared with gadolinium-enhanced MR imaging (32,34). DWI also showed limitations in detecting small viable tumors after TACE in an experimental animal study (35). DWI may thus improve the prognosis of patients with HCC by allowing prompt repeat TACE based on correct early prediction of recurrent HCC with equivalent quality to iodized-oil CT, but does not exceed the reliability of iodized-oil CT.

The difference in ADC values between responding and non-responding lesions before TACE produced controversial results in a study carried out by Yuan *et al* (33) and this study. A significantly higher pretreatment mean ADC was seen in non-responding lesions ($1.726\pm0.323 \times 10^{-3}$ mm^2/s) than in responding lesions ($1.294\pm0.185 \times 10^{-3}$ mm^2/s) in the study by Yuan *et al* (33), while no significant difference was evident in our study. Although the reason for this controversial result is unclear, all lesions showed early enhancement on dynamic contrast-enhanced CT in this study, while the presence of early enhancement is not clearly described in the study by Yuan *et al* (33). The response of HCC to TACE generally depends on the presence of early enhancement on contrast-enhanced CT, which may indicate a lower ADC value in the lesion due to less necrosis (33). HCC without enhancement on contrast-enhanced CT in the study by Yuan *et al* may thus have contributed to the discrepancy between the two studies.

DWI was not able to depict two tumors in our study population. DWI is known to have limitations such as relatively poor signal-to-noise ratio and high sensitivity to pulsatile or susceptibility artifacts, degrading the ability to detect lesions (10,36).

In conclusion, ADC, a new quantitative measurement from DWI, may allow effective evaluation of the efficacy of TACE for HCC and correctly reveal recurrent tumor. However, further refinement of MRI techniques is needed to properly clarify MRI susceptibility and motion artifacts.

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