Evaluating Local Hepatocellular Carcinoma Recurrence Post-Transcatheter Arterial Chemoembolization: Is Diffusion-Weighted MRI Reliable as an Indicator?

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Purpose: To evaluate the detectability of local hepatocellular carcinoma (HCC) recurrence after transcatheter arterial chemoembolization (TACE) by diffusion-weighted MR imaging in correlation with those of gadolinium-enhanced MR imaging.

Materials and Methods: Respiratory-triggered diffusion-weighted MR images (b factor, 500 s/mm²; number of averaging, six were obtained in 25 patients with 39 HCCs. Two independent radiologists evaluated diffusion-weighted MR images, gadolinium-enhanced MR images after TACE, and assigned confidence levels for postoperative HCC recurrence. Apparent diffusion coefficients (ADCs) in HCCs were also measured. Sensitivities and specificities were compared using an extension of the McNemar test. Observer performance was also determined by ROC curve analysis.

Results: Local recurrences in 14 HCCs and complete tumor necrosis in 25 HCCs after TACE were determined. Sensitivity for the detection of local HCC recurrence was higher on gadolinium-enhanced MR imaging (82%) than on diffusion-weighted MR imaging (60.7%) for the two readers in combination and separately (P < 0.05). Specificities were comparably high for both sequences. Az values were higher for gadolinium-enhanced MR images (0.92) than for diffusion-weighted MR images (0.74) for readers in combination and separately (P < 0.05). Mean ADC values showed an increase after TACE (P < 0.001).

Conclusion: Diffusion-weighted MR imaging was not found to be a reliable predictor of local HCC recurrence after TACE as compared with gadolinium-enhanced MR imaging.

Key Words: liver; diffusion; MRI

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MATERIALS AND METHODS

Patients

Our institutional review board approved this retrospective study and patient informed consent was not required. We retrospectively searched our patient records, and identified 25 patients (18 men and 7 women; 48–79 years of age; mean age, 60.2 years) who underwent MR imaging 1–3 (mean, 2.1) weeks before and 2–6 (mean, 3.2) months after TACE. Before TACE, 39 HCCs (5–39 mm [mean, 16 mm]) were proven present in these 25 patients by percutaneous tumor biopsy (n = 6), by a combination of previous histologic proof by biopsy at initial diagnosis 6–12 months before TACE, by findings of tumor growth or development on radiologic images and tumor marker (alpha fetoprotein or PIVKA II) increases (n = 19), or otherwise by a combination of radiologic findings and tumor marker increases without histologic proof (n = 13). Local tumor recurrence after TACE was determined by confirming tumor growth on follow-up computed tomography (CT) or MR images obtained within 6–9 months (mean, 7.4 months) of TACE and by increases in the levels of serum tumor markers. In some HCCs, previous lipiodolization associated with TACE hampered the diagnosis of recurrent tumors, but we carefully evaluated tumor enhancement in the hepatic arterial phase or washout in the equilibrium phase referring to unenhanced CT images. All 25 patients enrolled had chronic liver damage due to type-B (n = 3) or type-C (n = 22) viral hepatitis.

MR Imaging

MR imaging was performed using a 1.5-T superconducting MR system (Intera Achieva Nova Dual 1.5T; Philips Medical Systems, Best, the Netherlands) and a 4-channel phased-array body multi-coil, and all images were obtained in a transaxial plane with a field of view of 38 cm. The MR imaging protocol consisted of T1-weighted fast field-echo (repetition time [TR] ms/echo time [TE] mess; 220/4.6 [in-phase], 2.3 [out-of-phase], 320 × 224 [frequency × phase encoding] matrix, receiver bandwidth of 523.2 Hz per pixel, a parallel imaging reduction factor of 2, 3-mm interval with no intersectional gap, received breath hold acquisitions for 30 slices per breath hold); fat-suppressed respiratory-triggered T2-weighted turbo spin-echo (1200–3600 [effective TR]/80 [effective TE], echo train length of 21, 512 × 256 matrix, received bandwidth of 210 kHz per pixel, two signals acquired, and a 3–4 min acquisition time); and breath-hold gadolinium-enhanced double hepatic arterial, portal venous, and equilibrium phase imaging with fat-suppressed three-dimensional spoiled turbo field-echo imaging (3.3/1.1, 15° flip angle, 352 × 230 matrix, 6-mm acquisition slice thickness reconstructed at 3-mm interval with no intersectional gap, received bandwidth of 434.3 kHz per pixel, reduction factor of 2, one signal acquired, 60 slices per 12 s). Test bolus imaging was performed in the abdominal aorta at the level of the first lumbar vertebral body. Coronal 20-mm-thick single-section two-dimensional fast field-echo images (14/1.0 [TR/TE], 1-s acquisition time) were obtained every second after initiating an intravenous bolus injection of 1 mL of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany), and this was followed by a flush with 15 mL of sterile saline solution. The central k-space lines of the four phases were filled at 6, 18, 55, and 180 s after contrast arrival in the abdominal aorta, and predominantly represented the early hepatic arterial, late hepatic arterial, portal venous, and equilibrium phases, respectively.

Diffusion-Weighted MR Imaging

Before contrast injection, respiratory-triggered diffusion-weighted MR imaging was performed using a single-shot echo-planar sequence (3700/96 ms [TR/TE], 320 × 320 matrix, received bandwidth of 210 kHz per pixel, two signals acquired, and a 3–4 min acquisition time). Spectral presaturation with inversion recovery for fat suppression was used to exclude chemical shift artifacts. The isotropic motion-probing gradient pulses were placed along three orthogonal oblique directions, which achieved a shorter echo time and improved signal-to-noise ratio (Gradient Overplus; Philips Medical System, Best, the Netherlands).

Chemoembolization Technique

TACE was performed by two interventional radiologists with 7 and 10 years of clinical experience, respectively, using a digital flat panel detector angiography system (Innova 4100; GE Healthcare, Milwaukee, WI). A sheath introducer was placed using the Seldinger approach in the right common femoral artery; a 5 French (F) angiographic catheter (Clinical, Miami, FL) was advanced into the common hepatic artery; and a 2.2–2.4 F coaxial catheter (Prograte; Trumo; Medical, Somerset, NJ) was advanced over 0.0016-inch guidewire (Glidewire; Terumo Medical, Somerset, NJ) into the desired hepatic arterial branch.

The chemoembolization material used throughout was an emulsion of 20–50 mg of epirubicin (Pharmorubicin; Pharmacia & Upjohn, Milan) dissolved in 2 mL of nonionic contrast material (Iopamiron 370; Schering, Berlin) and 4–6 mL of iodized poppy-seed oil (Lipiodol Ultra Fluide; Laboratoires Guerbet). The ratio of iodized oil volume to epirubicin solution volume was maintained at 2 or greater, thus ensuring the stability of the water-in-oil emulsion. The dose of emulsion administered was dependent on tumor size. After confirming by fluoroscopy that the emulsion had been properly delivered to the tumor concerned, gelatin sponge particles ranging in volume from 1 to 27 mm³ (Spojel; Asteras, Tokyo) were applied until the feeding arteries were fully embolized. All patients underwent unenhanced CT immediately after TACE (Light Speed Ultra 16; GE Healthcare) to confirm iodized oil distribution in liver and tumors.

Image Analysis

MR images obtained after TACE were retrospectively reviewed by two blinded radiologists by consensus (S.G. and H.K. who had 7 and 10 years, respectively, of post-training experience at interpreting body MR images).
Readers measured lesion sizes using an electronic caliper on an image viewer, recorded sites, and then subjectively evaluated the signal intensities of individual tumors on diffusion-weighted MR images and their enhancement characteristics on gadolinium-enhanced MR images, using a 5-point scale: 1, hypointense; 2, mildly hypointense; 3, isointense; 4, mildly hyperintense; and 5, hyperintense.

Confidence levels for probable recurrence on diffusion-weighted images and gadolinium-enhanced images were separately assigned for each lesion using a four-point scale: 1, definitely not recurrent; 2, possibly not recurrent; 3, possibly recurrent; and 4, definitely recurrent. A confidence level 1 was assigned when a lesion was hypointense on diffusion-weighted images and hypointense on gadolinium-enhanced images obtained during the hepatic arterial to equilibrium phase. Level 4 was assigned when a lesion was hyperintense on diffusion-weighted images, hyperintense on hepatic arterial phase images, and wash out on portal venous or equilibrium phase images. Confidence levels 2 and 3 were assigned based on radiologist subjective judgment.

**Apparent Diffusion Coefficients**

A radiologist (Y.T. with 4 years of posttraining experience at interpreting body MR images) reviewed all images on a postprocessing workstation (Advantage Workstation 4.2, GE Healthcare) and established a region of interest in each lesion on ADC mapping images to determine its ADC value. Care was taken to contain almost entire lesions.

**Statistical Analysis**

Sensitivity for lesion detection was determined from the number of lesions assigned a score 3 or 4. Likewise, specificity was determined by the number assigned a score of 1 or 2. We compared sensitivities and specificities, using an extension of the McNemar test. For each imaging sequence, a receiver operating characteristic (ROC) curve was fit to each radiologist's confidence rating using a maximum-likelihood estimation determined using LABMRMC1.0B software (Metz CE, University of Chicago, Chicago, IL). Observer performance for each imaging sequence was evaluated by calculating the area under the ROC curve (Az). Differences between averaged Az values were estimated using “jackknife dispersion” and analysis of variance. P values of less than 0.05 were considered significant.

To assess interobserver variability at interpreting images, κ statistics for multiple observers were used to measure degree of agreement. A κ value of up to 0.20 represented slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and a value of 0.81 or greater almost perfect agreement.

**RESULTS**

Local tumor recurrence after TACE occurred for 14 of the 39 HCCs in eight patients. Thirty-seven HCCs in 24 patients were detected by followup MR imaging, and two HCCs in one patient by contrast enhanced CT.

On diffusion-weighted images, areas of recurrence after TACE showed hyperintensity in 57%, while completely necrotic areas in 8% (P < 0.001). However, on gadolinium-enhanced hepatic arterial-phase images, areas of tumor recurrence after TACE showed hyperintensity in 86%, but completely necrotic areas were never hyperintense (P < 0.001).

Sensitivities for tumor detection are shown in Figure 1. The sensitivities of diffusion-weighted MR images were 64, 57, and 61% for readers 1, 2, and both readers, respectively, while those of gadolinium-enhanced MR images were 86%, 78%, and 82% for readers 1, 2, and overall, respectively. Sensitivity for the detection of local tumor recurrence was greater (P < 0.05) with gadolinium-enhanced imaging than with diffusion-weighted imaging in both readers and readers overall (P < 0.05).

**Figure 1.** Bar chart showing mean sensitivities for the detection of local tumor recurrence with diffusion-weighted imaging (white bar) and gadolinium (gd) -enhanced imaging (striped bar). Sensitivities of diffusion-weighted imaging were 64, 57, and 61% for readers 1, 2, and overall, respectively, while those of gadolinium-enhanced imaging were 86%, 78%, and 82% for readers 1, 2, and overall, respectively. Sensitivity for the detection of local tumor recurrence was greater (P < 0.05) with gadolinium-enhanced imaging than with diffusion-weighted imaging in both readers and readers overall (P < 0.05).

Specificity was comparably high for both sequences in all readers, without significant differences.

**Figure 2.** Bar chart showing mean specificities with diffusion-weighted imaging (white bar) and gadolinium (Gd) -enhanced imaging (striped bar). Specificities for the detection of local tumor recurrence were comparably high with both sequences in all readers, without significant differences.
Mean $Az$ values for tumor detection are shown in Figure 3. The $Az$ values of diffusion-weighted imaging were 0.82, 0.66, and 0.74 for readers 1, 2, and overall, respectively, and those of gadolinium-enhanced imaging were 0.96, 0.89, and 0.92, respectively. $Az$ values were greater ($P < 0.05$) with gadolinium-enhanced imaging than with diffusion-weighted imaging in reader 2 and in readers overall.

The changes in ADC values in HCCs pre- to post-TACE are shown in Figure 5. Mean ADC values showed a significant increase after TACE ($P < 0.05$).

**DISCUSSION**

The administration of TACE mixed with iodized oil and anticancer agents followed by the application of gelatin sponge particles causes ischemic damage to HCCs, and results in hemorrhage or coagulation induced tumor necrosis. Although contrast-enhanced CT is able to reveal residual or recurrent tumors as areas of hypervascularity, it is often difficult to assess correctly contrast enhancement in such tumors adjacent to retained iodized oil on CT, because of beam-hardening artifacts caused by iodized oil. Moreover, because MR imaging is barely influenced by the presence of iodized oil, viable tumors are better depicted by gadolinium-enhanced MR imaging. Ito et al (6) reported that gadolinium-enhanced MR imaging well reveals tumor hemodynamics, and that it is helpful for evaluating the therapeutic efficacy of TACE with iodized oil for the treatment of HCC.

Kamel et al (13) evaluated histopathologically determined tumor necrosis after TACE, although the HCCs evaluated in this study were fairly larger (2–18 cm [mean, 7 cm]) than ours (5–39 mm [mean, 16 mm]). However, although they concluded that diffusion-weighted imaging better quantified tumor necrosis area after chemoembolization than gadolinium-enhanced MR imaging, in the present study, most locally recurrent tumors were pathognomonically detected on gadolinium-enhanced multiphasic MR images. In fact, only 2 of the 14 locally recurrent HCCs lacked hyperintensity during the hepatic arterial-dominant phase, and, therefore, were not detected correctly by either reader. However, these nodules showed clear washout in the portal and equilibrium phases when they were re-examined. Consequently in the present study, the detect-
ability of local tumor recurrence after TACE was greater by gadolinium-enhanced MR imaging than by diffusion-weighted MR imaging. Although diffusion-weighted MR imaging was more straightforward because of no need for breath holding or contrast material administration, we would recommend gadolinium-enhanced MR imaging as a baseline tool for the evaluation of HCC after TACE. Regarding the current role of diffusion-weighted imaging in hepatic MR imaging, diffusion-weighted imaging may have additional values in the diagnosis of hepatic diseases especially in patients gadolinium-enhanced MR imaging is contraindicated due to renal dysfunction, allergic tendency, difficulty in breath holding, and so on.

Figure 6. A 63-year-old man with hepatocellular carcinoma (HCC) in the anterior-superior segment of right hepatic lobe. A: Diffusion-weighted image obtained before transcatheter arterial chemoembolization (TACE) shows ill-demarcated area of slight hyperintensity corresponding to HCC (arrows). B: Gadolinium-enhanced image obtained during hepatic arterial phase before TACE shows patchy areas of hypervascularity corresponding to HCC (arrows). C: Unenhanced computed tomography image obtained immediately after TACE shows dense accumulations of iodized oil to HCC (arrows). D: Diffusion-weighted image obtained after TACE shows area of diffuse hyperintensity in HCC, but there are no clear findings of tumor recurrence. E: Gadolinium-enhanced image obtained during hepatic arterial phase after TACE shows a small focus of hypervascularity ventrally in HCC, which reveals local HCC recurrence (arrow).
The high observed diagnostic performance of gadolinium-enhanced MR imaging was probably due to the following. First, because we treated comparatively small HCCs (5–39 mm [mean, 16 mm]) using TACE, HCCs lapsed into entire necrosis showing homogeneous hypovascularity on gadolinium-enhanced MR images, which allowed tiny local recurrent tumors to be visualized with excellent contrast. Second, we used a high-resolution three-dimensional T1-weighted MR sequence (352 × 230 matrix, 6-mm acquisition slice thickness at 3-mm interval with no intersectional gap) and ran this sequence after test-bolus imaging to optimize the scan timing for 4-phase MR imaging (Fig. 6A–E), and these highly dedicated MR imaging techniques may have contributed to the achieved high observer performance levels recorded for tumor detection.

Diffusion-weighted MR imaging visualizes water-molecule diffusion or the Brownian motion of water protons in biologic tissues (14), which provides an insight on water composition within malignant tumors and tumor viability. Viable tumor cells have intact membranes that restrict water-molecule diffusion, whereas in necrotic tumors disrupted membranes allow higher levels of diffusion. Chen et al. (12) reported that ADC values in HCCs after TACE showed significant increases in all cases in their clinical study, and concluded an evaluation of ADC values might be useful for assessing the early therapeutic responses of large HCCs after TACE; tumor necrosis was determined by ADC increases and by signal intensity changes on diffusion-weighted MR images accompanied by ADC maps. Significant increases in ADC values were also observed after TACE in the present study, but ADC values varied widely and these increases did not contribute noticeably to the accurate diagnosis of tumor necrosis by any cut-off points.

Taouli et al. (8) found that ADC values depend on b factors, that is, ADC values approximated to the true values of tissues in question when high b factors were used, whereas ADCs were affected by intravoxel perfusion and were usually overestimated when a low b factor was applied. (15). Thus, we avoided using low b factors in the present study. Although high b factors of up to 1000 s/mm² were required to determine virtually true ADCs, we used a middle-range b factor of 500 s/mm², because liver contours were obscured due to weak signals in the liver when high b factors were used, which hampered radiologist interpretation in the clinical setting.

This study has several limitations. First, we had little histological information on the HCCs, because most patients in our study had been proven to have HCC by tumor biopsy before initial diagnosis. Second, the single-shot echo-planar imaging technique used in the present study had spatial resolution as low as 7 × 3.3 × 1.7 mm. Future MR imager developments such as higher magnetic field strength (16) or the use of multichannel body surface coils may resolve these issues. Because some of HCC nodules in our study were as small as 5 mm in size, it was reasonable that gadolinium-enhanced MRI with greater spatial resolution outperformed DWI in the detection. However, we infer that partial volume averaging effect fairly contributed to the favorable contrast with diffusion-weighted images.

In conclusion, diffusion-weighted MR imaging was not found to be a reliable predictor of local HCC recurrence after TACE as compared with gadolinium-enhanced MR imaging. Thus, we recommend that gadolinium-enhanced MR imaging be used as a first-line tool for the evaluation of HCC tumor viability after TACE and that diffusion-weighted MR imaging be considered a supplementary sequence in clinical practice.

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