Unresectable Hepatocellular Carcinoma: Serial Early Vascular and Cellular Changes after Transarterial Chemoembolization as Detected with MR Imaging¹

Ihab R. Kamel, MD, PhD
 Eleni Liapi, MD
 Diane K. Reyes, BA, RT
 Marianna Zahurak, MS
 David A. Bluemke, MD, PhD
 Jean-François H. Geschwind, MD

Purpose:

To prospectively assess serial changes in contrast material-enhanced and diffusion-weighted (DW) magnetic resonance (MR) imaging values within 1 month after transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma (HCC).

Materials and Methods:

Institutional review board approval was obtained for this prospective HIPAA-compliant study. MR imaging was performed before and within 24 hours after TACE in 24 patients with HCC (21 male, three female; mean age, 59 years and 62 years, respectively). Serial MR imaging was subsequently performed 1, 2, 3, and 4 weeks after therapy. The imaging protocol included fast spin-echo T2-weighted MR imaging, breath-hold DW echo-planar MR imaging, and breath-hold unenhanced and contrast-enhanced T1-weighted three-dimensional fat-suppressed gradient-recalled-echo MR imaging in the arterial and portal venous phases. Tumor size, enhancement, and apparent diffusion coefficient (ADC) values were recorded before and sequentially after treatment. Regression models for the correlated data were used to assess changes in these parameters over time after TACE.

Results:

Mean tumor size was 7.5 cm and was unchanged up to 4 weeks after therapy. Reduction in tumor enhancement in the arterial phase occurred immediately after TACE, with a consistent reduction occurring 1–3 weeks after therapy ($P = .001$). Reduction in tumor enhancement in the portal venous phase also occurred immediately after TACE, with a consistent reduction occurring 1–3 weeks after therapy ($P = .0003$). The increase in tumor ADC value was significant 1–2 weeks after therapy ($P = .004$), borderline significant 3 weeks after therapy, and insignificant 24 hours and 4 weeks after therapy.

Conclusion:

Significant reduction in tumor enhancement occurred within 24 hours after TACE and persisted up to 4 weeks after TACE. Lesser changes in the ADC value appeared 1 week after TACE, persisted through 2 weeks after TACE, and became less apparent 3 and 4 weeks after TACE. No change in tumor size was recorded during the follow-up period.

© RSNA, 2009

¹ From the Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins Hospital, 601 N Caroline St, Baltimore, MD 21287. Received December 29, 2007; revision requested February 22, 2008; revision received August 13; final version accepted September 24. Supported in part by a grant from the Cardiovascular and Interventional Radiology Research and Education Fund.

Address correspondence to I.R.K. (e-mail: ikamel@jhmi.edu).

Hepatocellular carcinoma (HCC) is one of the most lethal malignancies worldwide, with more than 1 million new cases being diagnosed annually. In the United States, the number of new HCC cases that are diagnosed annually is increasing, primarily because of an increasing incidence of hepatitis C infection (1,2), an aging population, and an increasing incidence of nonalcoholic steatohepatitis. Unfortunately, HCC is diagnosed in most patients at a time when curative surgical resection or organ transplantation cannot be performed because of advanced disease or substantial impairment of liver function. Unresectable HCC is difficult to treat because of underlying hepatic cirrhosis and its sequelae, associated impairment in liver function, and resistance of HCC to conventional chemotherapy and radiation therapy (3). To our knowledge, no standard treatment for unresectable HCC exists in the United States. However, there is a growing reliance on the use of locoregional therapies—such as radiofrequency ablation, cryotherapy, transarterial chemoembolization (TACE), and transarterial radioembolization—to treat unresectable HCC (4–6). The goal of these treatments is to induce cytoreduction and cellular necrosis (7–9). TACE exposes the tumor to high concentrations of the chemotherapeutic agents for a prolonged period of time, while at the same time minimizing systemic toxicity (10,11). Prior studies have shown survival benefits in patients with HCC, with cumulative survival probability superior to that achieved

with the best supportive care or systemic chemotherapy (10–14).

Early assessment of the effectiveness of TACE is critical in determining the success of treatment and in helping guide future therapy. Change in tumor size on computed tomographic (CT) or magnetic resonance (MR) images is the accepted criterion with which to assess response to chemotherapy. Reduction in tumor size is a standard and validated parameter used to assess response to chemotherapy according to the Response Evaluation Criteria in Solid Tumors, or RECIST (15,16). One must note, however, that in the early posttreatment period after locoregional therapy, tumors may be nonviable even if they do not change in size (17). Reduction of tumor enhancement has been used as a biomarker of disease response, as proposed by the European Association for the Study of Liver Disease (18). Other authors have suggested that the decrease in tumor enhancement was associated with a favorable response to therapy after TACE (17,19).

Diffusion-weighted (DW) MR imaging and apparent diffusion coefficient (ADC) maps can be used to investigate tumor viability at the cellular level. Prior studies have shown that ADC values of tumors treated with locoregional therapy increase after treatment, suggesting increasing cellular necrosis (17,19). However, the early temporal changes in tumor enhancement and ADC values after TACE are unknown. Knowledge of these early changes would substantially contribute to patient care and outcome by enabling a rapid in vivo assay of treatment efficiency so that therapy could be optimized and ineffective treatment could be discontinued. In the current study, our objective was to prospectively assess serial changes in contrast material-enhanced

and DW MR imaging values within 1 month after TACE in patients with unresectable HCC.

Materials and Methods

Study Cohort

This prospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by our institutional review board. Informed consent was obtained from each patient before he or she participated in the study. The study was open for enrollment from March 9, 2004, to January 17, 2006. During this period, our liver tumor board discussed the care of 120 patients with HCC who underwent one or more cycles of TACE. Criteria for performing TACE included a confirmed diagnosis of unresectable HCC in patients with or without minimally impaired liver function. Patients excluded from TACE were those with an Eastern Cooperative Oncology Group performance score greater than 2; encephalopathy; severe variceal bleeding, severe ascites, or both; significant thrombocytopenia; prolonged impaired renal function; acute renal failure (an abrupt increase in serum creatinine level of 50% or more with respect to the baseline level or an absolute increase in the serum creatinine concentration of at least 0.5 mg/dL to a level of more than 1.5 mg/dL); or severe liver failure (advanced Child-

Advance in Knowledge

- Transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma induces early and persistent changes in tumor vascularization followed by delayed and transient changes in the apparent diffusion coefficient value, without systematic changes in tumor size, indicating that functional imaging parameters may be useful indicators of the success of therapy.

Implication for Patient Care

- Functional MR imaging techniques that depict vascularization and cellularity should be incorporated into the early assessment of therapy response in patients with hepatocellular carcinoma who undergo TACE.

Published online

10.1148/radiol.2502072222

Radiology 2009; 250:466–473

Abbreviations:

ADC = apparent diffusion coefficient

DW = diffusion weighted

HCC = hepatocellular carcinoma

TACE = transarterial chemoembolization

Author contributions:

Guarantors of integrity of entire study, I.R.K., J.F.H.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, I.R.K., E.L.; clinical studies, I.R.K., E.L., D.K.R., D.A.B., J.F.H.G.; statistical analysis, I.R.K., M.Z.; and manuscript editing, all authors

Authors stated no financial relationship to disclose.

See also the editorial by Padhani in this issue.

Pugh score C). Our study group included all patients with HCC who were undergoing treatment for the first time and who had undergone dynamic contrast-enhanced and DW MR imaging before TACE and 24 hours and 1, 2, 3, and 4 weeks after TACE. Of the 120 patients who underwent treatment, only 24 fulfilled these inclusion criteria. Patients with well-defined and infiltrative tumors were included in the study. However, patients with small tumors (<1 cm in diameter) ($n = 12$) and those with tumors in the liver dome ($n = 17$) were excluded from our study because these tumors were difficult to detect with DW MR imaging. Patients who had undergone chemoembolization previously ($n = 29$) were also excluded because they may have partially responded to initial therapy. Seventeen patients were not asked to enroll in the study because they were already participating in a different clinical trial during the study enrollment period, while the remaining 21 patients declined to participate.

Diagnosis of HCC was confirmed at biopsy in 11 patients and by determining that all typical clinical, imaging, and laboratory findings were present in 13 patients. Typical clinical findings include the presence of liver cirrhosis and its complications. Typical imaging findings include the presence of a hypervascular mass on images acquired with arterial phase CT or MR imaging; this mass appears hypovascular to the liver on portal venous phase CT and MR images. Typical laboratory findings in patients with HCC include an elevated α -fetoprotein level (>400 ng/mL).

Chemoembolization Technique

An experienced interventional radiologist (J.F.H.G.) performed all TACE procedures in accordance with our standard institutional protocol. A 5.0-F micropuncture introducer set (Cook, Bloomington, Ind) was used to access the right common femoral artery with the Seldinger technique. After a 0.035-inch Bentson guidewire (Cook) was advanced into the abdominal aorta, the needle was exchanged for a 5-F vascular sheath (Cordis, Miami, Fla), which was placed in the right common femoral artery. Then, a 5-F Glidecath Simmons-1 catheter (Terumo, Somerset, NJ) was advanced through the

sheath into the aorta, and elective angiography of the celiac axis was performed. The catheter was advanced into the desired hepatic artery branch. (The desired branch depended on the tumor location.) TACE included administration of a solution that contained 100 mg of cisplatin (Platinol; Bristol-Myers Squibb, Princeton, NJ), 50 mg of doxorubicin (Adriamycin; Pharmacia Upjohn, Kalamazoo, Mich), and 10 mg of mitomycin C (Mitomycin C; Bedford Laboratories, Bedford, Ohio) in a 1:1 mixture with iodized oil (Savage Laboratories, Melville, NY), followed by infusion of 300–500- μ m-diameter microsphere particles (Embosphere; Biosphere Medical, Rockland, Mass) until stasis was achieved.

MR Imaging Technique and Parameters

All patients underwent baseline and follow-up MR imaging performed with a 1.5-T MR unit (CV/i; GE Medical Systems, Milwaukee, Wis) and a phased-array torso coil. The imaging protocol included (a) axial T2-weighted fast spin-echo imaging (repetition time msec/echo time msec, 5000/100; 256×256 matrix; 8-mm section thickness; 2-mm intersection gap; 32-kHz receiver bandwidth), (b) axial single-shot breath-hold gradient-echo DW echo-planar imaging (5000–6500/110, 128×128 matrix, 8-mm section thickness, 2-mm intersection gap, 50 or 750 sec/ mm^2 b value, 64-kHz receiver bandwidth, 18 sections acquired during a 25-second breath hold), and (c) axial breath-hold unenhanced and contrast-enhanced (0.1 mmol gadodiamide per kilogram of body weight, Omniscan; Amersham, Princeton, NJ) T1-weighted three-dimensional fat-suppressed spoiled gradient-echo imaging (5.1/1.2, 320–400-mm field of view, 192×160 matrix, 4–6-mm section thickness, 64-kHz receiver bandwidth, 15° flip angle) in the arterial and portal venous phases (20 and 60 seconds, respectively).

Image Evaluation

The images of each patient were transferred to a picture archiving and communication system (Advantage; GE Healthcare, Chicago, Ill) and interpreted by two experienced MR radiologists (I.R.K., E.L.; 8 and 4 years of experi-

ence, respectively) in the same reading session to ensure careful comparison of preprocedural and sequential postprocedural MR imaging findings. The single largest targeted tumor was evaluated in each patient to ensure independent sampling. In all cases, unenhanced images were subtracted from hepatic arterial phase and portal venous phase images to allow better assessment of tumor enhancement. A reader (I.R.K.) used electronic calipers to record the size of the targeted tumor (maximal tumor diameter) on the subtracted portal venous phase images. The two readers visually assessed the percentage of tumor enhancement for the two subtracted phases in consensus. The percentage of enhancement was based on the percentage of the total area of enhancement seen on the axial image with the largest tumor size and was recorded in 5% increments ranging from no enhancement to 100% enhancement. Areas of tumor enhancement were considered viable, and areas that were unenhanced were considered necrotic.

Pixel-based ADC maps were generated on the same workstation. ADC values were calculated with linear regression analysis of the function $S = S_0 \times \exp(-b \times \text{ADC})$, where S is the signal intensity with a b value of 750 sec/ mm^2 , and S_0 is the signal intensity with a b value of 50 sec/ mm^2 . One reader (I.R.K.) measured mean ADC of the tumor by drawing a region of interest over the whole HCC and using image subtraction as the reference with which to accurately identify the tumor margins. ADC of background liver parenchyma was recorded by drawing a region of interest (at least 50 pixels) in the uninvolved lobe of the liver. Similarly, ADC of the spleen was recorded by drawing a region of interest (at least 50 pixels) over the midspleen. These measurements were obtained at baseline and sequential examinations.

Statistical Analysis

The primary statistical end points of this study were area of tumor enhancement in the arterial and portal venous phases, and tumor ADC value at baseline, 24 hours, and 1, 2, 3, and 4 weeks after therapy.

This resulted in six repeated measurements per patient for each imaging parameter. Regression models for correlated data were used to assess changes in the previously mentioned parameters over time after TACE. Estimates were obtained by using the generalized estimating equation (20). A compound symmetric covariance structure was assumed for these regression models; this implied that the aspect of covariance between repeated measurements was due to patient contribution irrespective of time. Means and 95% confidence intervals calculated with the generalized estimating equation were recorded before therapy and each week after therapy.

Weekly changes across MR imaging techniques were depicted with box plots. In these box plots, the length of the box is the interquartile range of data and depicts the spread of the middle 50% of observations. The horizontal line inside the box is the median. The lines extending from the box (ie, from upper and lower quartiles) are adjacent values. The upper adjacent value (AV_{up}) was obtained as follows: $AV_{up} = Q_{up} + (1.5 \cdot IQR)$, where Q_{up} is the upper quartile and IQR is interquartile range. The lower adjacent value (AV_{low}) was obtained as follows: $AV_{low} = Q_{low} - (1.5 \cdot IQR)$, where Q_{low} is the lower quartile. Any value lying outside of this range is displayed as an open circle and can be considered an outlier. Box plots were generated by using R software (R Project, version R-2.5.0; R Foundation for Statistical Computing, Vienna, Austria), and all other statistical computations were performed by using an SAS

package (SAS, version 9; SAS Institute, Cary, NC). All *P* values were two sided, and all confidence intervals were at the 95% level. *P* values less than .05 were considered to indicate a significant difference.

Results

Demographic Data

This study included 24 patients (mean age, 60 years $\pm$ 13 [standard deviation]), 21 of whom were male (mean age, 59 years $\pm$ 14) and three of whom were female (mean age, 62 years $\pm$ 17); HCC had been diagnosed in all patients. Each patient underwent one selective chemoembolization session in either the right ($n = 17$) or the left ($n = 7$) lobe. All procedures were performed successfully, without immediate (within 24 hours after chemoembolization) complications. Of the 127 MR studies evaluated, 24 were obtained at baseline, and 103 were obtained at follow-up (mean of four studies per patient). Not all patients underwent imaging at each follow-up examination because of low performance status ($n = 8$) or lack of transportation to our facility ($n = 9$). The numbers of patients who were imaged within 24 hours and 1, 2, 3, and 4 weeks after TACE were 23, 19, 22, 19, and 20, respectively.

Imaging Findings

Mean tumor diameter at baseline was 7.5 cm. The reported mean tumor diameter, mean enhancement in the arte-

rial and portal venous phases as measured on subtracted images, and mean ADC values at baseline and subsequent time intervals are shown in the Table 1. These values were compared with baseline values, and *P* values were calculated. An immediate and significant decrease in tumor enhancement in the arterial phase occurred within 24 hours after chemoembolization, with the maximum reduction in enhancement occurring at 1–3-week follow-up. There was a similar immediate and significant decrease in tumor enhancement during the portal venous phase at 24-hour follow-up, with the maximum reduction in enhancement also occurring at 1–3-week follow-up. Reduction in tumor enhancement on arterial and portal venous phase images continued throughout follow-up until 4 weeks after TACE (Figs 1, 2).

Changes in tumor ADC value were smaller and occurred later in the follow-up period than did changes in arterial and portal venous enhancement. At 24 hours after TACE, the increase in tumor ADC value was small and insignificant ($P = .11$). However, the increase in tumor ADC value was significant at 1- and 2-week follow-up ($P = .004$). The increase in tumor ADC value was of borderline significance at 3-week follow-up ($P = .06$) and was not significant at 4-week follow-up ($P = .19$). Tumor size at baseline was not significantly different from tumor size at any of the follow-up periods. ADC values of the uninvolved liver and spleen at follow-up were un-

Serial Changes after TACE

Time Point	Enhancement in Arterial Phase		Enhancement in Venous Phase		ADC Value		Tumor Diameter	
	Mean (%)	<i>P</i> Value	Mean (%)	<i>P</i> Value	Mean (mm ² /sec $\cdot$ 1000)	<i>P</i> Value	Mean (cm)	<i>P</i> Value
Baseline	72 (62, 82)	...	89 (81, 97)	...	1.86 (1.71, 2.02)	...	7.5 (6.1, 9.0)	...
24-Hour follow-up	38 (25, 51)	.001	48 (34, 62)	.0003	1.94 (1.80, 2.09)	.11	7.7 (6.3, 9.1)	.41
1-Week follow-up	35 (22, 48)	.001	45 (30, 59)	.0004	2.13 (1.99, 2.27)	.004	7.9 (6.5, 9.3)	.15
2-Week follow-up	35 (21, 48)	.001	44 (30, 59)	.0003	2.11 (1.95, 2.27)	.004	7.8 (6.3, 9.3)	.40
3-Week follow-up	35 (22, 48)	.001	44 (30, 58)	.0003	2.07 (1.88, 2.25)	.06	7.7 (6.4, 9.1)	.51
4-Week follow-up	36 (23, 49)	.001	45 (31, 59)	.0002	1.95 (1.77, 2.13)	.19	7.5 (6.1, 8.9)	.88

Note.—Data in parentheses are 95% confidence intervals. In this study, 23, 19, 22, 19, and 20 patients underwent follow-up MR imaging 24 hours and 1, 2, 3, and 4 weeks, respectively, after TACE. *P* values were calculated with generalized estimating equations.

Figure 1

Figure 1: A–E, Serial changes in gadolinium enhancement of a mass (arrow) on subtracted T1-weighted gadolinium-enhanced portal venous phase images (left: 5.1/1.2), DW MR images (middle: 6500/110), and ADC images (right) after TACE. A, Baseline images. Left: A 2.5-cm mass in left lobe shows almost complete (100%) enhancement. Middle: Hyperintense mass is visible. Right: ADC = 0.00172 mm²/sec. B, At 24 hours after TACE. Left: Mass shows significant enhancement reduction (–50%). Middle: Mass is isointense. Right: ADC = 0.00180 mm²/sec. C, At 1 week after TACE. Left: Mass shows no enhancement. Middle: Mass is isointense. Right: ADC = 0.00203 mm²/sec. D, Left: At 2 weeks after TACE. Mass shows no enhancement. Middle: Mass is isointense (arrow). Right: ADC = 0.00210 mm²/sec. E, At 4 weeks after TACE. Left: Mass shows no enhancement. Middle: Mass is isointense (arrow). ADC = 0.00179 mm²/sec. Tumor remains unchanged in size.

changed compared with those obtained at baseline ($P \geq .05$).

Discussion

Our results show significant temporal changes in arterial and portal venous enhancement immediately (within 24 hours) after treatment, with the maximum decrease in enhancement occurring 1–3 weeks after therapy. This trend remained until 4 weeks after therapy. Changes in ADC lagged behind, and the increase in the ADC value of targeted tumors was significant at 1- and 2-week follow-up. This increase was of borderline significance 3 weeks after therapy and was no longer significant 4 weeks after treatment. Of note, no change in tumor size was detected during the 1-month follow-up period. Immediate (within 24 hours after TACE) assessment of posttreatment cellular and vascular changes is possible; however, the emphasis should be on monitoring changes in tumor enhancement since the ADC value and size changes may be limited. MR imaging performed

1–2 weeks after TACE yields the maximum difference in tumor enhancement and ADC value when compared with baseline values. At 3–4-week follow-up, only reduction in tumor enhancement persists, whereas increase in tumor ADC value is of borderline significance or is insignificant.

It is critical that physicians who are caring for patients with cancer be able to assess early tumor response after therapy because an early favorable response generally indicates that the therapy was effective and may result in a substantial survival benefit, partially because local control of the disease has been achieved (21,22). More importantly, withholding treatment once imaging response has been achieved could prevent toxicities related to overtreatment. Early identification of treatment failure is also critical in patient care, since a repeat TACE cycle can be performed before disease progression occurs if liver function is maintained. However, to our knowledge, there are no standardized criteria with which to assess treatment response after TACE.

Change in tumor size as defined ac-

cording to the Response Evaluation Criteria in Solid Tumors is the standard for noninvasive imaging assessment that is used to guide clinical decision making after chemotherapy (15). However, the validity of tumor measurements has been questioned in view of the emergence of new anticancer therapies that are geared toward tumor dormancy rather than tumor disappearance (17). In addition, a decrease in viable cell mass shortly after TACE is not necessarily reflected by a change in tumor size, and tumors may not decrease in size despite the fact that they are not viable (23,24). We documented a lack of change in tumor size 4 weeks after therapy, similar to what has been reported in the literature.

Recent studies have demonstrated the value of vascular and cellular biomarkers that could be used to assess treatment response. Changes in these biomarkers occur in vivo within hours or days of exposure to antineoplastic agents, and they potentially could be used to assess early tumor response. The molecular changes include contrast enhancement and ADC changes at DW MR imaging. Contrast enhancement is a reflection of cellular viability (25–27): Areas of tumor enhancement are considered viable, whereas unenhanced regions reflect tissue necrosis, as suggested by the European Association for the Study of Liver Disease. To accurately assess tumor enhancement, we used the image subtraction techniques described by Yu and Rofsky (28). The advantages of using subtraction imaging to assess HCC lesions include increased depiction of enhancing lesions that are hyperintense on unenhanced T1-weighted MR images. The disadvantages of this technique include image misregistration that results in spurious peripheral enhancement. However, none of the patients included in this study had substantial misregistration artifacts.

DW MR images and ADC maps provide insight into the molecular water composition and the degree of tumor viability at the cellular level (21,22). Viable tumors are highly cellular, and these cells have an intact cell membrane, thus restricting the motion of water molecules and resulting

Figure 2

Figure 2: Box plots show serial changes in ADC values (black boxes) and arterial (red boxes) and portal venous (blue boxes) enhancement. The length of the box is the interquartile range of data and indicates the spread of the middle 50% of the observations. The median is indicated by the horizontal line inside the box.

in a decrease in the ADC value. On the other hand, cellular necrosis causes increased membranous permeability allowing free diffusion of water molecules and a marked increase in the ADC value. This technique enables us to detect early cellular necrosis (21,22). DW MR imaging has been used to assess tumor response after chemotherapy and radiation therapy (29); it also has been used as a biomarker when assessing tumor response to therapy before changes in tumor size occur. Furthermore, ADC values add a quantifiable measure of tumor cell death by directly indicating the state of water diffusion within the tumor. Our results show that ADC changes are transient and lag behind changes in tumor enhancement. Peak changes occur 1–2 weeks after therapy, and changes become less significant 3–4 weeks after therapy. This is likely due to tissue dehydration resulting from cellular necrosis.

Cross-sectional imaging is typically performed 4–6 weeks after therapy to determine, on the basis of changes in tumor size, if the tumor responded to therapy. However, the optimum time after TACE for patients to undergo imaging is unknown. Animal studies showed that ischemia and cell membrane damage occur almost immediately after TACE, resulting in the release of enzymes (lactic dehydrogenase and aspartate aminotransferase) and water before complete cell necrosis (30). Imaging should be performed during the interval that demonstrates detectable differences between cells that are completely necrotic and those that are in the reparative process or transition zone. Our results show it is likely that imaging performed 1–2 weeks after TACE would reveal the maximum detectable changes in tumor enhancement and ADC values after therapy.

This study had several limitations. The sample was small, with possible selection bias since we included only 24 of 120 patients whose care was discussed by our liver tumor board during the enrollment period. Moreover, not all patients underwent all five follow-up MR imaging examinations. It is possible but unlikely that the variation in contrast enhancement or ADC values was due to the fact that a different number of stud-

ies were obtained at each time point. Another limitation of our study was that we did not group patients according to whether they responded to treatment. It is possible that responders had more significant changes in tumor enhancement and ADC values than did nonresponders. However, our objective was to assess temporal changes after TACE to determine the optimum time to perform follow-up imaging—not to determine the success of therapy, which has already been proved to prolong patient survival (10–14). Patients often undergo multiple TACE cycles for lesions that may not respond to initial treatment, and the temporal changes after repeat treatment are unknown and were not evaluated in this study. Additional studies may be performed to assess these changes after multiple treatment cycles.

In conclusion, our study provided information about early changes in vascular and cellular MR findings after TACE. In vivo monitoring of these dynamic changes suggests that maximum changes in tumor enhancement and ADC values occur 1–2 weeks after therapy. Imaging can be performed immediately (within 24 hours) or 3–4 weeks after therapy, and tumor response at these time points may be assessed by evaluating changes in tumor enhancement. However, at these time points, a minimal change or no change in ADC value is anticipated. In addition, changes in tumor size may not occur in the early follow-up period.

References

1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745–750.
2. American Cancer Society. Cancer facts and figures. Atlanta, Ga: American Cancer Society, 2006.
3. Carr BI. Hepatic artery chemoembolization for advanced stage HCC: experience of 650 patients. *Hepatogastroenterology* 2002;49:79–86.
4. Ahmed M, Goldberg SN. Thermal ablation therapy for hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13(9 pt 2):S231–S244.
5. Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13(9 pt 2):S211–S221.
6. Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology* 1998;27:1578–1583.
7. Rilling WS, Drooz A. Multidisciplinary management of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13(9 pt 2):S259–S263.
8. Head HW, Dodd GD 3rd. Thermal ablation for hepatocellular carcinoma. *Gastroenterology* 2004;127(5 suppl 1):S167–S178.
9. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004;127(5 suppl 1):S179–S188.
10. Solomon B, Soulen MC, Baum RA, Haskal ZJ, Shlansky-Goldberg RD, Cope C. Chemoembolization of hepatocellular carcinoma with cisplatin, doxorubicin, mitomycin-C, ethiodol, and polyvinyl alcohol: prospective evaluation of response and survival in a U.S. population. *J Vasc Interv Radiol* 1999;10:793–798.
11. Soulen MC. Chemoembolization of hepatic malignancies. *Oncology (Williston Park)* 1994;8:77–84.
12. Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. *Radiology* 1989;170:783–786.
13. Ngan H, Lai CL, Fan ST, Lai EC, Yuen WK, Tso WK. Transcatheter arterial chemoembolization in inoperable hepatocellular carcinoma: 4-year follow-up. *J Vasc Interv Radiol* 1996;7:419–425.
14. Higuchi T, Kikuchi M, Okazaki M. Hepatocellular carcinoma after transcatheter hepatic arterial embolization: a histopathologic study of 84 resected cases. *Cancer* 1994;73:2259–2267.
15. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
16. Tsuchida Y, Therasse P. Response evaluation criteria in solid tumors (RECIST): new guidelines. *Med Pediatr Oncol* 2001;37:1–3.
17. Kamel IR, Bluemke DA, Eng J, et al. The role of functional MR imaging in the assessment of tumor response after chemoembolization

- in patients with hepatocellular carcinoma. *J Vasc Interv Radiol* 2006;17:505–512.
18. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208–1236.
 19. Kamel IR, Bluemke DA, Ramsey D, et al. Role of diffusion-weighted imaging in estimating tumor necrosis after chemoembolization of hepatocellular carcinoma. *AJR Am J Roentgenol* 2003;181:708–710.
 20. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130.
 21. Ross BD, Chenevert TL, Rehemtulla A. Magnetic resonance imaging in cancer research. *Eur J Cancer* 2002;38:2147–2156.
 22. Ross BD, Moffat BA, Lawrence TS, et al. Evaluation of cancer therapy using diffusion magnetic resonance imaging. *Mol Cancer Ther* 2003;2:581–587.
 23. Lim HK, Han JK. Hepatocellular carcinoma: evaluation of therapeutic response to interventional procedures. *Abdom Imaging* 2002;27:168–179.
 24. Takayasu K, Arii S, Matsuo N, et al. Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. *AJR Am J Roentgenol* 2000;175:699–704.
 25. Murakami T, Nakamura H, Hori S, et al. Detection of viable tumor cells in hepatocellular carcinoma following transcatheter arterial chemoembolization with iodized oil: pathologic correlation with dynamic turbo-FLASH MR imaging with Gd-DTPA. *Acta Radiol* 1993;34:399–403.
 26. Castrucci M, Sironi S, De Cobelli F, Salvioni M, Del Maschio A. Plain and gadolinium-DTPA-enhanced MR imaging of hepatocellular carcinoma treated with transarterial chemoembolization. *Abdom Imaging* 1996;21:488–494.
 27. Bartolozzi C, Lencioni R, Caramella D, Mazzeo S, Ciancia EM. Treatment of hepatocellular carcinoma with percutaneous ethanol injection: evaluation with contrast-enhanced MR imaging. *AJR Am J Roentgenol* 1994;162:827–831.
 28. Yu JS, Rofsky NM. Dynamic subtraction MR imaging of the liver: advantages and pitfalls. *AJR Am J Roentgenol* 2003;180:1351–1357.
 29. Mardor Y, Pfeffer R, Spiegelmann R, et al. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. *J Clin Oncol* 2003;21:1094–1100.
 30. Geschwind JF, Artemov D, Abraham S, et al. Chemoembolization of liver tumor in a rabbit model: assessment of tumor cell death with diffusion-weighted MR imaging and histologic analysis. *J Vasc Interv Radiol* 2000;11:1245–1255.