Four-dimensional Transcatheter Intraarterial Perfusion MR Imaging for Monitoring Chemoembolization of Hepatocellular Carcinoma: Preliminary Results

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PURPOSE: Angiographic endpoints for chemoembolization of hepatocellular carcinoma (HCC) are subjective, and optimal endpoints remain unknown. Transcatheter intraarterial perfusion (TRIP) magnetic resonance (MR) imaging, when performed in a combined MR/interventional radiology (MR-IR) suite, offers an objective method to quantify intraprocedural tumor perfusion changes, but was previously limited to two spatial dimensions. This study prospectively tested the hypothesis that a new volumetric acquisition over time, four-dimensional TRIP MR imaging, can measure HCC perfusion changes during chemoembolization.

MATERIALS AND METHODS: Seven men (mean age, 53 years; range, 42–65 y) with eight tumors (mean size, 2.5 × 2.4 cm^2; diameter range, 1.5–5.2 cm) underwent chemoembolization in an MR-IR suite between February and December 2007, with intraprocedural tumor perfusion reductions monitored with four-dimensional TRIP MR imaging. Microcatheter chemoembolization was performed with a 1:1 mixture of chemotherapy agent and emulsifying contrast agent, followed by the administration of gelatin microspheres. Pre- and post-chemoembolization time–intensity curves were generated for each tumor. Semiquantitative measures of tumor perfusion, including area under the curve (AUC), peak signal intensity (SI), time to peak SI, and maximum upslope (MUS), were calculated, and mean differences before and after chemoembolization were compared with paired *t* tests.

RESULTS: Four-dimensional TRIP MR imaging–monitored chemoembolization was successful in all cases. Calculated AUCs before and after chemoembolization (439 vs 221, $P = .004$, 50% reduction), peak SI (32 vs 19, $P = .012$, 41% reduction), and MUS (11 vs 3, $P = .028$, 73% reduction) showed significant reductions after chemoembolization. Time to peak SI did not significantly change (23 sec vs 36 sec, $P = .235$, 57% increase).

CONCLUSIONS: Four-dimensional TRIP MR imaging can successfully measure semiquantitative changes in HCC perfusion during MR-IR–monitored chemoembolization. Future studies may correlate changes in these objective functional parameters with tumor response.

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Abbreviations: AUC = area under the curve, DSA = digital subtraction angiography, 4D = four-dimensional, IR = interventional radiology, MUS = maximum upslope, SACE = subjective angiographic chemoembolization endpoint, SI = signal intensity, TIC = time–intensity curve, TRIP = transcatheter intraarterial perfusion, 2D = two-dimensional

ALTHOUGH chemoembolization is an established treatment for unresectable hepatocellular carcinoma (HCC) (1,2), the optimal angiographic endpoints for this procedure remain unknown. Currently, there is no definitive literature consensus regarding which is the preferable degree of tumor embolization (3): stasis (ie, complete cessation of antegrade blood flow to tumor) or substasis (ie, reduc-

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tion of antegrade blood flow to tumor). In addition, the relationship between angiographic endpoints and tumor therapeutic response remains undetermined. In general, substasis angiographic endpoints are endorsed to reduce potential complications and difficulties presented by complete or excess embolization. These include accelerated liver failure (4,5), elimination of future arterial access to tumor should repeat liver-directed intraarterial therapy be necessary, and possible induction of cancer angiogenesis and tumor recurrence (6,7). As subjective angiographic endpoints for chemoembolization have been shown to vary widely among operators (8), accurate and objective determination of substasis endpoints remains a challenge for interventional radiologists.

In contrast to digital subtraction angiography (DSA), magnetic resonance (MR) imaging allows more objective and reliable assessment of tumor function during transcatheter liver-directed embolotherapies (9). We previously demonstrated that transcatheter intraarterial perfusion (TRIP) magnetic resonance (MR) imaging, which uses direct catheter-based intraarterial injections of gadolinium contrast agent, may be employed to measure functional changes in first-pass perfusion during hepatic tumor embolization in rabbits (10,11). This technology has recently undergone clinical translation in a combined MR/DSA unit (termed an MR–interventional radiology [IR] suite) for intraprocedural monitoring and quantification of tumor perfusion changes during chemoembolization (8,12), but was limited by two-dimensional (2D) acquisition protocols. We have since implemented an improved approach termed four-dimensional (4D) TRIP MR imaging, which serially monitors perfusion levels during chemoembolization using three spatial and one time dimension by imaging a volume of treated liver every 2 seconds with MR fluoroscopy. In this study, we tested the hypothesis that 4D TRIP MR imaging can be used to measure semiquantitative perfusion changes in HCC during MR-IR–monitored chemoembolization.

MATERIALS AND METHODS

This prospective study was approved by our hospital's institutional review board, and was in compliance with the Health Insurance Portability and Accountability Act. All patients provided written informed consent.

Clinical Setting, Patients, and Tumors

Between February and December 2007, seven patients with surgically unresectable HCC presenting for chemoembolization at a single university-affiliated hospital in a large metropolitan area were enrolled for study. All patients were deemed candidates for chemoembolization based on discussion at a weekly institutional multidisciplinary conference. Chemoembolization inclusion and exclusion criteria were modified from Brown et al (13). Inclusion criteria consisted of (i) age greater than 18 years, (ii) Eastern Cooperative Oncology Group performance status of 2 or lower, (iii) Child-Pugh class A or B disease, (iv) focal or multifocal HCC, (v) estimated glomerular filtration rate greater than 30 mL/min, (vi) no contraindications to MR imaging, and (vii) submission of informed consent. No patients met exclusion criteria of (i) life expectancy less than 6 months, (ii) Eastern Cooperative Oncology Group performance status of 3 or higher, (iii) Child-Pugh class C disease, (iv) uncorrectable coagulopathy (ie, International Normalized Ratio >1.5), (v) total bilirubin level greater than 4.0 mg/dL, (vi) serum creatinine level greater than 2.0 mg/dL, (vii) uncorrectable thrombocytopenia (platelet count $<50{,}000/\mu L$), or (viii) contraindications to MR imaging. Patients with portal vein thrombosis were included if superselective segmental chemoembolization was technically feasible.

The diagnosis of HCC was established noninvasively based on the presence of a hepatic mass at least 2 cm in diameter with characteristic imaging findings in the setting of liver cirrhosis (14). Surgical unresectability was determined by attending transplant surgery physicians and consisted of portal vein thrombosis in two patients. The remaining patients underwent chemoembolization to maintain eligibility for future intended liver transplantation.

Patient Demographics and Tumor Characteristics

Seven patients (all men; mean age 53 years; age range, 42–65 y) were included. Underlying liver disease included alcoholic cirrhosis ($n = 2$), hepatitis C virus ($n = 3$), and hepatitis B virus ($n = 1$), as well as cirrhosis related to hemochromatosis ($n = 1$). Liver disease was classified as Child-Pugh class A ($n = 2$) or B ($n = 5$). Mean Model for End-stage Liver Disease score was 12 (range, 7–19). Eastern Cooperative Oncology Group performance status was 0 ($n = 1$) or 1 ($n = 6$). Okuda stages included stage 1 ($n = 2$) and stage 2 ($n = 5$), and Cancer of the Liver Italian Program stages were early ($n = 1$) and intermediate ($n = 6$).

Eight total tumors were treated. All tumors were focal and circumscribed in nature, and were located in segments 2 ($n = 1$), 4 ($n = 1$), 6 ($n = 1$), 7 ($n = 2$), or 8 ($n = 3$). Mean tumor size was 2.5×2.4 cm^2 (diameter range, 1.5–5.2 cm). Two patients had portal vein thrombosis. Mean α-fetoprotein level was 6,936 ng/dL (range, 1–48,285 ng/dL). Six tumors had not been previously treated, whereas two tumors had undergone previous chemoembolization. Although some patients in this study were candidates for radiofrequency ablation therapy as a "bridge" to liver transplantation based on HCC size and location, chemoembolization was selected as the optimal locoregional therapy in these patients during institutional multidisciplinary conference discussion.

MR-IR Unit

All chemoembolization procedures were performed in a dedicated MR-IR suite (Miyabi; Siemens, Erlangen, Germany) that contains a flat-panel DSA system integrated with a 1.5-T Espree MR imaging scanner via a moving table. Patients were transferred between the IR angiography table and MR imaging scanner according to institutional safe transfer protocol in which an itemized checklist was systematically reviewed by physician operators, angiographic technicians, and angiography nurses before patient relocation to account for all present ferromagnetic devices and prevent inadvertent