A Comparison of Chemoembolization Endpoints Using Angiographic versus Transcatheter Intraarterial Perfusion/MR Imaging Monitoring

Robert J. Lewandowski, MD, Dingxin Wang, BS, James Gehl, BBA, Bassel Atassi, MD, Robert K. Ryu, MD, Kent Sato, MD, Albert A. Nemcek, Jr, MD, Frank H. Miller, MD, Mary F. Mulcahy, MD, Laura Kulik, MD, Andrew C. Larson, PhD, Riad Salem, MD, MBA, and Reed A. Omary, MD, MS

PURPOSE: Transcatheter arterial chemoembolization (TACE) is an established treatment for unresectable liver cancer. This study was conducted to test the hypothesis that angiographic endpoints during TACE are measurable and reproducible by comparing subjective angiographic versus objective magnetic resonance (MR) endpoints of TACE.

MATERIALS AND METHODS: The study included 12 consecutive patients who presented for TACE for surgically unresectable HCC or progressive hepatic metastases despite chemotherapy. All procedures were performed with a dedicated imaging system. Angiographic series before and after TACE were reviewed independently by three board-certified interventional radiologists. A subjective angiographic chemoembolization endpoint (SACE) classification scheme, modified from an established angiographic grading system in the cardiology literature, was designed to assist in reproducibly classifying angiographic endpoints. Reproducibility in SACE classification level was compared among operators, and MR imaging perfusion reduction was compared with SACE levels for each observer.

RESULTS: Twelve patients successfully underwent 15 separate TACE sessions. SACE levels ranged from I through IV. There was moderate agreement in SACE classification ($\kappa = 0.46 \pm 0.12$). There was no correlation between SACE level and MR perfusion reduction ($r = 0.16$ for one operator and 0.02 for the other two).

CONCLUSIONS: Angiographic endpoints during TACE vary widely, have moderate reproducibility among operators, and do not correlate with functional MR imaging perfusion endpoints. Future research should aim to determine ideal angiographic and functional MR imaging endpoints for TACE according to outcome measures such as imaging response, pathologic response, and survival.

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Abbreviations: AUC = area under the curve, DSA = digital subtraction angiography, HCC = hepatocellular carcinoma, SACE = subjective angiographic chemoembolization endpoint, TACE = transcatheter arterial chemoembolization, TIMI = Thrombolysis In Myocardial Infarction, TRIP = transcatheter intraarterial perfusion.

PRIMARY and secondary hepatic malignancies continue to plague clinical oncologists. Unfortunately, most patients are not candidates for an operative cure at presentation (1,2). Traditional chemotherapeutic regimens offer no survival benefit compared with best supportive care for patients with hepatocellular carcinoma (HCC) (3–9). Liver-directed therapies, of which transcatheter arterial chemoembolization (TACE) is the most widely accepted, have evolved in the treatment of HCC. Recent randomized controlled studies have demonstrated improved survival benefit for those undergoing TACE versus best supportive care (10,11). TACE has also become an established treatment for those with progressive hepatic metas-

From the Departments of Radiology (R.J.L., D.W., J.G., B.A., R.K.R., K.S., A.A.N., F.M., M.F.M., L.K., A.C.L., R.S., R.A.O.), Biomedical Engineering (D.W., A.C.L., R.A.O.), and Medicine (M.F.M., L.K., R.S.), Feinberg School of Medicine, and Robert H. Lurie Comprehensive Cancer Center (M.F.M., A.C.L., R.S., R.A.O.), Northwestern University, 676 North St. Clair Street, Suite 800, Chicago, Illinois 60611. Received April 2, 2007; final revision received June 18, 2007; accepted June 20, 2007. **Address correspondence to** R.J.L.; E-mail: r-lewandowski@northwestern.edu

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tases despite standard-of-care chemotherapy (12–20). However, there is no published consensus regarding the preferred angiographic endpoint for TACE: stasis to antegrade blood flow or to a substasis level (21). Although unproven, a substasis endpoint may be safer and more efficacious because excessive embolization may result in arterial occlusion or liver failure (22).

Transcatheter intraarterial perfusion (TRIP) magnetic resonance (MR) imaging is an innovative first-pass perfusion technique that employs direct catheter-based intraarterial injections of contrast agent into the targeted hepatic artery before and after TACE. TRIP MR imaging can be used to verify distribution of injected chemoembolic material before delivery and to monitor changes in tumor perfusion after liver embolotherapy (23). It differs from conventional dynamic contrast agent–enhanced MR imaging because TRIP MR imaging uses catheter-directed intraarterial injections of gadolinium, whereas dynamic contrast agent–enhanced MR imaging uses intravenous injections of gadolinium. A preclinical study in the VX2 rabbit liver tumor model has validated the utility of TRIP MR imaging to monitor iterative changes in liver tumor perfusion during embolization (23). This technique has been translated clinically in the context of interventional radiologic MR suites, which combine interventional radiologic radiographic digital subtraction angiography (DSA) with adjacent MR imaging scanners. TRIP MR imaging offers an objective, quantitative intraprocedural method to compare subjective angiographic endpoints of TACE.

Current radiographic methods cannot assess functional endpoints of TACE. By fusing intraprocedural TRIP MR imaging information with traditional radiographically guided delivery of TACE, we aim to improve the success and reduce the variability of such therapies. In this prospective clinical study, we tested the hypothesis that angiographic endpoints during TACE for HCC or progressive hepatic metastases are measurable and reproducible. To accomplish this, we compared subjective radiographic versus objective MR endpoints of TACE.

Table 1
Study Sample Demographics

Demographics	No. of Patients
Age (y)	
<69	10 (83)
≥69	2 (17)
Ethnic group	
White	8 (67)
Black	1 (8)
Asian	2 (17)
Hispanic	1 (8)
Sex	
Male	7 (58)
Female	5 (42)

Note.—Values in parentheses are percentages.

MATERIALS AND METHODS

Clinical Setting and Patients

Our local institutional review board approved this prospective study. From March through November 2006, we enrolled 12 consecutive patients with surgically unresectable HCC or progressive hepatic metastases despite standard-of-care chemotherapy who presented at a single university-affiliated hospital in a large metropolitan area. All patients were deemed TACE candidates at a weekly institutional multidisciplinary tumor conference. Inclusion and exclusion criteria were modified from the report of Brown et al (24). Included patients met the following criteria: (i) age greater than 18 years, (ii) Eastern Cooperative Oncology Group performance status no greater than 2, (iii) Child-Pugh class A/B disease in cases of HCC, (iv) focal or multifocal hepatic malignancy, (v) no contraindications to MR imaging, and (vi) informed consent. We excluded patients with (i) life expectancy less than 6 months, (ii) Eastern Cooperative Oncology Group performance status of 3 or greater, (iii) Child-Pugh class C disease, (iv) uncorrectable coagulopathy (International Normalized Ratio >1.5), (v) total bilirubin level greater than 4.0 mg/dL, (vi) serum creatinine >2.0 mg/dL; (vii) uncorrectable thrombocytopenia (platelet count <50,000/μL), or (viii) contraindications to MR imaging (eg, pacemaker, cochlear implant). Patients with portal vein thrombosis were enrolled if superselective segmental TACE was technically feasible (25).

Table 2
Tumor Characteristics of Study Sample

Tumor Characteristics	No. of Patients
Lesion distribution (measurable)	
Unilobar	6 (50)
Bilobar	6 (50)
Replacement (%)	
0–25	10 (84)
26–50	1 (8)
51–75	1 (8)
>75	0 (0)
Morphology	
Uninodular and <50%	9 (75)
Multinodular and <50%	3 (25)
Massive or >50%	0 (0)
Portal vein thrombosis	
None	11 (92)
Unilobar	0 (0)
Main	1 (8)
Cirrhosis	
No	2 (17)
Yes	10 (83)
Infiltrative	
No	10 (83)
Yes	2 (17)

Note.—Values in parentheses are percentages.

Demographics, tumor characteristics, baseline liver function, and staging of enrolled patients' disease are detailed in **Tables 1–3**.

The diagnosis of HCC was established by biopsy and/or noninvasively based on a tumor larger than 2 cm in diameter with characteristic imaging findings (26) in the setting of cirrhosis with an serum α-fetoprotein level of at least 400 ng/mL (27). Patients were deemed to have unresectable disease by an attending transplant surgeon or surgical oncologist for the following reasons: (i) concurrent comorbidities including cardiac or respiratory compromise, (ii) recurrent or multilobar disease, (iii) cirrhosis or portal hypertension, (iv) vascular invasion, (v) high tumor burden, and/or (vi) contraindications to general anesthesia. The diagnosis of progressive hepatic metastatic disease was established by biopsy and cross-sectional imaging.

MR Procedure Suite

We performed all TACE procedures with use of a dedicated inter-