Published in final edited form as:

Acad Radiol. 2011 July 1; 18(7): 828–836. doi:10.1016/j.acra.2011.02.016.

Intra-procedural Transcatheter Intraarterial Perfusion MRI as a Predictor of Tumor Response to Chemoembolization for Hepatocellular Carcinoma

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Abstract

Rationale and Objectives—To prospectively test the hypothesis that transcatheter intraarterial perfusion magnetic resonance imaging (TRIP-MRI) measured semi-quantitative perfusion reductions during transcatheter arterial chemoembolization of hepatocellular carcinoma (HCC) are associated with tumor response.

Materials and Methods—Twenty eight patients (mean age 63 years; range 47–87 years) with 29 tumors underwent chemoembolization in a combined MR-interventional radiology suite. Intra-procedural tumor perfusion reductions during chemoembolization were monitored using TRIP-MRI. Pre- and post-chemoembolization semi-quantitative area under the time-signal enhancement curve (AUC) tumor perfusion was measured. Mean tumor perfusion pre- and post-chemoembolization were compared using a paired t-test. Imaging follow-up was performed one to three months after chemoembolization. We studied the relationship between short-term tumor imaging response and intra-procedural perfusion reductions using univariate and multivariate analysis.

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Financial support, disclosures, and conflicts of interest:

No other disclosures or conflicts of interest.

Results—Intra-procedural AUC perfusion value decreased significantly after chemoembolization (342.1 versus 158.6 arbitrary unit, $P < 0.001$). Twenty six patients with 27 HCCs ($n = 27$) had follow-up imaging at mean 39 days post-chemoembolization. Favorable response was present in 67% of these treated tumors according to necrosis criteria. 15 of 16 (94%) tumors with 25–75% perfusion reductions showed necrosis treatment response compared to only 3 of 11 (27%) tumors with perfusion reductions outside the above range ($P = 0.001$). Multivariate logistic regression indicated that intra-procedural tumor perfusion reduction and Child-Pugh class were independent factors associated significantly with tumor response ($P = 0.012$ and 0.047 , respectively).

Conclusion—TRIP-MRI can successfully measure semi-quantitative changes in HCC perfusion during chemoembolization. Intra-procedural tumor perfusion reductions are associated with future tumor response.

Keywords

Transcatheter intraarterial perfusion magnetic resonance imaging (TRIP-MRI); transcatheter arterial chemoembolization; hepatocellular carcinoma (HCC); tumor response; functional embolic endpoint

Introduction

Early identification of tumor response to transcatheter arterial chemoembolization may facilitate efficient assessment of treatment efficacy, timing of repeat therapy, and patient prognosis. Radiological HCC response assessment by conventional computed tomography (CT) or magnetic resonance imaging (MRI) typically occurs 1–3 months after chemoembolization. Although several studies have identified early vascular and cellular changes using dynamic-contrast enhanced (DCE) and diffusion-weighted (DW) MRI as potential markers for early tumor response assessment (1–4), few studies have explored intra-procedural functional imaging biomarkers that may objectively predict future tumor response at the time of chemoembolization procedures.

Intra-procedural MRI allows objective assessment of tumor functions during transcatheter liver-directed embolotherapies (5). We previously demonstrated that transcatheter intraarterial perfusion (TRIP)-MRI, which uses direct catheter-based intraarterial injections of gadolinium (Gd) contrast, may be clinically employed for intra-procedural monitoring and quantification of tumor perfusion changes during chemoembolization when performed in a combined MR / digital subtraction angiography (DSA) unit (termed MR-IR suite) (6–9). TRIP-MRI serially monitors tumor contrast uptake during chemoembolization, providing reliable objective measurement of tumor perfusion prior to and following therapy (7–9).

In this study, we aimed to investigate the relationship between intra-procedural tumor perfusion reductions and tumor response to chemoembolization. We prospectively tested the hypothesis that changes in semi-quantitative TRIP-MRI tumor perfusion obtained during chemoembolization may be used to predict future tumor response.

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 for procedures.

Clinical setting and patients characteristics

Between February 2006 and January 2010, 28 patients with surgically unresectable HCC presenting for MR-IR monitored chemoembolization at a single university-affiliated hospital in a large metropolitan area were prospectively enrolled for this study. Inclusion criteria consisted of (a) age greater than 18 years, (b) surgically unresectable HCC, (c) Eastern cooperative oncology group (ECOG) performance status ≤ 2 , (d) Child-Pugh class A or B liver disease, (e) focal or multi-focal measurable HCC, (f) less than 50% overall liver tumor burden, (g) ability to maintain adequate breath hold (30 seconds), (h) ability to lay supine greater than thirty minutes, (i) ability to undergo angiography and selective visceral catheterization, (j) ability to provide informed consent, and (k) no contraindications to MRI. Exclusion criteria consisted of (a) life expectancy less than six months, (b) uncorrectable coagulopathy (international normalized ratio greater than 1.5), (c) total bilirubin greater than 4.0 mg/dL, (d) serum creatinine greater than 2.0 mg/dL, (e) uncorrectable thrombocytopenia (platelet count less than 50,000 per μ L). Patients with portal vein thrombosis were included if superselective segmental chemoembolization was technically feasible. The HCC study sample was limited to tumor treated in a single chemoembolization session to reduce bias related to differences in treatment session number in the same tumor.

The diagnosis of HCC was established by percutaneous biopsy or non-invasively based upon the presence of a hepatic mass greater than 2 cm diameter with characteristic imaging findings in the setting of liver cirrhosis (10). Surgical unresectability was determined by multidisciplinary consensus at tumor conference comprised of surgical and medical oncology, transplant surgery, hepatology, and interventional radiology.

Patient demographic and tumor characteristic information is presented in Table 1.

MR-IR suite

All chemoembolization procedures were performed in a dedicated MR-IR suite (Miyabi, Siemens AG Healthcare Sector, Erlangen, Germany) that contains a flat panel Artis dTA digital subtraction angiography (DSA) unit integrated with a 1.5 T MAGNETOM Espree MR imager via a moving table. Patients were transferred between the IR angiography table and MRI scanner according to an institutional safe transfer protocol that accounted for all ferromagnetic devices.

Chemoembolization procedures

Chemoembolization was performed by a single Certificate of Added Qualification certified interventional radiologist with over 15 years of clinical experience. Patients were prepared and draped in standard sterile fashion while supine on the angiographic procedure table, and routine arterial access was gained via the right common femoral artery. Initial mapping visceral angiography was then performed using a 5 French visceral catheter (cobra, Sos, or Simmons). Subsequent lobar or segmental angiography in the tumor vascular distribution was performed using a coaxially placed 2.8 French microcatheter (Renegade Hi-Flo; Boston Scientific, Natick MA) after vessel selection with a 0.016 inch diameter guidewire (Headliner; Terumo Medical, Aliso Viejo CA). Catheter position was confirmed using DSA with iohexol (Omnipaque-300; Amersham Health, Princeton NJ) injection. After selecting the appropriate catheter position for chemoembolization, patients were transferred to the adjacent MRI on a moving table. Vascular catheters were covered using a sterile drape to allow for placement of an MR torso array coil. Pre-chemoembolization MRI was then performed.

Following MRI, patients were transferred back to the IR angiography table for chemoembolization. Chemoembolization was performed via the coaxially placed

microcatheter with a 1:1, 20 mL volume solution of chemotherapy agents (100 mg cisplatin, 30 mg mitomycin C, and 30 mg doxorubicin) and emulsifying contrast (Ethiodol; Savage Laboratories, Melville NY). The chemotherapy suspension was injected under direct fluoroscopic observation. Chemoembolization was then concluded by injecting 500–700 μ m diameter tris-acryl gelatin microspheres (Embosphere; Biosphere Medical, Rockland MA) mixed with iohexol. Completion angiography was performed after microsphere embolization. Angiographic endpoint was graded based upon the subjective chemoembolization endpoint (SACE) classification (6) and determined at the discretion of the attending interventional radiologist.

After chemoembolization, patients were again transferred to the MRI scanner for post-chemoembolization completion MRI. After scanning, all catheters and vascular access devices were removed, and hemostasis was achieved with manual compression or a vascular closure device (Angio-Seal, St. Jude Medical, St. Paul MN; or StarClose, Abbott Vascular, Abbott Park IL). Finally, post-chemoembolization non-contrast abdominal computed tomography was obtained to assess the distribution of the injected chemotherapy emulsion.

Intra-procedural MRI

After patient transfer from the IR angiography table to the MRI scanner, patients underwent MRI in supine position using a body array coil. Axial and coronal T1- and T2- weighted turbo spin echo (TSE) localization scans were performed to determine optimal slice positions for subsequent TRIP-MRI. Localization scans were repeated after each MR-IR transfer to ensure consistent slice positions for serial TRIP-MRI measurements.

3D TRIP-MRI was performed using 2D saturation-recovery (SR) gradient echo (GRE) imaging (7) and 4D TRIP-MRI was performed using 3D GRE imaging (13, 14) respectively, in axial orientations, providing full spatial coverage of the targeted liver segments. These imaging sequences were optimized to provide rapid serial acquisition of T1-weighted images for first-pass contrast enhanced MR imaging with a relatively linear relationship between signal and contrast agent concentration (5). 3D TRIP-MRI scan parameters were: TR / TE = 2.4 / 1.2 msec, 8 mm slice thickness, and 10–14 slices. 4D TRIP-MRI scan parameters were: TR / TE = 4.0 / 1.7 msec, 5 mm slice thickness, and 24–28 partitions. Other common parameters included: 15° flip angle, 192 $\times$ 128 matrix, 380–450 mm field of view, and generalized autocalibrating partially parallel acquisition factor, 2. TRIP-MRI slice positions were repeatedly sampled for 40 seconds with 2.2 – 2.5 second sampling rate for each 2D stack or 3D slab. Five seconds after beginning TRIP image acquisition, the interventional radiologist hand injected gadopentetate dimeglumine (Gd; Magnevist, Berlex, Montville, NJ) through the indwelling hepatic artery catheter. Each TRIP-MRI contrast injection was tailored based upon targeted vessel caliber and blood flow rates. Lobar hepatic artery injections used 10 mL of 20% Gd solution at 2 mL/sec, while segmental injections used 5 mL of 20% Gd at 1 mL/sec. These injection protocols were designed to demonstrate perfusion to the targeted liver segments, while avoiding reflux of injected contrast agent into non-targeted angiographic territories. Immediately prior to Gd injection, patients were instructed to breath hold for the following 30 seconds to minimize respiratory motion during first-pass imaging. To maintain consistency, each patient underwent the same TRIP-MRI scan and contrast injection protocol before and after chemoembolization.

Following each TRIP-MRI scan, 2D multi-slice T1-weighted GRE scans were performed for conventional contrast enhanced delayed phase imaging of the liver.

MRI perfusion data analysis

TRIP-MRI series were exported to a Siemens workstation for analysis. Based upon intra-procedural anatomic findings and prior diagnostic images, we chose TRIP-MRI slice positions at the center of each tumor. A region-of-interest (ROI) encompassing the entire tumor within this central slice was selected by consensus of two observers under the guidance of the attending interventional radiologist who performed all chemoembolization procedures in this study. We then plotted the average time-signal intensity enhancement curves from all voxels within the ROI for all dynamic TRIP-MRI series. Each pre-chemoembolization TRIP-MRI series was evaluated to determine the optimal post-injection time interval for measurement. We selected the signal integration interval beginning with the initiation of signal enhancement and closing just beyond peak signal enhancement. Subsequently, tumor perfusion was measured by calculating area under the time-signal enhancement curve (AUC) as semi-quantitative perfusion parameter. To maintain consistency, pre- and post-chemoembolization TRIP-MRI series were analyzed with identical time interval for AUC calculations. We calculated the change in tumor perfusion after chemoembolization as the percentage reduction from pre-chemoembolization values.

Tumor response evaluation

Patients underwent follow-up imaging (contrast enhanced MRI or triphasic CT) one to three months post-procedure to assess response to chemoembolization in the treated lesions. Follow-up imaging analysis was performed independently of the TRIP-MRI perfusion analysis by a board certified interventional radiologist well-versed in the radiographic response assessments following liver-directed locoregional therapies. Size criteria, assessed according to World Health Organization (WHO) guidelines (11), and necrosis response criteria were used to assess tumor response at the first post-chemoembolization imaging follow-up within 3 months unless patients underwent liver transplantation. WHO guideline is based on the cross product of the greatest perpendicular axes of a measurable mass. For each lesion, objective tumor response was defined as either a complete response (CR), defined as complete disappearance of a measurable lesion, or partial response (PR), defined as a 50% decrease from baseline for WHO criteria. Progressive disease (PD) was defined as 25% increase in baseline for WHO criteria. Stable disease (SD) was defined as neither PR nor PD. Necrosis response criteria vary from WHO criteria by accounting for tumor necrosis via estimates of the area of non-enhancement with contrast CT or MRI. Tumor necrosis was suggested to have utility in response assessment by the Barcelona-2000 European Association for the Study of the Liver (EASL) Conference (12), and this particular response assessment methodology was developed by our group and is now published in several series (13–16). Necrosis response criteria CR and PR were defined as 100% decrease in the amount of enhancing tissue in the treated lesion and $\geq 50\%$ decrease in the amount of enhancing tissue in the treated lesion, respectively (13–16). Necrosis response criteria SD encompassed $< 50\%$ decrease to $\leq 25\%$ increase in the amount of enhancing tissue in the treated tumor (13–16). Necrosis response criteria PD was defined as $> 25\%$ increase in amount of enhancing tissue in the treated lesion and/or new enhancement in the previously treated lesion warranting further locoregional therapy (13–16).

Statistical analysis

Semi-quantitative AUC perfusion values measured before and after chemoembolization were first compared using paired t-test to evaluate the intra-procedural reduction in tumor perfusion. We then performed exploratory analyses to identify how intra-procedural tumor perfusion reduction may relate to tumor response. The tumor response was defined as CR or PR in this study. A scatter plot was used to indicate the relationship between semi-quantitative AUC reductions and tumor response. We categorized HCC samples into four groups by percentage intra-procedural perfusion reduction quartiles and calculated the

response rate for each group. We subsequently combined tumors in the two AUC reduction quartiles with the highest response rates into one group and the remaining tumors into another group. The pre-chemoembolization patient and tumor characteristics between the two groups were compared using t-test for continuous variables and the Fisher exact test for categorical variables to assess for baseline differences. Univariate and multivariate analyses were conducted to identify factors associated with tumor response. Independent categorized variables, including age (older than 65 years), gender, tumor size (diameter greater than 3.0 cm), tumor number (greater than 1), Child-Pugh class (higher than A), ECOG performance status (greater than 0), American Joint Committee on Cancer (AJCC) stage (greater than 1), elevated baseline serum alpha fetoprotein (AFP) level (greater than 200 ng/mL (17)), elevated bilirubin level (greater than 1.3 mg/dL (18)), and preferred intra-procedural AUC reductions (with high response rate), were evaluated by univariate analysis using two-tailed Fisher exact test. Multivariate analysis was performed using multiple logistic regression to further evaluate factors that indicated significance in the univariate analysis. Nonsignificant variables in the univariate analyses were excluded from the multivariate model. Tumor number and size would not be included in multivariate analysis if AJCC stage entered multivariate analysis, because they were covered by means of AJCC staging. Baseline bilirubin would not be studied in multivariate analysis if Child-Pugh class was selected into multivariate model, because bilirubin was captured by Child-Pugh class. Total serum albumin and ascites levels were not assessed separately in these analyses because they represent components of Child-Pugh score. Statistical analyses were performed by using SPSS software package (Version 17, SPSS Inc., Chicago IL). A P-value less than 0.05 was considered to indicate statistical significance.

Results

Intra-procedural TRIP-MRI

Representative diagnostic pre-chemoembolization contrast-enhanced T1-weighted MR images are shown in Figure 1. Segmental or lobar chemoembolization were successfully performed to treat 29 separate HCC foci in 28 patients. No procedure-related complications were encountered. Intra-procedural TRIP-MRI was technically successful in all cases as was subsequent time-signal enhancement curve generation. Reductions in tumor perfusion were manifested from the decreased degree and rate of tumor contrast uptake in the TRIP-MRI images series immediately following therapy (Fig. 2a, b). The post-chemoembolization noncontrast-enhanced CT images confirmed chemotherapy ethiodized oil contrast accumulation within these treated regions (Fig. 2c). Calculated pre- and post-chemoembolization AUC (342.1 versus 158.6 arbitrary unit, $P < 0.001$) showed statistically significant reductions after chemoembolization. The median reduction in tumor perfusion is 55% (mean: 52%, range: 0% – 96%).

Tumor imaging response

1–3 month imaging follow-up post-chemoembolization was available in 27 of the 29 treated tumors. One patient underwent orthotopic liver transplantation before the first imaging follow-up. Another patient with a solitary treated HCC did not undergo post-chemoembolization radiographic imaging within the first 17 months after treatment, and was defined as lost to short-term imaging follow-up. Two tumors in these two patients were therefore excluded from response analysis. Representative post-chemoembolization follow-up contrast-enhanced T1-weighted MR images are shown in Figure 3. For the 27 tumors with imaging follow-up, Table 2 presents response according to WHO and necrosis response criteria at mean 39 days (median 35 days, range 20–78 days) following chemoembolization. Although no tumors responded to treatment according to WHO guidelines, the response rate (combined PR and CR) was 67% using necrosis response criteria.

Association between intra-procedural tumor perfusion reduction and tumor response

Scatter plot demonstrated an inverted U-shaped relationship between intra-procedural AUC perfusion reductions and tumor response by necrosis response criteria (Fig. 4a). When AUC reductions were partitioned into quartile subsets and assessed for tumor response by group, the two groups with 25–50% and 50–75% perfusion reductions had the highest response rate (Table 3, Fig. 4b). All tumors in the 25–50% perfusion reduction group showed PR, while the 50–75% perfusion reduction group had the best CR rate (Table 3). 15 of 16 (94%) tumors in the combined 25–75% tumor perfusion reduction group achieved tumor response by necrosis criteria, compared to 3 of 11 (27%) tumors in the combined < 25% and > 75% perfusion reduction group (Table 4). Furthermore, no significant difference between the two groups in baseline characteristics were found, suggesting the degree of chemoembolization induced blood flow reduction might be an important factor contributing to the difference in rate of tumor necrosis. The univariate analysis indicated only the intra-procedural perfusion reduction (25–75% versus < 25 and > 75%, $P = 0.001$) and Child-Pugh class (A versus B, $P = 0.004$) were significantly related to tumor response (Table 4). The multivariate analysis demonstrated that both intra-procedural tumor perfusion reduction and Child-Pugh class were independent factors associated significantly with tumor response ($P = 0.012$ and 0.047 , respectively, Table 4).

Discussion

Chemoembolization represents a liver-directed intraarterial treatment for HCC with established survival benefit (19–22) and is now recognized as the standard of care for intermediate-stage HCC (21–23). This therapy exploits the discrepancy in blood supply between hypervascular neoplastic tissue, which derives 90–100% of its blood flow from the hepatic artery, and non-tumorous liver parenchyma, which is predominantly perfused by the portal vein, to deliver a combination of chemotherapeutic drugs and embolic agents to tumors (21–23). While embolic materials slow blood flow through tumor and sequester chemotherapy medications to achieve high local drug concentrations, embolization also results in regional tissue ischemia. Ensuing localized hypoxia increases expression of intra-tumoral angiogenic factors, including vascular endothelial growth factor (VEGF), which drives cancer angiogenesis and endothelial cell proliferation (24, 25). In this manner, over-embolization during chemoembolization with complete elimination of forward arterial blood flow may promote induction of tumor recurrence and treatment failure.

There is no definitive literature consensus regarding the preferable degree of tumor embolization during chemoembolization (26). In general, some degree of embolization is desirable to achieve mild tumor devascularization and increased chemotherapy retention (27). For this reason, partial blood flow reduction endpoints are endorsed during chemoembolization. Preservation of antegrade arterial blood flow also subdues potential complications presented by complete or over-embolization. Aside from hypoxia-driven tumor angiogenesis, these complications include accelerated liver failure (28, 29) and elimination of future arterial access to tumor should repeat liver-directed intraarterial therapy become necessary. Our study was therefore motivated to understand the relationship between intra-procedural perfusion reduction and tumor response. Furthermore, we aimed to investigate the predictive value of intra-procedural perfusion imaging for future tumor chemoembolization response.

In the present prospective study, we used TRIP-MRI to successfully monitor semi-quantitative HCC perfusion reductions during MR-IR monitored chemoembolization in 29 tumors. We measured statistically significant decreases in tumor AUC perfusion following therapy. Using necrosis response criteria, our analyses indicated a statistically significant increase in tumor response for intra-procedural perfusion reduction of 25–75%. In this

subset, 94% of tumors showed imaging response, as compared to the subset with less than 25% or greater than 75% perfusion reductions, where just 27% of tumors showed response. Moreover, baseline characteristics between the two treated groups had no statistically significant difference. In our samples, 25–75% tumor AUC reduction and Child-Pugh class A were independent factors associated significantly with improved tumor response.

Our study shows an overall 67% necrosis criteria response rate at mean 39 days after chemoembolization. This percentage is consistent with the rates reported by large scale clinical studies approximating 43.5%–64% necrosis criteria response (14, 30). However, in stratified comparison, the 94% response rate in tumors with 25–75% perfusion reduction is higher than the literature reported values, while the 27% response rate in the rest tumor samples is notably much lower. The use of necrosis response criteria to evaluate tumor response to chemoembolization is supported by several clinical findings. First, the relationship between necrosis response and HCC pathological necrosis after chemoembolization is confirmed in explanted liver samples (31). Second, necrosis response shows significant correlation to AFP response (larger than 50% AFP reduction) post-chemoembolization in patients with greater than 200 ng/mL baseline AFP (17). Third, at median 1.6 months, necrosis response is a favorable and significant prognosticator of patient survival following locoregional liver-directed therapies including chemoembolization (13). Additionally, necrosis response evaluation typically at one-month imaging follow-up is among the earliest radiographic therapeutic response assessments performed in clinical routine. Necrosis response serves as an early conventional surrogate for therapeutic benefit and influences subsequent clinical decisions.

The inverted U-shaped relationship between intra-procedural AUC perfusion reduction and necrosis response suggests that: 1) within the initial perfusion reduction range (e.g. 0–55%), increased embolization level typically improves response; 2) intermediate embolization level (25–75%) with partial perfusion reduction can be effective; and 3) over-embolization may reduce chemoembolization efficacy. In addition, complete response is concentrated in the tumor samples with 50–75% perfusion reduction. These observations provide further evidence that middle to upper level partial reductions in blood flow may be more effective in producing tumor necrosis. Our findings also suggest the potential use of intra-procedural TRIP-MRI as a functional imaging biomarker to predict follow-up anatomic response one to three months after therapy.

There were several important limitations to this study. First, our semi-quantitative TRIP-MRI scans provided differences in relative tumor perfusion following chemoembolization, rather than employing absolute quantitative measurements, such as the forward volume transfer constant (K^{trans}) (32). These quantitative approaches may allow direct comparison of absolute differences in perfusion between patients rather than just relative changes within the same patient (9, 33). Clinical studies using these methods are currently ongoing to further explore the relationship between MR tumor perfusion changes and clinical outcomes. Second, the exploratory nature and the small sample size of this study limit the statistical conclusion validity, and a larger sample size is required to compare outcomes with perfusion categories that are smaller than the proposed quartile ranges. Third, TRIP-MRI is capable of assessing perfusion in the vascular distribution distal to the catheter tip. It cannot assess perfusion due to collateral arterial (26, 28, 34) or portal venous supply, unless a follow-up intravenous injection of contrast agent is performed after the post--chemoembolization TRIP-MRI scan (35). Fourth, TRIP-MRI is most applicable to focal tumors with circumscribed margins because of the need to define tumor margins for ROI creation and subsequent time-signal enhancement calculation. Fifth, correlation of the perfusion data with as yet validated necrosis response criteria somewhat limits the ability to generalize the conclusions obtained herein. However, these necrosis response criteria are strongly

supported by radiological – pathological correlation data (31), and are therefore felt to represent legitimate measures of tumor response. Finally, we did not assess the relationship of tumor perfusion with patient survival due to our limited sample size. The complexity of patient survival, which depends upon tumor burden, liver functional impairment, overall health status, and response to treatment (36), calls for a larger study group.

In summary, semi-quantitative TRIP-MRI, performed within an integrated MR-IR unit, can be successfully used to monitor changes in HCC perfusion during chemoembolization. This approach offers the ability to measure intra-procedural changes in tumor perfusion, and may potentially serve as an objective predictor of future tumor response at the time of chemoembolization procedure. There was increased tumor response by necrosis criteria when relative perfusion was reduced by 25–75%. Although these results suggest that intermediate tumor perfusion reductions yield improved tumor response, additional studies will be required to verify these findings. Such studies should incorporate absolute quantitative perfusion parameters to correlate effect on patient management, tumor response, and patient survival.

Acknowledgments

Supported by National Institutes of Health NCI grants No. R01 CA126809 and No. R01 CA134719.

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Figure 1. 65-year-old man with liver cirrhosis related to hemochromatosis and unifocal HCC. Post-contrast arterial phase T1-weighted MR scan (a) obtained prior to chemoembolization reveals segment 8 HCC (arrow). Venous phase image (b) shows typical tumor washout.

Figure 2.

Pre- (a) and post-chemoembolization (b) contrast-enhanced TRIP-MR images for tumor shown in Figure 1 show dramatic reduction in tumor contrast uptake (arrow) after embolization. Pre- and post-chemoembolization tumor AUC perfusion in this patient reduced from 439 to 136 (arbitrary unit, 69.1% reduction). Immediate post-procedure noncontrast-enhanced CT scan demonstrated excellent uptake of chemotherapy emulsion within the targeted lesion (arrow).

Figure 3. Arterial phase (a) and venous phase (b) post-contrast T1-weighted MR scans performed 28 days following chemoembolization for tumor shown in Figures 1 and 2 demonstrates necrosis criteria complete response in segment 8 tumor (arrow).

Figure 4.

Graphs show relationship between intra-procedural TRIP-MRI perfusion (AUC) reduction and tumor response based on necrosis response criteria. (a) Scatter plot between perfusion reduction and necrosis criteria tumor response demonstrates an inverted U-shaped relationship, suggesting an intermediate embolization level is able to induce desirable tumor necrosis. (b) Bar graph of tumor response rates categorized by perfusion reduction level indicates greater percentage of tumor response can be achieved with 25–75% perfusion reduction as compared to < 25% or > 75% perfusion reduction.

Table 1

Patient demographic and tumor characteristics

Characteristic	Patient number (n = 28)
Gender	
Male	21
Female	7
Age (year)	
Mean $\pm$ Standard Deviation	62.7 $\pm$ 10.4
HCC Etiology	
Alcoholic	5
Hepatitis B virus	1
Hepatitis C virus	13
Other	9
AFP	
> 200 ng/mL	8
$\leq$ 200 ng/mL	20
Child-Pugh Class	
A	16
B	12
ECOG Performance Status	
0	9
1	19
AJCC Stage	
1	17
2	5
3	6
Okuda Stage	
1	9
2	18
3	1
CLIP Stage	
0	7
1	11
2	7
3	1
4	2
Tumor Morphology	
Unifocal	18
Multifocal	10
Distribution	

Characteristic	Patient number (n = 28)
Unilobar	22
Bilobar	6
Size of Targeted Lesion (cm)	
Mean $\pm$ Standard Deviation	4.0 $\pm$ 2.7
Diagnosis Method	
Biopsy	11
Imaging	17

ECOG = Eastern Cooperative Oncology Group, AJCC = American Joint Committee on Cancer, CLIP = Cancer of the Liver Italian Program, AFP = alpha fetoprotein

Table 2

Tumor imaging response

Response	CR	PR	SD	PD
WHO	0	0	25	2
Necrosis	7	11	7	2

WHO = World Health Organization, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

Table 3
Relationship between tumor necrosis imaging response and MR perfusion reduction

Perfusion Reduction	Necrosis Response				
	CR	PR	SD	PD	Combined CR/PR
< 25% (n = 6)	0	1	4	1	1
25–50% (n = 4)	0	4	0	0	4
50–75% (n = 12)	6	5	1	0	11
> 75% (n = 5)	1	1	1	2	2
					3

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

Table 4

Analyses of Factors Associated with Tumor Response

Variable	Necrosis Response		P-Value	
	CR/PR (n = 18, 67%)	SD/PD (n = 9, 23%)	Univariate Analysis*	Multivariate Analysis#
Perfusion Reduction			0.001	0.012
25–75%	15 (94%)	1 (6%)		
< 25 or > 75%	3 (27%)	8 (73%)		
Child-Pugh Class			0.004	0.047
A	13 (93%)	1 (7%)		
B	5 (38%)	8 (62%)		
Age (year)			1.000	
≤ 65	10 (67%)	5 (33%)		
> 65	8 (67%)	4 (33%)		
Gender			0.653	
Male	14 (70%)	6 (30%)		
Female	4 (57%)	3 (43%)		
Tumor size (cm)			0.683	
≤ 3.0	9 (75%)	3 (25%)		
> 3.0	9 (60%)	6 (40%)		
Tumor number			0.692	
= 1	10 (62.5%)	6 (37.5%)		
> 1	8 (73%)	3 (27%)		
ECOG performance status			0.667	
0	7 (78%)	2 (22%)		
> 0	11 (61%)	7 (39%)		
AJCC stage			0.683	
I	9 (60%)	6 (40%)		
> I	9 (75%)	3 (25%)		
Serum AFP (ng/mL)			1.000	
≤ 200	13 (68%)	6 (32%)		
> 200	5 (62.5%)	3 (37.5%)		

Variable	Necrosis Response		P-Value	
	CR/PR (n = 18, 67%)	SD/PD (n = 9, 23%)	Univariate Analysis*	Multivariate Analysis#
Serum bilirubin (mg/dL)				0.193
≤ 1.3	8 (89%)	1 (11%)		
> 1.3	10 (56%)	8 (44%)		

* Fisher's Exact Test;

Multivariate Logistic Regression

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ECOG = Eastern Cooperative Oncology Group, AJCC = American Joint Committee on Cancer, AFP = alpha fetoprotein