Transcatheter Intraarterial Perfusion MRI is an Intra-procedural Imaging Biomarker to Predict Survival during Chemoembolization of Hepatocellular Carcinoma

Dingxin Wang[1,2], Ron Gaba[3], Brian Jin[4], Robert Lewandowski[4,5], Robert Ryu[4], Kent Sato[4], Laura Kulik[6], Mary Mulcahy[5,7], Andrew Larson[4,5], Riad Salem[4,5], and Reed Omary[4,5]

[1]Siemens Medical Solutions USA, Inc., Minneapolis, Minnesota, United States, [2]Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, Minnesota, United States, [3]Department of Radiology, University of Illinois at Chicago, Chicago, Illinois, United States, [4]Department of Radiology, Northwestern University, Chicago, Illinois, United States, [5]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, United States, [6]Department of Hepatology, Northwestern University, Chicago, Illinois, United States, [7]Department of Medicine, Northwestern University, Chicago, Illinois, United States

Introduction: Hepatocellular carcinoma (HCC) is the third most common cause of cancer death worldwide. With established survival benefits, transcatheter arterial chemoembolization (TACE) is widely accepted as the first-line therapy for intermediate-stage unresectable HCC [1]. Intra-procedural imaging biomarkers predictive of overall survival (OS) during TACE could potentially further enhance the benefits of TACE, as intra-procedural prognostic factors could be used to guide the selection of optimal therapeutic endpoints at the time of treatment. Transcatheter Intraarterial Perfusion (TRIP)-MRI, using catheter-directed intraarterial contrast injections, offers an objective approach to monitor intra-procedural tumor perfusion changes during TACE in a combined clinical MR/X-ray DSA unit [2, 3]. Recent clinical studies have suggested that chemoembolization endpoints can affect treatment outcome [4] and indicated that intra-procedural perfusion changes measured by TRIP-MRI can predict tumor necrosis imaging response to TACE [5]. In this study, we tested the hypothesis that TRIP-MRI monitored tumor perfusion changes during TACE can predict OS in patients with unresectable HCC.

Methods: In this prospective IRB-approved study, 51 consecutive HCC patients underwent TACE procedures within a Siemens Miyabi MR-DSA suite. Each patient was catheterized under DSA guidance and transferred to a 1.5T Siemens MAGNETOM Espree MR scanner for baseline TRIP-MRI measurements. After moving back to DSA unit, patients underwent DSA-guided TACE. Patients were then returned to MRI for repeat TRIP-MRI. 3D or 4D TRIP-MRI were performed using 2D saturation-recovery spoiled-gradient-echo (GRE) sequence (TR/TE/TI = 2.4/1.2/90 ms, 10-14 slices, 8mm thickness), or 3D GRE sequence (TR/TE = 4.0/1.7 ms, 24-28 slices, 5mm thickness), respectively. Other common parameters included: 15° flip angle, 192×128 matrix, 380-450 mm FOV, 670 Hz/pixel BW, and GRAPPA acceleration factor 2. Dynamic images were acquired for 35 sec after intraarterial injection of 5 or 10 mL 20% Gd-DTPA contrast (Magnevist, Berlex). Imaging parameters were chosen to provide a relatively linear relationship between signal intensity and tissue contrast agent concentration. Tumor regions-of-interest in the central slice of each tumor were drawn on TRIP-MRI image series to generate time-signal enhancement curve. Area-under-the-curve (AUC) was measured as semi-quantitative perfusion parameter and percentage tumor perfusion change was calculated [2]. For multiple tumors treated within same TACE section, size weighted average percentage perfusion reduction was calculated. The endpoint of this study was OS. We studied the correlation between intra-procedural tumor percentage perfusion reduction and OS. Univariate analysis using Kaplan-Meier method with the log-rank test and multivariate analyses using Cox proportional hazards model were conducted to investigate factors associated with OS (α=0.05).

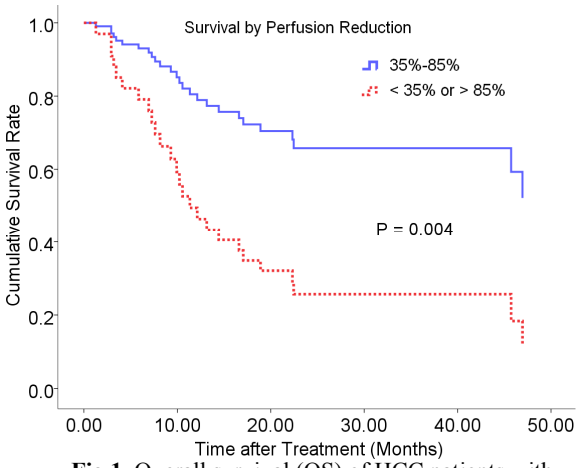

Fig 1. Overall survival (OS) of HCC patients with 35-85% and < 35 or >85% tumor perfusion reduction during TACE adjusted for CLIP score.

Results: Fifty patients had TRIP-MRI monitored TACE successfully performed and were eligible for the analysis. The 25th, 50th, and 75th percentiles of intra-procedural perfusion percentage reduction were 31.5%, 51.1%, and 68.1%. At the time of analysis, 26 of the total 50 patients have deceased. The median OS was 45.7 months (95% CI, 5.6-85.8 months). Patients with 35-85% intra-procedural tumor AUC reductions (n = 32) showed significantly improved median OS compared to patients with AUC reductions outside this range (n = 18) (46.9 [95% CI, not available] versus 10.6 [95% CI, 6.4-19.9] months, P=0.012). The cumulative survival rates in the preferred and non-preferred perfusion reduction groups at 1 and 2 years after TACE were 78.1% and 64.6% versus 50.0% and 26.7%. Univariate analysis indicated that Child-Pugh class (A vs. B, P = 0.033), United Network for Organ Sharing (UNOS) stage (T1/T2 vs. T3/T4a/T4b/N/M, P = 0.009), Cancer of the Liver Italian Program (CLIP) score (< 2 vs. ≥ 2, P = 0.006), and intra-procedural tumor AUC reduction (35-85% vs. < 35 or > 85%, P = 0.012) had significant effects on OS. Multivariate analysis indicated the following factors were independent positive prognosticator of overall survival: CLIP score less than 2 (hazard ratio = 0.27, 95% CI, 0.12-0.64, P = 0.003) and 35-85% intra-procedural tumor perfusion reduction (hazard ratio = 0.31, 95% CI, 0.14-0.69, P = 0.004) (**Table 1**). Figure 1 illustrates the survival distribution function by intra-procedural tumor perfusion reduction adjusted for covariates.

Table 1. Prognostic Factors Associated with Overall Survival

Factor	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Perfusion Reduction						
35-85% (n=32)	0.38	0.18-0.83	**0.012**	0.31	0.14-0.69	**0.004**
< 35 or > 85% (n=18)	1			1		
CLIP Score						
< 2 (n=26)	0.33	0.14-0.75	**0.006**	0.27	0.12-0.64	**0.003**
≥ 2 (n=24)	1			1		
UNOS Stage						
T1/T2 (n=29)	0.36	0.16-0.80	**0.009**			
T3/T4a/T4b/N/M (n=21)	1					
Child-Pugh Class						
A (n=30)	0.66	0.45-0.98	**0.033**			
B (n=20)	1					

Conclusion: Our study shows the evidence of association between intra-procedural tumor perfusion reduction during TACE and OS. TACE provided better survival benefit when relative perfusion reduction was 35-85%. The present results also suggest that TRIP-MRI performed within an integrated MR-DSA unit may serve as an intra-procedural imaging biomarker to predict survival at the time of TACE procedure.

References: [1] Lewandowski, Radiology 2010 [2] Larson, Radiology 2008 [3] Wang, JMRI 2010 [4] Jin, AJR 2011 [5] Wang, Acad Radiol. 2011

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