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Magnetic resonance imaging features predictive of an incomplete response to transarterial chemoembolization in patients with hepatocellular carcinoma

A STROBE-compliant study

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Abstract

To identify pretreatment magnetic resonance imaging (MRI) features associated with an incomplete response (IR) to transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC).

The medical records of 89 patients with HCC who had undergone a first TACE were reviewed retrospectively. The size, visual attenuation in the arterial phase, signal intensity (SI) on T1-, T2-, and diffusion-weighted images, and apparent diffusion coefficient (ADC) values of each lesion were evaluated on pretreatment images. The response to TACE was routinely assessed at 4 weeks post-treatment by 4-phase computed tomography. The HCC patients were classified as complete or incomplete responders based on the arterial–phase enhancement of the target lesion.

In multivariate analysis, larger lesion diameter ($P = .004$, OR = 1.06 per millimeter, 95% CI = 1.02–1.11), faint enhancement on arterial phase ($P = .021$, OR = 3.24, 95% CI = 1.22–9.14), and non-low SI on T1-weighted images ($P = .016$, OR = 3.36, 95% CI = 1.29–9.32) were significantly associated with increased odds of an IR to TACE in HCC patients.

An iso-to-high T1-weighted SI by pretreatment MRI was an independent predictor of an incomplete response to TACE in patients with HCC, in addition to faint arterial enhancement and lesion size.

Abbreviations: αFP = alpha-fetoprotein, AASLD = American Association for the Study of Liver Diseases, APASL = Asia-Pacific Association for the Study of the Liver, CI = confidence interval, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma, IR = incomplete response, MRI = magnetic resonance imaging, OR = odds ratio, PD = progressive disease, PR = partial response, RFA = radiofrequency ablation, SD = stable disease, SI = signal intensity, TACE = transarterial chemoembolization.

Keywords: hepatocellular carcinoma, imaging predictors, transarterial chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and the third leading cause of cancer-related death.[1] Liver transplantation and surgical resection are curative for HCC and have good survival rates; however, few patients with HCC qualify for these curative modalities.[2] Transarterial chemoembolization (TACE) is widely used as a bridge to liver transplantation, or as a palliative treatment.[3] Patients with HCC who respond poorly to TACE may undergo radiofrequency ablation (RFA), resection, or systemic chemotherapy.[4] Therefore, prediction of the response to TACE is crucial for therapeutic planning: early repeat treatment for remnant viable tumor delayed retreatment to reduce toxicity or conversion to other local-regional treatment modalities.

Regarding the pretreatment imaging features of HCC, Hu et al showed that lesion size, vascularity and number, and portal vein invasion, were significantly independently associated with the response to TACE.[5] Kwan et al reported that avid enhancement and a wide feeding artery diameter on angiography were significantly predictive of a good response to TACE.[6] However, few studies have evaluated pretreatment magnetic resonance imaging (MRI) findings predictive of the response to TACE. Therefore, in this study, we assessed the pretreatment MRI features associated with an incomplete response (IR) to TACE in patients with HCC.

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2. Materials and methods

2.1. Patients

This study was approved by the institutional review boards of Soonchunhyang University Bucheon Hospital where the patient data were collected. Informed consent was waved because the study involved only retrospective images or case record reviews. From January 2013 to December 2015, 196 patients who underwent TACE for HCC in our institution were analyzed retrospectively. All of these patients underwent CT and MRI within 3 months before TACE and follow-up CT within 6 weeks after TACE. We excluded 107 patients because of:

1) previous TACE (n = 21),
2) inappropriate protocol or imaging quality of CT and/or MRI for diagnosis of HCC (n = 83), and
3) a history of systemic chemotherapy, RFA, or radiation therapy before TACE or during the follow-up period (n = 3).

Patients undergoing hepatectomy were not excluded. The final study population comprised 89 patients (73 males and 16 females, mean age 60.1 ± 9.3 years). Causes of liver disease, the latest serum alpha-fetoprotein (αFP) levels and Child-Pugh scores before TACE were reviewed by 1 radiologist (LMH) from patients' medical records.

2.2. Imaging

CT examinations were performed on one 16- and two 64-multidetector CT scanners (Somatom Scope and Somatom Definition Flash [Siemens Healthcare] and Discovery CT750 HD [GE Healthcare], respectively). The tumor characteristics and response were evaluated by CT using a 4-phase protocol (non-enhanced phase, arterial phase [20–30 s], portal venous phase [60 s], and delayed venous phase [80 s]) within 12 weeks before and 6 weeks after TACE, respectively.

MRI was performed using a 3-Tesla system (Signa HDxt; GE Healthcare) within 3 months before the initial TACE. The protocol consisted of a breath-hold T2-weighted single-shot fast spin-echo sequence, a respiratory-triggered fat-suppressed T2-weighted fast spin-echo sequence, a breath-hold T1-weighted dual-echo (in-phase and opposed phase) sequence, respiratory-triggered diffusion-weighted sequences, and dynamic contrast-enhanced fat-suppressed 3D T1-weighted sequences using liver acquisition with volume acceleration (LAVA; GE Healthcare). Before and after the administration of gadoxetic acid (Primovist; Bayer Schering Pharma), dynamic T1-weighted unenhanced, early arterial phase (10 s), late arterial phase (35 s), portal venous phase (60 s), transitional phase (3 min), and hepatobiliary phase (20 min) images were acquired. Images in which the unenhanced phase was subtracted from the early arterial and late arterial phases were also obtained. The pulse sequence is listed in Table 1.

2.3. Diagnosis of HCC

HCC can be diagnosed non-invasively by contrast-enhanced CT or MRI. The American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Asia-Pacific Association for the Study of the Liver (APASL), Korean Liver Cancer Study Group, and the National Cancer Center (KLCSG-NCC) have issued guidelines for imaging diagnosis of HCC. Although there is no consensus, these guidelines have the following criteria in common: arterial phase hyperenhancement and venous or delayed phase washout.[7–15] But according to the APASL or KLCSG guidelines, nodules smaller than 1 cm can be diagnosed as HCC. Not to include subcentimeter HCCs in this study, we diagnosed HCC by radiological evaluation with reference to the AASLD or EASL guidelines, or by histological evaluation before TACE.

2.4. Image analysis

HCC lesions detected by pre-TACE imaging, and that underwent selective embolization via the feeding artery on angiography, were chosen as target lesions. In patients with multiple HCC lesions, the most distinct one was selected for evaluation and the multiplicity of HCC was recorded for comparison. Tumor location was assessed in terms of the liver segment and the position within a segment.

Two radiologists with 7 (LMH) and 4 (CSY) years of experience in abdominal imaging reviewed the pre-TACE MR images and follow-up CT images of the target lesions. On pre-TACE MRI,

Table 1

Sequence parameters for 3-T MR imaging.

Parameter	T2-weighted	Fat-suppressed T2-weighted	3D T1-weighted dual-echo (in/out phases)	Diffusion-weighted	Contrast enhanced Fat-suppressed 3D T1-weighted (5 phases)
Sequence type	SSFSE breath hold	FSE repiratory triggered	GRE breath hold	repiratory triggered	LAVA breath hold
No. of sections acquired	30∼40	30∼40	(92∼100)*2(In/Out Phases)	30∼40	92∼100
Section thickness, mm	5(∼6)	5(∼6)	4.4 (interpolated display thickness 2.2)	5(∼6)	4.4 (interpolated display thickness 2.2)
Intersection gap, mm	1	1	0	1	0
Field of view, cm^2	40	40	40	40	40
Matrix	384*224	320*320	256*224 (interpolated display matrix 512)	128*128	300*200
Repetition time, msec	1350	10000	4	50 - 10000 400 - 10000 800 - 16000	4.4
Echo time, msec	47.5	71	1.1, 2.2	50 - 36.8 400 - 50.7 800 - 58.6	1.3
b values used, sec/mm^2	NA	NA	NA	0, 50, 400, 800	NA

FSE = fast spin echo, GRE = gradient echo, LAVA = liver acquisition with volume acceleration, NA = not accepted, SSFSE = single shot fast spin echo.

Table 2

Baseline characteristics (n = 89).

Variable	Value
Age, yr	60.1 ± 9.3
Sex	
Male	73 (82.0%)
Female	16 (18.0%)
Causes of liver disease	
HBV	53 (59.6%)
HCV	15 (16.9%)
Alcoholic	17 (19.1%)
Etc	4 (4.4%)
Multiplicity of HCC	
Single	29 (32.6%)
Multiple	60 (67.4%)
αFP, ng/mL	1501.4 ± 5667.14
Child-Pugh score	5.9 ± 1.11

Data were reported as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.
αFP = alpha-fetoprotein.

each HCC lesion was evaluated in terms of size, enhancement (faint or intense), and heterogeneity (homogenous or heterogeneous) in the arterial phase, and the presence and timing (portal venous and transitional phases) of washout and the signal intensity (SI) (high, iso-, or low relative to the liver parenchyma) on T1WI, T2WI, and hepatobiliary-phase images. Diffusion-weighted image (DWI) SI and apparent diffusion coefficient (ADC) values were calculated by drawing a region of interest (ROI) that encompassed the entire lesion. The presence of portal vein invasion and the presence of intratumoral fat component were also evaluated.

Treatment response was assessed at 4 weeks after TACE by 4-phase CT. The responses to TACE were categorized according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [16] as follows: complete response (CR), disappearance of any intratumoral arterial enhancement; partial response (PR), ≥30% decrease in the diameter of the viable (enhancement in the arterial phase) portion of a target lesion (taking the baseline diameter of the target lesion as a reference); progressive disease (PD), ≥20% increase in the diameter of the viable portion of a target lesion (taking as reference the baseline diameter of the target lesion); and stable disease (SD), any cases not categorized as PR or PD. Next, the HCC patients were reclassified into complete and incomplete responder groups; the complete responder group comprised patients with a CR and the incomplete responder (IR) group comprised those with a PR or SD. There was no case of PD.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software (ver. 14.0; SPSS Inc., Chicago, IL). A kappa statistic was recorded for interobserver agreement. Univariate and multivariate logistic regression analyses were performed to identify the pretreatment imaging features associated with a response to TACE. For logistic regression analyses, consensus data by 2 radiologists were used. Of the variables (including known predictive factors such as tumor size and arterial enhancement) subjected to univariate analyses, those with a $P < .05$ were used in the multivariate logistic regression model. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated.

3. Results

Eighty-nine HCCs of 89 patients were included in this study. Of the 89 enrolled patients, 46 showed a CR to TACE, as indicated by compact lipiodol uptake on follow-up CT. Thirty-four patients showing a PR and 9 showing SD, were reclassified into the incomplete responder group. The basic characteristics of patients are listed in Table 2.

Interobserver agreement regarding the treatment response was excellent (κ = .932). Interobserver agreement rates for pre-TACE MR findings of target lesions were good to excellent (Table 3).

Table 3

MRI features according to treatment response.

Variable	Total (N = 89)	CR (N = 46)	IR (N = 43)	Interobserver agreement (κ)
AP enhancement				0.685
Faint	33 (37.1%)	12 (26.1%)	21 (48.8%)	
Intense	56 (62.9%)	34 (73.9%)	22 (51.2%)	
Enhancement pattern on AP				0.794
Homogeneous	49 (55.1%)	30 (65.2%)	19 (44.2%)	
Heterogeneous	40 (44.9%)	16 (34.8%)	24 (55.8%)	
Wash-out				0.629
Absent	9 (10.1%)	3 (6.5%)	6 (14.0%)	
Present	80 (89.9%)	43 (93.5%)	37 (86.0%)	
PV invasion				0.848
Absent	71 (79.8%)	42 (91.3%)	29 (67.4%)	
Present	18 (20.2%)	4 (8.7%)	14 (32.6%)	
T1SI				0.893
High	6 (6.7%)	3 (6.5%)	3 (7.0%)	
Iso	29 (32.6%)	11 (23.9%)	18 (41.9%)	
Low	54 (60.7%)	32 (69.6%)	22 (51.2%)	
T2SI				0.771
High	78 (87.6%)	41 (89.1%)	37 (86.0%)	
Iso	10 (11.2%)	5 (10.9%)	5 (11.6%)	
Low	1 (1.1%)	0 (0.0%)	1 (2.3%)	
HBP SI				0.787
High	2 (2.2%)	2 (4.3%)	0 (0.0%)	
Iso	12 (13.5%)	8 (17.4%)	4 (9.3%)	
Low	75 (84.3%)	36 (78.3%)	39 (90.7%)	

Data were reported as frequency (percentage) for categorical variables.
AP = arterial phase, CR = complete response, HBP = hepatobiliary phase, IR = incomplete response, PV = portal vein, SI = signal intensity.

Table 4

Logistic regression analysis for incomplete response on treatment.

Variable	Univariable	
	OR (95% CI)	*P* value
Age, yr	1.02 (0.97–1.06)	.498
Sex		
Male	1.00 (Reference)	
Female	1.09 (0.36–3.25)	.882
αFP, ng/mL	1.00	.228
Child-Pugh score	1.40 (0.97–2.126)	.122
MRI features		
Tumor size, mm	1.05 (1.02–1.1)	.01
AP enhancement		
≥moderate	1.00 (Reference)	
≤Mild	2.7 (1.13–6.74)	.028
Enhancement pattern		
Homogeneous	1.00 (Reference)	
Heterogeneous	2.37 (1.02–5.66)	.048
PV invasion		
Absent	1.00 (Reference)	
Present	5.07 (1.63–19.31)	.008
T1SI		
Low	1.00 (Reference)	
Non-low	2.18 (0.92–5.28)	.078
T2SI		
High	1.00 (Reference)	
Non-high	1.33 (0.37–4.96)	.659
Diffusion restriction		
Absent	1.00 (Reference)	
Present	0.52 (0.17–1.48)	.228
HBP SI		
Non-low	1.00 (Reference)	
Low	2.71 (0.83–10.58)	.117

αFP = alpha-fetoprotein, AP = arterial phase, CI = confidence interval, HBP = hepatobiliary phase, OR = odds ratio, PV = portal vein, SI = signal intensity.

In univariate analyses, lesion size, intensity, and heterogeneity of arterial enhancement, incidence of portal vein invasion, and T1-weighted SI differed significantly between the complete and incomplete responder groups (Table 4). Multiplicity of HCCs, serum αFP levels, and Child-Pugh scores, and causes of cirrhosis were not different between 2 groups. There were no significant differences in incidence of intratumoral fat component, ADC values or SIs on T2-weighted images, hepatobiliary phase images, or DWI between the 2 groups. Five variables found to be significant in univariate analyses were included in the multivariate logistic regression model. In the multivariate analysis, larger diameter ($P = .004$, OR = 1.06 per millimeter, 95% CI = 1.02–1.11), faint arterial-phase enhancement ($P = .021$, OR = 3.24, 95% CI = 1.22–9.14), and non-low SI on T1WI ($P = .016$, OR = 3.36, 95% CI = 1.29–9.32) were significantly associated with increased odds of an IR (Table 5).

Table 5

Logistic regression analysis for incomplete response on treatment.

Variable	Multivariable	
	OR (95% CI)	*P* value
Tumor size, mm	1.06 (1.02–1.11)	.004
AP enhancement		
Intense	1.00 (Reference)	
Faint	3.24 (1.22–9.14)	.021
T1SI		
Low	1.00 (Reference)	
Non-low	3.36 (1.29–9.32)	.016
Goodness-of-fit	AIC = 109.13	
	$P = .541$ by H–L test	

AP = arterial phase, CI = confidence interval, H–L test = Hosmer–Lemeshow test, OR = odds ratio.

4. Discussion

TACE is used to control tumor growth, improve survival, palliate symptoms, and provide neoadjuvant therapy for patients with unresectable HCC.[17] A recent meta-analysis showed a survival benefit of TACE;[18] however, this differs among patients and according to the tumor characteristics.[19] Therefore, determination of pretreatment imaging factors predictive of a response to TACE is important. Compact lipiodol uptake, evaluated by dynamic CT 1 month after treatment, is reportedly associated with improved survival in patients with unresectable HCC.[20] Furthermore, the ADC ratio at 1 month after TACE is predictive of progression-free survival.[21] Therefore, the 1-month response to TACE may be associated with disease-free survival and, possibly, other outcomes. However, few studies have aimed to identify pretreatment MRI findings predictive of a response to TACE in patients with HCC.

Although HCCs typically have a low SI on T1-weighted images, some show iso- or hyper-intensity relative to the liver parenchyma. Fats, high concentrations of proteins or copper, hemorrhage, and glycogen in tumors can lead to T1 shortening and result in hyperintensity on T1-weighted images.[22,23] Also, a higher SI on T1-weighted images has been reported to be related to greater histological differentiation of HCC.[24] Therefore, relatively well-differentiated HCC lesions with iso-to-high SI on T1-weighted images have less prominent feeding arteries and tend to respond poorly to TACE. Moreover, tumor uptake of lipiodol decreases with increasing amounts of fat or copper in the tumor. Our study revealed that an iso-to-high T1 SI on pretreatment MRI was an independent predictor of an IR to TACE. But our patients did not undergo follow-up MRI after TACE. Treatment response was assessed by follow-up CT and we couldn't evaluate whether MRI features of HCCs including T1 SI were changed after TACE. In addition, we only evaluated the 1-month response to TACE, so further studies are needed to assess the relationships between the MRI features and the disease-free survival in patients with HCCs.

Further studies are needed to assess the relationship between the SI on T1-weighted images and the response to TACE in patients with HCC.

We analyzed HCC lesions in which the tumor-specific feeding vessel was visualized by angiography. In contrast, HCC lesions diagnosed by pre-TACE imaging, but not visualized by angiography, were excluded, as were those first detected by angiography. This enabled us to accurately evaluate the efficacy of TACE for HCC lesions.

Unlike those who previously received TACE, RFA, systemic chemotherapy, or radiation therapy, patients undergoing hepatectomy were included in this study; the former therapies might affect the hepatic vascular system and the tumor response. Hepatectomy rarely affects the remnant liver parenchyma or vascular system, and so we did not need to take into account possible alterations of the vasculature.

In conclusion, an iso-to-high SI on T1-weighted pretreatment MRI, in addition to faint arterial enhancement and larger tumor

size, was an independent predictor of an IR to TACE in patients with HCC. Although further studies with larger populations, and preferably involving multiple centers, are required, our results will enable the HCC patients likely to benefit least from TACE to be identified.

Author contributions

Conceptualization: Min Hee Lee, Hae Kyung Lee.
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