Diffusion-weighted Magnetic Resonance Imaging in Hepatocellular Carcinoma as a Predictor of a Response to Cisplatin-based Hepatic Arterial Infusion Chemotherapy

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Abstract

This study aimed to identify the utility of diffusion-weighted magnetic resonance (MR) imaging with an apparent diffusion coefficient (ADC) map as a predictor of the intrahepatic response of hepatocellular carcinoma (HCC) to cisplatin-based hepatic arterial infusion chemotherapy (HAIC). We retrospectively evaluated 113 consecutive patients with HCC who underwent gadoxetic acid-enhanced and diffusion-weighted MR imaging. The appropriate cutoff for the tumor-to-liver ADC ratio was determined to be 0.741. Of the 113 patients, 51 (45%) presented with a tumor-to-liver ADC ratio < 0.741. Evaluation of the intrahepatic treatment response after 2-3 cycles of HAIC in these 51 patients revealed that 20 patients (39%) experienced an objective response to HAIC. On the other hand, only 10 of the 62 patients with a tumor-to-liver ADC ratio ≥ 0.741 (16%) experienced an objective response. Thus, the objective response rate was significantly higher in patients with a tumor-to-liver ADC ratio < 0.741 than in those with a tumor-to-liver ADC ratio ≥ 0.741 (P = 0.006). Multivariate logistic regression analysis using parameters including perfusion alteration, percentage of a non-enhancing portion, and tumor-to-liver ADC ratio revealed that a tumor-to-liver ADC ratio < 0.741 (odds ratio 3.03; P = 0.015) is the sole predictor of an objective response to HAIC. Overall survival rates were significantly higher in patients with objective responses to HAIC than in those without objective responses (P = 0.001 by log-rank test). In conclusion, patients with unresectable HCC with a tumor-to-liver ADC ratio < 0.741 showed a favorable intrahepatic response to HAIC. Therefore, diffusion-weighted MR imaging can play a critical role as a predictor of response to cisplatin-based HAIC in unresectable HCC.

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of malignancy-related death worldwide [1]. A considerable number of patients with advanced HCC receive only palliative treatments in East Asian countries, where hepatitis B virus (HBV) infection is prevalent and accounts for more than 70% of the patients [2]. To enhance survival outcomes, sorafenib and lenvatinib are typically administered in cases of advanced HCC with portal vein tumor thrombus (PVTT) or extrahepatic metastasis. However, these drugs are not exceptionally efficacious and may even have notable side effects [3; 4]. Furthermore, the latest immune checkpoint inhibitor monotherapy did not demonstrate increased survival compared with sorafenib in patients with unresectable HCC [5].

Advanced HCC cases can alternatively be treated through hepatic arterial infusion chemotherapy (HAIC), whereby the drug is administered directly through a port inserted into the liver, thus enabling tumor targeting with higher drug dosage and minimizing systemic adverse effects [2]. There is research evidence that, compared to sorafenib, both the objective response (OR) and survival outcomes are improved when HCC is treated through HAIC [2; 6; 7]. Moreover, recent studies demonstrated that reduction of the intrahepatic tumor by the use of HAIC in advanced HCC with PVTT or extrahepatic metastasis led to better survival outcomes [2; 8].

A non-invasive diagnosis of HCC is established by a characteristic radiological findings of arterial phase hyperenhancement (APHE) and portal venous or delayed phase “washout” on contrast-enhanced CT or MRI [9]. Recently, hepatocyte-specific contrast agents for liver MRI have been recognized as the critical tool for the detection of early HCCs. Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA, gadoxetic acid) is a commonly used hepatocyte-specific contrast agent and readily enters into hepatocytes 15-20 minutes after intravenous injection [10]. Hepatobiliary phase (HBP) imaging is obtained at

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this time. Recent studies have suggested that the biological behavior of HCC could be anticipated by examining irregular tumor margin, arterial rim enhancement, and signal intensity (SI) in HBP images [10; 11]. Diffusion-weighted imaging (DWI) was also reported to anticipate the biological behavior of HCC [11; 12]. DWI depends on the information of the diffusivity of water molecules reflecting the cellularity of the tumors [13]. However, evaluation of HCC treatment responses based on the detection of features in MR imaging has not been undertaken by many studies. In this study, we aimed to identify the utility of various MRI findings and DWI with an apparent diffusion coefficient (ADC) map as a predictor of the intrahepatic response of HCC to cisplatin-based HAIC.

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Methods

Study design and population

Ethical approval was obtained from the Institutional Review Board of Seoul St. Mary's Hospital (KC19RESI0912). A diagnosis of unresectable HCC was confirmed in every enrolled patient by the updated international guidelines [9; 14; 15]. HCC cases with PVTT or infiltrative tumors are usually treated with HAIC rather than sorafenib in the researcher's institution. The medical records of all cases that received an HCC diagnosis between January 2010 and December 2017 were reviewed by experienced hepatologists. The survival data of the patients continued to be followed up until December 2019. The inclusion criteria of this study were as follows: unresectable HCC cases undergoing HAIC monotherapy, age range of 20 – 80 years, Child-Pugh class A or B, Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, lack of indication of bone marrow inhibition (white blood cell $\geq 3000/\mu L$, hemoglobin ≥ 8 g/dL, and platelet count $\geq 7.5\times10^4/\mu L$), normal renal function with levels of serum creatinine < 2.0 mg/dL, diffusion-weighted, contrast-enhanced MR imaging before treatment, and response evaluation at least after 2 cycles of treatment. The study did not include cases in which HAIC was undertaken after sorafenib administration. Finally, 113 patients were enrolled in this study for analysis (Figure 1).

Diagnosis of HCC

Multiphasic CT, MRI, biochemical analysis of AFP, and additional biomarkers provided diagnostic information for HCC. The modified RECIST criteria were used to assess therapeutic response [3]. Tumors without arterial enhancement of the target lesions were determined to be in complete response (CR). Partial response (PR) was defined as a 30% reduction in the sum of viable target lesion diameters. Progressive disease (PD) was identified if augmentation of at least 20% was noted in the total viable target lesion

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diameters. If the findings were outside these definitions, the tumor response was considered a stable disease (SD). RECIST rather than mRECIST was used in cases of infiltrative HCCs because this type is classified by mRECIST as a non-target lesion. Likewise, during the assessment of tumor response, PVTT was not included because it was classified by mRECIST as a non-target lesion.

The Vp stages were employed to categorize the PVTT. Tumor invasion distal to the second portal vein branch was categorized as Vp1, tumor invasion of the second portal vein branch was categorized as Vp2, tumor invasion of the first portal vein branch was categorized as Vp3, and tumor thrombus occurrence in the main portal vein trunk or a branch of the portal vein contralateral to the main affected lobe was categorized as Vp4 [2].

HAIC protocol

The specific protocol of HAIC has been described previously [2]. Every HAIC process was conducted by two or more interventional radiologists with more than five years of experience. Two chemotherapeutic drugs were infused through the chemoport inserted into the femoral artery, 5-fluorouracil (5-FU) (500 mg/m^2) for three days and cisplatin (60 mg/m^2) on the second day. In cases where the disease did not progress or the therapy did not have severe complications, HAIC was repeated at the interval of 4-6 weeks. The Child-Pugh categorization was applied at every cycle to assess hepatic function, while follow-up multiphasic CT or MRI was applied after 2-3 therapy cycles to assess the response to therapy.

Qualitative and quantitative analyses of MR imaging

A 3-T MR system (verio, Siemens Healthcare, Erlangen, Germany) alongside a phased array coil with 8 channels serving as the receiver coil was employed for MR imaging. Breath-hold half Fourier Acquisition single-shot turbo spin echo, respiratory-triggered fast spin echo T2-

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weighted image with fat suppression and 3D T1-weighted in- and opposed-phase gradient echo with two-point Dixon reconstruction were obtained as previously described [16]. Meanwhile, contrast-enhanced study was performed using fat-suppressed 3D spoiled gradient-echo volume interpolated breath-hold examinations. After acquisition of unenhanced images, Gd-EOB-DTPA was injected with a dosage of 0.1mL/kg body weight and a flow rate of 1 mL/s through the antecubital vein followed by a 20-mL saline flush. Arterial phase (30- to 35-second delay), portal venous phase (65- to 85-second delay), transitional phase (3-minute delay), and HBP (20-minute delay) were acquired as previously described [17]. DWI with echo planar imaging using b values of 0, 50, 500 and 800 s/mm^2 were obtained and ADC maps were automatically generated using DWI with b values of 0 and 800 s/mm^2 [17].

An abdominal radiologist with 10-year-experience in abdominal MRI reviewed all images as well as the quantitative analysis. She recorded the number of tumors, the largest diameter on axial and coronal images, both lobe involvement, presence of portal vein tumor thrombus and involving segment, hepatic vein or inferior vena cava invasion, tumor type (expansile mass or infiltrative), APHE, targetoid enhancement, homogeneity of arterial enhancement, portal washout, proportion of non-enhancing portion, corona enhancement, presence of tumor's capsule, perfusion alteration and intralesional fat.

Quantitative measurement was undertaken regarding ADC values in lesions and circumscribing healthy parenchyma. Delineation of a region of interest was done on ADC maps for both healthy liver parenchyma and HCCs, steering clear of necrotic and cystic zones, artifacts, and blood vessels within the liver as far as manageable [17]. The regions of interest were drawn with similar size (3 cm^2) in both of tumors and healthy parenchyma and peripheral portion of the tumor was not included because of frequent partial volume artifact [17]. The region of interest was drawn in the largest tumor in the patients with multiple tumors. Ratio of tumor-to-liver ADC was calculated in each patient.

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Statistical analysis

Statistical analysis was performed using SPSS version 26 software (IBM Corp., Armonk, NY, USA). The chi-square test was used to evaluate discrete variables from the two cohorts. An independent t-test was employed to compare continuous variables between the two groups. A receiver operating curve was used to identify the cutoff value. Statistical significance was defined as $P < 0.05$. The Kaplan-Meier technique was adopted to approximate the overall survival (OS) without recurrence, while the log-rank test was applied for OS comparison. Determinants of objective responses were identified by conducting multivariate analysis alongside a Cox proportional hazard model.

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Results

Baseline characteristics

The baseline clinical characteristics of the enrolled patients are listed in Table 2. We divided all included patients into two groups according to the ADC tumor to liver ratio. The cutoff value of the ADC tumor to liver ratio (0.741) was determined by the receiver operating characteristic (ROC) curve. The patients were divided into two groups: patients with an ADC tumor to liver ratio < 0.741 (n = 50, low group) and an ADC tumor to liver ratio ≥ 0.741 (n = 63, high group). There were no differences in sex and etiology of HCC between the two groups, although patients in the low group tended to be younger (Table 2). There were no statistical differences in the maximal diameter, tumor number, and the presence of PVTT between the two groups. A considerable number of patients in both groups received other modalities of treatment (TACE, liver resection, RFA, or sorafenib) before HAIC. Regarding tumor markers, there was no statistical difference in serum AFP levels between the two groups. Before HAIC, the mean tumor ADC (unit, $1.10 \pm 0.29 \times 10^{-3}$ mm^2/s) of the high group was not significantly different from that of the low group (unit, $1.10 \pm 0.31 \times 10^{-3}$ mm^2/s), although the mean tumor to liver ADC ratio was significantly lower in the low group ($P < 0.001$) (Table 2). Moreover, the mean tumor to spleen ADC ratio was also significantly lower in patients in the low group ($P < 0.001$). For the other parameters detected in MR imaging (the amount of the non-enhancing portion, the presence of perfusion alteration, the presence of targetoid enhancement, the presence of blood product in the tumor, the presence of fatty change in the tumor, and the tumor signal after arterial enhancement), there were no statistical differences between the low and high groups.

Intrahepatic response according to the ADC tumor to liver ratio

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As indicated in Table 2, the optimal intrahepatic response to therapy was evaluated based on mRECIST following 2-3 HAIC cycles. In the low group, the number of patients who displayed CR or PR was 21 (42%) and SD or PD was 29 (58%). In the high group, the number of patients who displayed CR or PR was 11 (17%) and SD or PD was 52 (83%). There was a statistical difference between the objective response rate between the low and high groups ($P < 0.006$). Figure 2 shows that the tumor to liver ADC ratio of patients with an objective response was significantly lower than that of patients without an objective response ($P < 0.01$). However, there was no significant difference in OS between the patients with high tumor to liver ADC ratio and those with low values (data not shown) by log-rank test, although patients with objective responses showed better survival outcomes than those without (data not shown).

Factors affecting responses to HAIC

Table 3 delineates the factors affecting the responses to HAIC. Variables included in the logistic regression were as follows: age < 60 years, presence of PVTT as Vp0 to Vp2, AFP lower than 1000 ng/mL, non-enhancing portion of the tumor less than 50%, the presence of perfusion alteration, and the tumor to liver ADC ratio less than 0.741 (Table 3). Among all the factors, the tumor-to-liver ADC ratio was the only factor that had a significant effect on the objective responses to cisplatin-based HAIC (odds ratio: 3.208, 95% confidence interval: 1.288-7.878, $P = 0.012$) (Table 3). Figure 3 shows the MR imaging of a representative patient case with strong diffusion restriction and excellent response to HAIC. For the patient, the main tumor was located in the main portal vein, and the pretreatment ADC tumor to liver ratio was 0.36. After 5 cycles of HAIC, there was no viable tumor with diffusion restriction (Figure 3). The patient underwent subsequent liver transplantation after the achievement of

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CR by HAIC.

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Discussion

Advanced HCC with PVTT or extrahepatic metastasis usually shows poor prognosis, with the aim of treatment being limited to extending life and at the same time preserving the hepatic reserve. Advanced HCC in the BCLC staging system has typically been treated with the multikinase inhibitor sorafenib or lenvatinib [18]. However, these drugs have been shown to improve survival only slightly in cases of BCLC stage C disease. Moreover, when HBV is the cause of HCC, the prevalence of PVTT and more aggressive tumor features are higher than when other etiologies are the causes [2]. Recent work by our group has demonstrated that survival outcomes in advanced HCC cases are markedly improved by HAIC because it substantially alleviates the intrahepatic tumor burden, even in cases with Vp 3 or 4 PVTT [2]. Therefore, it is critical to choose patients who will potentially benefit from HAIC. In this study, we suggest that decreased ADC tumor to liver ratio may be a marker of an objective response to cisplatin-based HAIC.

DWI is now used in most of the cancers to predict treatment responses and to distinguish different tumor grades [13]. For instance, patients with breast cancer and a low pretreatment ADC tended to respond better to neoadjuvant chemotherapy [19]. Recent reports demonstrated that DWI helps distinguishing early HCCs from regenerative nodules in cirrhotic livers [20; 21]. Moreover, DWI predicted the pathologic grade of HCC because there was an inverse correlation between tumor grades and ADC values [22; 23; 24]. For patients treated with cisplatin-based HAIC, this strategy will also provide benefits to patients. Despite the known chemoresistance of HCC to cytotoxic drugs such as cisplatin [25; 26], there are certainly a group of patients that show dramatic responses to this treatment [27]. The reason there is a group of patients who show objective responses to this treatment will be identified when detailed multi-omics analyses are performed. Previous reports demonstrated that downregulated expression of specific genes may render susceptibility to cisplatin in HCC

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cell lines [25; 26]. This suggests that patients with downregulation of these genes in their tumors may show a good response to cisplatin-based HAIC. The molecular-radiologic correlation regarding cisplatin sensitivity in HCC requires further investigation.

There are a number of shortcomings to this study. One shortcoming is that the study was conducted in one institution, so there is a possibility of selection bias. Another shortcoming is the insufficient number of cases recruited. On the other hand, this is the first study to identify imaging biomarkers of HAIC in advanced HCC. Although comparable analyses were conducted on cases receiving sorafenib treatment during the same period, statistical analyses were not possible because only three of the over 250 cases displayed intrahepatic objective responses following sorafenib treatment.

In a recent clinical trial, lenvatinib was non-inferior to sorafenib in terms of overall survival in patients with unresectable HCC and caused a considerable decrease in the tumor burden when patients were responsive to the drug [28; 29; 30]. Therefore, the combined use of lenvatinib plus cisplatin-based HAIC may show the synergistic anti-cancer effects in advanced HCC. A future prospective clinical trial of lenvatinib plus cisplatin-based HAIC vs. lenvatinib only may show promising results in combination treatment. Investigation of the roles of DWI and contrast-enhanced MRI in lenvatinib plus HAIC will also be an area for interesting research.

In conclusion, our study demonstrated for the first time that patients with unresectable HCC with a tumor-to-liver ADC ratio < 0.741 showed a favorable intrahepatic response to HAIC. Therefore, diffusion-weighted MR imaging can play a critical role as a predictor of response to cisplatin-based HAIC in unresectable HCC.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions:

Pil Soo Sung: study design, data collection, data analysis, data interpretation, manuscript writing, and manuscript approval.

Moon Hyung Choi: data collection, data analysis, data interpretation, manuscript writing, and manuscript approval.

Hyun Yang, Ho Jong Chun, Jeong Won Jang, Jong Young Choi, Seung Kew Yoon, Joon-Il Choi, Young Joon Lee, Si Hyun Bae: data interpretation and manuscript approval.

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Table 1. MR Imaging Sequences and Parameters

Parameters	Sequence				
	HASTE T2WI	**Fast Spin Echo T2WI**	**T1-Weighted in/opposed phase**	**T1-weighted 3D GRE**	**DWI**
TR (msec)	600–1000	2000–6000	170–220	2.8-3.5	3500–4200
TE (msec)	80–140	100–140	2.6/1.3	1-1.2	40–50
Flip angle (º)	138	150–160	50–70	11	90/180
Slice thickness (mm)	6	6	6	2	8
Reconstruction interval (mm)	6	6	6	2	8
Acquisition matrix	320–400 × 150–180	380–450 × 180–220	250–300 × 120–170	256 x 156	140–160 × 90–120
Signal averages	1	1	1	1	5
b-values (s/mm^2)	N/A	N/A	N/A	NA	0, 50, 500

TR, repetition time; TE, echo time; HASTE, half-Fourier acquisition single-shot turbo spin-echo, T2WI = T2-weighted image, 3D = three-dimensional, GRE = gradient echo DWI = diffusion weighted image

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Table 2. Clinical parameters of study patients

Variables	ADC ratio < 0.741 (n = 50)		ADC ratio ≥ 0.741 (n = 63)		p
	No.	%	No.	%	
Age					0.02
< 60	36	72	31	49	
≥ 60	14	28	32	51	
Sex					0.074
Male	44	88	47	75	
Female	6	12	16	25	
Etiology					0.096
HBV	46	92	46	73	
HCV	1	2	7	11	
Alcohol	1	2	6	10	
HBV + HCV	0	0	1	2	
Others	2	4	3	5	
Serum AFP					0.257
< 1000 ng/mL	19	38	31	49	
≥ 1000 ng/mL	31	62	32	51	
Tumor maximal diameter					0.437
< 10 cm	17	34	27	43	
≥ 10 cm	33	66	36	57	
Tumor number					0.703
Single	23	46	26	41	
Multiple	27	54	37	59	
Portal vein tumor thrombus					0.829
Vp0, 1, 2	12	24	17	27	
Vp3, 4	38	76	46	73	
Extrahepatic metastasis					1
yes	11	22	13	21	
no	39	78	50	79	
Previous treatment					
TACE	20	40	26	52	
RFA	3	6	5	10	
TARE	1	2	3	6	
Liver resection	2	4	4	8	
Sorafenib	1	2	3	6	
Non-enhancing portion					0.005
< 50%	26	52	49	78	
≥ 50%	24	48	14	22	
Perfusion alteration				0	0.126
no	26	52	42	67	
yes	24	48	21	33	
Targetoid enhancement					0.599
no	44	88	53	84	
yes	6	12	10	16	
Blood product in tumor (T1)					0.852
no	26	52	34	54	
yes	24	48	29	46	
Fatty change in tumor					1
no	44	88	56	89	
yes	6	12	7	11	
Mean tumor ADC (unit, $\times 10^{-3}$ mm^2/s)	1.10 ± 0.29		1.10 ± 0.31		1
Mean liver ADC (unit, $\times 10^{-3}$ mm^2/s)	1.54 ± 0.35		1.26 ± 0.31		0.001
Mean spleen ADC (unit, $\times 10^{-3}$ mm^2/s)	1.05 ± 0.24		1.06 ± 0.19		0.757
Mean tumor to liver ADC ratio	0.63 ± 0.10		0.98 ± 0.23		0.001
Mean tumor to spleen ADC ratio	0.94 ± 0.25		1.16 ± 0.27		0.001

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Diffusion restriction					0.787
no	8	16	8	13	
yes	42	84	55	87	
Tumor signal after arterial enhancement					0.662
higher than parenchyma	45	90	56	89	
similar to liver parenchyma	2	4	4	6	
lower than liver parenchyma	3	6	3	5	
Homogenous enhancement				0	0.014
no	6	12	20	32	
yes	44	88	43	68	
Median HAIC session number	5.0 ± 3.3		4.3 ± 3.1		0.297
Response to HAIC					0.006
CR+PR	21	42	11	17	
SD+PD	29	58	52	83	

HAIC: Hepatic arterial infusion chemotherapy; HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alpha fetoprotein; BCLC: Barcelona Clinical Liver Cancer; TACE: transarterial chemoembolization; RFA: radiofrequency ablation; TARE: transarterial radioembolization; ADC: apparent diffusion coefficient

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Table 3. Factors affecting the responses to HAIC

Variables	logistic regression analysis for objective response	
	P	OR (95% CI)
Age (< 60)	0.427	0.682 (0.265-1.753)
Portal vein tumor thrombus (Vp0 to Vp2)	0.709	0.815 (0.278-2.389)
AFP (< 1000 ng/mL)	0.952	1.029 (0.41-2.582)
Non-enhancing portion < 50%	0.622	0.778 (0.287-2.112)
Presence of perfusion alteration	0.397	0.676 (0.273-1.673)
ADC ratio (tumor to liver) < 0.741	0.012	3.208 (1.288-7.989)

HAIC: Hepatic arterial infusion chemotherapy; AFP: alpha fetoprotein; ADC: apparent diffusion coefficient, OR: odds ratio. CI: confidence interval

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Figure Legends

Figure 1. Study population

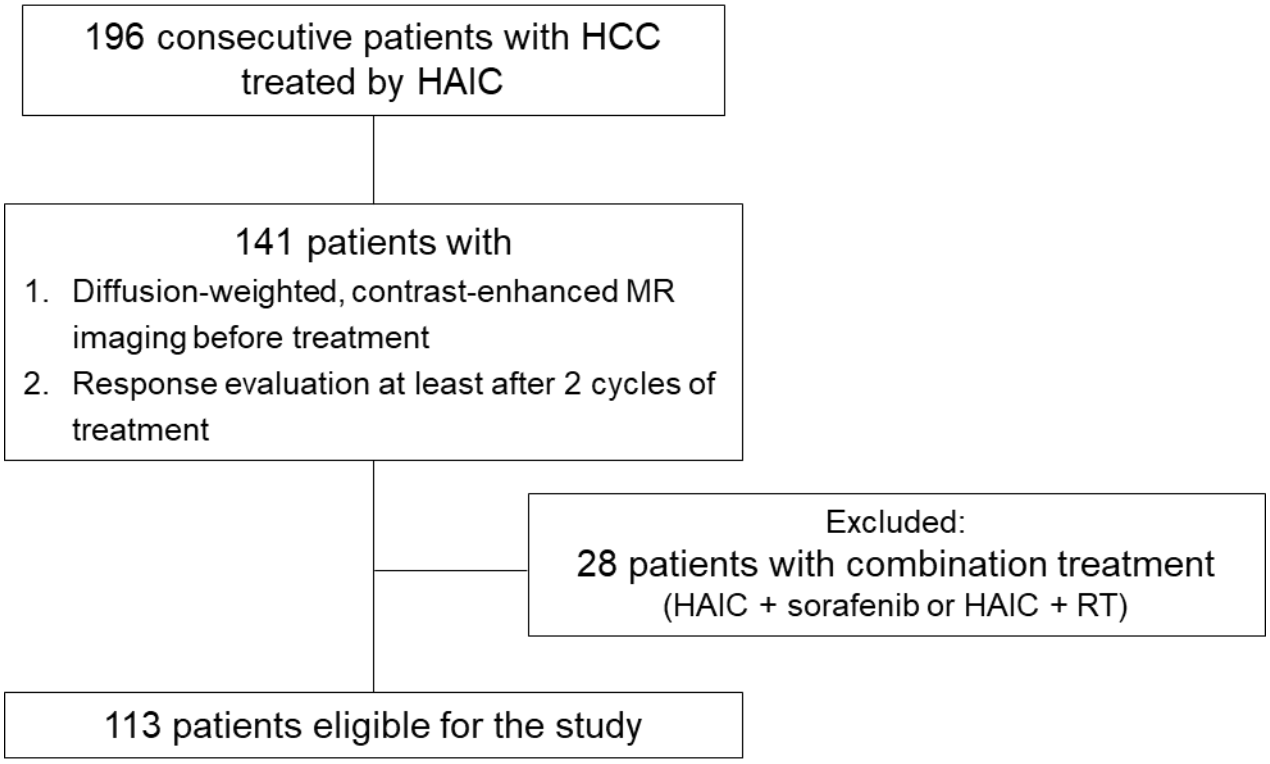

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Figure 2. Tumor to liver ADC ratio according to the response to HAIC

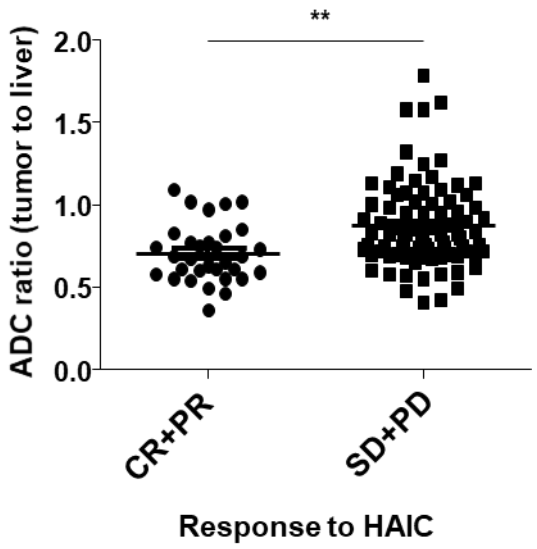

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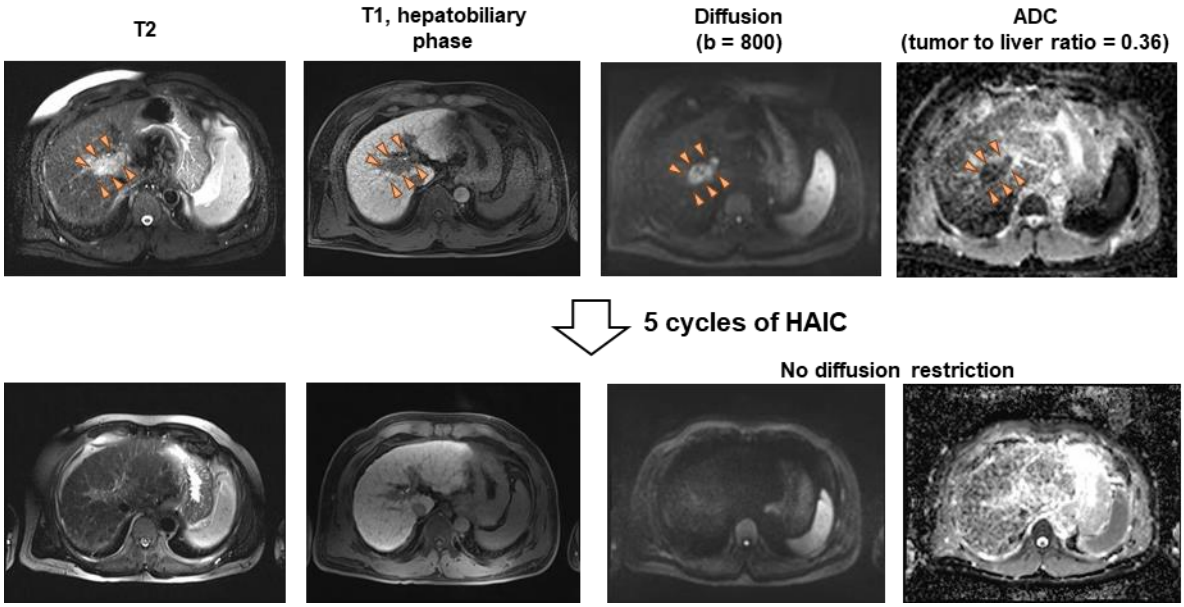
Figure 3. Representative patient case with strong diffusion restriction and good response to HAIC



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Abbreviations

ADC: apparent diffusion coefficient; HCC: hepatocellular carcinoma ; HAIC: hepatic arterial infusion chemotherapy; MR: magnetic resonance; HBV: hepatitis B virus; PVTT: portal vein tumor thrombus; OR: objective response; APHE: detected arterial phase hyperenhancement; PVP: portal venous phase; ECA: extracellular contrast agent; SI: signal intensity; DWI: diffusion-weighted imaging; HBP: acid-enhanced hepatobiliary phase; Gd-EOB-DTPA: Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; ECOG: Eastern Cooperative Oncology Group; CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease; 5-FU: 5-fluorouracil; ROC: the receiver operating characteristic