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Intravoxel Incoherent Motion Diffusion-Weighted Imaging of Hepatocellular Carcinoma: Is There a Correlation With Flow and Perfusion Metrics Obtained With Dynamic Contrast-Enhanced MRI?

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Abstract

Purpose—To assess the correlation between intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) metrics in hepatocellular carcinoma (HCC) and liver parenchyma.

Materials and Methods—Twenty-five patients with HCC (M/F 23/2, mean age 58 years) underwent abdominal MRI at 1.5 or 3.0T, including IVIM-DWI (with 16 b-values) and DCE-MRI (3D FLASH sequence, mean temporal resolution of 2.3 sec). IVIM-DWI parameters (pseudodiffusion coefficient, D^* , diffusion coefficient, D , and perfusion fraction, PF) were quantified in HCC lesions and liver parenchyma using a Bayesian fitting algorithm. DCE-MRI parameters (arterial flow, F_a , portal flow, F_p , total flow, F_t , mean transit time, MTT , distribution volume, DV , and arterial fraction, ART) were quantified using a dual-input single-compartment model. Correlations between IVIM-DWI and DCE-MRI parameters were assessed using a Spearman correlation test.

Results—Thirty-three HCC lesions (average size 5.0 ± 3.6 cm) were analyzed. D , D^* , and PF were all significantly lower in HCC vs. liver ($P < 0.05$). Significantly higher F_a and ART and lower F_p were observed in HCC vs. liver ($P < 0.001$). Significant moderate to strong negative correlations were observed between ART and D^* ($r = -0.443$, $P = 0.028$), ART and PF ($r = -0.536$, $P = 0.006$), ART and $PF \times D^*$ ($r = -0.655$, $P < 0.001$), F_a and PF ($r = 0.455$, $P = 0.023$), and F_a and $PF \times D^*$ ($r = -0.475$, $P = 0.018$) in liver parenchyma. There was no significant correlation between IVIM-DWI and DCE-MRI metrics in HCC lesions.

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Conclusion—IVIM-DWI and DCE-MRI provide nonredundant information in HCC, while they correlate in liver parenchyma. These findings may be secondary to predominant portal inflow in the liver and tortuous vasculature and tissue heterogeneity in tumors.

Hepatocellular carcinoma (HCC) is one of the fastest-rising cancer-related causes of death in the United States, as its incidence rate almost tripled in the last three decades.¹ While blood to the liver tissue is mainly supplied by the portal vein, the majority of HCC lesions are highly vascularized by arterioles only.² The arterial supply of HCC lesions provides the rationale for locoregional arterial chemoembolization or radioembolization in cases of unresectable HCC and for antiangiogenic therapies.^{3,4} In addition, the unique characteristics of HCC on contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) allow for diagnosis of HCC without tissue sampling in typical cases.⁵ Thus, imaging, including MRI, has a key role in the diagnosis of HCC. MRI can also be used for treatment planning and evaluation, since it provides a noninvasive characterization of HCC vascularization and flow.

Dynamic contrast-enhanced MRI (DCE-MRI) allows for estimation of tissue perfusion and permeability. Dynamic time–signal intensity data in liver tissue and tumors resulting from a DCE-MRI acquisition performed before, during and after injection of a gadolinium-based contrast agent can be processed and modeled using the pharmacokinetic model described by Materne et al.⁶ This model provides estimates for the arterial flow (F_a), portal flow (F_p), arterial fraction (ART), mean transit time (MTT), and distribution volume (DV) of the contrast agent and has been applied by multiple research groups to assess vasculature properties of both liver tissue^{7–9} and HCC.^{10–12} HCC has been shown to exhibit a significantly higher F_a and ART and lower F_p and DV than liver parenchyma.¹²

Another MRI method that provides parameters that reflect tissue perfusion is intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI). IVIM-DWI allows for simultaneous assessment of tissue diffusion and pseudodiffusion due to capillary blood flow.¹³ IVIM-DWI consists of a series of diffusion-weighted acquisitions with a wide range of b-values. Subsequently, a biexponential fitting algorithm is used to determine the perfusion fraction (PF or f), pseudodiffusion (D^* or D_p), and diffusion coefficient (D). IVIM-DWI has been used for the characterization of diffuse liver disease^{14–17} and HCC.^{18–20} Since IVIM-DWI allows for estimation of both perfusion and diffusion in a single measurement, it may possibly serve as a surrogate for enhancement and flow measurements and thereby eventually eliminate the need for contrast agent injection. Correlative studies between IVIM-DWI and enhancement obtained with contrast-enhanced imaging including DCE-MRI have been performed in brain tumors,²¹ head and neck cancer,^{22,23} lung cancer,²⁴ renal lesions,²⁵ cervical cancer,²⁶ and liver cirrhosis.²⁷ Variable results were found in these studies, ranging from no correlation^{24,27} to moderate to strong correlation^{22,23,25,26} between IVIM-DWI and (dynamic) contrast-enhanced MRI.

The objective of our study was to quantify IVIM-DWI and DCE-MRI parameters in HCC lesions and liver parenchyma and to assess the correlation between these quantitative techniques.

Materials and Methods

Patients

Patients with HCC were enrolled in this single-center prospective, Health Insurance Portability and Accountability Act (HIPAA)-compliant study approved by our institution's Institutional Review Board (IRB). Written informed consent was obtained from all subjects. Thirty consecutive patients with HCC diagnosed on routine imaging according to the American Association for the Study of Liver Diseases (AASLD) 2011 criteria⁵ were included between June 2013 to March 2015. From the 30 initial patients, five patients were excluded from the study because of severe motion artifacts on both the IVIM-DWI and DCE-MRI acquisitions ($n = 3$) or because of absence of either DCE-MRI ($n = 1$) or IVIM-DWI data ($n = 1$). Twenty-five patients were finally included in our patient cohort (M/F 23/2, mean age 58 years, range 30–70 years, cirrhotic/noncirrhotic 14/11), of which 24 had chronic liver disease (chronic hepatitis C, $n = 16$; chronic hepatitis B, $n = 7$; nonalcoholic steatohepatitis [NASH], $n = 1$). One patient had no previous history of liver disease and had HCC confirmed on pathology. Two patients underwent locoregional treatment with either transarterial chemoembolization (TACE) combined with radiofrequency ablation or TACE only before the MRI acquisition (range 111–133 days before MRI).

In order to assess test–retest repeatability of the MRI metrics, 10 patients underwent the MRI examination twice, either both examinations at 1.5T ($n = 8$), both at 3.0T ($n = 1$), and one examination at 1.5T and one at 3.0T ($n = 1$). Two of the 10 retest measurements were excluded because of motion artifacts on both the IVIM-DWI and DCE-MRI acquisition, leaving eight patients with nine HCC lesions for the test–retest analysis (one with both exams at 3.0T and 7 with both exams at 1.5T), with average time between scans of 5 days (range 1–9 days).

Image Acquisition

MRI was performed with 1.5T (Aera, Siemens Healthcare, Erlangen, Germany; $n = 19$) or 3.0T clinical systems (Skyra, Siemens Healthcare; $n = 6$), each equipped with a 32-channel spine and flexible body array coil for signal reception. All subjects were asked to fast for 6 hours, because of the previously described positive effect of postprandial increased glucose levels on portal blood flow.²⁸ In addition to IVIM-DWI and DCE-MRI, axial and coronal T_2 -weighted turbo-spin echo (HASTE) imaging, axial dual-echo chemical shift imaging, axial T_2^* mapping, 3D T_1 -weighted imaging before and at a delayed phase (~4 min) after injection of a gadolinium-based contrast agent and postcontrast axial fat-suppressed T_2 -weighted imaging were performed in all patients.

IVIM-DWI—IVIM-DWI was performed using an axial fat-suppressed, single-shot, spin-echo echo planar imaging (EPI) sequence with bipolar diffusion gradients (repetition time [TR] one respiratory cycle, echo time [TE] 74–81 msec, acquisition matrix 160×80 – 132 , reconstruction matrix 320×100 – 256 , field-of-view [FOV] 340 – 450×220 – 305 mm², parallel imaging [GRAPPA] acceleration factor 2, slice thickness 7 or 8 mm, 20–30 slices covering the entire liver). The acquisition was respiratory-triggered by positioning a 5mm coronal navigator slice on the dome of the liver, except for the first four patients at 3.0T in

whom the acquisition was done during free breathing. For those patients the TR was set to 4500 msec. The sequence was acquired with 16 different b-values (0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 175, 200, 400, 600, and 800 s/mm²).¹⁵ The number of averages (NA) was 1 for all b-values, except for b = 400 s/mm² (NA = 2), b = 600 s/mm² (NA = 3), and b = 800 s/mm² (NA = 4). The average acquisition time was 493 ± 186 seconds. Each nonzero b-value was sampled in three orthogonal diffusion directions. The images obtained at the different directions were combined into a mean diffusion-weighted image by the image reconstruction software of the scanner console using a three-pass trace. Patients were asked to breathe normally during the acquisition.

DCE-MRI—Before DCE-MRI, an inversion recovery Look–Locker (IR-LL) pulse sequence (180°inversion with 32 postinversion acquisitions, TIs = 42–1576.5 msec at 48 msec interval, TR = 2.25 msec, TE = 1.04 msec, FA = 8°, FOV 420 × 288mm², matrix 128 × 88, parallel imaging GRAPPA acceleration 2) was used to provide quantitative T_1 mapping in 1–2 slices through each lesion in one 18-second breath-hold. The DCE-MRI acquisition was performed during free breathing using an axial 3D FLASH sequence. Image parameters were: TR 2.68–2.74 msec, TE 0.97–1.07 msec, flip angle (FA) 9.5–11.5°, acquisition matrix 192 × 106–125, reconstruction matrix 384 × 264–312, FOV 370–401 × 254–325mm², 40 slices, interpolated slice thickness 4–5 mm, mean temporal resolution 2.3 seconds. One hundred volumes were acquired before, during, and after intravenous injection of half dose (0.05 mmol/kg) Gd-BOPTA (gadobenate dimeglumine; Bracco Diagnostics, Princeton, NJ), followed by a 25-mL saline flush, both at 5 mL/s. Half dose of the contrast agent was used to prevent saturation effects in the DCE-MRI acquisition.

Image Analysis

Image analysis was performed by two observers in consensus (observer 1, S.H., an MRI physicist with 5 years of experience, and observer 2, M.W., a body radiologist with 4 years of experience). A representative example of the region-of-interest (ROI) placement is shown in Fig. 1. HCCs were diagnosed by observer 2 according to the AASLD 2011 criteria⁵ (typical washin/washout) on standard MRI sequences and on prior clinical contrast-enhanced imaging studies (CT or MRI).

IVIM-DWI—The IVIM-DWI images were registered to the images acquired with a b-value of 0 s/mm² with a 3D rigid registration algorithm using open-source image analysis software (FireVoxel; CAI²R, New York University, New York, NY). Free-hand 3D ROIs were drawn in the HCC lesions and in the entire liver parenchyma. For the HCC lesions, an ROI was drawn by observer 2 in the entire lesion, including all slices on which the HCC lesion was identified. In order to avoid partial volume effects, the lesion boundaries were not included. The ROI in the liver parenchyma was drawn in all slices in which liver tissue was seen, excluding large vessels, lesions, and boundaries. For all ROIs, regions with major artifacts were excluded. ROIs were drawn on b = 150 s/mm², and then propagated to the images of the other b-values. ROI positioning was checked on the images of each b-value and corrected if necessary.

The biexponential IVIM model^{15,20} was fit to the mean signal curve in the ROI at different b-values to estimate the pseudodiffusion coefficient (D^*), diffusion coefficient (D), and perfusion fraction (PF). The IVIM equation is shown in Eq. (1), in which SI is the signal intensity at a certain b-value and SI_0 is the signal intensity at a b-value of 0 s/mm². The fitting procedure was done in MatLab R2015a (MathWorks, Natick, MA) using a Bayesian algorithm²⁹:

$$SI = SI_0 [PF e^{-bD^*} + (1 - PF) e^{-bD}] \quad (1)$$

In addition, the apparent diffusion coefficient (ADC) was determined by calculation of the slope of a linear fit through the logarithmic signal data at $b = 0$ s/mm² and all b-values above 150 s/mm² to avoid influence of perfusion on the ADC estimation.

DCE-MRI—Similar to the IVIM-DWI images, motion in the DCE-MRI acquisition was corrected using 3D registration in FireVoxel. 3D ROIs within the whole HCC lesions and the entire liver parenchyma were drawn on the registered images, in the same way as the ROI positioning in IVIM-DWI. In addition, ROIs were drawn in the portal vein (on the registered images) and abdominal aorta (on the unregistered images, at the level of the celiac trunk), each on five slices. ROIs were drawn on the arterial phase for HCC and aorta and on a portal venous phase for liver and portal vein. The ROIs were subsequently propagated to the other time-points and ROI positioning was checked on the different time-points. The ROIs in the liver parenchyma and the lesions drawn in the DCE-MRI images were matched as closely as possible to the ROIs drawn on IVIM-DWI images. Mean dynamic SI curves in the ROIs were exported and analyzed in MatLab. In order to reduce inflow artifacts in the mean SI curve in the aorta, a locally weighted linear least-squares fit with first-degree polynomial (LOWESS) was applied on the curve of the aorta, as described previously.³⁰ Outliers in the curves, eg, caused by respiratory or cardiac motion, were removed by eliminating data points after the enhancement peak for which the absolute difference in signal intensity with both the previous data point and the next data point was higher than 5 times the standard deviation (SD) of the SI before contrast agent injection.

The dynamic SI curves were converted to dynamic contrast agent concentration [CA] using the signal equation for a spoiled gradient recalled echo (SPGR) sequence, the precontrast T_1 values, and the contrast agent's relaxivity. For the liver and HCC lesions, average precontrast T_1 values were determined from the Look-Locker acquisition. For the portal vein and aorta, precontrast T_1 values were based on the literature.³¹ A hematocrit value of 0.45 was used for conversion from blood [CA] to plasma [CA]. Contrast agent relaxivity values of 8.1 mM⁻¹ s⁻¹ and 6.3 mM⁻¹ s⁻¹ were used at 1.5T and 3.0T, respectively.³²

A dual-input single-compartment model⁶ was used to model the contrast agent uptake kinetics in the liver and HCC. The model is described by the following formula:

$$C_t(t) = \int_0^t [k_{1a} C_a(t' - \tau_a) + k_{1p} C_p(t' - \tau_p)] e^{-k_2(t-t')} dt' \quad (2)$$

in which C_t , C_a , and C_p are the [CA] in the tissue, aorta, and portal vein, respectively; k_{1a} , k_{1p} , and k_2 are the aortic inflow rate constant, portal venous inflow rate constant, and the outflow rate constant, respectively; τ_a and τ_p are the delay between the aorta and portal vein and the liver/HCC, respectively. Fitting was done with different values of τ_a and τ_p ranging from 0 to 5 times the temporal resolution and subsequently the fit with the lowest residuals was selected.

The rate constants were converted to blood flow parameters by multiplication by $60 \text{ s/min} \times 100 \text{ g/mL} / (1 - \text{Hct}_{sv})$. Hct_{sv} is the hematocrit of small vessels, for which a constant value of 0.25 was assumed.^{6,33} This conversion resulted in estimated values for the arterial flow (F_a , mL/100 g/min), portal venous flow (F_p , mL/100 g/min), and total flow ($F_a + F_p$, mL/100 g/min). In addition, the arterial fraction ($\text{ART} = F_a/F_t$), the distribution volume fraction of the contrast agent through the tissue ($\text{DV} = [k_{1a} + k_{1p}]/k_2$) and the mean transit time (ie, the average time that it takes the contrast agent to transfer from the portal/aortic input to the venous output; $\text{MTT} = 1/k_2$, s) were determined.⁶

Statistical Analysis

Quantitative data are presented as mean $\pm$ SD. Fit quality of the DCE-MRI and IVIM-DWI curves was determined by calculation of the coefficient of determination R^2 . Differences in IVIM-DWI and DCE parameters between liver and HCC tissue were tested for significance using a Mann–Whitney U -test. The correlation between IVIM-DWI (D , D^* , PF , $PFxD^*$, and ADC) and DCE-MRI parameters (F_a , F_p , F_t , MTT , DV , and ART) was assessed by determination of the Spearman correlation coefficient, for both liver and HCC. For patients who underwent repeat measurements, only the first MRI exam was used for the analysis of differences between MRI parameters between liver and HCC and the correlation analyses. Repeatability of IVIM-DWI and DCE-MRI parameters was assessed by determination of the coefficient of variation (CV) and Bland–Altman limits of agreement (BA-LA) between repeat measurements. Parameter repeatability was considered excellent when CV was $<10\%$, good when CV was between 10 and 20%, acceptable when CV was between 20 and 30%, and poor when CV was $>30\%$.¹⁸ For all tests, the level of significance was set to 0.05. All analyses were performed using MatLab.

Results

Thirty-seven HCC lesions were identified in the included 25 patients with lesions distributed as follows: patients with one ($n = 16$), two ($n = 7$), three ($n = 1$), or four ($n = 1$) lesions. Four lesions were excluded from analysis because of motion artifacts ($n = 3$) or because of the lack of viable tumor tissue after locoregional treatment ($n = 1$). One other lesion was also previously treated, but only partially necrotic (30% necrosis) and was therefore included in the analysis. Thirty-three HCCs were finally included in the analysis; these had an average size of $5.0 \pm 3.6 \text{ cm}$ (range 1.0–14.2 cm). Thirty-two lesions corresponded to treatment-naïve HCC tumors, with 26/32 having no necrosis on imaging and 6/32 lesions showing a limited amount of necrosis ($<10\%$ [$n = 2$], $<20\%$ [$n = 4$]).

IVIM-DWI and DCE-MRI Parameters

Representative curves and corresponding fits in liver and HCC are shown in Fig. 2 for IVIM-DWI and DCE-MRI. Average IVIM-DWI and DCE-MRI parameters and corresponding R^2 fit quality values are displayed in Table 1 for liver and HCC lesions. D^* , D , and PF were all significantly lower in HCC compared to liver, while the ADC values of liver and HCC were not significantly different. The R^2 of the IVIM fitting procedure was lower in HCC lesions compared to liver. F_a and ART were significantly higher in HCC vs. liver, while F_p was significantly lower in HCC. No significant differences were observed for F_t , MTT , and DV between HCC and liver. Although overall good fitting was observed for DCE-MRI, the goodness-of-fit R^2 was significantly lower in HCC.

Parameter Repeatability

Average CV and BA-LA for IVIM-DWI and DCE-MRI parameters in liver parenchyma and HCC as obtained from test–retest measurements in eight patients are displayed in Table 2. For IVIM-DWI, excellent repeatability was observed for D , PF , and ADC in the liver parenchyma, while D^* showed acceptable repeatability. In HCC lesions, repeatability was excellent for D and ADC , good for PF , and poor for D^* .

For DCE-MRI, good repeatability was observed for F_t , MTT , and DV in the liver, while repeatability was poor for F_a , F_p , and ART . In HCC lesions, repeatability was excellent for ART , good for DV , and poor for F_a , F_p , F_t , and MTT .

Correlation Between IVIM-DWI and DCE-MRI Parameters

From the 30 assessed correlations between IVIM-DWI and DCE-MRI parameters, five were found to be significant in the liver (Fig. 3) and none in HCC lesions. In the liver, significant moderate to strong negative correlations were observed between ART and D^* ($r = -0.443$, $P = 0.028$), ART and PF ($r = -0.536$, $P = 0.006$), ART and $PF \times D^*$ ($r = -0.655$, $P < 0.001$), F_a and PF ($r = -0.455$, $P = 0.023$), and between F_a and $PF \times D^*$ ($r = -0.475$, $P = 0.018$). From all correlation analyses in the HCC lesions, the lowest P -value was observed for the correlation between F_a and PF ($r = 0.275$, $P = 0.122$; Fig. 3).

Discussion

In this study we quantified diffusion and perfusion/flow parameters in HCC and liver parenchyma and assessed the correlation between IVIM-DWI and DCE-MRI metrics. While some significant correlations were observed in the liver, no significant correlations between IVIM-DWI and DCE-MRI parameters were found in HCC lesions.

The significant correlations between IVIM-DWI and DCE-MRI parameters in the liver were associated with the predominant portal supply to the liver parenchyma. Decreased portal flow, which may be observed in cirrhosis, may be partially compensated for by an intrinsic mechanism in the liver known as the arterial buffer response,³⁴ shown as higher ART in cirrhotic livers compared to non-cirrhotic livers.⁸ The compensation for the loss of portal venous flow by the arterial buffer response is generally incomplete,³⁵ which may explain the negative correlations between ART and PF , D^* and $PF \times D^*$, and between F_a and PF and

PFxD* in the liver observed in our study. The lack of correlations between IVIM-DWI and DCE-MRI in HCC lesions suggests that IVIM-DWI is perhaps more sensitive to portal than to arterial flow, given the predominant arterial perfusion of HCC lesions.

The significant correlations between IVIM-DWI and DCE-MRI parameters in the liver were moderate to strong. This is in agreement with other correlative studies between IVIM-DWI and contrast-enhanced MRI where moderate to strong correlations were observed in head and neck cancer,^{22,23} renal lesions,²⁵ and cervical cancer.²⁶ However, other studies reported no significant correlations between IVIM-DWI and contrast-enhanced MRI in lung cancer²⁴ and liver cirrhosis.²⁷ The absence of significant correlations in the previous study in liver cirrhosis²⁷ is contradictory to our results. The discrepancy between that particular study and the present study may be the choice of b-values. Patel et al²⁷ used relatively few low b-values under 100 s/mm² (0, 50, and 100 s/mm²), while we used seven equally spaced b-values under 100 s/mm², which may allow for a better estimation of PF and D*.

The mixed findings on correlations between IVIM-DWI and DCE-MRI in the literature could be explained by the fact that IVIM-DWI and DCE-MRI do not share the same conceptual principles; IVIM-DWI measures the blood flow in the direction of the diffusion-encoding gradients, while DCE-MRI probes the pattern of blood delivery and distribution of contrast agent in the tissue, at a different temporal scale.²¹

The lack of correlation between IVIM-DWI and DCE-MRI in HCC may be related to the drastically altered hemodynamics in tumors, which make it considerably challenging to estimate capillary properties in cancerous tissue.²¹ D* is dependent on both blood velocity and mean capillary segment length,¹³ which are heterogeneous in the tortuous tumor vasculature. Indeed, we observed poor repeatability for D* in HCC lesions, which is consistent with recent studies on repeatability of IVIM-DWI metrics in liver and HCC¹⁸ and in liver metastases.³⁶ Moreover, the tissue in tumors is more heterogeneous compared to the homogeneous liver tissue, leading to different contributions of, for example, viable, hypoxic, and necrotic regions to the signal. Tumor heterogeneity could be addressed by histogram analysis of pixel-wise IVIM-DWI and DCE-MRI parameter maps. However, accurate DCE-MRI pharmacokinetic parameter mapping would have required a T_1 mapping sequence that covered the entire volume instead of the Look-Locker T_1 sequence that only covered 1–2 slices used in this study.

The IVIM-DWI^{19,37} and the DCE-MRI parameter values^{7–10,12} as well as the repeatability of these metrics^{7,15,18} are approximately similar to previously published values, both in liver parenchyma and in HCC lesions. The diffusion coefficient found in HCCs in our study tended to be slightly higher than previously reported in IVIM-DWI studies in HCC.^{18–20} This may be explained by differences in patient population and consequent variation in tumor grade distribution, as Woo et al have shown that IVIM-DWI parameters in HCC are dependent on tumor grade.²⁰ In addition, IVIM-DWI parameters have been shown to vary across MR systems.³⁸ The significant differences in IVIM-DWI metrics between liver parenchyma and HCC lesions and the absence of such a significant difference in the ADC suggest that IVIM-DWI may provide improved HCC characterization compared to ADC. The overall poor repeatability for D* and some DCE-MRI flow parameters in both liver and

HCC should be taken into account for clinical interpretation of abdominal IVIM-DWI and DCE-MRI, especially when assessing response to therapy.

Although the poor repeatability of D^* observed in the HCC lesions is inherent to IVIM-DWI measurements in tumors, also motion and distortion associated with the EPI sequence may affect parameter repeatability. IVIM-DWI with reduced distortion could possibly be acquired using readout-segmented EPI.³⁹ Limited motion was observed on the IVIM-DWI images, and residual motion and distortion was corrected by registration to the images at $b = 0$. The registration algorithm could potentially be more effective if it would be applied on the images of the individual directions before averaging, which were not available in our study, instead of on the trace-weighted images. Nevertheless, the excellent goodness-of-fit values observed in both liver and tumor tissue for IVIM-DWI indicates that motion and distortion had little effect on parameter estimation. Also for the IVIM-DWI acquisitions at 3.0T, excellent goodness-of-fit was observed in both liver and HCC, despite the free-breathing acquisition. The choice of b -values may significantly affect IVIM-DWI parameter estimation and repeatability, as shown in a recent study on IVIM-DWI data quality in normal and malignant liver tissue.⁴⁰ The results in that study indicate that estimation of D^* in liver tumors may slightly improve by spreading the b -values more evenly between the pseudodiffusion ($<150 \text{ s/mm}^2$) and diffusion ($>150 \text{ s/mm}^2$) range.

A Bayesian fitting algorithm^{15,41} was used for the analysis of IVIM-DWI data in our study. The Bayesian analysis accounts for measurement uncertainty by estimating probability functions for the parameters rather than global estimations of parameter values. The Bayesian method was shown to perform better than least-squares algorithms for the fitting of IVIM data.⁴¹ In other studies on IVIM-DWI of HCC, the Bayesian technique was also applied for the estimation of IVIM-DWI parameters.^{18,19}

After image registration of the DCE-MRI data, the curves in the aorta, portal vein, liver, and HCC were generally well defined, resulting in good fitting of the pharmacokinetic model in liver and HCC. Nevertheless, the goodness-of-fit R^2 values in the HCC lesions were significantly lower than in the liver, possibly explained by the fact that lesions are more prone to motion. Fit quality and test–retest repeatability of DCE-MRI could potentially be improved by using a less motion-sensitive DCE-MRI acquisition. Recently, a free-breathing radial DCE-MRI acquisition scheme using respiratory motion-resolved compressed sensing reconstruction was introduced, which exhibited high image quality and substantially reduced motion artifacts in the liver.⁴²

Our study has several limitations. While maximum effort was taken to match the ROIs placed in the DCE-MRI and DWI measurements, an exact geometric match could not be completely achieved. The DCE-MRI data were acquired in 3D, while the IVIM-DWI images were obtained using a multislice 2D acquisition. In addition, slice thickness differed between the acquisitions. Another limitation is that the T_1 map that was used for analysis of the DCE-MRI data was only performed in 1–2 slices, rather than covering the entire liver.

In conclusion, moderate to strong correlations between IVIM-DWI and DCE-MRI parameters were observed in the liver parenchyma, while no correlation was observed in

HCC lesions, possibly caused by the predominant portal blood flow in the liver and tortuous microvasculature and tissue heterogeneity in HCC lesions. These techniques thus provide nonredundant information on perfusion and microcirculation in HCC.

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FIGURE 1.

Image processing in a 61-year-old male patient with chronic hepatitis C and a 5-cm HCC in the right hepatic lobe. **a:** Axial DCE-MRI acquisition shows ROI placement in liver parenchyma (blue), HCC lesion (red), and aorta (green). **b:** Coronal reformat of axial DCE-MRI acquisition shows ROI in portal vein (yellow). **c:** Axial IVIM-DWI image shows ROI in the liver (blue) and HCC lesion (red) similar to DCE-MRI ROI placement.

FIGURE 2.

DCE-MRI input and fits (solid lines) and data points in liver and HCC (**a**) and IVIM-DWI fits and data points in liver and HCC (**b**) with corresponding estimated metrics. The curves originate from the ROIs from Fig. 1. The DCE-MRI curves and parameters indicate predominant portal and arterial flow in liver and HCC, respectively.

FIGURE 3.

Correlation plots between ART and D^* (a), ART and PF (b), ART and $\text{PF} \times D^*$ (c), F_a and PF (d), and F_a and $\text{PF} \times D^*$ (e) in the liver and between F_a and PF in HCC (f).

TABLE 1

Mean $\pm$ SD IVIM-DWI and DCE-MRI Parameters and Goodness-of-Fit (R^2) in the Liver ($n = 25$) and HCC Lesions ($n = 33$)

		Liver	HCC	<i>P</i>
IVIM-DWI	D*	95.9 $\pm$ 48.8	64.1 $\pm$ 42.8	0.010
	D	1.49 $\pm$ 0.27	1.36 $\pm$ 0.26	0.050
	PF	0.23 $\pm$ 0.06	0.18 $\pm$ 0.08	<0.001
	ADC	1.61 $\pm$ 0.25	1.57 $\pm$ 0.33	0.286
	R^2	0.99 $\pm$ 0.01	0.97 $\pm$ 0.06	<0.001
DCE-MRI	F _a	56.0 $\pm$ 33.0	196.3 $\pm$ 189.3	<0.001
	F _p	145.8 $\pm$ 128.2	71.3 $\pm$ 162.6	<0.001
	F _t	201.8 $\pm$ 126.7	267.6 $\pm$ 294.0	0.937
	MTT	24.2 $\pm$ 9.3	28.0 $\pm$ 19.4	0.912
	DV	54.0 $\pm$ 21.9	50.2 $\pm$ 30.3	0.221
	ART	33.6 $\pm$ 22.8	83.2 $\pm$ 22.5	<0.001
	R^2	0.97 $\pm$ 0.02	0.88 $\pm$ 0.09	<0.001

D*, pseudodiffusion coefficient (10^{-3} mm²/s); D, diffusion coefficient (10^{-3} mm²/s); PF, perfusion fraction; ADC, apparent diffusion coefficient (10^{-3} mm²/s); R^2 , coefficient of determination; F_a, arterial flow (ml/100 g/min); F_p, portal venous flow (ml/100 g/min); F_t, total flow (ml/100 g/min); MTT, mean transit time (s); DV, distribution volume fraction (%); ART, arterial fraction (%). *P*-values result from Mann–Whitney *U*-tests between liver and HCC parameter values. Significant *P*-values are bolded.

Test–Retest Repeatability of IVIM-DWI and DCE-MRI Parameters in HCC and Liver Parenchyma Expressed With the Coefficient of Variation (CV, %) and Bland–Altman Limits of Agreement (BA-LA, %) in Eight Patients With Nine HCC Lesions

TABLE 2

	Liver		HCC	
	CV (range)	BA-LA	CV (range)	BA-LA
IVIM-DWI				
D*	21.4 (4.6–42.8)	–73.8–73.7	52.4 (1.8–95.7)	–164.2–193.9
D	7.3 (0.4–19.8)	–31.3–26.8	8.7 (0.5–29.4)	–38.5–26.0
PF	5.2 (0.0–11.8)	–20.5–21.4	16.3 (0.6–47.3)	–65.5–56.8
ADC	5.6 (0.0–14.3)	–23.4–16.6	8.3 (0.0–29.2)	–41.1–18.6
DCE-MRI				
F _a	40.8 (8.1–118.5)	–146.4–166.7	32.7 (3.8–54.7)	–105.6–119.7
F _p	34.6 (4.4–141.4)	–177.9–100.6	92.2 (0–141.4)	–280.9–357.8
F _t	15.9 (1.3–55.1)	–80.5–44.7	34.4 (3.8–63.2)	–103.5–129.4
MTT	11.4 (1.5–27.4)	–40.6–47.1	30.7 (1.4–56.5)	–121.9–70.9
DV	11.9 (1.1–30.2)	–52.3–22.1	14.4 (3.9–50.9)	–65.6–39.7
ART	40.5 (0.6–116.9)	–116.6–175.0	7.0 (0–20.8)	–33.1–20.6

D*, pseudodiffusion coefficient ($10^{-3} \text{ mm}^2/\text{s}$); D, diffusion coefficient ($10^{-3} \text{ mm}^2/\text{s}$); PF, perfusion fraction; ADC, apparent diffusion coefficient ($10^{-3} \text{ mm}^2/\text{s}$); R^2 , coefficient of determination; F_a, arterial flow (ml/100 g/min); F_p, portal venous flow (ml/100 g/min); F_t, total flow (ml/100 g/min); MTT, mean transit time (s); DV, distribution volume fraction (%); ART, arterial fraction (%).