Evaluation of Hepatic Tumors Using Intravoxel Incoherent Motion Diffusion-Weighted MRI

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Background: This study aimed to evaluate the diagnostic value of the D value, D* value, and f magnitude for identifying benign and malignant hepatic tumors using intravoxel incoherent motion (IVIM) diffusion-weighted imaging (DWI).

Material/Methods: Data of 89 cases (123 lesions) with hepatic tumor confirmed by surgical pathology and postoperative follow-up were retrospectively collected. Among these cases, 40 cases were benign hepatic tumors (57 lesions) and 49 cases were malignant hepatic tumors (66 lesions). All subjects underwent conventional MRI with T1WI, T2WI, multib-value DWI, and dynamic enhanced LAVA scan. Diffusion-weighted images with 11 b values (0, 10, 20, 30, 50, 80, 100, 200, 400, 800, and 1000 s/mm²) were obtained to calculate true molecular diffusion (D), perfusion-related diffusion coefficient (D*), and perfusion fraction (f). The diagnostic performance in differentiating between malignant and benign hepatic lesions was analyzed.

Results: Malignant lesions had a significantly lower D value ([1.04±0.34]×10⁻³ mm²/s) and D* value ([16.5±7.7]×10⁻³ mm²/s) compared to benign lesions (D value: [1.70±0.55]×10⁻³ mm²/s, P<0.01; D* value: [21.7±9.9]×10⁻³ mm²/s, P<0.01). There was no statistically significant difference in f values between malignant (23.3±9.5) and benign lesions (33.5±14.9, P=0.13). In addition, D exhibited a better diagnostic performance than D* in terms of the area under the curve, sensitivity, and specificity when identifying malignancies from benign lesions.

Conclusions: D and D* are significant parameters for diagnosing hepatic tumors. Moreover, the D value is a more reliable parameter in distinguishing benign and malignant hepatic tumors.

MeSH Keywords: Diffusion Magnetic Resonance Imaging • Liver Diseases • Liver Neoplasms

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Background

With the rapid development of magnetic resonance imaging (MRI) technology such as improved MRI gradient performance, multichannel surface receiver coils, and parallel imaging techniques, functional MRI technology has brought revolutionary progress in the diagnosis and study of diseases [1]. Diffusion-weighted imaging (DWI) can reflect the pathological and physiological information of the lesion on the basis of the microscop-ic mobility of water, which is called the Brownian movement in organisms with various diseases, and it also has an important role in the identification of hepatic tumors [2–9]. Previous studies have suggested that the apparent diffusion coefficient (ADC) of hepatic tumor lesions has distinct differences between benign and malignant tumors, which can distinguish the property of a tumor [10,11]. However, inherent limitations exist in diagnosis based on a single exponential model, especially losing sight of the effect of the arteriole-capillary-ve-nule microcirculation in living tissues on ADC values [12]. In 1986, Le Bihan et al. proposed the principles of intravoxel in-coherent motion (IVIM) [10] and suggested that using a more sophisticated approach to describe the relationship between signal attenuation in tissues with increasing b value would enable quantitative parameters that separately reflect tissue diffusivity and tissue microcapillary perfusion to be estimat-ed. In 1988, Le Bihan et al. used a phantom that could show the effects of perfusion using DW imaging [13]. Yamada et al. initially applied IVIM to the abdomen in 1999 to evaluate the diffusion coefficient of lesions in the abdominal viscera [14].

IVIM can provide quantitative parameters for the movement of water molecules in tissues and reflect the perfusion condition of the tissue [15]. In fact, IVIM separates ‘diffusion’ and ‘perfusion’ through a special diffusion-weighted imaging sequence at the voxel level [15]. IVIM-DWI can be obtained through multiple b values, and emphasizes the combined application of the low b value (<200 s/mm²) and high b value (>2000 s/mm²) to accurately and effectively detect and measure the ADC value of lesions [16]. The IVIM-DWI technique can be used to estimate the diffusion coefficient of slow or nonperfusion-related diffusion-based molecular diffusion (D), the diffusion coefficient of fast or perfusion-related diffusion based diffusion (D*), and the perfusion-related diffusion fraction (f) in the voxel. D reflects tissue diffusivity and D* reflects microcapillary perfusion [17].

This research used the double exponential model to estimate the D value, D* value and f magnitude and compare the di-nostic performance of these parameters in hepatic tumors.

Material and Methods

Patients

This study was approved by the local ethics committee and written informed consent was obtained from each subject before the examination. From January 2014 to October 2014, a total of 103 subjects with suspicious hepatic tumors underwent multiple-b-value IVIM-DWI. A total of 123 focal hepatic lesions in 89 patients were included in this study after surgical pathologic confirmation. Among the 89 patients, 52 patients were male and 37 patients were female. Mean age was 69.7 years old with an age range of 39 to 85 years old. Patients with definite diagnosis were divided into 2 groups according to the extent of tumor progress: benign tumor group (40 cases, 57 lesions) and malignant tumor group (49 cases, 66 lesions). Final diagnoses were as follows: hemangioma (47 lesions in 31 cases), liver abscess (5 lesions in 4 cases), focal nodular hyperplasia (4 lesions in 4 cases), liver hamartoma (1 lesion in 1 case), hepatocellular carcinoma (40 lesions in 30 cases), metastatic liver tumor (20 lesions in 13 cases), and cholangiocarcinoma (6 lesions in 6 cases, Table 1). Primary tumors of the metastatic liver tumor were as follows: colorectal carcinoma (7 cases), pancreatic carcinoma (2 cases), gastric carcinoma (2 cases), breast cancer (1 case), and ampullary carcinoma (1 case). Size (given as mean±standard deviation and range) of the hepat-ic carcinoma, cholangiocarcinoma, metastatic liver tumor, hepato-cellular carcinoma, focal nodular hyperplasia, abscess and hamartoma were 3.11±1.92 cm (1.68–4.50 cm), 3.12±1.03 cm (1.95–6.43 cm), 1.72±1.35 cm (1.30–3.90 cm), 2.84±1.79 cm (1.50–7.50 cm), 3.17±1.74 cm (1.70–6.00 cm), 2.62±1.43 cm (1.60–5.00 cm), and 4.41 cm, respectively.

Inclusion criteria were as follows: (1) patients with focal liver lesions detected by computed tomography (CT) or ultrasound examination, (2) patients who were not contraindicated to the MR examination, (3) patients with focal hepatic lesion >2 cm in diameter, and (4) conclusive diagnosis of the lesion using either pathologic or aspiration biopsy confirmation.

Exclusion criteria were as follows: (1) patients who were treated by transarterial chemoembolization or radiofrequency ablation, (2) patients whose images were of unacceptable quality for the evaluation of focal hepatic lesions on DWI, (3) patients who are unable to tolerate the examination, and (4) patients who did not achieve a definite diagnosis.

MRI

MRI was performed using a 3.0T whole-body scanner (Discovery MR750, GE Healthcare Systems; Milwaukee, WI, USA) with a GE 8-channel phased-array coil. All subjects were subjected to...
**Table 1. Baseline characteristics of benign and malignant hepatic lesions.**

| Lesions                  | Number of patients | Malignant tumors |
|--------------------------|--------------------|------------------|
| Hemangioma (n=47)        | 40                 | 49               |
| Hepatocellular carcinoma | 40                 | 49               |
| Hepatapostema (n=5)      | 57                 | 66               |
| Metastatic liver tumor   |                    |                  |
| FNH (n=4)                |                    |                  |
| Cholangiocarcinoma (n=6) |                    |                  |
| Hamartoma (n=1)          |                    |                  |

FNH – focal nodular hyperplasia.

In order to achieve consistency of breathing extent and frequency, subjects were asked to hold their breath for 4–8 h before the examination and respiratory training was used to achieve consistency of breathing extent and frequency.

Routine MRI protocols consisted of transverse T1-weighted imaging (T1WI) using 3D gradient-echo pulse LAVA (liver acquisition with volume acceleration) sequences, transverse breath-trigger fat suppressed fast recovery fast spin-echo (FRFSE) T2-weighted imaging (T2WI), and coronal breath-trigger fat suppressed FRFSE T2WI. IVIM-DWI with respiratory triggering was performed with the following scanning parameters: TE=79 ms, TR=6000 ms, matrix size=128×160, FOV from 36×36 cm to 40×40 cm, slice thickness=7 mm, gap=1 mm and scanning time=256 s. Eleven b-values were used: 0, 10, 20, 30, 50, 80, 100, 200, 400, 800, and 1000 s/mm². For b values in ranges of 0–30 s/mm², 50–200 s/mm² and 400–1000 s/mm², NEX was 3, 2, and 6, respectively.

Transverse and coronal contrast-enhanced DWI imaging was performed with a 3D T1-weighted gradient-echo pulse LAVA sequence after the administration of gadopentetate dimeglumine (GD-DTPA; Beilu Pharmaceutical, Beijing, China) into the elbow vein at a dose of 0.1 mmol/kg with a rate of 2.5–3 ml/s by high-pressure syringe. The contrast agent was followed by an intravenous bolus administration of 20 ml of saline at the same rate. Scanning parameters were as follows: matrix size=288×192, slice thickness=2–5 mm, and the layer number of scanning ranged from 70 to 100. TR=3.7 ms, TE=1.7 ms, rotation angle=12° and breath holding time=12–17 s. The arterial, portal venous and delayed phase scans were performed 18–20 s, 55–60 s and 3 min after contrast injection, respectively.

**Image analysis**

Three diffusivity parameters were defined as follows: diffusion coefficient of slow or nonperfusion-related diffusion-based molecular diffusion (D, 10⁻⁹ mm²/s) represents true molecular diffusion, diffusion coefficient of fast or perfusion-related diffusion based diffusion (D*, 10⁻⁹ mm²/s) represents perfusion-related diffusion, and perfusion-related diffusion fraction (f, %) represents fractional volume occupied in the voxel by flowing spins. These diffusivity values were calculated using the IVIM model equation described by Le Bihan et al. [10]:

$$S_b/S_0 = (1-f) \times \exp(-bD) + f \times \exp(-b(D+D^*))$$

Sb is the signal intensity for a given b value and S0 is the signal intensity at b=0 s/mm². D was initially determined by the linear least square approach using DWI with a b-value >200 s/mm². D* and f were calculated by the nonlinear least-squares approach using the Nelder-Mead method. Figure 1 plots ln(Sb/S0) of relative signal intensity vs. b values from primary hepatocellular carcinoma. The signal attenuation curve shows a hockey-stick appearance at low b-values, which is indicative of a perfusion effect.

All acquired images were analyzed on a GE Advantage Workstation 4.6 using the local software of the machine Functool (GE Healthcare, Milwaukee, WI, USA) [18] prior to surgery and before pathologic results were known. Two clinically experienced radiologists with more than five years of experience in interpreting hepatic MR images, who were blinded to the final results, identified the lesions and assessed the diagnostic performance of each method. The lesions were categorized into three groups: benign, malignant, and indeterminate. The accuracy of each method was evaluated using the area under the receiver operating characteristic curve (AUC). The AUCs were compared using the DeLong method. The statistical significance level was set at p<0.05.

**Results**

The AUCs for the different methods are presented in Figure 2. The AUC for the IVIM-DWI method was significantly higher than those for the other methods (p<0.05). The diagnostic performance of the IVIM-DWI method was superior to that of the conventional MRI methods (P<0.05). The diagnostic performance of the IVIM-DWI method was also superior to that of the conventional MRI methods in terms of the accuracy of lesion detection (p<0.05).

**Discussion**

IVIM-DWI is a promising technique for the differential diagnosis of hepatic lesions. It provides additional information about tissue perfusion, which is important for the accurate evaluation of hepatic tumors. The high diagnostic performance of the IVIM-DWI method suggests that it could be a valuable tool for the differential diagnosis of hepatic tumors.

**Conclusion**

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histology or biopsy, evaluated each of the MR images independently. Decisions were obtained by consensus. Routine T1WI, T2WI, and dynamic enhanced LAVA T1WI were provided to confirm the location and size of the lesion when IVIM-DW images were evaluated (Figure 2A and Figure 3A, 3B). ROIs were placed on an image with b=0 (Figure 2B and Figure 3C). The software automatically copied the ROI to each image (b=10–1,000 s/mm²) and calculated the average of the signals within the ROI for each image while simultaneously recording the D value, D* value and f value, respectively (Figure 2C–2E and Figure 3D–3F). In focal hepatic lesions, ROIs were placed in order to avoid necrosis or hemorrhage, and ROIs were drawn as large as possible to cover the solid part of the lesions. Mean ROI area was 22.4–29.3 mm².

Statistical analysis

Data were analyzed using commercial software (IBM SPSS v.19, Armonk, NY; MedCalc v.12, Mariakerke, Belgium). Data were expressed as means ± standard deviation (SD). Shapiro-Wilk test was used to examine the normality. Diffusion parameters of benign and malignant tumors were compared by Mann-Whitney U test. Diffusion parameter results between malignant tumor types were compared by Kruskal-Wallis test followed by Bonferroni-corrected Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was performed for lesion discriminability between malignant and benign hepatic lesions. A P value <0.05 was considered statistically different.

Table 2. Comparison of IVIM Parameters between malignant and benign hepatic lesions (means ±SD).

|                      | Benign tumors | Malignant tumors | P value |
|----------------------|---------------|------------------|---------|
| D (10⁻³ mm²/s)       | 1.70±0.55     | 1.04±0.23        | <0.01   |
| D* (10⁻³ mm²/s)      | 217.7±9.9     | 165.7±7.7        | <0.01   |
| f (%)                | 33.5±14.9     | 23.3±9.5         | 0.13    |

D – true molecular diffusion; D* – perfusion-related diffusion coefficient; f – perfusion fraction.
Results

Both the D value ([1.04±0.34]×10⁻³ mm²/s) and D* value ([16.5±7.7]×10⁻³ mm²/s) in malignant lesions were significantly lower than in benign lesions (D value [1.70±0.55]×10⁻³ mm²/s, P<0.01; D* value [21.7±9.9]×10⁻³ mm²/s, P<0.01). There was no statistically significant difference in f value between malignant (23.3±9.5) and benign (33.5±14.9) lesions (P=0.13, Table 2).

Results of diffusion and perfusion-related parameters by tumor type are shown in Table 3. Cholangiocarcinoma presented significantly higher D values than metastatic liver tumor (P=0.021).
and hepatocellular carcinoma (P=0.002). Similarly, metastatic liver tumor had significantly lower D* values than cholangiocarcinoma (P=0.016) and hepatocellular carcinoma (P=0.001).

According to ROC analysis, the average area under the ROC curve for predicting malignant lesions was 0.88 (0.81–0.91) for D* value and 0.98 (0.94–1.00) for D value (P<0.05, Table 4). Optimal cutoff values calculated by ROC analysis (D, 1.295×10^{-3} mm²/s and D*, 21.85×10^{-3} mm²/s) provided sufficiently high sensitivity and specificity for both D (96.2% and 91.4%, respectively) and D* (90.6% and 82.9%, respectively) values (Table 4).

### Discussion

Functional MR images can reflect the random motion (Brownian movement) of water molecules in living tissue. However, quantitative ADC values can also be affected by physiological activity and the perfusion effect of the capillary network [19]. The double exponential model with multi-b-values separates the diffusion and perfusion (microcirculation) of water molecules. It more closely approximates the real ADC of the biological tissue, which reflects DWI better than the single exponential model [20].

The IVIM double exponential model assumes that tissue diffusion consists of 2 parts: Brownian movement (D) due to molecular diffusion, and fast perfusion movement (D*) due to blood flow in smaller vessels. D is the static tissue molecular diffusion (true diffusion coefficient), which is calculated by selecting the high b value (>200/mm²) and eliminating the perfusion component. D* denotes the perfusion-diffusion coefficient, which is the perfusion-related diffusion coefficient due to blood circulation. Perfusion composition of tissue microcirculation is sensitive to MR signal attenuation with low b values (<200/mm²) [21]. The perfusion fraction f represents the fractional volume occupied in the voxel by flowing spins linked to the intravascular component or to the microcirculation. D* is closely associated with blood vessel density in tumor tissues, and f value increases with the growth of the tissue perfusion component [22]. In this study, D* values were much greater than the corresponding D values, which indicate that D* is sensitive to MR signal attenuation when b value is low. The D, D*, and f values in our study are similar to a previous study in hepatic adenoma, hepatic cavernous hemangio-
oma, hepatocellular carcinoma, metastatic liver tumor, and cholangiocarcinoma patients [23]. However, the study of Ichikawa et al. [17] reported higher D, D*, and f values than those in our study. These may be due to the difference on the manual ROI drawing (manual ROI method) and the number of patients or lesions. The attribute of the hypovascularity of metastatic liver tumors in this study may also affect these outcomes.

In this study, we found both D and D* values in malignant lesions were significantly lower than in benign lesions, which is consistent with the findings of Ichikawa et al. [17]. This may due to the similar distribution of the samples. In contrast to our findings, the study of Doblas et al. [24] reported that pure diffusion coefficients (D) were significantly lower in malignant tumors than in benign tumors, while perfusion-related diffusion parameters (D*) did not significantly differ between these 2 groups, which was due to the large number of benign hepatic lesions (FNH and adenomas) in their study.

The D* value of metastatic liver tumors is lower than hepatocellular carcinoma and cholangiocarcinoma, which may be due to the hypovascular property of the metastatic liver tumor. Our findings are consistent with those of a previous study, which reported that D* and f values can reflect the condition of the blood supply, and these values are higher in hypervascular hepatic tumors than in hypovascular hepatic tumors [9].

This study also used the ROC curve to evaluate the diagnostic efficiency of D, D*, and f. The ROC curve presents the optimal threshold of D for the diagnosis of benign and malignant tumors is 1.295×10^{-3} mm²/s. Sensitivity (91.4%) and specificity (96.2%) of the D value are both relatively high for identifying the maximum AUC (0.976), indicating the highest diagnostic efficiency of the D value. These may be caused by the following. (1) The most obvious difference between benign and malignant tumors is the component of abnormal cell proliferation. Altered nucleo-cytoplasmic ratio and nuclear atypia in malignant tumor cell induce the limited diffusion of water
molecules and increase the true diffusion of the tissue. (2) The component separation of perfusion-diffusion and true molecular diffusion by the double exponential model resulted in the calculation, in which the D value is closer to the actual ADC of the biological tissue. The perfusion-diffusion is due to the irregular perfusion of the microcirculation in the blood capillary. The relatively small sample size and the selection of lesion types in this study may have affected interpretation of results. Therefore, further studies are warranted.

More realistic D, D*, and f values can be obtained by using more DWI images of low b values and high b values during IVIM imaging, contributing to the qualitative and quantitative identification of the diagnosis. D and D* are both valuable in the diagnosis of hepatic tumors, but D is more reliable in property identification. The diagnostic value of the perfusion parameter obtained by IVIM may reduce the dependency for liver contrast medium clinically. IVIM is an ideal examination method when dynamic enhanced scan period (arterial phase) fails or for contrast medium sensitivity, especially for senile patients and infants.

This study has several limitations. First, this is a retrospective study. Thus, there is an overbalance in the distribution of tumor types, which is limited by the subjects in the hospital. Second, using 3 parameters is unstable, in contrast to using a single parameter; which can easily cause errors in the D* value. In particular, when the f value is small (low perfusion proportion), the quality of the D* image decreases and the chance for more errors on the D* value is higher [25]. Third, the liver is a locomotive organ that can affect IVIM parameters [26,27]. Finally, multi-b-value technology prolongs scanning time, which is onerous for patients.

Conclusions

IVIM DWI can provide more essential D, D*, and f values by using sufficiently low b values and high b values, which contributes to the qualitative and quantitative diagnosis of hepatic tumors. The D value was proven to be a more reliable parameter than the D* value for distinguishing between malignant and benign hepatic lesions.

Conflict of interest

The authors declare that they have no conflict of interest.

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