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Intravoxel Incoherent Motion Diffusion Weighted Imaging for the Therapeutic Response of Transarterial Chemoembolization for Hepatocellular Carcinoma

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Abstract

Background: Intravoxel incoherent motion diffusion weighted imaging (IVIM-DWI) can not only observe the diffusion of tissue water molecules but also reflect the blood perfusion information of tissue microcirculation. IVIM-DWI has been applied in many clinical areas. However, few studies have addressed the use of IVIM-DWI for the evaluation of transarterial chemoembolization (TACE) response in hepatocellular carcinoma (HCC) patients. **Objectives**: The purpose of the present study was to explore the role of IVIM-DWI for the therapeutic response of TACE for HCC. **Materials and Methods**: Twenty patients underwent IVIM-DWI scan on a 3.0T magnetic resonance imaging instrument 1 - 3 days before and 30 to 40 days after TACE. The values of IVIM-DWI parameters, including standard apparent diffusion coefficient (ADC), pure diffusion coefficient (Dslow), pseudo-diffusion coefficient (Dfast) and perfusion fraction (f) were measured. The values of IVIM-DWI parameters before and after TACE were compared using paired t tests. The values between responsive and non-responsive groups were compared using independent-samples t test. $P < 0.05$ indicated statistical significance. **Results**: After TACE, the ADC and Dslow values in the tumors increased significantly, and the values of Dfast decreased significantly, while the values of f value did not change obviously. The ADC values in responsive group were remarkably higher than those in non-responsive group, the Dfast values in responsive group were significantly lower than those in non-responsive group, but the values of Dslow and f between the two groups were not different significantly. **Conclusions:** IVIM-DWI parameters can be used as potential

markers for the therapeutic response of TACE for HCC.

Keywords

Hepatocellular Carcinoma, Diffusion-Weighted Imaging, Intravoxel Incoherent Motion, Transarterial Chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide and is a serious threat to human life and health. Because HCC often has an occlusive onset, patients are often in the advanced stages of the disease when first seeking treatment and have lost the indications for surgical excision. Transarterial chemoembolization (TACE) has been proven to improve the survival time and life quality in HCC patients [1] [2] [3] [4] [5]. The accurate evaluation of TACE treatment response is conducive to the next step of developing personalized treatment programs. However, assessment of anatomic response in the early post-treatment period has been controversial because the absence of a reduction in tumor size does not mean an absence of response [6] [7] [8]. Magnetic resonance diffusion weighted imaging (DWI) can detect the free diffusion motion of water molecules in living tissue. It enables quantitative analyses by measuring the standard apparent diffusion coefficient (ADC) value. Thus, this technique can be used to evaluate TACE response for HCC [9]-[14]. But conventional DWI with a mono-exponential model could not separate perfusion and true diffusion-related effect. Intravoxel incoherent motion diffusion weighted imaging (IVIM-DWI), with a bi-exponential model, can not only observe the diffusion of tissue water molecules but also reflect the blood perfusion information of tissue microcirculation, compensating for the deficiencies of conventional DWI [15]. In recent years, IVIM-DWI has been applied in many clinical areas [16]-[26]. However, few studies have addressed the use of IVIM-DWI for the therapeutic response of TACE for HCC. The aim of the present study was to investigate the role of IVIM-DWI for the therapeutic response of TACE for HCC.

2. Materials and Methods

2.1. Patient Population

This study was approved by our institutional review board, and patient informed consent was obtained. In this study, TACE was performed in the intermediate-stage HCC patients who were not suitable candidates for surgical resection. Exclusion criteria were advanced-stage HCC in the BCLC classification, serum total bilirubin > 80 umol/L, history of severe heart or renal impairment, and iodine allergy. From January 2015 to December 2016, 20 patients with 31 HCC nodules were consecutively enrolled in this study, including 16 males and 4 fe-

males, aged 24 - 72 years, with an average age of 54.3 ± 10.4 years (Table 1). All patients had not received other antitumor treatments before receiving TACE treatment. HCCs were classified as either response group or non-response group according to morphological features. The HCC nodules with diameter reduction greater than 30% constituted the response group, nodules with diameter reduction less than 30% or increment constituted the non-response group.

2.2. MR Imaging

All patients received MRI examinations at 1 - 3 days before TACE and 30 - 40 days after TACE. The equipment used was a 3.0T magnetic resonance imaging (MRI) scanner (Discovery MR750, GE Medical Systems, Milwaukee, Wis., USA). Patients fasted for 4 hours and received breathing training before scanning. The scanning range was the full liver, from the top of the diaphragm to the lower edge of the liver. The scanning sequences were a breath-hold transverse axis fat-suppressed T1WI sequence, a respiratory-triggered fat-suppressed T2WI, and an IVIM-DWI (b = 0, 20, 40, 80, 100, 200, 400, 800, 1000) with a TR 3529 ms, TE 60.8 ms, matrix 128 × 160, FOV 40 cm, slice thickness 5 mm, and interslice gap 0.5 mm, respectively. Images were transferred to a GE ADW4.6 post-processing station and analyzed using Function-MADC software. The ADC, pure diffusion coefficient (Dslow), pseudodiffusion coefficient (Dfast) and perfusion fraction (f) values were measured for each patient. Various parameters were measured 3 times, and the average was taken.

2.3. TACE Procedure

The Seldinger technique is commonly used to puncture the right femoral artery. Under the guidance of a guide wire, a 5F angiographic catheter was placed in the celiac artery or hepatic artery for the performance of digital subtraction angiography (DSA). Subsequently, microcatheter superselective catheterization of the tumor-feeding artery was conducted. TACE was performed by administration of 5-fluorouracil (1000 mg) via the tumor-feeding artery, followed by lipiodol (Lipiodol UltraFluid, Laboratoire Guerbet, Aulnay-Sous-Bois, France) (5 to 20 ml)

Table 1. Clinical characteristics of the 20 patients.

Variable	Value
Age (yr)	54.3 (range 24 - 72)
Sex	
Men	16
Women	4
Size of tumor (cm)	6.4 (range 2.5 - 8.9)
Liver cirrhosis	19
HBV	19
Serum AFP (ng/mL)	14,082.1 (range 665.5 - 110,980.7)

HBV: Hepatitis B virus; AFP: alpha-fetoprotein.

with lobaplatin (40 mg) and adriamycin (40 mg) mixed chemoembolic emulsion and gelfoam particles. Chemobolization was terminated when the tumor stain disappeared or when the patient could no longer tolerate the procedure.

2.4. Statistical Analysis

SPSS 20.0 software was used to analyze the changes of IVIM-DWI parameters. The IVIM-DWI parameters of HCC nodules before and after TACE were compared using paired t test. The values between responsive and non-responsive groups were compared using independent-samples t test. $P < 0.05$ indicated statistical significance.

3. Results

After treatment with TACE, the ADC and Dslow values in the tumor increased remarkably (all $p < 0.01$), and the values of Dfast decreased significantly ($p < 0.01$), while the values of f did not change obviously ($p > 0.05$). Six HCC nodules were classified as responsive group, and 25 HCC nodules were non-responsive group. The ADC values in responsive group were evidently higher than those in non-responsive group ($p < 0.05$), the Dfast values in responsive group were significantly lower than those in non-responsive group ($p < 0.05$), but the values of Dslow and f between the two groups were not different significantly after TACE (all $p > 0.05$) (**Table 2** & **Table 3**) (**Figure 1** & **Figure 2**). The follow-up period was 1.6 to 3 months. TACE related complications and perioperative deaths have not occurred.

Table 2. Comparison of IVIM-DWI parameter levels before and after TACE treatment.

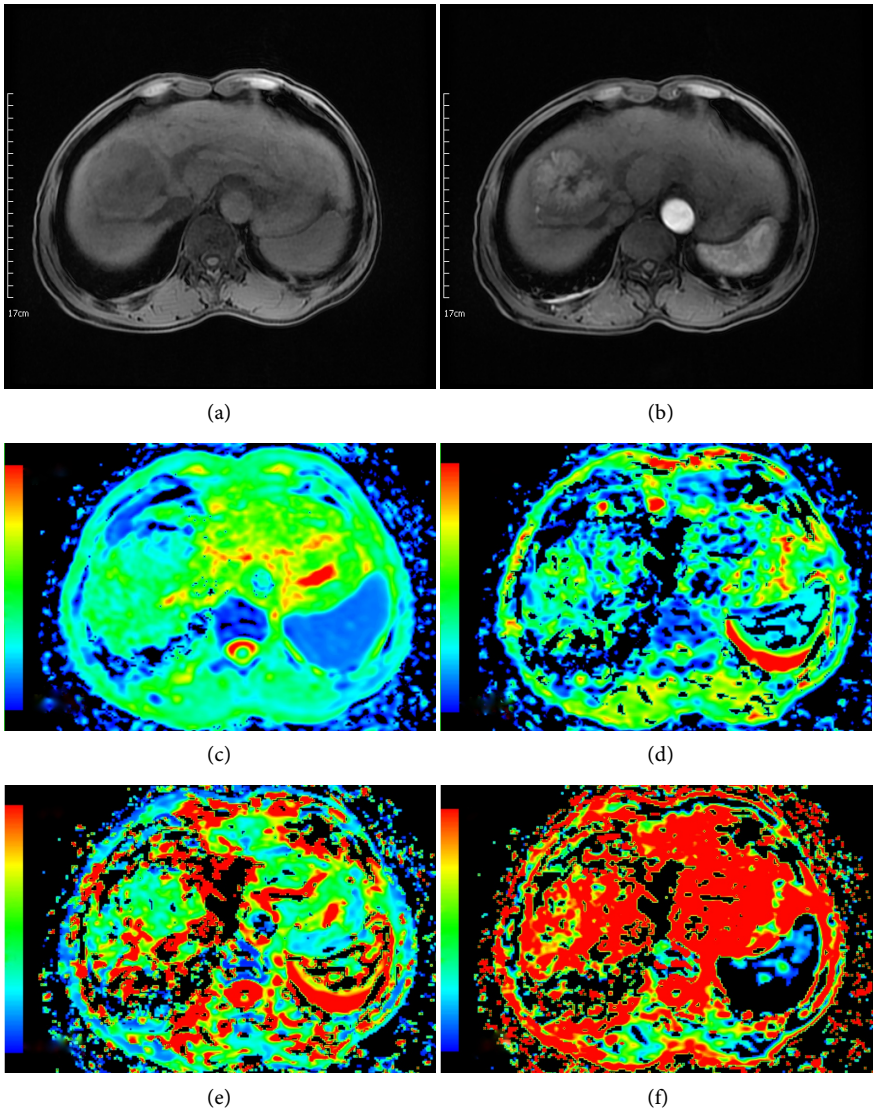
Parameters	Pre-TACE	Post-TACE	t	p
ADC (10^{-3} mm^2/s)	0.94 ± 0.17	1.23 ± 0.21	8.794	<0.01
Dslow (10^{-3} mm^2/s)	0.72 ± 0.14	0.91 ± 0.14	6.120	<0.01
Dfast (10^{-3} mm^2/s)	37.14 ± 7.96	28.29 ± 7.24	5.612	<0.01
f (%)	15.52 ± 3.33	15.45 ± 3.84	0.091	0.928

IVIM-DWI: intravoxel incoherent motion diffusion weighted imaging; TACE: transarterial chemoembolization; ADC: apparent diffusion coefficient; Dslow: pure diffusion coefficient; Dfast: pseudodiffusion coefficient; *f*: perfusion fraction.

Table 3. Comparison of IVIM-DWI parameter levels after TACE between responsive group and non-responsive group.

Parameters	Responsive group	Non-responsive group	t	p
ADC (10^{-3} mm^2/s)	1.42 ± 0.13	1.18 ± 0.19	2.769	0.010
Dslow (10^{-3} mm^2/s)	0.99 ± 0.10	0.87 ± 0.14	1.961	0.059
Dfast (10^{-3} mm^2/s)	22.16 ± 4.39	29.75 ± 7.06	2.506	0.018
f (%)	14.88 ± 3.22	15.58 ± 4.03	0.389	0.700

IVIM-DWI: intravoxel incoherent motion diffusion weighted imaging; TACE: transarterial chemoembolization; ADC: apparent diffusion coefficient; Dslow: pure diffusion coefficient; Dfast: pseudodiffusion coefficient; *f*: perfusion fraction.

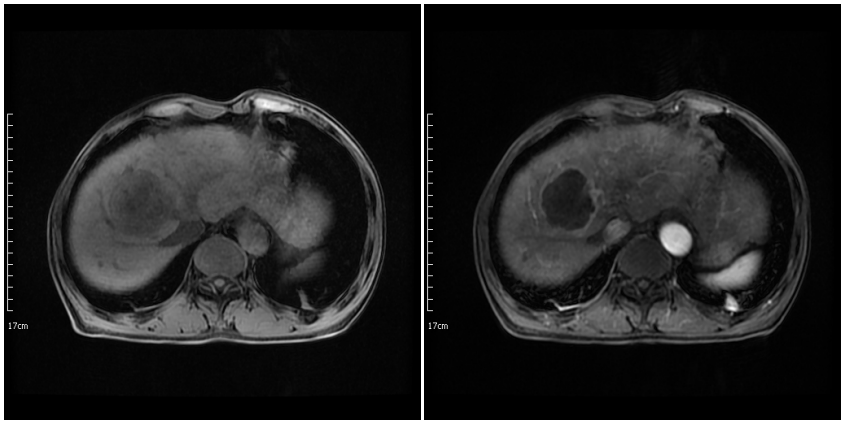


(a) (b)

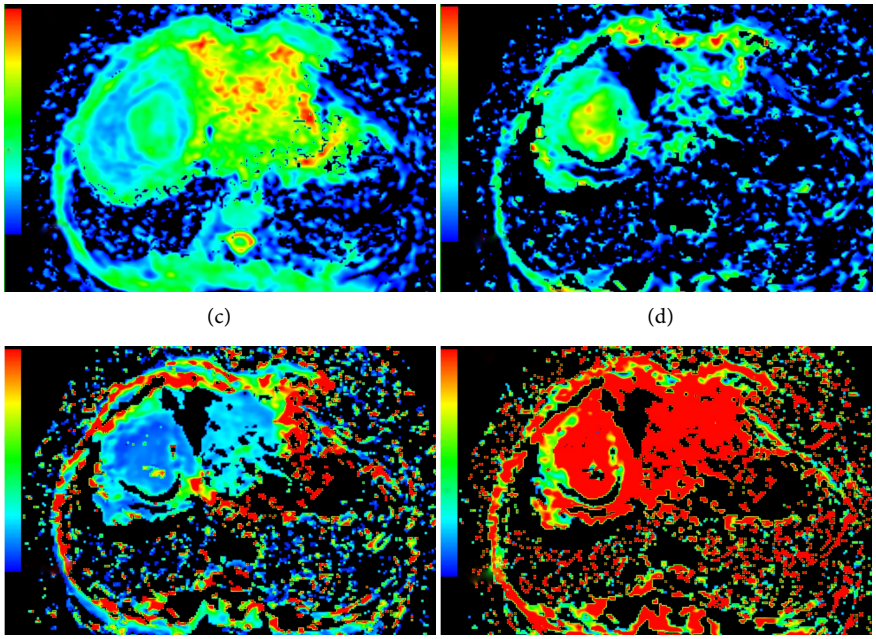
(c) (d)

(e) (f)

Figure 1. Axial MRI images of HCC patient before TACE treatment. (a) T1-weighted unenhanced image shows a hypointensive lesion in right lobe of liver. (b) Arterial phase contrast-enhanced image shows a heterogeneous enhanceed lesion. (c) ADC map. (d) Dslow map. (e) Dfast map. (f) f map.



(a) (b)



(c) (d)

(e) (f)

Figure 2. Axial MRI images of the same patient as in **Figure 1** after TACE treatment. (a) T1-weighted unenhanced image shows a hypointensive lesion in right lobe of liver. (b) Arterial phase contrast-enhanced image shows the central necrotic area and peripheral enhanced area in the lesion. (c) ADC map. (d) Dslow map. (e) Dfast map. (f) f map.

4. Discussion

Therapeutic response assessment of TACE is crucial for selecting the next treatment regimen and prognosis evaluation. Serun biomarkers often be used as indicators for the diagnosis and monitoring of tumor treatment progress [27] [28] [29]. Serum alpha-fetoprotein (AFP) is one of the most commonly used indicators for evaluating the response of TACE treatment. However, AFP values are always at normal levels in 30% of HCC patients [30]. For this group of patients, AFP values cannot be used to evaluate TACE response. Medical imaging plays an important role in response evaluation of tumor therapy [6] [31] [32] [33] [34] [35]. Currently, the value of functional imaging for tumor therapeutic response evaluation is increasingly being recognized [31]. Computed tomography (CT) can clearly show the deposition of high-density iodized oil in a lesion. However, the high-density iodized oil in the lesion interferes with the observation of residual tumor via enhanced CT. CT perfusion imaging has the ability to assess the perfusion changes in HCC tissues after chemoembolization, which can be used to evaluate the treatment response of TACE for HCC, but it will increase radiation exposure [6] [31].

With the development of functional MRI, it is possible to determine the metabolic status of tumor cells at an early stage before the appearance of tumor-related morphological changes. IVIM-DWI can show the molecular diffusion and microperfusion of the local capillary network in lesions by using quantitative indicators [15]. The commonly used parameters include the Dslow, Dfast and f values. The Dslow parameter of IVIM-DWI removes the effects of microcirculation

perfusion on ADC and can more accurately reflect the diffusion of water molecules within tissue. Dfast and f values mainly reflect tissue microcirculation capillary perfusion.

Park YS *et al.* studied 44 HCC patients using IVIM-DWI prior to TACE and CT after TACE as a reference standard. In total, 51 HCCs were analyzed: 37 were lipiodol good uptake (LGU) group and 14 were lipiodol poor uptake (LPU) group. ADC, D, and f values were not significantly different between these two groups. D* was significantly elevated in LGU than LPU. Their result indicated that the IVIM-DWI parameters would be helpful for predicting the lipiodol uptake [36]. Wu L *et al.* explore the threshold of IVIM parameters, ADC ratios 24 - 48 hours after TACE to assess early response in patients with unresectable HCC. They found that the ADC ratio and D ratio after TACE were independent predictors for response to TACE for HCC, and showed stronger association with PFS than mRECIST [37].

In this study, the values of ADC and Dslow of lesions after TACE treatment increased significantly, which may be related to the fact that the tumor cells undergo necrosis, leading to increased water diffusion capacity. The Dfast values in the lesion areas of HCC patients decreased after TACE, compared with the before-treatment values, which may be related to the fact that tumor blood supplies were blocked after TACE and the basement membrane of newly generated blood vessels was incomplete and the vessels had a small diameter, leading to slow blood flow. The value of f in this study did not change significantly after treatment, likely because Dfast and f values represent different aspects of perfusion; the former is primarily related to local tissue capillary velocity, and the latter is related to local tissue blood volume [36].

This study has the following limitations. Firstly, the number of cases collected in this study is small. Secondly, the images analyzed before and after TACE treatment may not be the same levels, which may be a potential source of error. Another limitation is that the relationship between the prognosis and changes of IVIM parameters after TACE treatment was not investigated in the HCC patients. In further studies, an increased number of cases should be studied. The prognosis of the patients with HCC should be followed up. In addition, because IVIM parameter measurement is susceptible to the b value and the selection of the b value is still controversial [38] [39], the selection of the b value needs to be further optimized or standardized.

5. Conclusion

In summary, IVIM-DWI parameters can be used as potential markers for the therapeutic response of TACE for HCC.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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