

Original Article

Role of diffusion-weighted magnetic resonance imaging and apparent diffusion coefficient values in the detection of gastric carcinoma

Jianxiao Liang^{1,2}, Hailian Lv³, Qingwei Liu⁴, Hongfu Li², Jiangquan Wang⁵, Engang Cui²

¹Shandong University, Jinan 250012, P. R. China; Departments of ²Radiology, ⁵Medical Services, Dongying People's Hospital, Dongying 257091, P. R. China; ³Department of MRI Division, Shengli Oilfield Central Hospital, Dongying 257034, P. R. China; ⁴Department of Radiology, Shandong Provincial Hospital, Jinan 250014, P. R. China

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Abstract: Objective: The study evaluated the applicability of diffusion-weighted magnetic resonance imaging (DW-MRI) and apparent diffusion coefficient (ADC) values in the diagnosis and staging of gastric carcinoma (GC). Methods: From December, 2013 to December, 2014, 35 GC patients were selected from the Department of Oncology. Carcinomatous gastric tissues were collected as the case group, and normal gastric tissues were collected as the control group. The DW-MRI examination was performed on a 3.0-T GE Signa Excite MRI scanner. The ADC values of carcinomatous and normal gastric tissues were measured. A statistical meta-analysis was further performed. Results: DW-MRI identified 75.0% (3/4) patients with T1, 75.0% (6/8) patients with T2, 86.4% (19/22) patients with T3, and 100.0% (1/1) patient with T4, showing an accuracy for T staging of 82.9% (29/35); identified 92.9% (13/14) patients of N0, 58.3% (7/12) patients of N1, 62.5% (5/8) patients of N2, and 100.0% (1/1) patients of N3, showing an accuracy for N staging of 74.3% (26/35). The average ADC value in the case group was apparently lower than the control group ($P < 0.001$); in the poorly differentiated group was lower than the moderately and well differentiated groups ($F = 111.1$, $P < 0.001$). Pairwise comparison of the average ADC value between the poorly, moderately and well differentiated groups showed statistical significance (all $P < 0.05$). Meta-analysis further confirmed a higher average ADC value in the case group than the control group (SMD = -4.136, 95% CI = -5.344~-2.928, $P < 0.001$). Conclusion: DW-MRI is proved to be an attractive, noninvasive, quantitative and useful technique in the diagnosis and staging of GC.

Keywords: Gastric carcinoma, diffusion-weighted magnetic resonance imaging, apparent diffusion coefficient, T staging, N staging, degree of differentiation, meta-analysis

Introduction

Gastric carcinoma (GC), developing from the lining of the stomach, is the fourth most common cancer and the second leading cause of cancer mortality in the world [1, 2]. It is estimated that, annually, more than 930,000 new cases of GC are being diagnosed and over 700,000 people die of it worldwide [3]. Early symptoms of GC include heartburn, upper abdominal pain, nausea and loss of appetite, and later symptoms include weight loss, yellow skin, vomiting, difficulty swallowing, and blood in the stool [4]. Numerous studies have showed that various factors, such as helicobacter pylori infection, dysplasia, male gender, cigarette smoking, alcohol consumption, iodine deficiency, dietary,

partial gastrectomy, Menetrier's disease may be significantly related to an increased risk of GC [5, 6]. The clinical manifestations of GC are not specific and not always present which results in difficult early diagnosis; while an accurate preoperative TNM staging is essential for choosing the treatment of GC [7]. Different techniques have been used for the preoperative diagnosis and staging of GC, such as endoscopy, ultrasonography (US), computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) [8]. However, due to their inefficiency, inaccuracy or the side effects, diffusion-weighted MRI (DW-MRI) is introduced as a replace technique for the preoperative diagnosis and staging of GC [7, 9].

Role of DW-MRI and ADC values in detecting GC

DW-MRI, a noninvasive diagnostic modality that achieves a substantial reduction of artifacts and an improvement of image quality, can measure the degree of microscopic mobility of water molecules within and between the intracellular and extracellular spaces [10]. Although the water molecular diffusion in tissues is not free, it can reflect the interactions with lots of barriers, for instance, giant molecules and membranes, which can indicate the microscopic details about tissue structures, either normal or in a morbid state [11]. With the technology of DW-MRI, we can track cellular aspect of the tissue resulting from visualization and measurement of the degree of water molecular diffusion in human body [12]. Generally, DW-MRI uses a pair of DW gradient pulses to produce signals that are sensitive to the localized diffusivity of water molecules and thus can indirectly measure the cell density of the tissue [8]. When water molecular diffusion is limited by cytotoxic damage from inflammation, wound, or neoplasm, the signal of DW-MRI presents high or bright; hereby, DW-MRI findings might act as an early predictor of biological abnormalities [13]. Furthermore, an apparent diffusion coefficient (ADC) of water can be calculated from the DW-MRI images, which depends on the presence of diffusion barriers in the water microenvironment [14]. The ADC value varies inversely with the cell density because elevated cell density restricts water molecules diffusion in the interstitial space [15]. In this regard, the changes of ADC values might be an independent marker of tumor location and pathologic type [16, 17]. In past few decades, DW-MRI has been widely used for diagnostic purposes and has been used for monitoring the clinical tumor responses for glioma, soft-tissue sarcoma, breast cancer, liver metastases, rectal cancer and GC, confirming the potential ability of DW-MRI to differential diagnosis of neoplasms [18, 19].

The present study evaluated the applicability of the DW-MRI and related ADC values in the diagnosis and staging of GC, and a meta-analysis was conducted to confirm the roles of DW-MRI and ADC values in the detection of GC.

Materials and methods

Ethics statement

The retrospective study was approved by the ethics committee of the People's Hospital of

Dongying City Shandong Province. The written informed consent was provided by each eligible patient and the study conformed to the Declaration of Helsinki [20].

Patients

From December, 2013 to December, 2014, a total of 35 patients (21 male and 14 female; age range: 38~75; mean age, 58.03 ± 9.12 years) with histologically confirmed GC were selected from the Department of Oncology of the People's Hospital of Dongying City Shandong Province. The diagnostic criteria of GC were as following: (1) abdominal discomfort at early stage, fatigue, backache, as well as nausea, vomiting and dysphagia after gastric obstruction at later stage in approximately 80% patients; (2) no clinical sign at early stage, abdominal mass by rectal touch, enlargement of the left supraclavicular lymph nodes, anemia, weight loss and occurrence of malignant ascites and cachexia at later stage; (3) X-ray Gas-Ba Double Enhancing clearly shows gastric contour, gastric motor, mucosal morphology, gastric emptying time, filling defect and niche; and (4) GC can be diagnosed by fiber endoscopy, exfoliative cytology, B ultrasound and CT examination [21]. The inclusion criteria were: (1) all patients received radical surgery; (2) GC with different degree of differentiation was histologically confirmed by postoperative pathology; and (3) all patients received routine MRI or DWI examination within 1 week preoperatively. The exclusion criteria for patients were: (1) artifacts on DWI affected the measurement of ADC values; and (2) patients received antitumor therapy before MRI. Among these 35 GC patients, 8 patients with carcinoma located in the cardia, 4 with carcinoma in the gastric fundus, 8 with carcinoma in the gastric body, and 15 with carcinoma in the gastric antrum. All patients had a clinical sign of gastral cavity pain, and partial patients had choked feelings when eating. Postoperative pathological outcomes revealed that there were 14 patients with poorly differentiated adenocarcinoma, 11 with moderately differentiated adenocarcinoma, and 10 with well differentiated adenocarcinoma. Carcinomatous gastric tissues were collected from the gastric wall of all patients as the case group ($n = 35$), and normal gastric tissues confirmed by pathological examination were collected > 2 cm from carcinoma lesion of all patients as the control group ($n = 35$).

Role of DW-MRI and ADC values in detecting GC

DW-MRI examination

All patients were advised to keep an empty stomach for 8-12 h before the DW-MRI examination. Adequate distention of the stomach was achieved by drinking 800-1000 mL of water prior to the examination, and pats on the back were conducted for all patients to minimize intragastric air. Anisodamine (20 mg) was injected intramuscularly to all patients 10 min before the examination to decrease gastrointestinal motility and to obtain high quality images on DW-MRI. Breath-holding was trained in all patients and then the DW-MRI examination was performed on a 3.0-T GE Signa Excite MRI scanner (Signa EchoSpeed Plus with EXCITE, General Electric Medical Systems, Milwaukee, WI, USA) with a maximum gradient strength of 40 mT/m and a slew rate of 150 T/(m × s). An 8-channel Torsopa phase array surface coil was employed in conjunction with an analytical software size estimation technique (ASSET). Conductor pad was utilized in all examinations. The DW-MRI examination was performed with all patients in a supine position and arms crossed above the head using the respiratory gating technique. DW-MRI was obtained using a single-shot echo-planar imaging (SS-EPI) sequence in the transverse plane during 2 breath-holdings, respectively. Imaging parameters for DW-MRI were: TR, 1500 ms; TE, 56 ms; bandwidth, 250 kHz; matrix size, 128 × 128; number of excitations (NEX), 2; field of view (FOV), 38 cm × 38 cm ~40 cm × 40 cm; section thickness, 6 mm; intersection gap, 1.5 mm. The array spatial sensitivity encoding technique (ASSET) was applied as the parallel imaging technique with an acceleration factor of 2. The motion-probing gradients (MPG) were placed along three orthogonal directions (x-, y- and z-axes), and the b-factor was 800 s/mm².

Image analysis

All DW-MRI data were transferred to GE-ADW4.3 workstation (Milwaukee, WI, USA). Post-processing for diffusion images were conducted by using the Functool 4.5.1 software (GE Medical Systems, Milwaukee, WI, USA). High quality of the DW image was determined by no obvious anamorphose, no artifact on DW-MRI making the ADC measurement impossible, and presence of discernable signal difference between the carcinomatous region and the

nearby normal gastric wall. An oval region of interest (ROI) was placed on the slice in which the largest area of the lesion was located, to enclose the high signal intensity area visible on DW-MRI. Another oval ROI was placed on the nearby apparently normal gastric wall. The ADC values of the ROI were read on the DWI and ADC maps, respectively, to record the signal intensity of the carcinomatous region and the nearby apparently normal gastric wall. All measurements were conducted by one same surgeon for more than 3 times, and means were obtained.

Histopathological evaluation

The DW-MRI preoperative staging was performed by two radiologist with more than 10 years of experience in the field of the clinical diagnosis of abdominal imaging according to the UICC/AJCC TNM classification [22]. T classification based on DW-MRI was as following: T1, no obvious lesion or submucosal layer to preserve the integrity; T2, invasion of all layers of gastric wall, smooth external boundary or slightly enhanced outer layer to preserve the integrity; T3, invasion of all layers of gastric wall, external boundary to present irregular or grid shape, or slightly enhanced outer layer to be damaged; T4, invasion of nearby tissues [23]. No serosa infiltration was determined by clear and smooth low-signal-intensity junctional zone between tumor and peripheral fat in phase scrambling gradient echo imaging. N classification based on DWI was as following: N0, no metastasis; N1, 1 to 2 metastatic lymph nodes; N2, 3 to 6 metastatic lymph nodes; N3, 7 or more metastatic lymph nodes [24].

Statistical analysis

SPSS 18.0 statistical software (IBM Corporation, Somers, NY, USA) was used for data analysis. All data were presented as mean ± standard deviation ($\bar{x} \pm s$). The *t* test was applied to compare ADC values between the case group and the control group after homogeneity test of variances using the Levene test. The *t* test was used under variance homogeneity and the *t'* test was used under variance heterogeneity. The analysis of variance (ANOVA) for a single-factor model was utilized to compare ADC values among poorly, moderately, and well differentiated groups. The comparison was conducted by using the Least Significant

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Table 1. T staging accuracy in diffusion-weighted magnetic resonance imaging (DW-MRI)

T staging	Pathological staging (n = 35)				Diagnostic accuracy (%)
	pT1 (n = 4)	pT2 (n = 8)	pT3 (n = 22)	pT4 (n = 1)	
DW-MRI					
T1	3	1	0	0	75.0%
T2	1	6	3	0	75.0%
T3	0	1	19	0	86.4%
T4	0	0	0	1	100.0%

pT1, pT2, pT3, pT4, T staging by postoperative pathological outcomes; T1, T2, T3, T4, T staging by DW-MRI.

Table 2. N staging accuracy in diffusion-weighted magnetic resonance imaging (DW-MRI)

N staging	Pathological staging (n = 35)				Diagnostic accuracy (%)
	pN0 (n = 14)	pN1 (n = 12)	pN2 (n = 8)	pN3 (n = 1)	
DW-MRI					
N0	13	4	1	0	92.9%
N1	1	7	2	0	58.3%
N2	0	1	5	0	62.5%
N3	0	0	0	1	100.0%

pN0, pN1, pN2, pN3, N staging by postoperative pathological outcomes; N0, N1, N2, N3, N staging by DW-MRI.

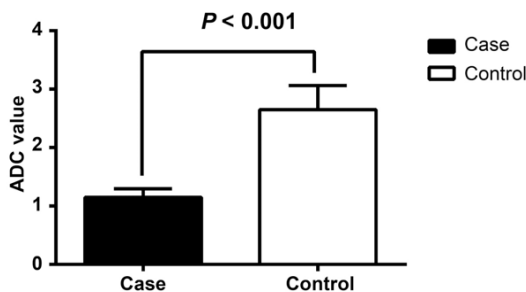


Figure 1. Comparison of average apparent diffusion coefficient (ADC) value between the case group and the control group.

Difference test (LSD-t) under variance homogeneity, and using the Tamhane's T2 under variance heterogeneity. All *P* values < 0.05 were considered statistically significant.

A Comprehensive Meta-Analysis version 2.0 software (CMA 2.0, Biostat Inc., Englewood, New Jersey, USA) was used to perform the statistical meta-analysis. The standard mean differences (SMD) with 95% confidence intervals (CI) was calculated by applying a fixed-effects model (Mantel-Haenszel method) or a random-

effects model (DerSimonian and Laird method), to evaluate the correlation of ADC value in DW-MRI with GC. The Z test was utilized to examine pooled effect size [25]. The forest plot was used to compare SMD with 95% CI between groups.

Results

T staging

In the 35 patients with GC that underwent surgery, postoperative pathological outcomes identified 4 patients (11.4%) with a stage of pT1, 8 (22.9%) with a stage of pT2, 22 (62.9%) with a stage of pT3, and 1 (2.9%) with a stage of pT4. The preoperative DW-MRI identified 75.0% (3/4) patients with a stage of T1, 75.0% (6/8) patients with T2, 86.4% (19/22) patients with T3, and 100.0% (1/1) patient with T4. The accuracy of DW-MRI in the determination of the T factor, according to the UICC/AJCC TNM classification, was 82.9% (29/35) (**Table 1**).

N staging

In the analysis of the N factor, we considered the lymph nodes according to the UICC/AJCC TNM classification. Using postoperative pathological staging, 14 out of 35 patients (40.0%) of pN0, 12 (34.3%) of pN1, 8 (22.9%) of N2, and 1 (2.9%) of N3 were identified. Employing DW-MRI, 92.9% (13/14) patients of N0, 58.3% (7/12) patients of N1, 62.5% (5/8) patients of N2, and 100.0% (1/1) patients of N3 were detected. The accuracy of DW-MRI in N staging was 74.3% (26/35) (**Table 2**).

ADC values in case group and control group

The average ADC value measured in carcinomatous gastric walls by DW-MRI was $(1.15 \pm 0.15) \times 10^{-3} \text{ mm}^2/\text{s}$. Comparison with normal gastric walls which showed an average ADC value of $(2.65 \pm 0.41) \times 10^{-3} \text{ mm}^2/\text{s}$ demonstrated that average ADC value in the case group was apparently lower than that in the control group (*P* < 0.001) (**Figure 1**).

ADC values in poor-, moderate- and well-differentiated adenocarcinoma

The locations of carcinoma were the cardia (n = 8), the gastric fundus (n = 4), the gastric body (n = 8), and the antrum (n = 15). On DW-MRI, the

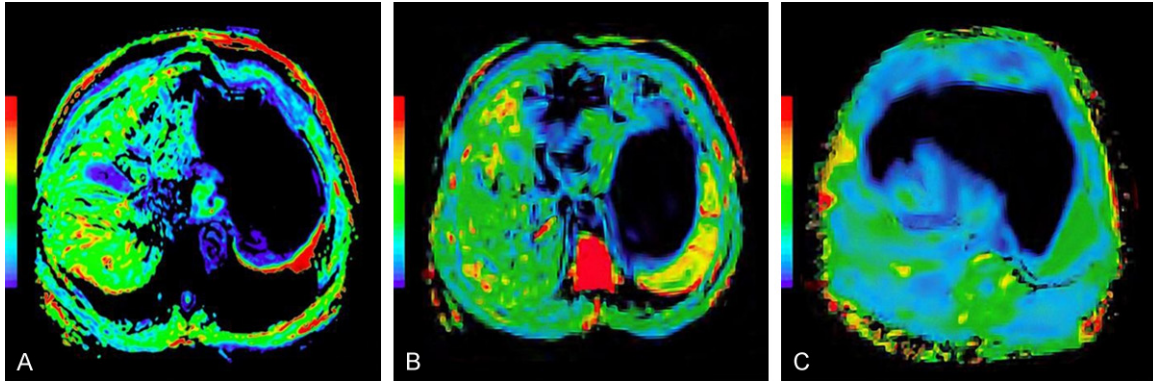


Figure 2. Apparent diffusion coefficient (ADC) map for the poor-differentiated carcinomatous area in the cardia (A), the moderate-differentiated carcinomatous area in the gastric body (B), and the well-differentiated carcinomatous area in the antrum (C).

Table 3. Average ADC values of poorly differentiated group, moderately differentiated group and well differentiated group

Degree of differentiation	ADC values ($\times 10^{-3} \text{ mm}^2/\text{s}$)	F	P
Poorly differentiated group	1.01 ± 0.06	111.1	< 0.001
Moderately differentiated group	$1.16 \pm 0.06^*$		
Well differentiated group	$1.35 \pm 0.04^{* \#}$		

ADC, apparent diffusion coefficient, *Compared with poorly differentiated group, $P < 0.05$; #Compared with moderately differentiated group, $P < 0.05$.

poor-differentiated carcinomatous area in the cardia showed low signal intensity in ADC map and the average ADC value was $(1.01 \pm 0.06) \times 10^{-3} \text{ mm}^2/\text{s}$ (**Figure 2A**); the moderate-differentiated carcinomatous area in the gastric body showed low signal intensity in ADC map and the average ADC value was $(1.16 \pm 0.06) \times 10^{-3} \text{ mm}^2/\text{s}$ (**Figure 2B**); the well-differentiated carcinomatous area in the antrum also displayed low signal intensity in ADC map and the average ADC value was $(1.35 \pm 0.04) \times 10^{-3} \text{ mm}^2/\text{s}$ (**Figure 2C**). Apparently, the average ADC value in the poorly differentiated adenocarcinoma was lower than that in the moderately differentiated adenocarcinoma and well differentiated adenocarcinoma. In addition, the ANOVA for a single-factor model proved that the differences were statistically significant ($F = 111.1$, $P < 0.001$). Pairwise comparison of the average ADC value between the poorly, moderately and well differentiated groups showed observably statistical significance (all $P < 0.05$) (**Table 3**).

Comparison of ADC value by meta-analysis

In total, 9 clinical studies, which reported the correlations of DW-MRI and ADC values with

GC, met our inclusion criteria for this meta-analysis [4, 7, 8, 26-31]. A total of 288 carcinomatous gastric tissues and 282 normal gastric tissues were involved in this meta-analysis. A random-effects model was utilized due to existing heterogeneity in each included study ($I^2 = 94.812\%$,

$P_h < 0.001$). Meta-analysis results showed a lower average ADC value in the carcinomatous gastric tissues than in the normal gastric tissues (SMD = -4.136, 95% CI = -5.344~-2.928, $P < 0.001$), as seen in **Figure 3**.

Discussion

In the present study, we utilized DWI sequences adding to the standard MRI protocol to reveal the utility of DW-MRI and ADC values in the preoperative diagnosis and staging of GC. The most important conclusion of the current study is that the ADC values in the case group was significantly lower compared to those in the control group, supporting that DW-MRI might be beneficial for characterizing and diagnosing GC by the aid of ADC measurements. This result was also confirmed by our meta-analysis showing an obvious lower average ADC value in the carcinomatous gastric tissues than in the normal gastric tissues. It has been well documented that DW-MRI could provide qualitative and quantitative functional information from the diffusion of water molecules, which mainly reflects the degree of cellularity of the tissue, and evidence has reported that various

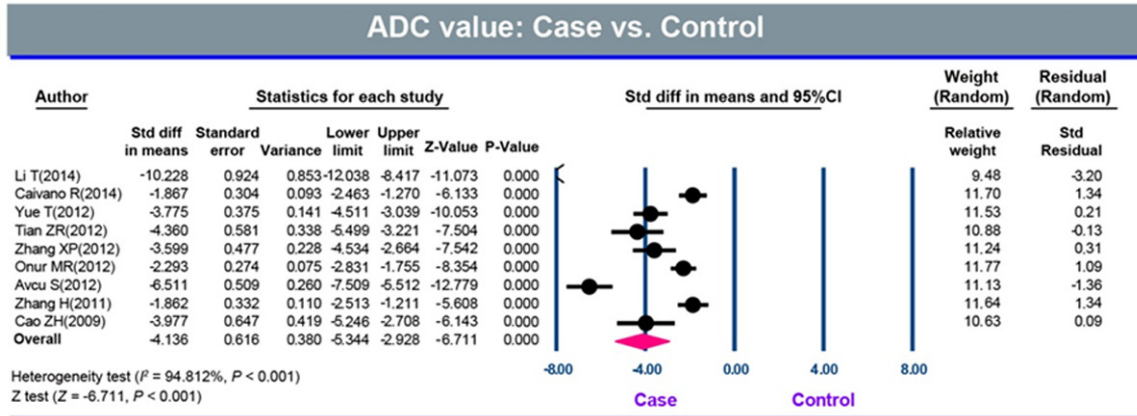


Figure 3. Forest plots of comparison of average apparent diffusion coefficient (ADC) value between carcinomatous gastric tissues and normal gastric tissues.

types of cancer have been evaluated by DW-MRI, such as breast cancer, head and neck cancer, and GC [32-34]. Moreover, ADC value, one of the most important advantages of DW-MRI to reflect the thermal diffusion of water molecules in biological tissues, has been reported to be reduced in various carcinomas [29]. Therefore, it is plausible that the mechanisms why malignant gastric tumors have lower ADC values are probably associated with a combination of higher cellularity, reduced extracellular space tortuosity, and tissue disorganization [7]. More specific, there is evidence in the literature revealing that the histopathological characteristics of gastric malignance, including high cellularity, cellular polymorphism, and increased mitoses may greatly result in a decrease in extracellular and intracellular spaces, and these cellular space reductions might restrict the free motion of water molecules, thereby leading to the decrease of ADC values [1]. These findings are in accordance with a previous study which also demonstrated that gastric tumors with a high cellular density have a relatively high intracellular/extracellular space volume ratio, and thus will produce a low ADC value on DW-MRI, which could provide a reference value for radiologists to evaluate GC [29]. This result suggests that ADC values reflected the histopathologic changes of the gastric wall by reducing with enhanced cellularity, acting as a potential diagnostic indicator of GC [7].

In addition, our results showed that DW-MRI allows diagnosing the gastric tumor even in T and N stage, leading to accurately predict the

resectability of surgery. In our analysis of the T factor and N factor, we found a relative high diagnostic accuracy of DW-MRI in identifying the invasion and metastasis of gastric tumor. In fact, analysis of the T factor is rather disappointing in the early stages of T1-T2. The cause, probably, is the difficult distension of the gastric wall in a few poorly cooperative patients and consequently a difficulty in identifying the layers [4]. It is therefore difficult to differentiate GC between pT1 and pT2; much more accurate diagnosis is the assessment of the extent extra-serosa (pT3) and the invasion of the surrounding structures (pT4). A case of T2 was overstaged by DW-MRI as T3, which was possibly because of an inadequate distension of the gastric walls in the patients and thereby difficulty in the identification of gastric structure [35]. In our analysis of the N factor, we found that DW-MRI shows a relative high diagnostic accuracy in evaluating of lymph node metastases, which is based on its principles of restriction pathological signal associated with cellularity [36]. In line with our findings, Kantarci et al. who studied 21 patients affected by GC using 1.5T DW-MRI, reported a sensitivity of 87% and a specificity of 100% [37]. Shinya et al. also considered that DW-MRI has the potential to be clinically effective for the evaluation of preoperative TNM staging of GC through a pilot study of a small sample of 15 patients [38].

Also, our results revealed that the average ADC value of poorly differentiated adenocarcinoma is apparently lower than that of moderately/well differentiated adenocarcinoma, showing that ADC has a potential for clinical apprecia-

tion in differentiating GC with different differentiation degree with good specificity. This finding is also resulted from the principle underlying DW-MRI that the thermal motion of water molecules in extracellular fluid enables the acquisition of images that reflect both histological structure and cellularity and therefore it can detect the changes of tissue structure at molecular level [39]. Therefore, poorly differentiated adenocarcinoma reflecting high degree of malignancy, of course, is correlated to lower ADC value which is related to higher cellularity, enhanced extracellular space tortuosity, and tissue disorganization [18].

In conclusion, DW-MRI is proved to be an attractive, noninvasive, quantitative and useful technique in the preoperative diagnosis and staging of GC. Additionally, ADC values could potentially serve as a biomarker to strengthen the diagnostic performance of GC. Moreover, DW-MRI was helpful in the T and N staging and differential diagnosis of GC with different degree of differentiation. The limitation of our study is mainly due to the small sample size, so a larger population study is needed to confirm our results.

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Address correspondence to: Jianxiao Liang, Department of Radiology, Dongying People's Hospital, Nanyi Road No. 317, Dongying 257091, P. R. China. E-mail: liuqingwei418@126.com

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