

Original Article

Use of diffusion-weighted imaging to evaluate histological factors and proliferative potential of gastric cancer

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Abstract: Objective: Gastric cancer is one of the most common malignant tumors. Non-inversional tool could improve the diagnosis and treatment of the cancer. The aim of this study was to evaluate the diagnostic value of diffusion-weighted imaging (DWI) for histological factors and Ki-67 antigen labelling index (LI) in gastric cancer. Methods: Eight-four DWI images of gastric cancer were analyzed retrospectively at b values of 0 and 1000 s/mm², respectively. Postoperative histological factors were obtained, including tumor TNM stage, histological type, and differentiation degree. Mean ADC values were calculated for the gastric cancers by two radiologists. Relations between ADC values and histological factors or Ki-67 LI were analyzed. The diagnostic cutoffs of ADC value were determined using ROC analysis and used to distinguish histological factors and Ki-67 LI of gastric cancer. Results: The ADC values in the tumors of different TNM stage, histological type, and Ki-67 LI were significantly different. They were significantly lower in higher TNM stage tumors, poorly differentiated adenocarcinomas or signet-ring cell carcinomas, and in the cancers with elevated Ki-67 LI. The ADC value was inversely correlated with Ki-67 LI ($r = -0.8146$, $P < 0.01$). The diagnostic cut-offs of ADC values to distinguish stage I, well differentiated adenocarcinoma and cancer with Ki-67 LI $< 47\%$ were 1.025, 1.042 and 0.961×10^{-3} mm²/s, respectively. Conclusions: ADC value may be helpful as a noninvasive tool for evaluating the histological factors and Ki-67 LI of gastric cancer.

Keywords: Gastric cancer, magnetic resonance imaging, diffusion-weighted imaging, Ki-67 antigen

Introduction

Gastric cancer is one of the most common malignant tumors, and its prognosis and survival rate are poor in patients with advanced-stage disease [1]. Classical pathological parameters such as histological type, differentiation grade, and tumor stage (T, N, and M stages) are associated with disease prognosis, and use of immunohistochemical biomarkers, such as p53, p27, CD133, and Ki-67, can significantly improve the prediction accuracy of oncological outcome models for gastric cancer patients [2-4].

Ki-67 is an established prognostic biomarker measuring cell proliferation for gastric cancer [5]. Ki-67 labeling index (LI) is shown to be related to the recurrence, progression, and survival in gastric cancer patients, independent of classical pathological parameters [2-4]. It is shown to be a more potent prognostic factor

than histological staging and pathological nodal status, and improved the predictive accuracy in a large cohort study when incorporated into the multivariate models containing the classical clinicopathological parameters [6]. Drawbacks of Ki-67 LI include relatively complicated procedures for immunohistochemistry assays and less objectivity in quantifying the positive cells.

Although CT is the choice modality for gastric cancer staging, it exposes patients to radiation. The accuracy of preoperative TNM staging in gastric cancer with MRI has been gradually improved and exhibited its superiority. Although gradient echo sequences show low linear signals in stomach and retinal layers, these signals disappear when the serosal infiltration of T3 cancer is applied. Therefore, the use of MRI for the preoperative staging of gastric cancer has become a predominant focus in recent years [7, 8].

DWI and gastric cancer

Table 1. MR sequences performed on patients with gastric cancer

Sequence	T2WI	DWI	e-THRIVE dynamic contrast enhanced
Plane	Axial	Axial	Axial
TR/TE (ms)	Shortest/80	3000/shortest	Shortest/shortest
Section thickness (mm)	5	5	4
Gap (mm)	1	1	1
FOV (cm)	36-40	36-40	36-40
NSA	2	2	1
Matrix	268×280	116×181	252×198
Fat suppression	None	Spectral inversion recovery	Spectral attenuated inversion recovery
Impulse sequence	Turbo spin-echo	Single-shot spin-echo echo-planar	T1 high-resolution isotropic volume excitation
Respiratory style	Respiratory-triggered	Free-breathing	Breath-holding

TR/TE: repetition time/echo time; FOV: field of view; NSA: number of signals averaged.

Diffusion-weighted imaging (DWI) is a variant of functional MRI, which measures the characteristics of water diffusion to reflect the integrity of cell membrane. It has been widely used in the management of patients with malignancies not only for diagnostic purposes but also for assessment and prediction of therapeutic responses and outcomes. Several studies have shown that apparent diffusion coefficient (ADC) might be useful as an imaging biomarker of assessing tumor aggressiveness [9-12]. For gastric cancer, it was shown that ADC is significantly related to pathological phenotypes, suggesting that it may be a biomarker to predict cancer aggressiveness clinically [7, 8].

This study was aimed to determine the relationship between ADC and pathological and immunohistochemical factors in gastric cancer, and to define the diagnostic cutoffs of ADC for TNM stage, histological type and differentiation grade of the cancer. The findings would provide new tool to diagnose gastric cancers and predict their biological behaviors following various therapies.

Material and methods

Patients

Ninety-seven consecutive patients were selected between September 2013 and October 2015 for this retrospective study. The included patients had histologically confirmed gastric cancer by gastroscopic biopsy at enrollment, undergone surgical resection without neoadjuvant therapy, with pathological reports of surgical specimens reporting the histological type and differentiation grade, primary MRI including DWI with tumor that are large enough (the

minimum diameter > 5 mm) to isolate the region of interest (ROI). Patients with poor DWI quality, such as artifacts (n = 8) and proven mucinous tumors (n = 5) were excluded.

Clinical and imaging data were retrieved from the patient database at the hospital. The study was approved by the Institutional Review Board of Affiliated Changshu Hospital of Soochow University and performed in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008. Written informed consent was obtained from each patient.

MRI technique

MR imaging was performed on all patients after fasting over eight hours to empty the gastrointestinal tracts. 10 mg of anisodamine (Mingsheng Pharmaceuticals Co., Ltd., Hangzhou, China) was given by intramuscular injection 10 minutes before the scan to reduce bowel peristalsis. Before anisodamine administration, the patients were interviewed to avoid those who are contraindicative to use anisodamine due to glaucoma, prostate gland hyperplasia and cardiac disease. Warm water (800-1000 ml) was orally administered within 5 min before MR imaging to fill the gastric cavity and the patients were instructed to breathe normally before MR scanning.

All patients were imaged with a 3T MRI scanner (Intera Achieva 3T, Philips Medical System, Best, The Netherlands) using a 16-channel phased-array surface coil positioned according to the tumor location. Patients were placed in the scanner in a supine position with the head scanned first. MR sequences are shown in

Table 2. Characteristics of patients and tumors used in this study

Group	N (%)
Age	63 (42-78) ^b
Gender	
Male	52 (61.9)
Female	32 (38.1)
TNM stage	
T ₁	5 (6)
T ₂	14 (16.7)
T ₃	50 (59.5)
T ₄	15 (17.9)
N ₀	32 (38.1)
N ₁	23 (27.4)
N ₂	8 (9.5)
N ₃	9 (10.7)
N ⁺ ^a	52 (61.9)
M ₀	76 (90.5)
M ₁	8 (9.5)
Histological type	
Poorly differentiated adenocarcinoma	44 (52.4)
Moderately differentiated adenocarcinoma	18 (21.4)
Well differentiated adenocarcinoma	8 (9.5)
Signet-ring cell carcinoma	14 (16.7)
Ki-67 LI	47 (13-64) ^b

^aTwelve specimens from palliative surgeries that could not completely meet the requirements for N staging were classified N⁺. ^bMedian (range).

Table 1; the b values of DWI were 0 and 1000 s/mm², respectively.

Histopathological analysis of the resected specimens was performed by a pathologist (Dr. Mei Wu), who was blinded to the MR findings. Pathologic reports were reviewed to determine the TNM stage, histological type and differentiation grade. Some specimens from the palliative surgeries that did not completely meet the requirements for N staging and were from lymph node-metastatic cancer were classified as N⁺. Histopathological staging of the tumors was performed based on the TNM classification of the American Joint Committee on Cancer (AJCC, 7th edition) [13].

Ki-67 labelling and analysis were performed as previously reported [14]. For immunohistochemical staining, the resected specimens were hydrated, washed in PBS, blocked with 3% BSA solution in the dark at room temperature for 30 min. The slides were then reacted to monoclonal antibody MIB-1 (dilution 1:200; Immunotech, Marseilles, France) at 4°C overnight. The slides were incubated with goat anti-rabbit horseradish peroxidase (HRP)-conjugated secondary antibody (1:5000, Santa Cruz

Biotechnology, USA), stained with diaminobenzidine and examined under a microscope. 1000 neoplastic nuclei in 10 randomly selected fields in each sample were examined for the presence or absence of distinct brown staining in the cytoplasm and the LI was calculated as percentage of the number of brown-colored cells over the total number of cells examined. Patients were divided into low or high expressers of Ki-67 antigen based on their median LI value as reported [15].

Image analysis

DWIs were loaded into a work station (Extended MR Workspace 2.6.3.4, Philips Medical Systems, Best, the Netherlands) and the corresponding ADC maps were

generated automatically. All MR images were carefully reviewed by two radiologists (Drs. Zhihua Lu and Libiao Ji), who had five and eight years of experience, respectively. The two radiologists were informed the locations of lesion but were blinded to other endoscopic and surgical pathological findings.

Mean ADC values were calculated for each sample in ROIs that were carefully selected within the solid parts of the lesion. The size and position of the ROIs were selected based on the consensus of two radiologists in connection with axial T2WIs and DWIs over the largest tumor area in a single section.

Statistical analysis

Correlation coefficient was calculated between Ki-67 LI and ADC value. To examine whether the ADC value is able to reflect histopathological difference, the differences in the ADC values between the different histopathological groups were tested using Student's t-test between low and high Ki-67 LI expressers and the Kruskal-Wallis test for patients with higher than third histopathological stages, types or differentiation grades. All the statistical analy-

Table 3. Relationships between ADC value and histological, and immunohistochemical factors

Group		n	Mean ADC (\pm SD)	P value
TNM stage	I	16	1.054 \pm 0.092	P = 0.000 ^a
	II	34	0.949 \pm 0.084	
	III	26	0.851 \pm 0.060	
	IV	8	0.893 \pm 0.061	
Histological type	Poorly differentiated adenocarcinoma	44	0.898 \pm 0.089	P = 0.000 ^a
	Moderately differentiated adenocarcinoma	18	0.964 \pm 0.075	
	Well differentiated adenocarcinoma	8	1.117 \pm 0.061	
	Signet-ring cell carcinoma	14	0.899 \pm 0.080	
Ki-67 LI	Low expression	32	0.988 \pm 0.104	P = 0.000 ^b
	High expression	32	0.874 \pm 0.076	

^aKruskal-Wallis test; ^bStudent's t-test.

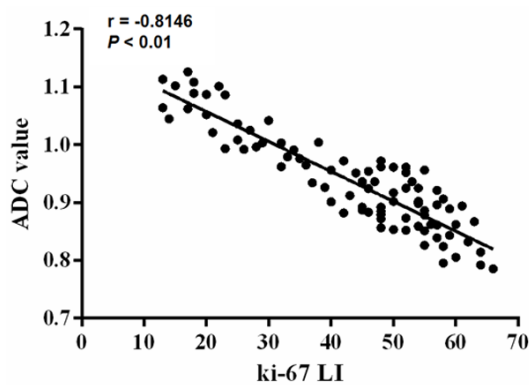


Figure 1. Correlation between ADC value and Ki-67 LI in 84 gastric cancers.

ses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Receiver operating characteristic curve (ROC) analysis was performed using the MedCalc software, and the diagnostic cutoffs of ADC value to distinguish TNM stage, histological type and differentiation grade were calculated. $P < 0.05$ was considered to be statistically significant.

Results

Clinical background

The final study population consisted of 84 patients with a median age of 63 years. The patient and tumor data are shown in **Table 2**. Among them, seventy-two patients underwent total or partial curative gastrectomy and 12 underwent palliative surgery (7 palliative resection and 5 partial gastrojejunostomy). Twelve specimens from the palliative surgery patients did not completely meet the requirements for N staging and were rated as N+. The histological types of the patients included adenocarcinoma

and signet-ring cell carcinoma. Based on the degree of differentiation, the carcinomas were classified as poorly, moderately and well differentiated adenocarcinomas and signet-ring cell carcinomas (**Table 2**).

Relationships between ADC value and histological or immunohistochemical factors

Correlations between the ADC value and histological or immunohistochemical factors were calculated (**Table 3**). Sixty-four patients were positive for Ki-67 antigen, accounting for 76.2% (64/84) of the study population, and the median Ki-67 LI was 47%. Based on the median value, the patients were divided into low expresser (Ki-67 LI < 47%) and high expresser (Ki-67 LI \geq 47%). Analyses showed that there were significant differences in the ADC values among TNM stages, histological types and Ki-67 LI (**Table 3**). ADC value was found inversely correlated with the Ki-67 LI ($r = -0.8146$, $P < 0.01$, **Figure 1**). Mean ADC values were significantly lower in patients with higher TNM stage, poorly differentiated adenocarcinoma or signet-ring cell carcinoma, and in cancer with elevated Ki-67 LI (**Figures 2-4**). The diagnostic cutoffs of ADC values to distinguish TNM stage, histological type and Ki-67 LI are shown in **Table 4**. We used these cutoffs to determine TNM stage, histological type and Ki-67 LI in the patients and the results are shown in **Table 4**. The sensitivities and specificities of the predictions were between 90.6 and 92.1% and 59.4 and 100%, respectively.

Discussion

Gastric cancer is heterogeneous tumor with poor prognosis that has variable behaviors,

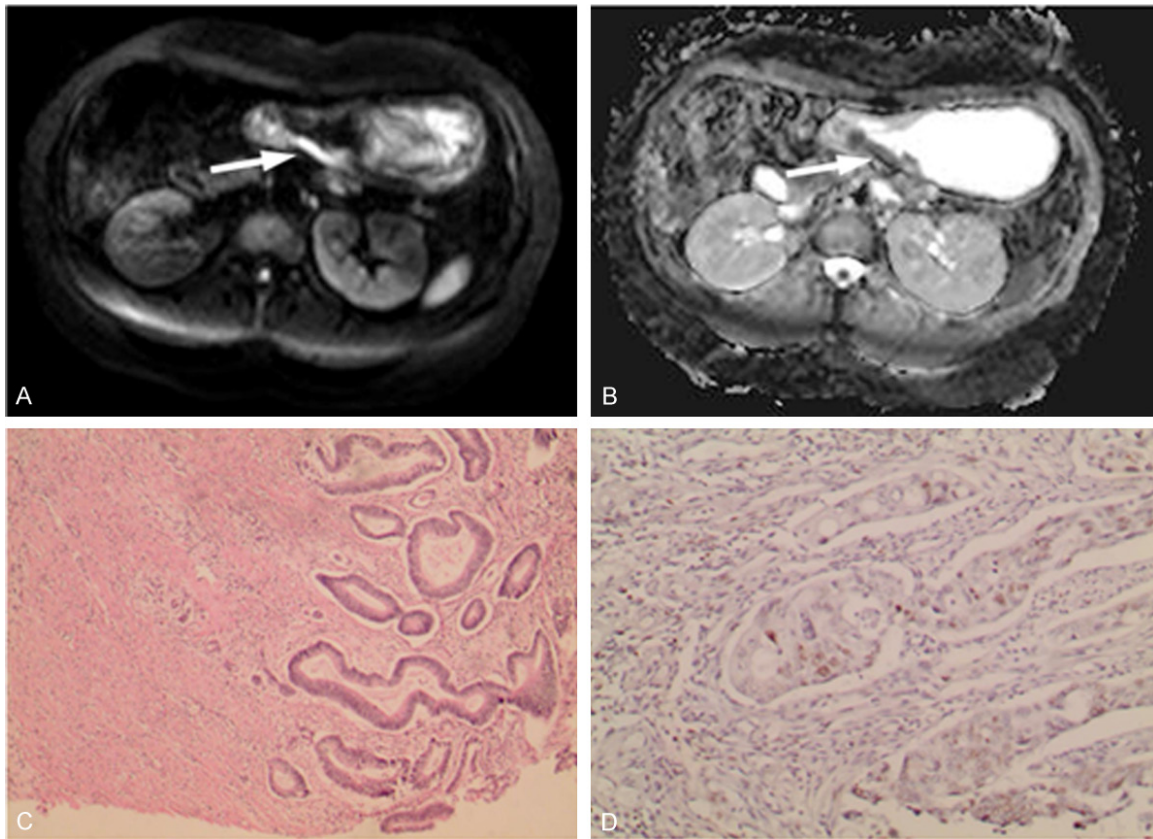


Figure 2. A sample of well differentiated adenocarcinoma pathologically diagnosed at stage $T_3N_0M_0$. A. Axial DWI showing the lesion with high signal intensity (SI) at the angulus of stomach (arrow); B. Corresponding ADC map showing the lesion as low SI (arrow) with a mean ADC value of $1.166 \times 10^{-3} \text{ mm}^2/\text{s}$; C. Micrograph of hematoxylin & eosin-stained well differentiated adenocarcinoma at a magnification of 200; D. Ki-67 staining of the tumor with a labelling index of 25% (magnification $\times 400$).

outcomes, and treatment responses. Many efforts have been made to predict the biological behaviors of the tumor for better treatment and prognosis. Classically, pathological factors such as TNM stage, histological type and differentiation grade, as well as immunohistochemical biomarkers, are frequently used for this purpose. Recently, several studies have shown that DWI may provide both morphological and functional indications that can be used to reflect the tumor biological behaviors by using the ADC value [9-12]. Therefore, DWI could potentially be useful as an imaging tool to assess tumor aggressiveness. Our results show that lower ADC values are strongly associated with higher TNM stage, poorly differentiated adenocarcinoma or signet-ring cell carcinoma, and with elevated Ki-67 LI.

Numerous clinicopathological factors may influence the prognosis of gastric cancer. TNM

staging can objectively reflect tumor biological behavior and disease progression, and has been well confirmed for its value in predicting prognosis of gastric cancer. In this study, we find that ADC value decreased with the increase in TNM stage, and varied significantly among different TNM stages. We speculate that after gastric mucosal epithelium damage, tumor cells are gradually enlarged and increase in number, while the nucleus/cytoplasm ratio increases as the depth of infiltration into stomach wall increases and lymph node metastasis occurs. As such, the space for water molecules to diffuse becomes smaller, leading to variation in the ADC value. ROC curve analysis reveals that AUC in stage I gastric cancer was 0.881 by cutting at a b value of $1.025 \times 10^{-3} \text{ mm}^2/\text{s}$. The mean ADC values in stage III and IV gastric cancer were similar, which may be due to the fact that there were more metastatic gastric cancer patients who received preoperative chemother-

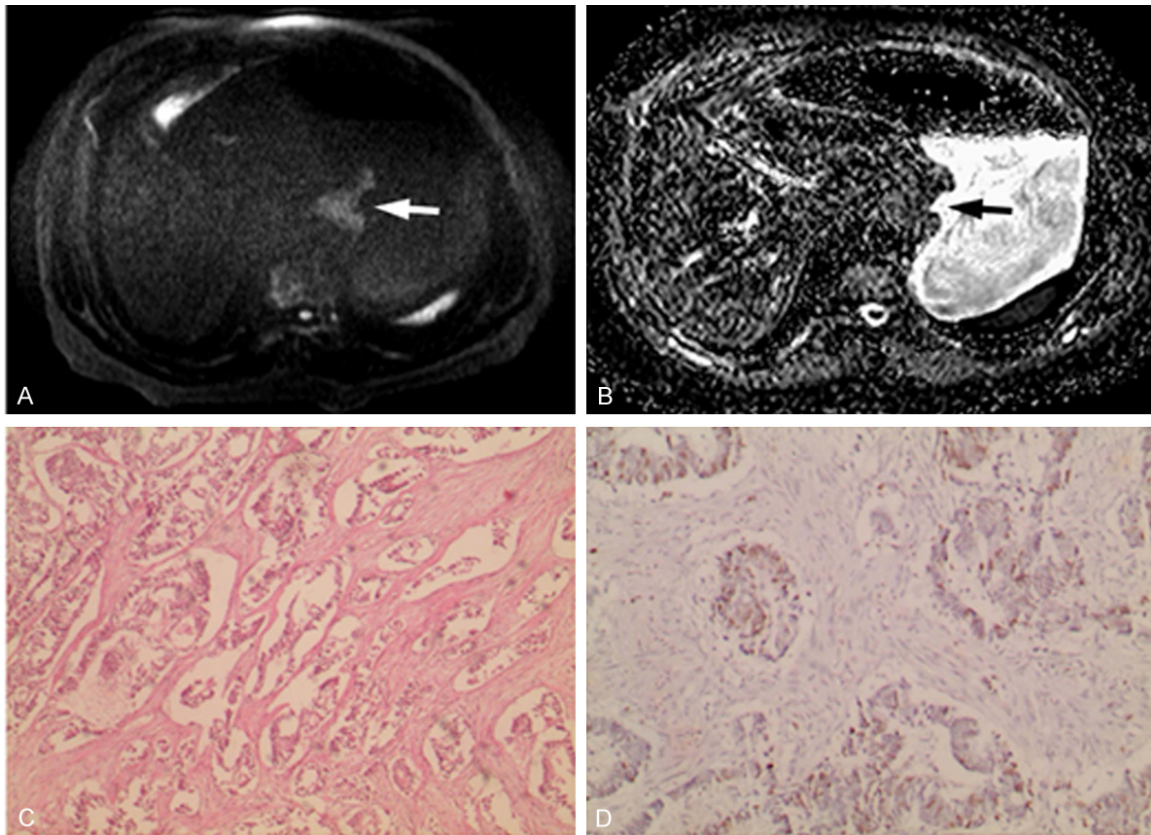


Figure 3. A sample of moderately differentiated adenocarcinoma pathologically diagnosed at stage $T_3N_0M_0$. A. Axial DWI showing the lesion with high signal intensity (SI) at the angulus of stomach (arrow); B. Corresponding ADC map showing the lesion as low SI (arrow) with a mean ADC value of $0.946 \times 10^{-3} \text{ mm}^2/\text{s}$; C. Micrograph of hematoxylin & eosin-stained well differentiated adenocarcinoma at a magnification of 200; D. Ki-67 staining of the tumor with a labelling index of 42% (magnification $\times 400$).

apy, resulting in fewer enrolled patients at M_1 stage. Our analysis shows that the patients with lower ADC value were at higher TNM stage, suggesting that this indicator can be used to screen patients for chemotherapy.

We find that mean ADC value declined at lower differentiation stage of adenocarcinoma. This may be attributed to increased density of tumor cell, higher nucleus/cytoplasm ratio and reduced intercellular space. In addition, signet-ring cell carcinoma was found to have lower mean ADC value with poorly differentiated adenocarcinoma (0.899 vs. 0.898). The cell size, density, and nucleus/cytoplasm ratio of Signet-ring cell carcinoma were similar to those of poorly differentiated adenocarcinoma, thus having similar ADC value. Clinicopathological study has confirmed that both signet-ring cell carcinoma and poorly differentiated adenocarcinoma have the worse prognosis [16]. Similar with early works [7], our findings demonstrate that ADC

value can reflect tumor pathological histological characteristics. ROC curve analysis shows that that sensitivity to diagnose well-differentiated adenocarcinoma is 92.1% with a specificity of 100%, and AUC is 0.976 at cutoff value of $1.042 \times 10^{-3} \text{ mm}^2/\text{s}$.

Integration of immunohistochemical features into risk stratification schemes is desirable in clinical practices because they offer may important information regarding tumor apoptosis and proliferation during antitumor therapy [17]. Tumor proliferation rate is a key prognostic factor. Ki-67 is a nuclear antigen that is generated during the proliferative phase of cell cycle and plays important roles in apoptosis and tumor proliferation related to prognosis [15]. In this study, we also analyzed the correlation between ADC values and Ki-67 LI. We find that with increased mitotic activity, there were more heterochromatin and higher nucleus/cytoplasm ratio, which probably results in reduced water

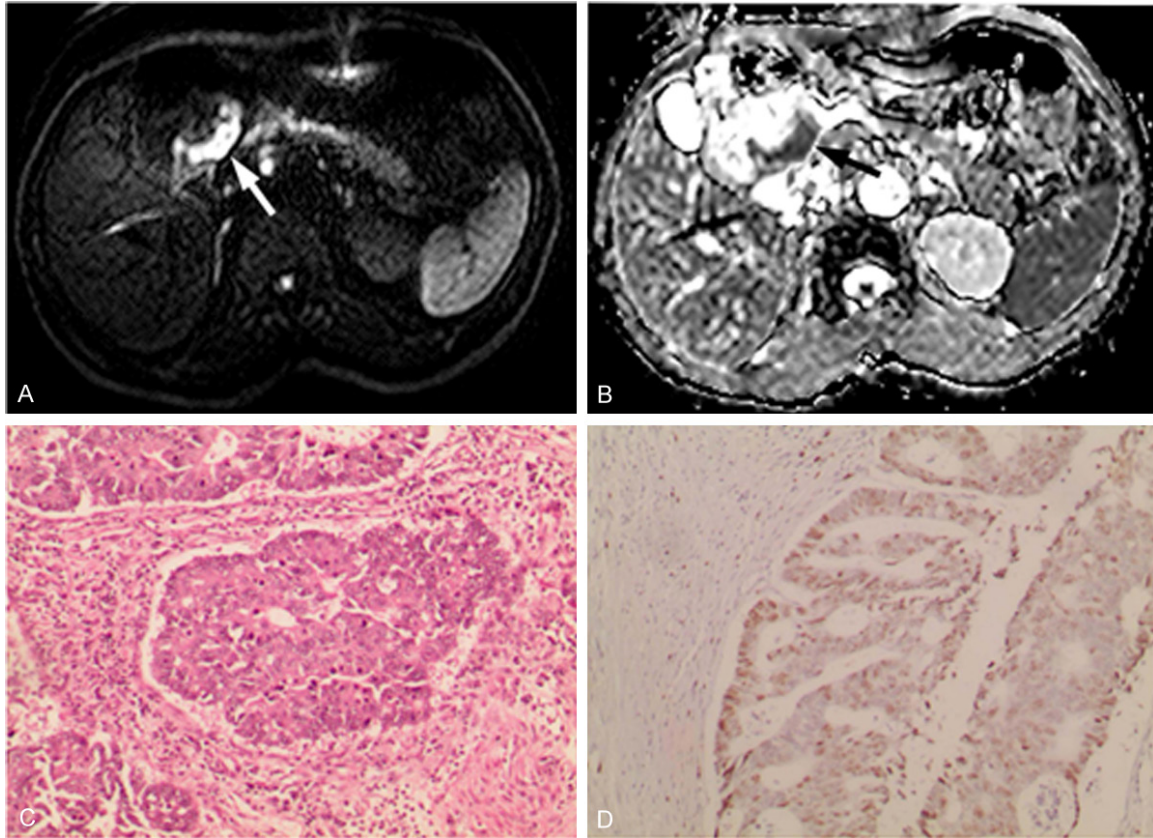


Figure 4. A sample of poorly differentiated adenocarcinoma pathologically diagnosed at stage T₃N₁M₀. A. Axial DWI showing the lesion with high signal intensity (SI) at the angulus of stomach (arrow); B. Corresponding ADC map showing the lesion as low SI (arrow) with a mean ADC value of 0.732×10⁻³ mm²/s; C. Micrograph of hematoxylin & eosin-stained well differentiated adenocarcinoma at a magnification of 200; D. Ki-67 staining of the tumor with a labelling index of 60% (magnification ×400).

Table 4. Diagnostic cutoff of ADC value to distinguish TNM stages, histological type, and Ki-67 LI

Group	Cut off	Sensitivity	Specificity	AUC	P value
Stage I/stage II to IV	1.025	91.2%	68.7%	0.881	< 0.0001
Well/non-well differentiated adenocarcinoma	1.042	92.1%	100%	0.976	< 0.0001
Low/high Ki-67 expression	0.961	90.6%	59.4%	0.805	< 0.0001

diffusivity and lower ADC value [18]. Several studies show that there are negative correlations between ADC value and Ki-67 LI in rectal cancer and bladder cancer [15, 19], although the relationship was unclear for gastric cancer. We find that ADC value is negatively correlated with Ki-67 LI. Although patients may be divided into low and high expressers for Ki-67 LI, there are still significant difference in ADC value within the low and high expressers. Nevertheless, we demonstrate that an ADC value and AUC of 0.961×10⁻³ mm²/s and 0.805 are a cutoff for lower expresser.

This study still has some limitations. Since mucous adenocarcinomas can produce a large number of myxoid substances, they are different from regular gastric cancers and have higher ADC value. They were excluded in this study. However, this results in reduced representation of our results over diverse cancers. Furthermore, as a retrospective study, most of the enrolled cases were poorly differentiated adenocarcinoma, leading to imbalanced case distribution. Finally, the partial volume effect of the liquid in the gastric lumen may affect ADC value accuracy for the small lesions. Since DWI thickness

was 5 mm in our study, the ADC values may be affected by partial volume effect for lesions less than 10 mm.

To sum up, we show that Ki-67 LI is significantly and negatively correlated with ADC value in gastric cancer; lower ADC values are strongly associated with higher TNM staging, lower differentiation degree, or signet-ring cell carcinoma, and with elevated Ki-67 LI. Our results demonstrate that ADC value could be useful as a noninvasive biomarker to predict the pathologic histological characteristics in gastric cancer.

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Disclosure of conflict of interest

None.

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References

- [1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90.
- [2] Saricanbaz I, Karahacioglu E, Ekinci O, Bora H, Kilic D and Akmansu M. Prognostic significance of expression of CD133 and Ki-67 in gastric cancer. *Asian Pac J Cancer Prev* 2014; 15: 8215-8219.
- [3] Ayed DB, Khabir A, Abid M, Bayroui MI, Gargouri A, Sellami-Boudawara T and Mokdad-Gargouri R. Clinicopathological and prognostic significance of p53, Ki-67, and Bcl-2 expression in Tunisian gastric adenocarcinomas. *Acta Histochem* 2014; 116: 1244-1250.
- [4] Calik M, Demirci E, Altun E, Calik I, Gundogdu OB, Gursan N, Gundogdu B and Albayrak M. Clinicopathological importance of Ki-67, p27, and p53 expression in gastric cancer. *Turk J Med Sci* 2015; 45: 118-128.
- [5] Gerdes J, Schwab U, Lemke H and Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. *Int J Cancer* 1983; 31: 13-20.
- [6] Sendler A, Gilbertz KP, Becker I, Mueller J, Berger U, Fink U, van Beuningen D and Siewert JR. Proliferation kinetics and prognosis in gastric cancer after resection. *Eur J Cancer* 2001; 37: 1635-1641.
- [7] Liu S, Guan W, Wang H, Pan L, Zhou Z, Yu H, Liu T, Yang X, He J and Zhou Z. Apparent diffusion coefficient value of gastric cancer by diffusion-weighted imaging: correlations with the histological differentiation and Lauren classification. *Eur J Radiol* 2014; 83: 2122-2128.
- [8] Liu S, Wang H, Guan W, Pan L, Zhou Z, Yu H, Liu T, Yang X, He J and Zhou Z. Preoperative apparent diffusion coefficient value of gastric cancer by diffusion-weighted imaging: correlations with postoperative TNM staging. *J Magn Reson Imaging* 2015; 42: 837-843.
- [9] Miller FH, Hammond N, Siddiqi AJ, Shroff S, Khatri G, Wang Y, Merrick LB and Nikolaidis P. Utility of diffusion-weighted MRI in distinguishing benign and malignant hepatic lesions. *J Magn Reson Imaging* 2010; 32: 138-147.
- [10] Kobayashi S, Koga F, Yoshida S, Masuda H, Ishii C, Tanaka H, Komai Y, Yokoyama M, Saito K, Fujii Y, Kawakami S and Kihara K. Diagnostic performance of diffusion-weighted magnetic resonance imaging in bladder cancer: potential utility of apparent diffusion coefficient values as a biomarker to predict clinical aggressiveness. *Eur Radiol* 2011; 21: 2178-2186.
- [11] Verma S, Rajesh A, Morales H, Lemen L, Bills G, Delworth M, Gaitonde K, Ying J, Samartunga R and Lamba M. Assessment of aggressiveness of prostate cancer: correlation of apparent diffusion coefficient with histologic grade after radical prostatectomy. *AJR Am J Roentgenol* 2011; 196: 374-381.
- [12] Costantini M, Belli P, Rinaldi P, Bufi E, Giardina G, Franceschini G, Petrone G and Bonomo L. Diffusion-weighted imaging in breast cancer: relationship between apparent diffusion coefficient and tumour aggressiveness. *Clin Radiol* 2010; 62: 1005-1012.
- [13] Washington K. 7th edition of the AJCC cancer staging manual: stomach. *Ann Surg Oncol* 2010; 17: 3077-3079.
- [14] Bae H, Yoshida S, Matsuoka Y, Nakajima H, Ito E, Tanaka H, Oya M, Nakayama T, Takeshita H, Kijima T, Ishioka J, Numao N, Koga F, Saito K, Akashi T, Fujii Y, Kihara K. Apparent diffusion coefficient value as a biomarker reflecting morphological and biological features of prostate cancer. *Int Urol Nephrol* 2014; 46: 555-561.
- [15] Kobayashi S, Koga F, Kajino K, Yoshita S, Ishii C, Tanaka H, Saito K, Masuda H, Fujii Y, Yamada T and Kihara K. Apparent diffusion coefficient value reflects invasive and proliferative potential of bladder cancer. *J Magn Reson Imaging* 2014; 39: 172-178.

DWI and gastric cancer

- [16] Adachi Y, Yasuda K, Inomata M, Sato K, Shirai-shi N and Kitano S. Pathology and prognosis of gastric carcinoma: well versus poorly differentiated type. *Cancer* 2000; 89: 1418-1424.
- [17] Mesko S, Kupelian P, Demanes DJ, Huang J, Wang PC and Kamrava M. Quantifying the ki-67 heterogeneity profile in prostate cancer. *Prostate Cancer* 2013; 2013: 717080.
- [18] Zhang XY, Sun YS, Tang L, Xue WC and Zhang XP. Correlation of diffusion-weighted imaging data with apoptotic and proliferation indexes in CT26 colorectal tumor homografts in balb/c mouse. *J Magn Reson Imaging* 2011; 33: 1171-1176.
- [19] Sun Y, Tong T, Cai S, Bi R, Xin C, Gu Y. Apparent diffusion coefficient (ADC) value: a potential imaging biomarker that reflects the biological features of rectal cancer. *PLoS One* 2014; 9: e109371.