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Original Article

Lymph node metastasis in patients with gastric cancer: a multi-modality, morphologic and functional imaging study

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Abstract: The aim of the study was to investigate the value of computed tomography (CT), magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI) for diagnosing lymph nodes metastasis before treatment in gastric cancer. Eighty-two patients with proven gastric cancer underwent CT, morphological MRI (T2WI) and DWI examinations. Two radiologists independently assessed these images for the presence of lymph nodes involvement. Pathologic findings were considered as "gold standard". Independent samples *t*-test was used for the comparisons of short diameters and ADC values between the positive lymph nodes and the negative lymph nodes. Diagnostic accuracy of these three imaging modalities was evaluated by area under the receiver operating characteristics (ROC) curve (AUC). The ADC value of the positive lymph nodes was (1.15 ± 0.01) × 10^{-3} mm^2/s, which was significantly lower than that of the negative lymph nodes (1.48 ± 0.01) × 10^{-3} mm^2/s (t = 18.70, P < 0.0001). The short diameter of the positive lymph nodes (1.54 ± 0.38 cm) was significantly greater than that of the negative lymph nodes (0.95 ± 0.12 mm) (t = 19.03, P < 0.001). The AUC for all imaging modalities combined (0.893) was significantly larger than that for each imaging modality alone (P < 0.05), and the AUC of DWI (0.797) was significantly larger than (P < 0.05) that of morphological MRI (0.733). There was no statistically significant difference between the AUCs of CT and morphological MRI (P = 0.462). In conclusion, CT, MRI and DWI combined present significantly higher accuracy than each imaging modality alone in the detection of lymph nodes involvement.

Keywords: Stomach neoplasms, lymph nodes, tomography, X-Ray computed, magnetic resonance imaging, diffusion weighted imaging, apparent diffusion coefficient

Introduction

Gastric cancer is the second most common malignancy following lung cancer worldwide [1, 2]. For patients especially in advanced stage, gastric cancer has a terrible influence on the quality of life due to the bad prognosis, which is determined by the tumor-node-metastasis (TNM) staging system [3, 4]. In particular, lymph node status has been established as one of the most important criteria for proper treatment strategy and prognosis of gastric cancer preoperatively [4, 5].

It has been reported that evaluations based only on computed tomography (CT) or morphological magnetic resonance imaging (MRI) are not sufficient evidence for the diagnosis of metastatic lymph nodes due to the relatively low detection rate [6-9]. Diffusion weighted imaging (DWI) is a valuable sequence used to define disease involvement. It can provide better characterization of soft tissues at a microscopic level and therefore reflect the pathological processes [10-12]. Several recent studies reported that DWI was a useful determinant in discriminating metastatic from benign lymph nodes in patients with gastric cancer [9], assessing preoperative or postoperative TNM staging accuracy [13, 14], and monitoring the response to treatment in local advanced gastric cancer [15]. However, there have been no prior studies that compared the diagnostic accuracies of CT, morphological MRI and DWI focused on the detec-

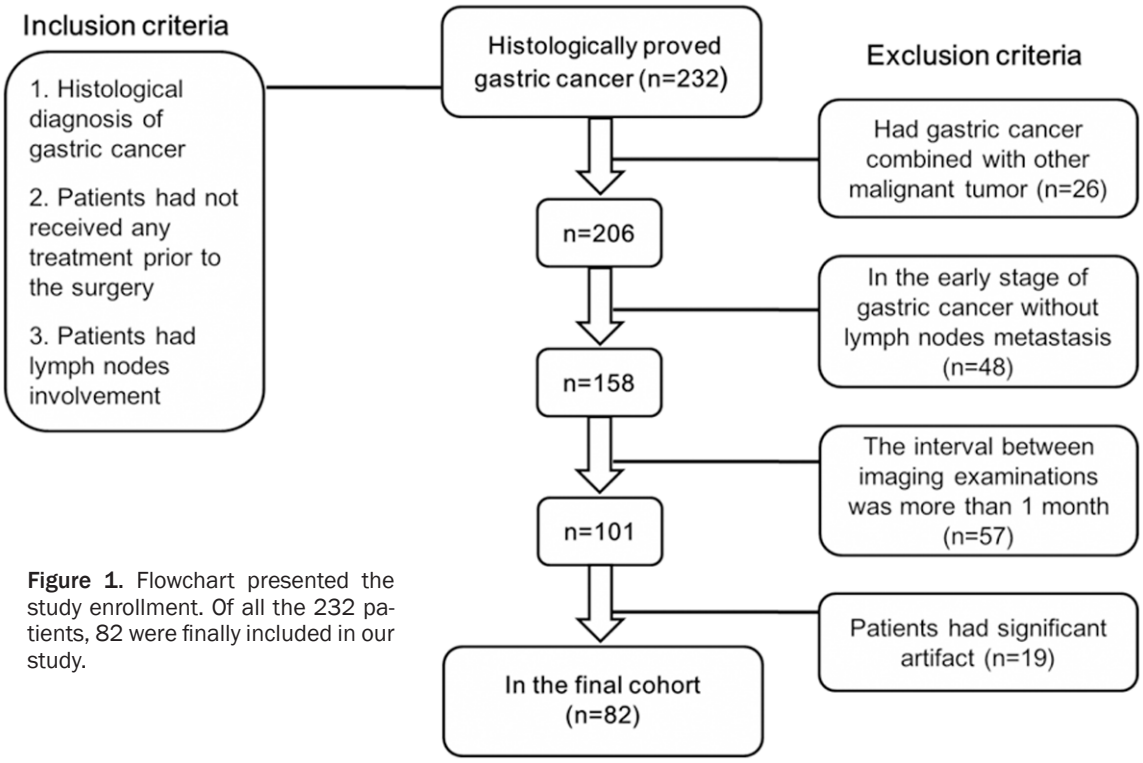

Figure 1. Flowchart presented the study enrollment. Of all the 232 patients, 82 were finally included in our study.

tion of metastatic lymph nodes. Hence, the purpose of our study is to compare the diagnostic accuracies of the three imaging modalities, CT, morphological MRI and DWI, for the detection of lymph nodes in patients with gastric cancer.

Materials and methods

Patient population

This study has received the institutional review board approval and a waiver of informed consent was obtained. From February 2014 to October 2015, 232 patients who underwent both CT and MRI examination in our hospital were pathologically confirmed gastric cancer. Among these cases, 82 patients (mean age 52 years, range 24-77; 65 male with a mean age of 57 years and age range of 24-77 years; 17 female with a mean age of 46 years and age range of 28-73 years) were finally enrolled based on the inclusion criteria: 1. Histological diagnosis of gastric cancer; 2. Patients had not received any treatment prior to the surgery; 3. Patients had lymph nodes metastasis. Finally, 150 patients were excluded due to various reasons: 1. Patients had gastric cancer combined with other malignant tumor (n = 26); 2. Patients were in the early stage of gastric cancer without lymph nodes metastasis (n = 48); 3. The interval between CT and MRI examinations for the same patient was more than one month (n = 57); 4. Images of the patients had significant artifact (n = 19). The case accrual process of this study is presented in **Figure 1**.

Imaging examination

Both CT and MRI examination were performed as routine examinations within two weeks before the surgery.

All CT scans were obtained with the dual-source computed tomography (DSCT) scanner (Somatom Definition Flash, Siemens Healthcare). Both unenhanced and contrast-enhanced CT images were obtained for all patients. Each patient was required to fast for at least 4 hours and drink 500 mL of tap water half an hour before procedure. 10 mg of intramuscular raceanisodamine hydrochloride injection was administered 15 minutes before the examination to reduce peristaltic bowel movement. CT scan was started at the level of the dome of the right hemidiaphragm to include the entire liver. All patients received an intravenous infusion of

nonionic iodinated contrast agent Iopamidol 370 at a flow rate of 3 mL/s by using a power injection. Contrast-enhanced CT scanning was started 45 s after initiation of the intravenous administration of contrast medium. The scanning parameters were: tube voltage of 120 KVp, tube current-time product of 280 mAs, section thickness of 5 mm, reconstruction interval of 5 mm, gantry rotation time of 0.5 s, pitch of 0.6 and a collimation of 64 × 1.2 mm. After scanning, the raw data were sent to a dedicated DSCT post processing workstation and reconstructed into axial, coronal and sagittal images with a 5-mm section thickness and a 5-mm interval.

MR examination was performed on a 3.0T MRI scanner (Siemens Magnetom Tim Trio MRI) using an 18-channel surface phased-array body coil. Before MR scanning, patients were asked to fast for 4-6 hours and ingest 500 ml of tap water for a distension of the stomach; and 15 minutes prior to the examination, 10 mg of raceanisodamine hydrochloride was intramuscularly administered. All patients underwent (1) axial T2-weighted TSE sequences (TR/TE 2000/81.0 ms; field of view 350 mm; slice thickness 5 mm with 1 mm interslice gap; flip angle 140°; one excitation and 30 slices in total), (2) DWI (TR/TE 7400/66 ms; field of view 380 mm; slice thickness 4 mm with 1 mm interslice gap; eight excitations; 80 slices; water excitation with *b*-values of 0 and 1000 s/mm^2). After the examination, all data were sent to a dedicated MRI (Leonardo; Siemens) image processing workstation for further analysis.

Image analysis

The retrospective analysis of images was performed by two abdominal radiologists, each with more than 10 years' experience in CT and MRI. The two radiologists independently reviewed the acquired CT and MR images without knowledge of the surgical and pathological findings of the resected lymph nodes. The third experienced radiologist with 20 years CT and MR expertise reviewed the images and made the decision in consensus when the former two observers had a disagreement in reading images. All CT and MR images were analyzed through picture archiving and communication system (PACS) monitors. The shape, border, short-axis diameter, CT attenuation, enhancement pattern, signal intensity and apparent diffusion coefficient (ADC) value of lymph nodes in CT and/or MRI were measured and recorded. The main diagnostic criteria used by the radiologists to determine the lymph nodes metastasis were as followed: lymph nodes were larger than 5 mm in the short-axis diameter, and/or showed central necrosis and/or indistinct nodal border and/or comparatively high density in contrast medium enhancement and/or showed iso-high/high signal intensity in DWI and iso-low/low signal intensity on ADC map [6, 16-20]. For each individual image examination, one author independently scored the likelihood of lymph nodes metastasis on a confidence level scale of 1-5 (1 = no lymph nodes metastasis, 2 = probably no lymph nodes metastasis, 3 = possible lymph nodes metastasis, 4 = probably lymph nodes metastasis, and 5 = definite lymph nodes metastasis) [21, 22]. With the reference of the morphological MR images, lymph nodes were identified on the DWI. A region of interest (ROI) was marked on the largest slice of each lymph node on the DW image (b = 0 mm/sec^2) as a reference. Then the ROI was pasted on the ADC map which was automatically generated in the workstation, with b = 1000 mm/sec^2. The ADC values were calculated by pixel-by-pixel monoexponential relationship ADC = log $(SI_0\text{-}SI_1)/b_1\text{-}b_0$ [23], where SI_0 and SI_1 were the signal intensity at b-value of b_0 = 0 and b_1 = 1000 sec/mm^2, respectively. The ADC value of each lymph node was calculated twice for accuracy. Special attention was paid to avoid the areas of focal signal intensity changes, susceptibility artifacts and necrosis.

The diagnostic accuracy of metastatic lymph nodes of gastric cancer was evaluated through CT and MRI, compared with the reference standard and the pathologic and surgical results.

Histopathological evolution

Patients underwent the extended lymphadenectomy procedure, which included total resection of lymph nodes in metastatic N1 and N2 stations, during which perigastric nodes (N1 station) in addition to the lymph nodes around the left gastric artery, the common hepatic artery, the coeliac axis, the splenic hilus and the splenic artery (N2 station) were removed [24, 25]. Moreover, primary tumor and perigas-

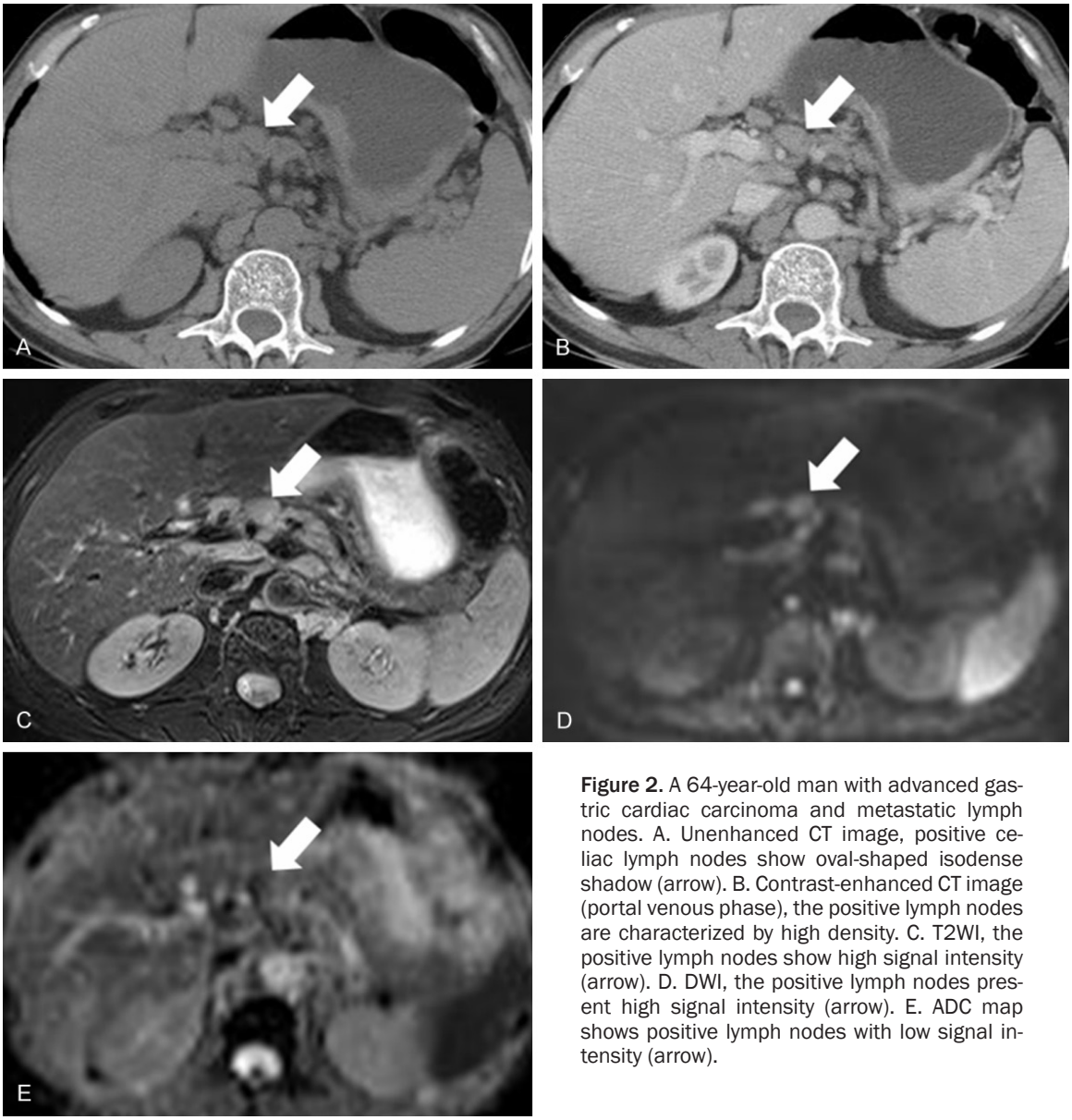

Figure 2. A 64-year-old man with advanced gastric cardiac carcinoma and metastatic lymph nodes. A. Unenhanced CT image, positive celiac lymph nodes show oval-shaped isodense shadow (arrow). B. Contrast-enhanced CT image (portal venous phase), the positive lymph nodes are characterized by high density. C. T2WI, the positive lymph nodes show high signal intensity (arrow). D. DWI, the positive lymph nodes present high signal intensity (arrow). E. ADC map shows positive lymph nodes with low signal intensity (arrow).

tric fat mixed with lymph nodes were dissected, as well.

A total of 2107 lymph nodes were resected in 82 patients and sent to the Department of Pathology in our hospital for further analysis. The specimens of lymph nodes were fixed in 4% neutral buffered formalin solution for 24 h, embedded in paraffin and then sectioned at a thickness of 5 μm. A careful search was made in each paraffin-slice of the lymph nodes to preferably confirm presence of metastasis. Each lymph node in pathologic examination was matched to the corresponding node visible on the CT and/or MRI ensured by the two radiologists mentioned above and an experienced pathologist (with 10 years of experience).

Statistical analysis

Interobserver agreement for nodal ADC value and short diameter measurements between the two radiologists was analyzed by calculating the intra-class correlation coefficient (ICC). Independent samples *t*-test was used for the comparisons of short diameters and ADC values between the positive lymph nodes and the negative lymph nodes. Receiver operating characteristics (ROC) curve analysis was employed for all imaging variables to predict lymph nodes

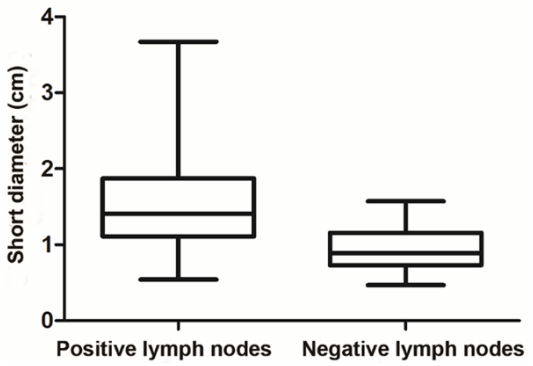

Figure 3. Box and whisker plot comparing the mean short diameter between the positive lymph nodes and the negative lymph nodes. The mean short diameter of the positive lymph nodes was significantly longer than those of the negative lymph nodes. The middle line represents the median. The central box represents the measurements from the lower to the upper quartile (25-75 percentiles). Whiskers indicate the range from the maximum to the minimum calculated the short diameter measurements.

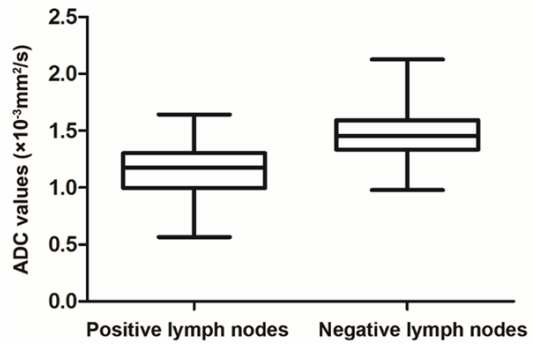

Figure 4. Box and whisker plot comparing the mean ADC value between the positive lymph nodes and the negative lymph nodes, respectively. The mean ADC value of positive lymph nodes was significantly lower than that of negative lymph nodes.

metastasis. The area under the ROC curve (AUC) was evaluated for models of lymph nodes metastasis prediction on the basis of the CT alone, morphological MRI alone and DWI alone. In addition, a model was constructed for all the prediction of lymph nodes metastasis on the basis of the three imaging modalities combined. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for predicting lymph nodes metastasis were calculated with 95% confidence intervals (95% CI). Statistical analyses were performed by using *Z* test. A *P* value less than 0.05 was considered statistically significant. All analyses were performed using SPSS statistical software program (Version 17.0 for Windows; SPSS, Inc., IL, USA).

Results

Inter-observer agreement in imaging analysis

The measurements in CT and MRI had good inter-observer reproducibility. Of all the lymph nodes in the positive group and the negative group, the agreement between the two observers was obtained in the ADC values and short diameters measurements with ICC of 0.861 (95% CI, 0.813-0.929) and 0.844 (95% CI, 0.791-0.915), respectively.

Imaging and pathologic results

After the CT and MRI examination, all patients underwent radical gastrectomy with extended lymphadenectomy procedure. Based on the identified 16 lymph nodes compartments (stations) surrounding stomach according to the guidelines of the Japanese Research Society for Gastric Cancer [24], positive group (472 LNs, 56 compartments, lymph nodes in each compartment were all metastatic based on the histopathology) and negative group (832 LNs, 167 compartments, LNs in each compartment were all non-metastatic based on the histopathology) were included and analyzed among all resected lymph nodes in our study. Representative case of the lymph nodes detected respectively by the three imaging modalities was showed in **Figure 2**.

Comparison of ADC values and short diameters between positive lymph nodes and negative lymph nodes

The ADC value of the positive lymph nodes was $(1.15 \pm 0.01) \times 10^{-3}$ mm^2/s, which was significantly lower than that of the negative lymph nodes $(1.48 \pm 0.01) \times 10^{-3}$ mm^2/s ($t = 18.70$, $P < 0.0001$). In addition, the short diameter of the positive lymph nodes (1.54 ± 0.38 cm) was significantly greater than that of the negative lymph nodes (0.95 ± 0.12 mm) ($t = 19.03$, $P < 0.001$) (**Figures 3**, **4**).

Evaluation of lymph node metastasis in CT, morphological MRI and DWI

The sensitivity, specificity, PPV, NPV and AUC of each imaging modality for detection of the posi-

Table 1. Sensitivity, specificity, PPV, NPV and AUC for detection of metastatic lymph nodes for each imaging modality

Imaging Modality	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
DSCT	72.7	66.7	61.6	76.9	0.753 (0.614 to 0.862)
Morphological MRI	72.7	70.0	64.0	77.8	0.733 (0.592 to 0.846)
DWI	77.3	70.0	65.4	80.8	0.797 (0.663 to 0.896)
All images combined	86.4	76.7	73.1	88.5	0.893 (0.776 to 0.962)

Note: In sensitivity, specificity, PPV and NPV, data are percentages.

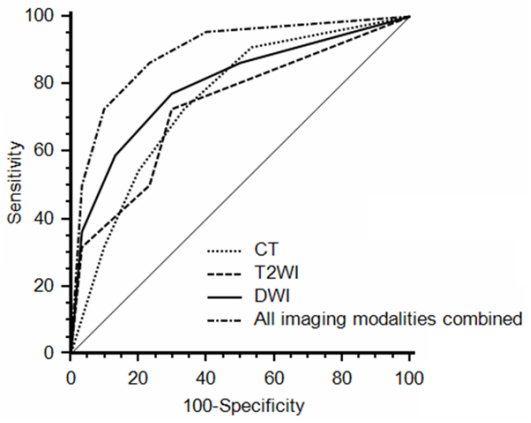

Figure 5. ROC curves for detection of lymph nodes involvement. The AUC of all imaging modalities combined (0.893, 95% CI: 0.776-0.962) was significantly larger than that of CT alone (0.753, 95% CI: 0.614-0.862) or morphological MRI alone (0.733, 95% CI: 0.592-0.846) or DWI alone (0.797, 95% CI: 0.663-0.896) ($P < 0.05$).

tive lymph nodes were showed in **Table 1**. The AUC of all images combined (0.893, 95% CI: 0.776-0.962) was significantly larger than that of CT images alone (0.753, 95% CI: 0.614-0.862) or morphological MR images alone (0.733, 95% CI: 0.592-0.846) or DW images alone (0.797, 95% CI: 0.663-0.896) ($z = 3.999$, 3.903 and 3.114, respectively, $P < 0.05$). DWI demonstrated greater diagnostic performance compared with morphological MRI ($z = 2.668$, $P < 0.05$). There was no significant statistical difference between the AUCs of CT and morphological MRI. ($z = 0.736$, $P = 0.462$, **Figure 5**).

Discussion

Gastric cancer is a common malignancy in the worldwide. Early-stage localized diseases can be cured by gastrectomy combined with extended lymphadenectomy (D2) [26, 27]; however, diseases at an advanced stage usually show local recurrence and/or distant metastases several years after the surgery. Not only the depth or extent of primary tumor invasion but also lymph node metastasis has been shown to be an important indicative factor that affects prognosis and treatment planning [5]. The presence of lymph node metastases is related with a reduction of the five year survival rate, despite the integration of adjuvant therapy to the surgery.

The conventional evaluation of lymph nodes involvement, like CT or morphological MRI, has been based mainly on morphological criteria (nodal size, border irregularity, configuration et al.). In gastrointestinal tumors, for instance, the widely accepted size criterion for lymph node metastasis is larger than 10 mm in diameter [28]. However, the accuracy of the criteria is insufficient, leading to the occurrence of false-positive or false-negative results, which has been shown to be a poor discriminator in differentiating metastatic from benign lymph nodes, especially when lymph nodes are in similar sizes. Accordingly, functional imaging is becoming increasingly essential in evaluation of lymph node metastasis [29].

DWI is a functional imaging technique whose contrast derives from the random motion of water molecules within tissues in vivo [10-12] and therefore considered to be a more ideal imaging modality. Cheng et al. [9] evaluated, by rigorous lesion-by-lesion pathologic-radiologic correlation, the accuracy of DWI and morphological MRI in nodal discrimination in gastric cancer, and showed DWI could provide great potential in effective discrimination of metastatic lymph nodes in gastric carcinoma. The characteristics of DWI on degree of restriction to water diffusion are partly related to the tissue cellularity and the integrity of cell membranes. The histopathological characteristics of malignancy are high cellular density correlated with numerous intact cell membranes. These features could diminish both the extracellular and intracellular spaces, and therefore cause a decrease in ADC values [10-12]. In addition to the high cellular density, fibrosis and peritumoral nodal immunoreactivity prob-

ably have contributed to the restricted water diffusion [30, 31]. In contrast, the ADC values of the benign lesions are usually on the high side exactly due to low cellularity compared with the former [10].

In our study, we respectively compared ADC values and short diameters between malignant lymph nodes and benign lymph nodes. We found that the ADC value of the positive lymph nodes was significantly lower than that of the negative lymph nodes, and the short diameter of the former was significantly greater than that of the latter, which was consistent with previous studies [9, 32, 33]. Furthermore, we characterized the evaluation of the accuracy of differentiating metastatic from benign lymph nodes combined with CT, morphological MRI and DWI. The results showed a similar accuracy between CT and morphological MRI. In this study, there was no significant difference in lymph node detection between CT and morphological MRI, but significant difference was found between DWI and CT or morphological MRI concerning the confidence of diagnosis with a sensitivity of 77.3% and specificity of 70.0%. In addition, when DWI was combined with the other two imaging modalities, the greatest predictive power was obtained with a sensitivity of 86.4%, specificity of 76.7% and AUC of 0.893 superior to each of the imaging modality. In terms of lymph node detection, previous studies have demonstrated DWI was superior to CT or morphological MRI [9, 34, 35], similar to ours.

The present study has several limitations. First, rigorous radiological-pathological correlations could not be performed because of the large number and complex anatomic location of lymph nodes in gastric cancer. Second, DW images were obtained with only 2 *b*-values (0 and 1000 s/m^2), although this is a frequently used strategy. In this sense, it is still not clear which are the optimal set of *b*-values and should be improved in future studies. Finally, our study was retrospective and validation was required in a prospective study.

In summary, DW images combined with CT and morphological MR images are significantly better than each imaging modality alone for detecting metastatic lymph nodes in gastric cancer, which is necessary for the assessment of lymph node metastasis to guide physicians to make appropriate treatment plan and evaluate prognosis.

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Disclosure of conflict of interest

None.

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