**Objective:** To determine whether gross tumor volume (GTV) and the maximum diameter of resectable cervical cancer at magnetic resonance imaging (MRI) could predict lymph node metastasis (LNM) and lymphovascular space invasion (LVSI).

**Materials and Methods:** A total of 315 consecutive patients with cervical cancer were retrospectively identified. Gross tumor volume and the maximum diameter of tumor were evaluated on MRI. Univariate and multivariate logistic regression analyses were performed to determine whether tumor size could predict LNM and LVSI. Cutoffs of GTV, maximum diameter, and the International Federation of Gynecology and Obstetrics (FIGO) classification of tumor were first investigated in 255 patients (group A) and then validated in an independent cohort of 60 patients (group B) using area under the receiver operating characteristic curve (AUC) analysis for predicting the presence of LNM and LVSI.

**Results:** Univariate analysis showed that GTV and the maximum diameter of tumor could predict LNM and LVSI (all \( P < 0.0001 \)). Multivariate analyses indicated GTV as an independent risk factor of LNM and LVSI (all \( P < 0.0001 \)). In group A, GTV, the maximum diameter, and the FIGO stage could identify LNM (AUC, 0.813, 0.741, and 0.69, respectively) and LVSI (AUC, 0.806, 0.751, and 0.684, respectively). In group B, GTV, the maximum diameter, and the FIGO stage could help identify LNM (AUC, 0.902, 0.825, and 0.759, respectively) and LVSI (AUC, 0.771, 0.748, and 0.700, respectively).

**Conclusions:** Gross tumor volume and the maximum diameter of resectable cervical cancer at MRI demonstrated capability in predicting LNM and LVSI, which were more accurate than FIGO stage.

**Key Words:** MRI, Tumor size, Cervical cancer, Lymph node metastasis, Lymphovascular space invasion
Cervical cancer is one of the most common diagnosed cancers and one of the leading causes of cancer death in females worldwide, especially in developing countries. The treatment of cervical cancer involves surgery and chemoradiotherapy, which depends on early detection and accurate staging, especially the lymph node involvement. Lymph node metastasis (LNM) is not only closely related to cervical cancer recurrence and distant metastasis, but also an independent factor in poor survival. Furthermore, lymphovascular space invasion (LVSI) not only was an independent influencing factor for LNM but also has been well considered for treatment cervical cancer now. Lymph node metastasis and LVSI were important prognostic factors for survival regardless of the disease extent. The accurate diagnosis of LNM and LVSI is currently considered an important prognostic factor for survival and making the choice of individualized treatment to the cervical cancer patients.

Conventional radiology is still extremely useful in diagnosing cervical cancer. The greatest restriction of using ultrasonic is the low sensitivity in detecting LNM. Magnetic resonance imaging (MRI) is a safe, repeatable, and effective imaging technique that has played a progressively important role in identifying the cervical tumor and its parametrial invasion. However, preoperatively detecting LNM has been a major drawback with a wide range sensitivity of 29% to 86% because it may be difficult to identify micrometastases lymph nodes that have normal size. Even if it used the expensive positron emission tomography/computed tomography for assessing regional LNM, the diagnostic accuracy is low in early-stage disease. After pathological correlations, the authors found that the positron emission tomography/computed tomography was falsely negative in 12% of 132 patients, especially for lymph nodes with 5 mm or less diameter. Previous studies reported that the gross tumor volume (GTV) of cervical cancer on MRI could be used for predicting the presence of histologic LNM and treatment outcome. It has been reported that the tumor volume and LVSI were all critical for selecting an appropriate therapeutic modality. The previously reported study also demonstrated that the tumor size of cervical cancer on MRI was important for preoperative staging and influenced management decisions. Therefore, our study was to retrospectively assess whether the tumor size of resectable cervical cancer on MRI could predict regional LNM and LVSI.

MATERIALS AND METHODS

Patients

The institutional ethics committee approved this study. Between December 2015 and June 2017, we retrospectively analyzed the data of patients with cervical cancer treated at 3 hospitals. Patients who met the following criteria were included: (1) had histologically confirmed cervical cancer and received radical hysterectomy with lymphadenectomy, (2) underwent dynamic MRI within 1 week before surgery, and (3) without preoperative chemoradiotherapy or radiotherapy. Consequently, this study involved 315 patients. Then these patients were divided into 2 cohorts. In the development cohort (group A), data in 255 patients were used to develop the GTV cutoff values in identifying LNM and LVSI. In the validation cohort (group B), data in 60 patients were used to validate the developed cutoff values of tumor size. The average age was 48 years (range, 29–74 years) in group A. The average age was 48.5 years (range, 31–70 years) in group B.

Magnetic Resonance Imaging

The patients undertook the examinations with standard body coil on 3.0-T Magnetom (Siemens, Munich, Germany) scanners. Imaging included sagittal 5-mm fast-spin echo T2-weighted images (echo time [TE], 90 milliseconds; repetition time [TR], 4600 milliseconds; number of excitations 2), and axial 5-mm T2-weighted and T1-weighted images (TE, 10 milliseconds; TR, 212 milliseconds; number of excitations 2). The diffusion-weighted imaging was performed in axial plane with b values of 0, 300, 500, and 800 s/mm² using the following parameters: TR, 4007 milliseconds; TE, 55 milliseconds; slice thickness, 5 mm; and field of view, 34 cm. Gadolinium-enhanced fat-suppressed T1-weighted axial images and sagittal images were performed after approximately 20-mL (a total of 0.2 mmol/kg of body weight) gadodiamide (gadopentetate dimeglumine; Consun, Guangzhou, China) injected via a pressure injector at a dosage of 2 mL/s followed by a 20-mL saline solution flush. It took approximately 30 minutes to complete all these MRI scans.

Tumor volume and the maximum diameter of tumor were evaluated quantitatively on the T2-weighted images. Two experienced radiologists who were blinded to each other’s results and patient information independently analyzed the MR images. According to the previous reports, tumor volume was calculated by multiplying the sum of tumor areas by the section thickness. Tumor area was manually outlined on the sagittal or axial T2-weighted image images along the border of the each suspected tumor slice (Fig. 1). The true maximum diameter of tumor is the longest diameter measured on both sagittal and transversal MR images.

Lymph Node Dissection and Histologic Evaluation

The removed lymph nodes included the nodes around the external, internal, and common iliac vessels; in the obturator fossa; and in retroperitoneal space. The mean number of nodes resected during surgery across this patient population was 36 (range, 20–58). The primary tumor and nodes were sliced and marked with hematoxylin and eosin, and
immunohistochemistry. The experienced pathologists microscopically observed the presence of LNM and LVSI.

Statistical Analysis
All statistical analyses were supported with SPSS (version 17.0; SPSS, Chicago, IL). Significant difference was considered if \( P < 0.05 \). The MRI data were used to test interobserver reproducibility of the measurements. In these 315 patients, interobserver reproducibility of tumor size measurements was assessed using coefficient of variation (CV). Variability was considered slight when the %CV was less than 10%, and the final result was the average value of the 2 measurements. If the %CV surpassed 10%, the observers completed additional 2 measurements. Moreover, the final result was the average of the 4 measurements.

Univariate and Multivariate Analyses of Clinicopathological Factors Correlated With LNM and LVSI

The correlation between clinicopathological factors and LNM is shown in Table 1. The correlation between clinicopathological factors and LVSI is shown in Table 2. The distributions of GTV and the maximum diameter of tumor stratified by N stage and LVSI are shown in Figure 2. Histology type could not predict the LNM and LVSI. There was no difference between ages for predicting LVSI (\( P = 0.903 \)). There was a significant difference between ages for predicting LNM (\( P = 0.005 \)). Tumor differentiation, International Federation of Gynecology and Obstetrics (FIGO) category, the maximum diameter of tumor, and GTV could predict the LNM and LVSI (all \( P < 0.05 \)). Multivariate analysis showed GTV as an independent risk factor related to LNM (\( P < 0.001 \); odds ratio, 1.286) and LVSI (\( P < 0.001 \); odds ratio, 1.406).

ROC Analyses of GTV and the Maximum Diameter of Resectable Cervical Cancer for Predicting the Presence of LNM and LVSI

As illustrated in Table 3 and Figures 3A, B, in the development cohort, the maximum diameters of tumor cutoff value in identifying the presence of LNM and LVSI were 2.75 cm (AUC, 0.741; sensitivity, 80.2%; specificity, 61.4%; accuracy, 67.0%) and 2.90 cm (AUC, 0.751; sensitivity, 68.4%; specificity, 67.4%; accuracy, 60.8%), respectively. The cutoff values of GTV in identifying the presence of LNM and LVSI were 5.17 cm\(^3\) (AUC, 0.813; sensitivity, 75.6%; specificity, 76.0%; accuracy, 75.7%) and 6.41 cm\(^3\) (AUC, 0.806; sensitivity, 60.2%; specificity, 93.4%; accuracy, 76.0%), respectively. The figures show that the AUC value of FIGO for identifying the presence of LNM and LVSI is less than that of GTV and the maximum diameter. In the development cohort, the AUC values of FIGO for identifying the presence of LNM and LVSI were 0.69 and 0.684, respectively.

As illustrated in Table 3 and Figures 3C, D in the validation cohort, when compared with data in the development cohort, the AUCs of GTV obtained in the validation cohort in the identification of LNM and LVSI were 0.902 and 0.771, respectively. The AUCs of the maximum diameter
TABLE 1. Univariate analysis of clinicopathological factors and gross tumor size of resectable cervical cancer correlated with regional LNM

| Variables                           | Negative (n =169) | Positive (n = 86) | P     |
|-------------------------------------|-------------------|-------------------|-------|
| Age, year                           |                   |                   | 0.005 |
| <50                                 | 93 (58.9)         | 65 (41.1)         |       |
| ≥50                                 | 76 (78.4)         | 21 (21.6)         |       |
| Histology type                      |                   |                   | 0.566 |
| Adenocarcinoma                      | 14 (66.8)         | 9 (33.2)          |       |
| Squamous cell carcinoma             | 155 (60.9)        | 77 (39.1)         |       |
| Tumor differentiation               |                   |                   | 0.002 |
| Poorly differentiated               | 85 (59.0)         | 59 (41.0)         |       |
| Moderately differentiated           | 36 (67.9)         | 17 (32.1)         |       |
| Highly differentiated               | 48 (82.8)         | 10 (17.2)         |       |
| FIGO category                       |                   |                   | <0.0001|
| IB1                                 | 62 (92.5)         | 5 (7.5)           |       |
| IB2                                 | 41 (60.3)         | 27 (39.7)         |       |
| IIA1                                | 36 (64.3)         | 20 (35.7)         |       |
| IIA2                                | 10 (45.5)         | 12 (54.5)         |       |
| IIB                                 | 20 (47.6)         | 22 (52.4)         |       |
| Maximum diameter of tumor, cm <4   | 154 (69.1)        | 69 (30.9)         | <0.0001|
| ≥4                                  | 15 (46.9)         | 17 (53.1)         |       |
| GTV, cm³                            |                   |                   | <0.0001|
| <3.9                                | 108 (85.0)        | 19 (15.0)         |       |
| ≥3.9                                | 61 (47.7)         | 67 (52.3)         |       |
| LVIAbsent                           | 133 (75.1)        | 44 (24.9)         | <0.0001|
| Present                             | 36 (46.2)         | 42 (53.8)         |       |

Numbers in parentheses are the percentages.

obtained in the validation cohort in the identification of LNM and LVI were 0.825 and 0.748, respectively. In Figures 3C, D also show that the AUC value of FIGO is less than that of GTV and the maximum diameter in identifying the presence of LNM and LVI in the validation cohort. In the validation cohort, the AUC values of FIGO in identifying the presence of LNM and LVI were 0.759 and 0.700, respectively.

**DISCUSSION**

Lymph node metastasis and LVI are not only closely related to cervical cancer recurrence and distant metastasis, but also independent factors for poor survival. Consequently, the accurate assessment of LNM and LVI plays a significant role in prognosis assessment and treatment. Our results suggest that the tumor size measured on MRI could be a potential alternative way for preoperative distinguishing N stages and identifying LVI of cervical cancer. The presence of LNM and LVI is the most important risk factor that affects survival and prognosis, which are not involved in FIGO classification. Previous studies have performed to evaluate the risk of LNM in cervical cancer. Several prognostic factors including FIGO stage, lymphatic permeation, and tumor histologic type have been demonstrated to be associated with LNM in cervical cancer. Our study was consistent with these published reports. Moreover, we found that GTV and the maximum diameter were more accurate than FIGO stage in predicting LNM or LVI in this study.

As for the protocol of our study, we claimed the maximum diameter of tumor to assess the N stages and identify LVI of cervical cancer for the first time. In the revised FIGO

### TABLE 2. Univariate analysis of clinicopathological factors and gross tumor size of resectable cervical cancer correlated with LVI

| Variables                           | Negative (n =177) | Positive (n =78) | P     |
|-------------------------------------|-------------------|------------------|-------|
| Age, year                           |                   |                  | 0.903 |
| <50                                 | 107 (67.7)        | 51 (32.3)        |       |
| ≥50                                 | 70 (72.2)         | 27 (27.8)        |       |
| Histology type                      |                   |                  | 0.352 |
| Adenocarcinoma                      | 14 (60.9)         | 9 (39.1)         |       |
| Squamous cell carcinoma             | 163 (70.3)        | 69 (29.7)        |       |
| Tumor differentiation               |                   |                  | 0.014 |
| Poorly differentiated               | 95 (66.0)         | 49 (34.0)        |       |
| Moderately differentiated           | 29 (54.7)         | 24 (45.3)        |       |
| Highly differentiated               | 53 (91.4)         | 5 (9.6)          |       |
| FIGO category                       |                   |                  | <0.0001|
| IB1                                 | 55 (82.1)         | 12 (17.9)        |       |
| IB2                                 | 57 (83.8)         | 11 (16.2)        |       |
| IIA1                                | 35 (62.5)         | 21 (37.5)        |       |
| IIA2                                | 10 (45.5)         | 12 (54.5)        |       |
| IIB                                 | 20 (47.6)         | 22 (52.4)        |       |
| Maximum diameter of tumor, cm <4   | 162 (72.6)        | 61 (27.4)        | <0.0001|
| ≥4                                  | 15 (46.9)         | 17 (53.1)        |       |
| GTV, cm³                            |                   |                  | <0.0001|
| <3.9                                | 162 (77.2)        | 29 (22.8)        |       |
| ≥3.9                                | 162 (77.2)        | 29 (22.8)        |       |
| LNM                                 |                   |                  | <0.0001|
|Absent                               | 133 (78.7)        | 36 (21.3)        |       |
|Present                              | 44 (51.2)         | 42 (48.8)        |       |

Numbers in parentheses are the percentages.
staging for cervical cancer, the accurate division of tumor size (the maximum diameter with a cutoff of 4 cm) has been used for staging. As suggested in the published article, tumor diameter was correlated with FIGO stage, LNM, and tumor recurrence rate. It is mostly reported that the larger the tumor diameter, the broader the surrounding invasion and the

**FIGURE 2.** Box plots show the correlation between the GTV (in centimeters cube) and N stage (A), the maximum diameter of tumor (in centimeters) and N stage (B), and the distributions of GTV (C) and the maximum diameter of tumor (D) stratified by LVSI.

**TABLE 3.** ROC analysis for tumor size of resectable cervical cancer for detecting LNM and LVSI

| Group                        | Cutoff Value | AUC  | Sensitivity | Specificity | PPV  | NPV  | Accuracy |
|------------------------------|--------------|------|-------------|-------------|------|------|----------|
| Development cohort (n = 255) |              |      |             |             |      |      |          |
| N0 vs N1                    |              |      |             |             |      |      |          |
| GTV                          | 5.17 cm³     | 0.813| 0.756       | 0.760       | 0.613| 0.859| 0.757    |
| Maximum diameter            | 2.75 cm      | 0.741| 0.802       | 0.614       | 0.510| 0.857| 0.670    |
| LVSI (+) vs (−)              |              |      |             |             |      |      |          |
| GTV                          | 6.41 cm³     | 0.806| 0.602       | 0.934       | 0.601| 0.934| 0.760    |
| Maximum diameter            | 2.90 cm      | 0.751| 0.684       | 0.674       | 0.633| 0.843| 0.608    |
| Validation cohort (n = 60)  |              |      |             |             |      |      |          |
| N0 vs N1                    |              |      |             |             |      |      |          |
| GTV                          | 5.17 cm³     | 0.902| 0.789       | 0.853       | 0.714| 0.897| 0.833    |
| Maximum diameter            | 2.75 cm      | 0.825| 0.842       | 0.610       | 0.531| 0.928| 0.716    |
| LVSI (+) vs (−)              |              |      |             |             |      |      |          |
| GTV                          | 6.41 cm³     | 0.771| 0.600       | 0.850       | 0.600| 0.825| 0.750    |
| Maximum diameter            | 2.90 cm      | 0.748| 0.750       | 0.625       | 0.500| 0.833| 0.748    |

NPV, negative predictive value; PPV, positive predictive value.
greater risk of LNM. The maximum diameter of tumor at MRI could be used for identifying the presence of LNM and L VSI in resectable cervical cancer patients with cutoff value of 2.75 and 2.90 cm, respectively. The previously reported studies confirmed that the tumor diameter of at least 25 mm on MRI could be an independent risk factor for parametrial invasion in cervical cancer with FIGO stage IB1. Our study confirmed the previously mentioned results that the maximum diameter of resectable cervical cancer correlated with regional LNM and L VSI.

In this study, we found that GTV was not only correlated with regional LNM and L VSI, but also an independent risk factor to detect the occurrence of LNM and L VSI. These results suggest that GTV based on MRI could be a potential alternative technique for the preoperative identifying L VSI and distinguishing N stages of cervical cancer. The “objective” MRI compared with “subjective” visual assessment had decreased observer dependence and increased diagnostic performance in evaluating cervical cancer. The previous investigator showed that the similar index (metabolic tumor volume) also could predict the tumor relapse and the survival of patients with cervical cancer. Previous studies found that tumor volume of head-neck cancer and endometrial cancer on MRI was the most important independent factor associated with the tumor grade and overall survival. Our results showed that GTV could help identify the presence of LNM and L VSI with cutoff values of 5.17 and 6.41 cm³, respectively. The probably pathological mechanism could be that L VSI was mainly around the tumor. The larger the GTV, the deeper the surrounding invasion and there was more likely to involve L VSI and the more frequent the incidence of LNM. Com pared with traditional FIGO classification, GTV of cervical cancer measured on MRI could be more accurate and objective for predicting the LNM. Owing to the subjectivity of the different gynecologic oncologists with different work experience, there may be different clinical FIGO stage for the same cervical cancer patients. Therefore, the noninvasive MRI assessment of LNM and the L VSI plays an important role in determining whether these patients should undergo extensive lymphadenectomies.
In our study, there were also some limitations. First of all, this study only included the cervical cancer patients who received lymphadenectomy and the patients who did not undergo lymphadenectomy were excluded from this study. Our inclusion criteria might be provided in case selection bias. Despite this limitation, our study indicated that GTV and the maximum diameter of resectable cervical cancer at MRI could predict the presence of LNM and LVSI. Second, we have not routinely assessed imaging features including parametrial invasion or size of lymph nodes on the MRI in this article. However, many previous studies had demonstrated that MRI features could help differentiate the stage of cervical cancer, but with low sensitivity (29%–86%) in detecting LNM for its incapability to detect micrometastases in normal-sized nodes. In our future study, we would like to compare the accuracy of tumor size or node size in predicting the N stage.

In conclusion, GTV and the maximum diameter of resectable cervical cancer at MRI demonstrated to be helpful in quantitatively predicting the presence of LNM and LVSI, which were more accurate than FIGO stage in predicting LNM or LVSI. We believe that preoperative assessment of the status of lymph nodes and LVSI is important in formulating individualized treatment plan for the individual cases.

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