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## Predictive Value of [<sup>18</sup>F]FDG PET/CT for Lymph Node Metastasis in Rectal Cancer

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[<sup>18</sup>F]Fluorodeoxyglucose ([<sup>18</sup>F]FDG) Positron emission tomography/computed tomography (PET/CT) is commonly used for rectal cancer staging, but improved diagnostic methods for nodal metastases are needed. We aimed to evaluate whether the combination model of the metabolic tumor volume of primary tumor (T\_MTV) and maximum standardized uptake value of lymph node (N\_SUVmax) on pretreatment [<sup>18</sup>F]FDG PET/CT could improve nodal metastases prediction in rectal cancer. We enrolled a total of 166 rectal cancer patients who underwent pretreatment [<sup>18</sup>F]FDG PET/CT and surgical resection without neoadjuvant treatment between January 2009 and August 2016. Visual and semiquantitative PET/CT parameters were obtained. Associations between clinicopathological, PET/CT-derived variables and nodal metastases were evaluated by logistic regression analysis. Nodal metastases were confirmed histologically in 68 of the 166 patients (41%). Uni- and multivariate analyses demonstrated T\_MTV and N\_SUVmax were independent predictive factors for nodal metastases. The c-statistics of the combination model was 0.806 (Standard Error, 0.034; 95% Confidence Interval, 0.737–0.863), which showed significant improvement compared to T\_MTV (0.698,  $P = 0.0002$ ) or N\_SUVmax (0.720,  $P = 0.0008$ ) alone. T\_MTV and N\_SUVmax are independently correlated with nodal metastases. Furthermore, the combination model showed improved performance for risk prediction; thus, [<sup>18</sup>F]FDG PET/CT might have a role in rectal cancer staging and treatment planning.

Colorectal cancer (CRC) is one of the most common malignancies, and it is the second leading cause of death from cancer in the United States. It is estimated that 135,430 new cases developed and 50,260 deaths occurred in 2017<sup>1</sup>. Identifying lymph node (LN) metastases is one of the most important steps for staging rectal cancer because it helps guide therapeutic decisions and determine the long-term outcome<sup>2,3</sup>.

Clinically, LN size, measured by computed tomography (CT) or magnetic resonance imaging (MRI), is the most common criteria used to determine pathologic LNs. An LN with greater than 1 cm short-axis diameter is considered pathologic; however, the upper limit of benign LNs differs depending on the anatomic location and tumor type<sup>4,5</sup>. Furthermore, nodal metastases can occur in normal-sized LNs less than 1 cm<sup>6</sup>. Thus, nodal staging based on LN size shows low sensitivity in identifying small metastatic LNs in patients with rectal cancer using conventional imaging modalities<sup>7,8</sup>.

Positron emission tomography (PET)/CT with [<sup>18</sup>F]Fluorodeoxyglucose ([<sup>18</sup>F]FDG) has been widely used for staging, restaging, and detection of recurrent disease in rectal cancer<sup>9–11</sup>. Although the specificity of [<sup>18</sup>F]FDG PET/CT in detecting nodal metastases has been known to be excellent, its sensitivity is relatively low<sup>12</sup>. Nodal [<sup>18</sup>F]FDG uptake findings alone could play a strong independent predictive factor for LN metastases. If the hypermetabolic LN, which show high [<sup>18</sup>F]FDG uptake, is observed in [<sup>18</sup>F]FDG PET/CT, this strongly suggests LN metastases, but not all hypermetabolic LNs are LN metastases. Normal vascular structures such as venous flexus or inflammatory reactive LNs were sometimes misinterpreted as metastatic LNs in CRC<sup>12,13</sup>. Although, strict criteria for the diagnosis of LN metastases in [<sup>18</sup>F]FDG PET/CT could reduce false-positive rates but decrease the sensitivity. Thus, sole use of nodal [<sup>18</sup>F]FDG uptake finding is imperfect for identifying LN metastases, and better predictive tools are needed.

Recently, metabolic tumor volume (MTV), as a volumetric parameter of PET/CT, has been suggested to be a predictive marker of survival outcomes in CRC<sup>14,15</sup>. Previous studies show that MTV could be a promising

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Variables	All patients (N = 166)	LN metastasis (–) (N = 98)	LN metastasis (+) (N = 68)	P value
Age, years	66.7 ± 10.6	67.1 ± 9.3	66.0 ± 12.2	0.560
Sex				0.202
Male	94 (56.6%)	60 (61.2%)	34 (50.0%)	
Female	72 (43.4%)	38 (38.8%)	34 (50.0%)	
Pre-operative CEA, ng/ml	5.7 ± 21.8	6.1 ± 27.0	5.1 ± 11.0	0.757
Pathologic tumor size, cm	4.6 ± 5.4	4.3 ± 6.8	5.0 ± 2.2	0.362
Pathologic T stage				<0.001
Tis	2 (1.2%)	2 (2.0%)	0 (0.0%)	
T1	25 (15.1%)	24 (24.5%)	1 (1.5%)	
T2	44 (26.5%)	34 (34.7%)	10 (14.7%)	
T3	77 (46.4%)	34 (34.7%)	43 (63.2%)	
T4	18 (10.8%)	4 (4.1%)	14 (20.6%)	
Pathologic N stage				<0.001
N0	98 (59.0%)	98 (100.0%)	0 (0.0%)	
N1	40 (24.1%)	0 (0.0%)	40 (58.8%)	
N2	28 (16.9%)	0 (0.0%)	28 (41.2%)	
AJCC stage				<0.001
0	2 (1.2%)	2 (2.0%)	0 (0.0%)	
I	58 (34.9%)	58 (59.2%)	0 (0.0%)	
II	38 (22.9%)	38 (38.8%)	0 (0.0%)	
III	67 (40.4%)	0 (0.0%)	67 (98.5%)	
IV	1 (0.6%)	0 (0.0%)	1 (1.5%)	
Histologic grade*				0.318
Well differentiated	3 (1.8%)	3 (3.1%)	0 (0.0%)	
Moderate differentiated	154 (94.5%)	91 (93.8%)	63 (95.5%)	
Poorly differentiated	5 (3.1%)	2 (2.1%)	3 (4.5%)	
Undifferentiated	1 (0.6%)	1 (1.0%)	0 (0.0%)	
PET/CT parameters				
Tumor SUVmax	15.3 ± 7.7	14.3 ± 7.6	16.7 ± 7.7	0.041
Tumor MTV	24.1 ± 22.6	19.0 ± 16.9	31.4 ± 27.5	0.001
Nodal FDG uptake finding				<0.001
Negative	127 (76.5%)	92 (93.9%)	35 (51.5%)	
Positive	39 (23.5%)	6 (6.1%)	33 (48.5%)	
Nodal SUVmax	1.1 ± 2.5	0.2 ± 0.6	2.4 ± 3.5	<0.001

**Table 1.** Patient Characteristics. CEA = Carcinoembryonic Antigen; AJCC = American Joint Committee on Cancer (7th ed.); PET/CT = Positron Emission Tomography/Computed Tomography; SUVmax = maximum standardized uptake value; MTV = Metabolic Tumor Volume; \*Grade cannot be assessed in three patients with mucinous carcinoma.

predictor for LN metastasis<sup>16–18</sup>, however, no studies have attempted to develop a prediction model for LN metastases status in rectal cancer using both MTV of the primary tumor (T\_MTV) and [<sup>18</sup>F]FDG-avid LN findings.

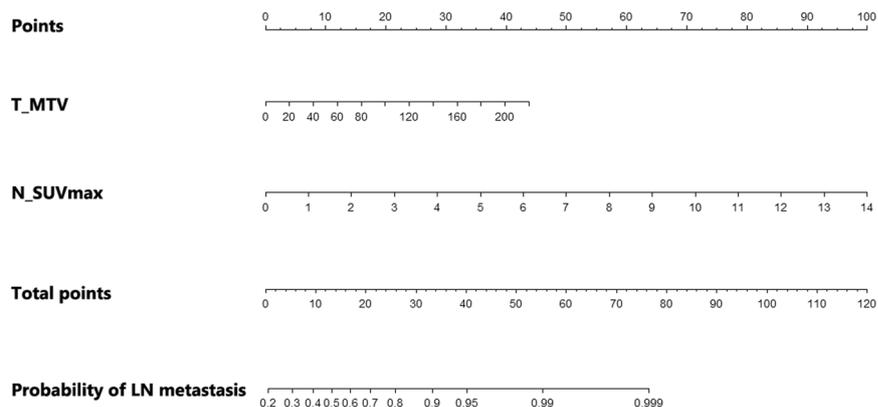
The purpose of this retrospective study was to determine whether the combination model of T\_MTV and maximum standardized uptake value (SUVmax) of the LN (N\_SUVmax), measured by [<sup>18</sup>F]FDG PET/CT, could improve the prediction of LN metastases in patients with rectal cancer.

## Results

**Patient Characteristics.** A total of 166 patients with rectal cancer who received curative surgical resection were retrospectively analyzed. The characteristics of the enrolled patients (mean age, 66.7 ± 10.6 years) and the associations with LN metastases are listed in Table 1. LN metastases were confirmed histologically in 68 patients (41%), and 98 patients (59%) presented with no LN metastases. Although the majority of patients were diagnosed with 7th American Joint Committee on Cancer (AJCC) stage I–III cancer, two patients with pathologic stage Tis were classified as stage 0, and one patient with distant metastasis was classified as stage IV. The stage IV patient had 6 nodal metastases (N2a) and underwent a low anterior resection of a single hepatic metastasis and left hepatectomy. Pathologic stages according to the 7th AJCC and PET parameters, such as SUVmax of primary tumor (T\_SUVmax), T\_MTV, and N\_SUVmax, were significantly different between the two groups; however, no significant differences were found with respect to pre-operative carcinoembryonic antigen (CEA), pathologic tumor size, and histologic grade. Thirty-nine of the 166 patients (23.5%) showed positive nodal uptake by [<sup>18</sup>F]FDG PET/CT findings. Of these 39 patients, 33 (84.6%) had histologically confirmed LN metastases. On the contrary, LN metastases were confirmed histologically in 35 (27.6%) of the 127 patients with negative nodal FDG uptake.

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	0.991 (0.962–1.020)	0.538		
Sex				
Male				
Female	1.579 (0.845–2.951)	0.152		
Pre-operative CEA, ng/ml	0.998 (0.983–1.013)	0.785		
Pathologic tumor size, cm	1.024 (0.961–1.092)	0.463		
PET/CT parameters				
Tumor SUVmax	1.043 (1.001–1.088)	0.046		
Tumor MTV	1.033 (1.014–1.054)	<0.001	1.022 (1.001–1.043)	0.038
Nodal SUVmax	2.356 (1.637–3.392)	<0.001	2.181 (1.523–3.125)	<0.001

**Table 2.** Uni- and multivariate logistic regression analyses for regional lymph node metastases. OR = Odds Ratio; CI = Confidence Interval; CEA = Carcinoembryonic Antigen; PET/CT = Positron Emission Tomography/Computed Tomography; SUVmax = maximum standardized uptake value; MTV = Metabolic Tumor Volume.

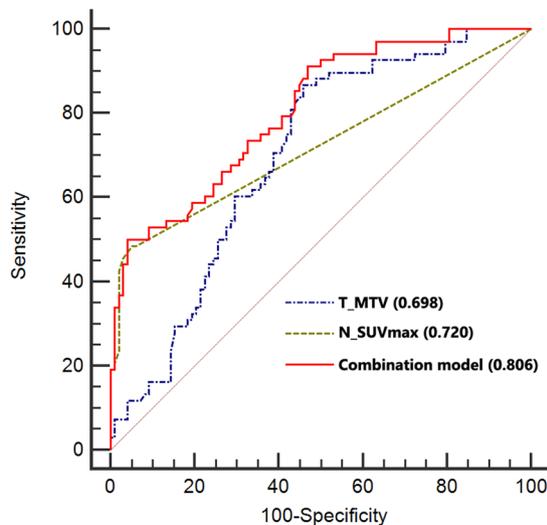


**Figure 1.** Nomogram for predicting the probability of regional LN metastasis using pretreatment [ $^{18}\text{F}$ ]FDG PET/CT parameters. First, the number of points for each parameter – T\_MTV and N\_SUVmax – should be determined by drawing a vertical line from the exact value of variables to the points row. Subsequently, total points can be obtained by sum of two variables. The individual predictive probability of regional LN metastasis can be calculated by drawing a vertical line from the total points row to the probability of regional LN metastasis. LN = lymph node; [ $^{18}\text{F}$ ]FDG = [ $^{18}\text{F}$ ]Fluorodeoxyglucose; PET/CT = Positron Emission Tomography/Computed Tomography; T\_MTV = metabolic tumor volume of primary tumor; N\_SUVmax = maximum standardized uptake value of regional LN.

For detecting LN metastases, [ $^{18}\text{F}$ ]FDG PET/CT had a sensitivity of 48.5%, a specificity of 93.9%, a positive predictive value of 84.6%, and a negative predictive value of 72.4%.

**Uni- and Multivariate Analyses.** Univariate logistic regression analysis revealed that T\_SUVmax, T\_MTV, and N\_SUVmax were significantly associated with LN metastases (Table 2). In the multivariate analysis, both T\_MTV (odds ratio [OR], 1.022; 95% confidence interval [CI], 1.001–1.043;  $P = 0.038$ ) and N\_SUVmax (OR, 2.181; 95% CI, 1.523–3.125;  $P < 0.001$ ) were found to be significant predictive factors; otherwise, T\_SUVmax was justifiably removed from the stepwise model. These two independent parameters were used to construct a nomogram for risk prediction of LN metastasis (Fig. 1). To use the nomogram, the points for each parameter should be determined by drawing a vertical line from the exact value of the variables to the points row. Then, total points are calculated by arithmetic sum. Finally, the individual predictive probability of LN metastasis can be obtained by drawing a vertical line from the total points row to the probability of LN metastasis row.

**Comparison of LN Metastasis Prediction Performance.** When LN metastases prediction performance was analyzed using receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC) was 0.698 for T\_MTV (Standard Error [SE], 0.040; 95% CI, 0.622–0.767) and 0.720 for N\_SUVmax (SE, 0.033; 95% CI, 0.646–0.787). We were able to build an improved prediction model that combined T\_MTV and N\_SUVmax. The c-statistics of combined model was 0.806 (SE, 0.034; 95% CI, 0.737–0.863), and it showed significant improvement in accuracy of LN metastases prediction compared to T\_MTV ( $P = 0.0002$ ) or N\_SUVmax ( $P = 0.0008$ ) alone (Fig. 2). However, no significant difference was found between T\_MTV and N\_SUVmax ( $P = 0.64$ ).



**Figure 2.** Graphs of ROC curve analysis show significant additional value of T\_MTV for predicting regional LN metastasis in rectal cancer. Although comparison of AUC between N\_SUVmax (0.720) and T\_MTV (0.698) was not significant ( $P=0.64$ ), c-statistics when T\_MTV was added to N\_SUVmax (0.806) showed significant improvement in accuracy of risk prediction for LN metastasis (0.806 for c-statistics of combination model vs. 0.698 for T\_MTV;  $P=0.0002$ , 0.806 for c-statistics of combination model vs. 0.720 for N\_SUVmax;  $P=0.0008$ ). ROC = receiver operating characteristic; T\_MTV = metabolic tumor volume of primary tumor; LN = lymph node; AUC = area under the curve; N\_SUVmax = maximum standardized uptake value of regional LN.

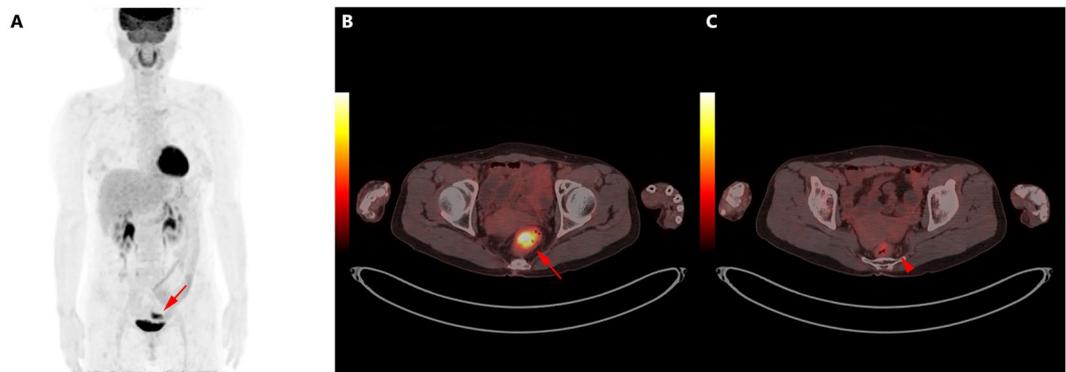
## Discussion

In the current study, we assessed the diagnostic value of metabolic parameters measured by [ $^{18}\text{F}$ ]FDG PET/CT for the prediction of LN metastases in patients with rectal cancer. Our results demonstrated that nodal [ $^{18}\text{F}$ ]FDG uptake findings were highly specific for LN metastases status, but it had a limitation due to its relatively low sensitivity. To overcome this limitation, we used metabolic parameters such as T\_MTV and N\_SUVmax for precise diagnosis of LN metastases. T\_MTV and N\_SUVmax are independent predictive factors for LN metastases in patients with rectal cancer. Moreover, the combination of both parameters significantly improved LN metastases prediction beyond each independent parameter alone (Fig. 3).

The sensitivity of [ $^{18}\text{F}$ ]FDG PET/CT was found to be relatively low (48.5%), although the specificity was high (93.9%). This finding is similar to that in previous studies, which showed poor sensitivity for detecting LN metastases<sup>12,19</sup>. In this study, we excluded the patients who had received neoadjuvant treatment, since any treatment before surgical resection could affect the histopathologic results, including the initial LN status. If these advanced rectal cancer patients who underwent neoadjuvant chemotherapy were included in the present study, the LN detectability of [ $^{18}\text{F}$ ]FDG PET/CT may be improved because the majority of these patients have shown high nodal [ $^{18}\text{F}$ ]FDG uptake.

Jo *et al.* have shown that MTV and total lesion glycolysis of the primary tumor, which are volumetric parameters of [ $^{18}\text{F}$ ]FDG PET/CT, were useful predictive factors for LN metastasis in patients with rectal cancer<sup>16</sup>. However, they only focused on metabolic activity of the primary tumor and did not use visual or semiquantitative information from [ $^{18}\text{F}$ ]FDG-avid LNs as a possible predictive factor for LN metastasis. In contrast, we evaluated not only metabolic information from the primary tumor, but also the LN's own metabolic activity, for LN metastases prediction. For semiquantitative analysis of [ $^{18}\text{F}$ ]FDG-avid LNs, we adopted N\_SUVmax which is the most widely accepted parameter of [ $^{18}\text{F}$ ]FDG PET/CT. Because SUVmax is a simple measurable metabolic parameter, and the application of metabolic volume parameter has a limitation in small volumes<sup>20</sup>. Tsunoda *et al.* demonstrated that N\_SUVmax could improve the accuracy of preoperative LN metastases detection when compared to nodal diameter<sup>12</sup>. Concordantly, N\_SUVmax was an independent prognostic factor for LN metastases in this study. We, therefore, have incorporated N\_SUVmax as well as T\_MTV for LN metastases prediction. Additionally, the combination of T\_MTV and N\_SUVmax could improve LN metastases prediction in patients with rectal cancer.

The present study also suggested that T\_MTV could be a useful complementary predictive factor itself for LN metastases. Recently, several studies have shown that volumetric parameters measured by [ $^{18}\text{F}$ ]FDG PET/CT are useful for the evaluation of therapeutic response or prognostication in a variety of malignancies<sup>21–25</sup>; T\_MTV can be used as a predictive factor for LN metastases in lung, endometrial, and uterine cervical cancers<sup>18,26,27</sup>. Our result is consistent with previous studies in that T\_MTV obtained by [ $^{18}\text{F}$ ]FDG PET/CT could be an effective marker of total tumor burden and may reflect the aggressiveness of cancer associated with LN metastases. A previous meta-analysis identified numerous histopathological factors that may be correlated with LN metastases in primary CRC<sup>28</sup>. However, no single histopathological feature reliably predicted LN metastases, and these factors can be evaluated only after surgery. Considering the feasibility of [ $^{18}\text{F}$ ]FDG PET/CT in the pre-operative setting



**Figure 3.** (A) Sixty-two-year-old female patient diagnosed with rectal cancer. (B) [ $^{18}\text{F}$ ]FDG PET/CT showed that intense [ $^{18}\text{F}$ ]FDG uptake in the rectum (T\_SUVmax; 10.7, T\_MTV; 13.7 ml). (C) Small LNs without significant [ $^{18}\text{F}$ ]FDG uptake were observed in the pericolic space, however, 3 of 24 resected LNs were histologically confirmed LN metastases. [ $^{18}\text{F}$ ]FDG = [ $^{18}\text{F}$ ]Fluorodeoxyglucose; PET/CT = Positron Emission Tomography/Computed Tomography; T\_SUVmax = maximum standardized uptake value of primary tumor; T\_MTV = metabolic tumor volume of primary tumor; LN = lymph node.

of rectal cancer, [ $^{18}\text{F}$ ]FDG PET/CT could be used as a non-invasive and pre-operative diagnostic tool for assessment of LN status in patients with rectal cancer.

The status of LN metastases is the most important prognostic factor in patients with rectal cancer. The five-year survival rate for patients with node-negative rectal cancer is 70–80%, whereas it is only 30–60% in node-positive rectal cancer. Accordingly, LN status assessment remains one of main factors used in determining neoadjuvant treatment in patients with rectal cancer<sup>29</sup>. Although [ $^{18}\text{F}$ ]FDG PET/CT can affect staging and treatment strategies, the current evidence is not considered strong enough to recommend the routine use of [ $^{18}\text{F}$ ]FDG PET/CT for initial staging<sup>30,31</sup>. The main reason for this is the lack of additional diagnostic value of [ $^{18}\text{F}$ ]FDG PET/CT. In that regard, the improved diagnostic performance of the combination model for predicting LN metastases may be helpful in selecting patients who should receive neoadjuvant treatment. Additionally, [ $^{18}\text{F}$ ]FDG PET/CT might be helpful in determining risk-adapted treatment and long-term patient outcome by providing more accurate information regarding LN status. A multi-institutional, large prospective study is necessary for the combination model of T\_MTV and N\_SUVmax on pretreatment [ $^{18}\text{F}$ ]FDG PET/CT to be accepted as a significant prognostic factor in patients with rectal cancer.

This study had a few limitations. First, the single-center retrospective design of this study might be subject to selection bias. Further studies are needed to validate the results of the present study. Second, physiologic [ $^{18}\text{F}$ ]FDG uptake in the gastrointestinal tract may cause overestimation of T\_MTV. Therefore, we adopted an absolute SUV threshold of 2.5 for MTV measurement, which was a widely used cutoff value in several previous studies and could reduce inter- and intra-observer variation in delineation of tumor volume using a software-assisted automatic method<sup>21,32</sup>. Lastly, we did not correct for a partial volume effect, which may have underestimated the value of SUVmax; this is because partial volume correction is generally too complex to use in daily clinical practice. New and feasible partial volume correction methods would be helpful in achieving precise quantification and clinical application<sup>33,34</sup>. Despite these limitations, we have shown that the combination of T\_MTV and N\_SUVmax could be an attractive strategy to further improve the diagnostic performance of [ $^{18}\text{F}$ ]FDG PET/CT for LN metastases in patients with rectal cancer.

In conclusion, T\_MTV and N\_SUVmax were independent prognostic factors for the prediction LN metastases in rectal cancer patients. Furthermore, our prediction model using T\_MTV and N\_SUVmax could provide a more precise prediction of LN metastases. The use of N\_SUVmax in combination with T\_MTV on preoperative [ $^{18}\text{F}$ ]FDG PET/CT could be a useful tool for initial staging and treatment planning in patients with rectal cancer.

## Methods

**Patients.** Between January 2009 and August 2016, the medical records of 296 consecutive patients who underwent surgery for rectal cancer and had a preoperative [ $^{18}\text{F}$ ]FDG PET/CT were evaluated retrospectively. Of these, patients who received neoadjuvant chemoradiotherapy (n = 96), endoscopic tumor removal prior to surgery (n = 24), or long delayed interval over than 1 month between [ $^{18}\text{F}$ ]FDG PET/CT and surgery (n = 10) were excluded. A total of 166 patients were enrolled in this study. Surgery (160 patients with anterior resection, 4 with abdominoperineal resection, 1 with Hartmann's operation, and 1 with total proctocolectomy) was performed by experienced colorectal surgeons, which included total mesorectal excision and at least 14 LNs were harvested. All of the patients were pathologically staged according to the 7th AJCC staging system<sup>35</sup>. The Institutional Review Board of Keimyung University Dongsan Medical Center approved this retrospective study and waived the requirement to obtain informed consent (2018-04-008).

**Positron Emission Tomography.** [ $^{18}\text{F}$ ]FDG PET/CT scan was performed using an integrated PET/CT system (Discovery STE; GE Healthcare, Milwaukee, WI, USA or Biograph mCT; Siemens Medical Systems, Knoxville, TN, USA). All patients fasted for at least 6 hours before [ $^{18}\text{F}$ ]FDG injection, and the blood glucose levels were below 150 mg/dL. Patients were encouraged to rest during the [ $^{18}\text{F}$ ]FDG uptake period. Images were

acquired 60 minutes after 5.5 MBq/kg (Discovery STe) or 4.0 MBq/kg (Biograph mCT) of FDG was administered intravenously. First, low-dose CT scan (Discovery STe; peak voltage of 120 kVp and slice thickness of 3.75 mm, Biograph mCT; peak voltage of 120 kVp and slice thickness of 3 mm) was acquired for attenuation correction. Immediately following the CT scan, PET scan was obtained with an acquisition time of 3 min per bed position for Discovery STe and 1.5 min per bed position for Biograph mCT in 3D mode. PET images were reconstructed using an ordered-subset expectation maximum iterative reconstruction algorithm.

**Image Analysis.** [<sup>18</sup>F]FDG PET/CT images were retrospectively interpreted in consensus by two experienced nuclear medicine physicians. First, LN metastases status was visually assessed and categorized into one of two groups. The metastatic LNs were categorized as positive, which showed increased [<sup>18</sup>F]FDG uptake from the surrounding background activity on PET regardless of size on CT. Subsequently, the volume of interest (VOI) of the primary tumor and LNs were manually drawn, and T\_SUVmax and N\_SUVmax were measured only in patients with positive [<sup>18</sup>F]FDG uptake for semiquantitative analyses. We assigned the SUVmax as 0 to patients with negative [<sup>18</sup>F]FDG uptake of the primary tumor or LNs. The SUVmax was calculated using the following formula: SUVmax = maximum activity in the region of interest (MBq/g)/[injected dose (MBq)/body weight (g)]. T\_MTV, obtained with an SUV threshold of 2.5, was used to define the VOI.

**Statistical Analysis.** Numeric data are expressed as mean ± standard deviation. Univariate and multivariate logistic regression analyses were performed to identify significant variables associated with LN metastasis. The prediction model of LN metastases, with the combination of significant parameters, was developed by using multivariable logistic regression modeling. A nomogram was established to be a graphic representation of the LN metastases prediction model based on the result of multivariate logistic regression analysis. The additional value of risk prediction for LN metastases was evaluated using c-statistics, and DeLong method was used to compare the difference between the AUC<sup>36</sup>. Statistical analyses were performed using MedCalc for Windows, version 18.2.1 (MedCalc Software, Ostend, Belgium) and R version 3.4.3 software (<http://www.r-project.org>, R Foundation for Statistical Computing, Vienna, Austria). All *P* values < 0.05 were considered statistically significant.

### Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Additional Information

**Competing Interests:** The authors declare no competing interests.

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