Predictive Value of $^{18}$F-FDG PET/CT for Lymph Node Metastasis in Rectal Cancer

Sung Hoon Kim$^1$, Bong-II Song$^2$, Beong Woo Kim$^1$, Hae Won Kim$^1$, Kyoung Sook Won$^1$, Sung Uk Bae$^2$, Woon Kyung Jeong$^2$ & Seong Kyu Baek$^2$

$^{18}$F]Fluorodeoxyglucose ($^{18}$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 $^{18}$F-FDG PET/CT could improve nodal metastases prediction in rectal cancer. We enrolled a total of 166 rectal cancer patients who underwent pretreatment $^{18}$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, $^{18}$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. 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.

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. Furthermore, nodal metastases can occur in normal-sized LNs less than 1 cm. Thus, nodal staging based on LN size shows low sensitivity in identifying small metastatic LNs in patients with rectal cancer using conventional imaging modalities. Positron emission tomography (PET)/CT with $^{18}$F-Fluorodeoxyglucose ($^{18}$F-FDG) has been widely used for staging, restaging, and detection of recurrent disease in rectal cancer. Although the specificity of $^{18}$F-FDG PET/CT in detecting nodal metastases has been known to be excellent, its sensitivity is relatively low. Nodal $^{18}$F-FDG uptake findings alone could play a strong independent predictive factor for LN metastases. If the hypermetabolic LN, which show high $^{18}$F-FDG uptake, is observed in $^{18}$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. Although, strict criteria for the diagnosis of LN metastases in $^{18}$F-FDG PET/CT could reduce false-positive rates but decrease the sensitivity. Thus, sole use of nodal $^{18}$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. Previous studies show that MTV could be a promising marker of survival outcomes in CRC.

$^1$Department of Nuclear Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea. $^2$Department of Surgery, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea. Correspondence and requests for materials should be addressed to B.-I.S. (email: song@dsmc.or.kr)
predictor for LN metastasis; 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 [18F]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 [18F]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 [18F]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                          | All patients (N = 166) | LN metastasis (−) (N = 98) | LN metastasis (+) (N = 68) | P value |
|------------------------------------|------------------------|----------------------------|-----------------------------|---------|
| Age, years (mean ± SD)             | 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.
For detecting LN metastases, [18F]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 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.

**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 (\( P = 0.64 \)).

### Table 2. Uni- and multivariate logistic regression analyses for regional lymph node metastases.

| 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                              |                     |                       |                     |                     |
| 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 (1.637–3.932) | \( < 0.001 \)         | 2.181 (1.523–3.125) | \( < 0.001 \)        |

Notes: 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 [18F]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; [18F]FDG = [18F]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.
Discussion

In the current study, we assessed the diagnostic value of metabolic parameters measured by \(^{18}\)F-FDG PET/CT for the prediction of LN metastases in patients with rectal cancer. Our results demonstrated that nodal \(^{18}\)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 \(^{18}\)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\(^{12,19}\). 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 \(^{18}\)F-FDG PET/CT may be improved because the majority of these patients have shown high nodal \(^{18}\)F-FDG uptake.

Jo et al. have shown that MTV and total lesion glycolysis of the primary tumor, which are volumetric parameters of \(^{18}\)F-FDG PET/CT, were useful predictive factors for LN metastasis in patients with rectal cancer\(^{16}\). However, they only focused on metabolic activity of the primary tumor and did not use visual or semiquantitative information from \(^{18}\)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 \(^{18}\)F-FDG-avid LNs, we adopted N\(_{SUVmax}\) which is the most widely accepted parameter of \(^{18}\)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\(^{20}\). Tsunoda et al. demonstrated that N\(_{SUVmax}\) could improve the accuracy of preoperative LN metastases detection when compared to nodal diameter\(^{12}\). 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 \(^{18}\)F-FDG PET/CT are useful for the evaluation of therapeutic response or prognostication in a variety of malignancies\(^{21-25}\). T\(_{MTV}\) can be used as a predictive factor for LN metastases in lung, endometrial, and uterine cervical cancers\(^{16,26,27}\). Our result is consistent with previous studies in that T\(_{MTV}\) obtained by \(^{18}\)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\(^{28}\). However, no single histopathological feature reliably predicted LN metastases, and these factors can be evaluated only after surgery. Considering the feasibility of \(^{18}\)F-FDG PET/CT in the pre-operative setting.
of rectal cancer, [18F]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 and clinical application.33,34. Despite these limitations, we have shown that the combination of T_MTV and N_SUVmax on pretreatment [18F]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 [18F]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.21,32. 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.33,34. 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 [18F]FDG PET/CT for LN metastases in patients with rectal cancer.

Figure 3. (A) Sixty-two-year-old female patient diagnosed with rectal cancer. (B) [18F]FDG PET/CT showed that intense [18F]FDG uptake in the rectum (T_SUVmax; 10.7, T_MTV; 13.7 ml). (C) Small LNs without significant [18F]FDG uptake were observed in the pericolic space, however, 3 of 24 resected LNs were histologically confirmed LN metastases. [18F]FDG = [18F]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.
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.** $[^{18}F]$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 $[^{18}F]$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 $T_{\text{SUVM}}$ and $N_{\text{SUVM}}$ were measured only in patients with positive $[^{18}F]$FDG uptake for semiquantitative analyses. We assigned the SUVmax as 0 to patients with negative $[^{18}F]$FDG uptake of the primary tumor or LNs. The SUVmax was calculated using the following formula: $\text{SUV}_{\text{max}} = \frac{\text{maximum activity in the region of interest (MBq/g)}}{[\text{injected dose (MBq)/body weight (g)}]}$. $T_{\text{MTV}}$, 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. 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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Author Contributions
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