Preoperative Standardized Uptake Value of Metastatic Lymph Nodes Measured by ^{18}F-FDG PET/CT Improves the Prediction of Prognosis in Gastric Cancer

Bong-Il Song, MD, Hae Won Kim, MD, Kyoung Sook Won, MD, Seung Wan Ryu, MD, Soo Sang Sohn, MD, and Yu Na Kang, MD

Abstract: This study assessed whether preoperative maximum standardized uptake value (SUVmax) of metastatic lymph nodes (LNs) measured by ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) could improve the prediction of prognosis in gastric cancer.

One hundred fifty-one patients with gastric cancer and pathologically confirmed LN involvement who had undergone preoperative ^{18}F-FDG PET/CT prior to curative surgical resection were retrospectively enrolled. To obtain nodal SUVmax, a transaxial image representing the highest ^{18}F-FDG uptake was carefully selected, and a region of interest was manually drawn on the highest ^{18}F-FDG accumulating LN. Conventional prognostic parameters and PET findings (primary tumor and nodal SUVmax) were analyzed for prediction of recurrence-free survival (RFS) and overall survival (OS). Furthermore, prognostic accuracy of survival models was assessed using c-statistics.

Of the 151 patients, 38 (25%) experienced recurrence and 34 (23%) died during follow-up (median follow-up, 48 months; range, 5–74 months). Twenty-seven patients (18%) showed positive ^{18}F-FDG nodal uptake (range, 2.0–22.6). In these 27 patients, a receiver-operating characteristic curve demonstrated a nodal SUVmax of 2.8 to be the optimal cutoff for predicting RFS and OS. The univariate and multivariate analyses showed that nodal SUVmax (hazard ratio [HR] = 2.71, $P < 0.0001$), pathologic N (pN) stage (HR = 2.58, $P = 0.0058$), and pathologic T (pT) stage (HR = 1.77, $P = 0.0191$) were independent prognostic factors for RFS. Also, nodal SUVmax (HR = 2.80, $P < 0.0001$) and pN stage (HR = 2.28, $P = 0.0222$) were independent prognostic factors for OS. A predictive survival model incorporating conventional risk factors (pT/pN stage) gave a c-statistic of 0.833 for RFS and 0.827 for OS, whereas a model combination of nodal SUVmax with pT/pN stage gave a c-statistic of 0.871 for RFS ($P = 0.0355$) and 0.877 for OS ($P = 0.0313$).

Nodal SUVmax measured by preoperative ^{18}F-FDG PET/CT is an independent prognostic factor for RFS and OS. Combining nodal SUVmax with pT/pN staging can improve survival prediction precision in patients with gastric cancer.

Abbreviations: ^{18}F-FDG PET/CT = ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography, HR = hazard ratio, LN = lymph node, OS = overall survival, pN = pathologic N, pT = pathologic T, RFS = recurrence-free survival, SUVmax = maximum standardized uptake value.

INTRODUCTION

Gastric cancer is the second leading cause of cancer mortality worldwide with higher incidence rates in Northeast Asia, Eastern Europe, and South America.[1] Although the mortality associated with gastric cancer has steadily declined, a substantial number of advanced gastric cancer patients still have poor outcomes.[1,2]

To date, depth of tumor invasion, level of lymph node (LN) metastasis, and stage of disease are the most significant prognostic factors for predicting recurrence.[3–5] However, preoperative assessment of the optimal method to predict prognosis in gastric cancer is not well established. Developing effective methods for the preoperative risk stratification of gastric cancer is necessary to select an optimal treatment for gastric cancer.

In recent decades, ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) has been widely used to assess various malignancies.[6] Several studies have revealed that ^{18}F-FDG PET can be important in staging, response evaluation, relapse monitoring, and tumor recurrence prediction in patients with gastric cancer.[7–15] However, ^{18}F-FDG uptake by the primary tumor may not be useful for survival prediction in gastric cancer patients. ^{18}F-FDG is not a cancer-specific agent, and as a result, many benign lesions such as gastritis, polyps, and normal gastric mucosa can demonstrate moderate-to-intense ^{18}F-FDG uptake.

LN metastasis is another important prognostic factor for gastric cancer.[16,17] However, ^{18}F-FDG PET for the diagnosis of LN involvement is limited in determining the extent of lymphadenectomy due to its low sensitivity.[8] However, relatively high specificity could provide a clinical benefit in initial therapy selection. Nevertheless, the prognostic value of ^{18}F-FDG uptake by metastatic LNs has not been well investigated in patients with gastric cancer.

The objective of the present study was to investigate the prognostic value of preoperative SUVmax of metastatic LNs measured by ^{18}F-FDG PET/computed tomography (CT) for recurrence-free survival (RFS) and overall survival (OS) in

patients with LN involvement gastric cancer prior to curative surgical resection.

PATIENTS AND METHODS

Patients

We retrospectively reviewed medical records of all gastric cancer patients who underwent ^{18}F-FDG PET/CT for a staging work-up before treatment at our institution between January 2008 and December 2010. Of these cases, patients with microscopic or macroscopic residual disease after surgical treatment, distant metastases, or other cancers and patients who had received any neoadjuvant therapy prior to surgical treatment of gastric cancer were excluded. Finally, 151 patients with LN involvement gastric cancer who had undergone curative surgical resection were enrolled in this study. Curative surgical resection was defined by the absence of tumor macroscopically or microscopically after operation. In this study, all patients received radical gastrectomy along with D2 lymphadenectomy (advanced gastric cancer) and D1 + β or D2 lymphadenectomy (early gastric cancer). Patients had routinely been followed up every 3 months for the first year, every 6 months for the second year, and yearly thereafter. Recurrences were evaluated by physical examination, esophagogastroduodenoscopy, ultrasonography, contrast-enhanced CT, ^{18}F-FDG PET/CT, magnetic resonance imaging, or histological biopsy. This retrospective study was approved by the institutional review board (2014-04-002), which waived the requirement of informed consent.

^{18}F-FDG PET/CT Acquisition Protocol and Image Analysis

^{18}F-FDG PET/CT scans were obtained using a Discovery STE PET/CT scanner (GE Healthcare, Milwaukee, WI) within 1 month before surgical resection. All patients fasted for at least 6 hours before the study. After the venous blood glucose level was managed to be <8.3 mmol/L (150 mg/dL), a dose of approximately 5.5 MBq/kg of ^{18}F-FDG was intravenously injected, and imaging was performed 60 minutes later. Additionally, patients were requested to drink at least 500 mL of water prior to scanning to distend the stomach. Before PET, a low-dose CT scan was acquired from the skull vertex to proximal thighs (peak voltage of 120 kV, automated tube current ranging from 60 to 150 mA, and a slice thickness of 3.75 mm without contrast enhancement for attenuation correction). Immediately following the CT scan acquisition, the PET data were acquired with an acquisition time of 3 minutes per bed position in 3-dimensional mode. The CT data were used for attenuation correction and PET images were reconstructed using an ordered-subset expectation maximum iterative reconstruction algorithm.

Image display and analysis was performed using an Advantage Workstation 4.3 (GE Healthcare) providing multiplanar reformatted images. All of the ^{18}F-FDG PET/CT images were retrospectively interpreted by 2 experienced nuclear medicine physicians and a consensus was reached. First, all of the ^{18}F-FDG PET/CT images were visually evaluated and categorized as either positive or negative based on their ^{18}F-FDG uptake findings. Primary tumors were characterized as positive for ^{18}F-FDG uptake with abnormally increased ^{18}F-FDG uptake exceeding the physiologic uptake by adjacent normal stomach wall and corresponding to lesions on esophagogastroduodenoscopy. Focally increased ^{18}F-FDG uptake lesions that did not correspond to cancer lesions on esophagogastroduodenoscopy and histopathological findings were judged to be negative for ^{18}F-FDG uptake.

In addition, no visible significantly increased ^{18}F-FDG uptake or diffusely increased ^{18}F-FDG uptake indiscernible from physiological stomach wall uptake was defined as negative for ^{18}F-FDG uptake. In the case of metastatic LNs, focally increased ^{18}F-FDG avid LNs that correspond to metastatic LNs on histopathological results were regarded as positive for ^{18}F-FDG uptake. However, in the case of suspicious ^{18}F-FDG avid metastatic LNs with a low ^{18}F-FDG uptake (SUVmax < 2), we decided that these metastatic LNs were negative for ^{18}F-FDG uptake.

Subsequently, the SUVmax was measured only in patients with positive primary tumors and ^{18}F-FDG avid metastatic LNs for quantitative analysis. Circular regions of interest were manually drawn over the maximum ^{18}F-FDG uptake lesions corresponding to the primary tumor and ^{18}F-FDG avid metastatic LNs on the attenuation-corrected transaxial ^{18}F-FDG PET images to obtain the SUVmax within these regions of interest. We assigned the SUVmax as 1.0 to patients with negative ^{18}F-FDG uptake of the primary tumor or LNs. The SUVmax was calculated using the following formula:

$$SUVmax = \frac{\text{maximum activity in region of interest (MBq/g)}}{\text{injected dose (MBq)/body weight (g)}}.$$

Clinicopathologic and Survival Data

Clinicopathologic data considered to be potentially important to prognosis were collected from the patients' medical records. Data included age at surgery, sex, perineural invasion, histopathological subtypes, Lauren histotype, pathologic T (pT) stage, and pathologic N (pN) stage. pT and pN classifications were in accordance with the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer.[18] In addition, the short-axis diameter of regional LNs identified with preoperative abdominal CT was included for survival analysis. RFS was defined as the interval from surgery to tumor recurrence or final medical examination for recurrence evaluation if recurrence did not occur. All patients with tumor recurrence were confirmed by pathology or at clinical follow-up. OS was calculated from the date of surgery to the date of death or last follow-up at our medical center.

Statistical Analysis

Numeric data are expressed as the mean ± standard deviation. The relationship between nodal SUVmax and N stage was evaluated using the analysis of variance test. The optimal cutoff LN size, primary tumor SUVmax, and nodal SUVmax for the prediction of recurrence and death were determined using receiver-operating characteristic (ROC) curve analysis. RFS and OS were calculated using the Kaplan–Meier method. Variables that significantly affected RFS and OS were investigated by the multivariate analysis using Cox regression model. The 95% confidence interval (CI) was determined for each parameter. The additional value of nodal SUVmax for prognostication was evaluated using c-statistics. Statistical analyses were performed using MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium). *P* values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics and ^{18}F-FDG PET/CT Findings

A total of 151 patients with LN involvement gastric cancer treated with curative surgical resection were retrospectively

analyzed. Overall, 38 of the 151 patients (25%) experienced recurrence during the clinical follow-up period (median follow-up, 48 months; range, 5–74 months). Of the 38 patients with recurrent disease, 34 (23%) died.

Characteristics of enrolled patients are summarized in Table 1. A total of 122 patients (81%) showed positive ^{18}F-FDG uptake by primary tumors and 27 (18%) showed positive uptake by metastatic LNs. The mean nodal SUVmax of these 27 patients was 4.9 ± 4.8 (range, 2.0–22.6). Of the 38 patients with recurrent disease, 18 (47%) showed positive nodal ^{18}F-FDG uptake and 20 (53%) showed negative nodal ^{18}F-FDG uptake. Of the 20 patients who showed disease recurrence but negative nodal ^{18}F-FDG uptake, 13 (65%) revealed small LN size

≤ 5 mm. Of the 34 patients who had died, 18 (53%) showed positive nodal ^{18}F-FDG uptake and 16 (47%) showed negative nodal ^{18}F-FDG uptake. Of the 16 patients who died but showed negative nodal ^{18}F-FDG uptake, 11 (69%) had a LN size ≤ 5 mm.

Among the 151 patients, 48 (32%) were N1 stage, 38 (25%) were N2 stage, and 65 (43%) were N3 stage. The mean nodal SUVmax was significantly different among the N stage groups ($P = 0.006$) and was increased by increases in the N stage. Mean nodal SUVmax was 1.14 ± 0.61 in N1 stage, 1.67 ± 2.36 in N2 stage, and 2.12 ± 3.24 in N3 stage, respectively. There were 15 patients (10%) in stage I, 50 (33%) in stage II, and 86 (57%) in stage III according to tumor node metastasis staging (Table 1).

Survival Analysis

At the time of analysis, 38 patients (25%) demonstrated recurrence and 34 (23%) died during the median follow-up of 48 months (range, 5–74 months). The median RFS and OS times were 36 and 48 months, respectively. Kaplan–Meier analysis revealed that positive nodal uptake was associated with significantly shorter RFS and OS compared with negative nodal SUVmax (Figure 1). In positive nodal uptake patients, an ROC curve demonstrated an optimal cutoff for nodal SUVmax of 2.8 to predict RFS and OS. Then, this LN-positive group was divided into 2 groups using this cutoff. Statistically significant differences of RFS and OS in a stepwise manner in accordance with groups with higher nodal SUVmax were observed between each grade by log-rank test (Figure 2).

Univariate analysis revealed that pT stage (1, 2, 3, 4), pN stage (1, 2, 3), LN size (≤ 5 vs >5 mm), perineural invasion (− vs +), primary tumor SUVmax (≤ 4.5 vs >4.5), and nodal SUVmax (<2.0, 2.0–2.8, >2.8) were significantly associated with RFS and OS (Table 2). On the multivariate analysis using Cox proportional hazards models, nodal SUVmax (hazard ratio [HR] = 2.71; 95% CI, 1.76–4.17; $P < 0.0001$), pN stage (HR = 2.58; 95% CI, 1.32–5.05; $P = 0.0058$), and pT stage (HR = 1.77; 95% CI, 1.10–2.84; $P = 0.0191$) were independent prognostic factors for RFS, and nodal SUVmax (HR = 2.80; 95% CI, 1.80–4.36; $P < 0.0001$) and pN stage (HR = 2.28; 95% CI, 1.13–4.61; $P = 0.0222$) were independent prognostic factors for OS (Table 3). Although, LN size, perineural, and primary tumor SUVmax were significantly correlated with RFS and OS on univariate analysis, these parameters were not independent prognostic factors for RFS and OS on multivariate analysis.

When analyzing pT and pN stage in all patients, c-statistics were 0.833 and 0.827 for RFS and OS, respectively. Combining nodal SUVmax with pT/pN stage gave a c-statistic of 0.871 for RFS ($P = 0.0355$) and 0.877 for OS ($P = 0.0313$) (Figure 3).

As positive nodal uptake was significantly associated with poor prognosis, an analysis of adjuvant chemotherapy effects within subgroup of 27 patients who showed positive nodal uptake on ^{18}F-FDG PET/CT was performed. Of these 27 patients, 9 (33.3%) received adjuvant chemotherapy and 14 received regular checkups without adjuvant chemotherapy. There was no statistical difference of RFS and OS between the 2 groups. The estimated median RFS was 15 months (95% CI, 7–19) in the surgery-only group versus 12 months (95% CI, 9–18) in the group receiving adjuvant chemotherapy ($P = 0.4495$), and the estimated median OS was 22 months (95% CI, 16–27) in the surgery-only group versus 17 months

TABLE 1. Patient Characteristics

Characteristics	n or Median $\pm$ SD
Age, y	58 ± 12.4 (range, 25–85)
Sex	
Male	95 (63%)
Female	56 (37%)
Perineural invasion	
No	66 (44%)
Yes	85 (56%)
Histopathological subtype	
Tubular	117 (78%)
Signet-ring cell	23 (15%)
Mucinous	8 (5%)
Lymphoepithelioma-like carcinoma	3 (2%)
Lauren histotype	
Intestinal	44 (29%)
Nonintestinal	107 (71%)
Pathologic T stage[*]	
T1	32 (21%)
T2	31 (21%)
T3	32 (21%)
T4	56 (37%)
Pathologic N stage[*]	
N1	48 (32%)
N2	38 (25%)
N3	65 (43%)
Lymph node size, mm	5.0 ± 5.5 (range, 3.0–60.0)
≤ 5	98 (65%)
>5	53 (35%)
TNM stage	
I	15 (10%)
II	50 (33%)
III	86 (57%)
Adjuvant chemotherapy	
No	118 (78%)
Yes	33 (22%)
Primary tumor FDG uptake	
Positive	122 (81%)
Negative	29 (19%)
Lymph node FDG uptake	
Positive	27 (18%)
Negative	124 (82%)

AJCC = American Joint Committee on Cancer, FDG = fluoro-2-deoxy-D-glucose, SD = standard deviation, TNM = tumor node metastasis.

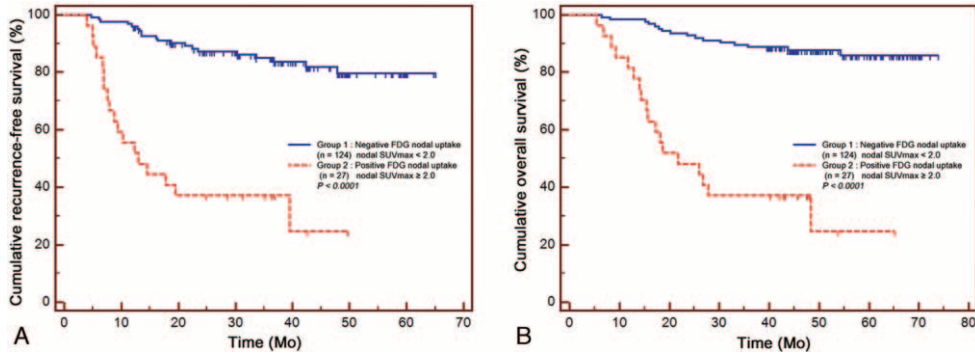[*] According to AJCC staging manual (seventh edition).

FIGURE 1. (A) Cumulative recurrence-free survival curves and (B) overall survival curves according to the ^{18}F-FDG uptake by metastatic lymph node. ^{18}F-FDG = ^{18}F-fluoro-2-deoxy-D-glucose.

(95% CI, 14−28) in the group receiving adjuvant chemotherapy ($P = 0.2180$).

DISCUSSION

In this study, we evaluated the value of preoperative nodal SUVmax on ^{18}F-FDG PET/CT to predict outcomes in gastric cancer with LN involvement. Our results demonstrate that nodal SUVmax is an independent prognostic factor for recurrence and death after curative surgical resection. Although the detection rate of ^{18}F-FDG PET/CT for LN involvement was only 18%, comparing nodal SUVmax to established prognostic factors by multivariate analysis demonstrated an independent association. Furthermore, incorporation of nodal SUVmax with conventional risk factors (pT/pN stage) improved survival prediction beyond conventional staging alone.

Yun et al[8] reported that ^{18}F-FDG PET had sensitivities and specificities of 34% and 96% for N1 and N2 disease and 50% and 99% for N3 disease, respectively. In our study, 27 of the 151 patients (18%) showed positive uptake by metastatic LNs. This difference could be due to patient selection. We excluded patients with residual disease, distant metastases, or those who received neoadjuvant therapy prior to resection.

Many studies have shown that SUVmax of primary lesions can assist in predicting recurrence. Most studies found that FDG uptake by primary gastric cancer lesion is an independent prognostic factor for tumor recurrence following resection.[14,15,19] Kim et al[14] demonstrated that pretreatment primary tumor SUVmax has a significant predictive value for progression-free survival in gastric cancer. However, nodal SUVmax was not investigated for prognostication and they included patients with stage IV disease who have significantly worse prognosis than those with lower stage disease. Lee et al[15] revealed that positive ^{18}F-FDG uptake by gastric cancer lesions is an independent and significant prognostic factor for recurrence after resection. However, they did not use nodal SUVmax for prognostication. Recently, Coupe et al[19] have reported that ^{18}F-FDG positive primary tumors and positive LNs were associated with inferior OS and remained an independent predictor on multivariate analysis. They included patients who received neoadjuvant chemotherapy; the pathologic results of primary tumor and metastatic LNs may be different after therapy. In subgroup analysis of patients following curative surgery, ^{18}F-FDG positive primary tumor was not a significant prognostic factor on multivariate analysis whereas positive LNs had a significant negative impact on RFS and OS by multivariate analysis. Although positive LNs were only statistically significant prognostic factors in patients who underwent surgery, there was no definite cutoff value for nodal SUVmax in that study.

The results of our study showed that primary tumor SUVmax was significantly associated with RFS and OS on univariate analysis, which was not preserved on multivariate analysis. On the contrary, nodal SUVmax was the most significant predictive factor for RFS and OS on both analyses, and an optimal cutoff value for nodal SUVmax was determined as 2.8. Furthermore, analyzing differences in the area under the ROC curve showed a significant improvement in the accuracy of risk prediction for RFS and OS rates when nodal SUVmax incorporated established risk factors (pT stage and pN stage) in
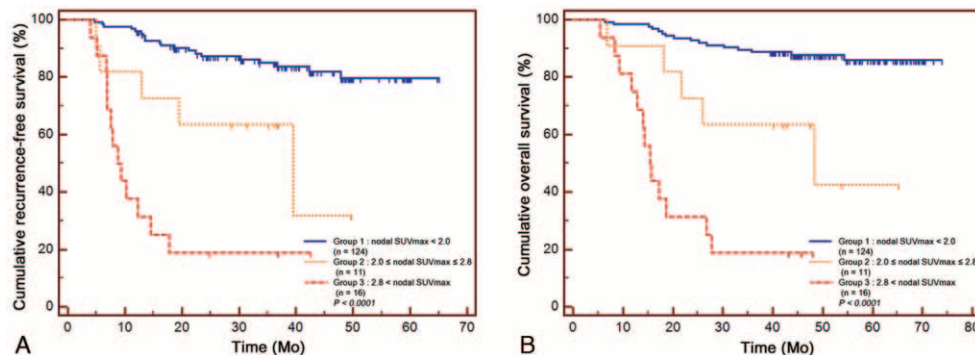

FIGURE 2. (A) Cumulative recurrence-free survival curves and (B) overall survival curves according to the nodal SUVmax (<2.0, 2.0−2.8, >2.8). SUVmax = maximum standardized uptake value.

TABLE 2. Univariate Analysis of Prognostic Factors for RFS and OS

Variable	n	RFS Hazard Ratio (95% CI)	P Value	OS Hazard Ratio (95% CI)	P Value
Age, y			0.3136		0.3572
<50	36	—		—	
≥50	115	0.71 (0.34–1.48)		1.25 (0.58–2.72)	
Sex			0.9427		0.8078
Male	95	—		—	
Female	56	1.02 (0.53–1.98)		1.09 (0.54–2.19)	
Perineural invasion			0.0001		0.0005
No	66	—		—	
Yes	85	4.91 (2.60–9.27)		4.20 (2.14–8.24)	
Histopathological subtype			0.7014		0.5837
Tubular	117	—		—	
Signet-ring cell	23	1.31 (0.55–3.11)		1.34 (0.52–3.43)	
Mucinous	8	0.90 (0.23–3.49)		0.48 (0.12–1.94)	
Lymphoepithelioma-like carcinoma	3	—			
Lauren histotype			0.2947		0.2571
Intestinal	44	—		—	
Nonintestinal	107	1.51 (0.75–3.05)		1.61 (0.77–3.36)	
Pathologic T stage			<0.0001		<0.0001
T1	32	—		—	
T2	31	3.26 (1.28–8.28)		3.15 (1.16–8.53)	
T3	32	7.97 (3.10–20.51)		5.37 (1.97–14.62)	
T4	56	20.26 (8.62–47.64)		17.81 (7.16–44.28)	
Pathologic N stage			<0.0001		<0.0001
N1	48	—		—	
N2	38	9.75 (4.30–22.12)		8.20 (3.44–19.53)	
N3	65	28.37 (13.55–59.40)		24.94 (11.41–54.53)	
Lymph node size, mm			0.0038		0.0062
≤5	98	—		—	
>5	53	2.47 (1.24–4.92)		2.48 (1.20–5.12)	
Primary tumor SUVmax			<0.0001		<0.0001
≤4.5	79	—		—	
>4.5	72	5.11 (2.69–9.73)		6.29 (3.19–12.41)	
Nodal SUVmax			<0.0001		<0.0001
<2.8	124	—		—	
2.0–2.8	11	3.52 (0.95–13.10)		4.28 (1.08–16.86)	
>2.8	16	10.80 (2.61–44.64)		13.26 (2.99–58.82)	
Adjuvant chemotherapy			<0.0001		0.0001
No	118	—		—	
Yes	33	3.46 (1.58–7.58)		3.60 (1.55–8.37)	

CI = confidence interval, OS = overall survival, RFS = recurrence-free survival, SUVmax = maximum standardized uptake value.

our study. These results suggest that FDG uptake by metastatic LNs could provide risk stratification in gastric cancer. It might be possible to differentiate aggressive phenotypes by preoperative ^{18}F-FDG PET/CT. Conventional risk factors including tumor invasion depth and extent of LN involvement are sometimes difficult to evaluate before surgery; therefore, ^{18}F-FDG PET/CT as a noninvasive evaluation method could provide additional value in predicting prognosis.

^{18}F-FDG uptake reflects both tumor biology and size for lesions <2 cm.[20] LN size would influence ^{18}F-FDG uptake and could be a potential prognostic factor. Tokunaga et al[21] revealed that patients with enlarged LNs (a short-axis diameter measuring ≥15 mm) conferred worse outcomes. In the present study, an ROC curve demonstrated a LN size of 5 mm to be the optimal cutoff. Differences in LN size cutoff values might reflect patient

selection. They excluded patients who received adjuvant chemotherapy. Although, large LN size patients showed poorer prognosis than small LN size patients on univariate analysis, LN size lost prognostic significance on multivariate analysis in our study. Also, Coupe et al[19] reported that lymphadenopathy on CT scans did not result in a significant difference in OS. These results suggest that metabolic information measured by ^{18}F-FDG PET/CT is more important than enlargement of metastatic LNs. However, underestimation of nodal SUVmax might have happened in 13 patients with disease recurrence and 11 patients who died because of absent nodal ^{18}F-FDG uptake within small-sized LNs.

In this study, we show that metabolic information of metastatic LNs represented by nodal SUVmax is more important than primary tumor lesion for predicting survival in gastric

TABLE 3. Multivariate Analysis of Prognostic Factors for RFS and OS

Variable	RFS			OS		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Pathologic T stage (1, 2, 3, 4)	1.77	1.10−2.84	0.0191	1.66	1.00−2.74	0.0501
Pathologic N stage (1, 2, 3)	2.58	1.32−5.05	0.0058	2.28	1.13−4.61	0.0222
Perineural invasion (no vs yes)	0.90	0.33−2.46	0.8374	1.02	0.39−2.69	0.9631
Lymph node size (≤5 vs >5 mm)	0.79	0.40−1.56	0.5036	0.78	0.38−1.61	0.5097
Primary tumor SUVmax (≤4.5 vs >4.5)	1.48	0.61−3.63	0.3894	1.87	0.69−5.10	0.2231
Nodal SUVmax (<2.0, 2.0−2.8, >2.8)	2.71	1.76−4.17	<0.0001	2.80	1.80−4.36	<0.0001

CI = confidence interval, OS = overall survival, RFS = recurrence-free survival, SUVmax = maximum standardized uptake value.

cancer. Malignant cells are well known to exhibit increased glucose uptake and consumption.[22] Glucose transporter 1 (GLUT-1) plays an important role in response for basal glucose uptake and its expression correlates with the rate of glucose metabolism. Overexpression of GLUT-1 has been observed in many cancers including gastric cancer.[23−25] Moreover, Kawamura et al[26] identified positive GLUT-1 expression of primary tumors was associated with depth of invasion, lymphatic permeation, vascular invasion, LN metastases, hepatic metastases, and peritoneal dissemination in gastric cancer. In addition, GLUT-1 expression levels of primary tumor were correlated with poor prognosis. Recently, Kim et al[27] reported that GLUT-1 expression of metastatic LNs is the most important predictive factor for ^{18}F-FDG uptake by metastatic LNs, but they did not mention an association between GLUT-1 expression of metastatic LNs and prognosis. The ability of metastasized tumor cells to invade lymphatic vessels is a more powerful prognostic factor than primary tumor features. Several authors emphasize that ^{18}F-FDG uptake by LNs is an important prognostic factor in patients with invasive ductal breast,[28] oral squamous cell,[29] cervical,[30] and endometrial cancers.[31] In line with these investigations, we presently report that high nodal SUVmax is significantly associated with poor prognosis in gastric cancer.

Despite many studies have demonstrated that postoperative adjuvant chemotherapy was associated with a significant improvement in OS compared with surgery alone,[32−34] there is no individualized adjuvant therapy approach according to

^{18}F-FDG PET/CT findings. Although part of patients with an expected poor prognosis received adjuvant chemotherapy in our study, the results of subgroup analysis on positive nodal uptake patients did not support the benefit of adjuvant chemotherapy. However, because the results of our study are a retrospective single-center study, further studies are needed to compare the prognosis between treatments in patients with positive nodal uptake on ^{18}F-FDG PET/CT. On the contrary, the results of the British MAGIC trial revealed that perioperative chemotherapy improved OS in patients who received perioperative chemotherapy compared with patients treated by surgery only.[35] Furthermore, a large clinical PRODIGY trial that evaluated the docetaxel + oxaliplatin + S-1 regimen as neoadjuvant chemotherapy in advanced gastric cancer is currently ongoing.[36] However, neoadjuvant chemotherapy benefit represented different outcome according to tumor location and Lauren histotype.[37,38] Considering prognostic significance of nodal SUVmax in gastric cancer, further controlled prospective studies with more patients are required to clarify nodal SUVmax to be accepted as a treatment personalization technique for prediction of those patients requiring neoadjuvant therapy in gastric cancer.

There are several limitations to this study. First, only node-positive patients who underwent curative surgical resection of gastric cancer were enrolled in this study. This may limit the generalizability and preclude application of risk stratification to patients without LNs metastases. Second, partial-volume effects
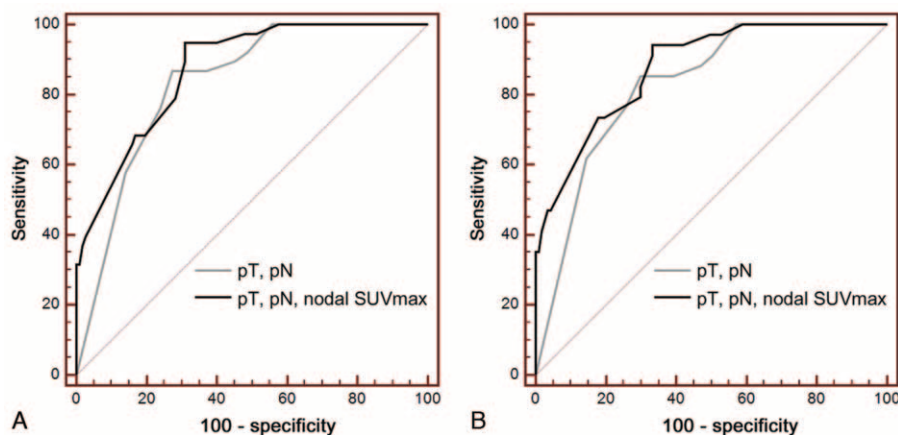

FIGURE 3. Graphs of receiver-operating characteristic curve analysis show an additional value of nodal SUVmax for predicting (A) recurrence-free survival and (B) overall survival rates. pN = pathologic N, pT = pathologic T, SUVmax = maximum standardized uptake value.

could affect ^{18}F-FDG uptake of small-sized LNs in patients with LN sizes of <2.0 cm by underestimating nodal SUVmax. Finally, the results of this study might be subject to selection bias stemming from its retrospective design. In this study, medical insurance did not cover adjuvant chemotherapy therapy in gastric patients with LN involvement. Consequently, the rate of adjuvant chemotherapy is low. This lower rate of chemotherapy could influence outcomes.

CONCLUSIONS

The present study revealed that nodal SUVmax on preoperative ^{18}F-FDG PET/CT is a significant independent predictor of RFS and OS after curative resection in gastric cancer patients with LN involvement. Combining nodal SUVmax with pT/pN stage might provide a more precise prognostic prediction. Thus, ^{18}F-FDG PET/CT might be useful for risk stratification before surgery and possibly aid in treatment selection.

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