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A Comparison Study of Esophageal Findings on ^{18}F-FDG PET/CT and Esophagogastroduodenoscopy

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Abstract
Purpose The aim of this study was to compare the esophageal findings of 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography–computed tomography (^{18}F-FDG PET/CT) and esophagogastroduodenoscopy (EGD).
Methods We retrospectively reviewed ^{18}F-FDG PET/CT and EGD findings of 369 subjects who underwent medical examination between January 2014 and December 2014. The range and intensity of esophageal ^{18}F-FDG uptake were visually analyzed. The maximum standardized uptake value (SUV_{max}) of the esophagus and around the esophagogastric (EG) junction was measured. EGD results were provided by the gastroenterologist. We compared the esophageal findings obtained using ^{18}F-FDG PET/CT and EGD.
Results There were typical linear FDG uptakes in ^{18}F-FDG PET/CT patients who underwent EGD the same day. In visual analysis of the range and intensity of the ^{18}F-FDG uptake, the patients who underwent ^{18}F-FDG PET/CT and EGD on the same day showed relatively diffuse and discernible ^{18}F-FDG uptake in the esophagus. Reflux esophagitis was diagnosed in 59 subjects, and 27 of these were classified as higher than Los Angeles classification A. With an increasing degree of reflux esophagitis observed on EGD, the SUV_{max} in the esophagus and around the EG junction was also increased.
Conclusion Our study showed that FDG uptake at the esophagus or the EG junction might be clinically significantly related to esophagitis. However, EGD performed before ^{18}F-FDG PET/CT on the same day may affect the esophageal ^{18}F-FDG uptake.

Keywords Positron emission tomography · Esophagogastroduodenoscopy · Esophagus · Reflux esophagitis · Physiologic activity

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Introduction

Positron emission tomography (PET) with 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is a useful modality in the diagnosis of various medical conditions and is being increasingly used worldwide. ^{18}F-FDG, a radionuclide glucose analog, accumulates in the cells with glycolytic activity. Therefore, FDG PET is a sensitive tool for detecting various malignancies; however, cellular FDG uptake is not limited to the malignant process alone [1–5]. There are a number of benign conditions, including physiologic uptake and normal variants of many organs, or inflammatory processes, in which cells show ^{18}F-FDG uptake. Thus, for a more accurate interpretation of the ^{18}F-FDG PET/CT findings, it is important to know about the benign conditions in which ^{18}F-FDG uptake increases. Thus far, although there have been many studies on physiologic ^{18}F-FDG uptake and ^{18}F-FDG uptake in benign diseases [6–10], some physiologic or inflammatory findings are not well understood.

Physiologic ^{18}F-FDG uptake and ^{18}F-FDG uptake in benign disease of the stomach are well described because the diseases of the stomach are relatively common and diverse [11]; however, few studies have evaluated ^{18}F-FDG uptake in the esophagus [12, 13]. The prevalence of gastroesophageal reflux disease (GERD) is very high worldwide [14, 15] and has increased rapidly during recent years in Korea [16]. GERD has a variety of clinical manifestations, and sometimes

the symptoms can be severe. In addition, previous studies have reported that reflux esophagitis increases the risk of esophageal adenocarcinoma [17–20]. However, despite the high prevalence and importance of GERD and reflux esophagitis, only few studies have assessed the correlation between reflux esophagitis and ^{18}F-FDG uptake so far [21].

The purpose of this study was to compare the findings of esophageal ^{18}F-FDG PET/CT and esophagogastroduodenoscopy (EGD), with the focus on reflux esophagitis. We also analyzed clinical factors that could affect esophageal FDG uptake.

Materials and Methods

Subjects

We retrospectively enrolled 369 subjects who underwent ^{18}F-FDG PET/CT and EGD between January 2014 and December 2014. Subject history was recorded for proper interpretation of the ^{18}F-FDG PET/CT data. Subjects who had undergone esophagus or stomach surgery as well as those with poor registration on ^{18}F-FDG PET/CT were excluded. Most of the subjects underwent ^{18}F-FDG PET/CT and EGD on the same day per the protocols defined at our health check-up center. EGD was performed first, followed by ^{18}F-FDG PET/CT scanning. For subjects who underwent ^{18}F-FDG PET/CT and EGD on different days, if the time between the two procedures was >1 month, the subjects were excluded.

^{18}F-FDG PET/CT

^{18}F-FDG PET/CT scans were performed using a PET/CT scanner (Biograph mCT 20 Excel, Siemens). All patients were fasted for at least 6 h, and the peripheral blood glucose level was confirmed to be ≤140 mg/dl before FDG injection. ^{18}F-FDG was intravenously administered at 5.5 MBq/kg of body weight. PET/CT scanning from the skull base to the mid-thigh was performed 60 min after intravenous injection of FDG. After the initial low-dose CT study, a standard PET protocol was used for scanning, with an acquisition time of 2 min per bed position. The acquired images were reconstructed using the iterative True X + TOF algorithm.

Image Analysis

^{18}F-FDG PET/CT images were interpreted on interactive workstations by two board-certified nuclear medicine physicians, and any equivocal cases were resolved by consensus. Readers were blinded to the results of EGD at the time of the PET image review. Image interpretation was based on visual and semiquantitative analysis using the attenuation-corrected PET emission images. The intensity of the focal ^{18}F-FDG uptake was expressed as the maximum standardized uptake value (SUV_{max}).

The range and intensity of esophageal involvement were visually analyzed. Visual grading of the ranges was divided into grade 0 to 3 (0=no discernible or focal uptake; 1=less than one-third of the esophagus; 2=more than one-third of the esophagus; 3=nearly or entire esophagus). The intensity of the esophageal uptake was also visually analyzed and divided into grade 0 to 3 (0=no discernible uptake; 1=minimal uptake; 2=similar to liver uptake; 3=higher than liver uptake).

The SUV_{max} values of the esophagus and around the esophagogastric (EG) junction were measured, and the specific locations were recorded. If ambiguous, the board-certified radiologist confirmed the location of the EG junction. Some cases with poor registration were excluded after this step.

EGD Analysis

EGD results were provided by the gastroenterologist. All subjects were fasted from 9 p.m. the previous day until the endoscopic procedures had been performed by experienced endoscopists. Reflux esophagitis was diagnosed and graded according to the Los Angeles classification. Hiatus hernia and other minor findings, including Barrett's esophagus, were also recorded.

Statistical Analysis

Differences in variables between subject groups were analyzed using the Mann-Whitney and Student t-test as well as one-way ANOVA test. Optimal cutoff values for continuous variables were determined using receiver-operating characteristic (ROC) curve analysis. Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc.), and $p<0.05$ was considered statistically significant.

Results

Subject Characteristics

Of a total of 369 subjects, 33 with advanced cancer status, history of gastrectomy or esophagectomy, or poor registration on ^{18}F-FDG PET/CT and 16 with a >1-month interval between ^{18}F-FDG PET/CT and EGD were excluded. Ten subjects with minor findings on EGD were also excluded. Of the remaining 310 subjects, 262 had undergone ^{18}F-FDG PET/CT and EGD on the same day. According to the health check-up

protocol followed at our check-up center, EGD was performed first, followed by ^{18}F-FDG PET/CT (Fig. 1).

EGD Findings

Reflux esophagitis was diagnosed in 59 (19.03 %) subjects, with 27 (8.71 %) of them classified as having higher than Los Angeles classification A. Hiatus hernia was diagnosed in 15 (4.84 %) subjects on EGD; other minor findings included esophageal polyp, esophageal diverticulum, glycogenic acanthosis, heterotopic gastric mucosa, Barrett's esophagus, Mallory-Weiss tear, and esophageal submucosal tumor.

Correlation Between Prior EGD and Esophageal Uptake in ^{18}F-FDG PET/CT

In several subjects who underwent ^{18}F-FDG PET/CT and EGD on the same day, typical linear FDG uptake was observed (Fig. 2), and visual analysis of the range and intensity of the ^{18}F-FDG uptake showed relatively diffuse and discernible ^{18}F-FDG uptake in the whole esophagus (Table 1). However, there were no significant statistical differences in the SUV values (Table 2).

Correlation Between SUV and Esophagitis Severity by the Los Angeles Classification

As the degree of reflux esophagitis observed on EGD increased, a greater value of the SUV_{max} in the esophagus and around the EG junction was observed (Figs. 3, 4 and Table 2). Figure 4 and Table 2 show the statistical significance of SUV parameters according to the severity of esophagitis.

ROC curve analysis was performed to determine the optimal cutoff in cases of reflux esophagitis classified as greater than Los Angeles classification A. When the cutoff for the

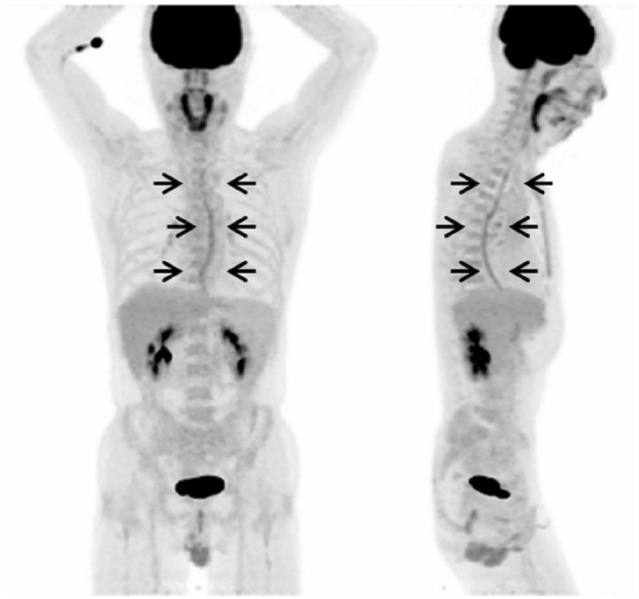

Fig. 2 Typical findings of subjects who underwent PET-CT and EGD on the same day; typical linear FDG uptake was observed in subjects who underwent ^{18}F-FDG PET/CT and EGD on the same day

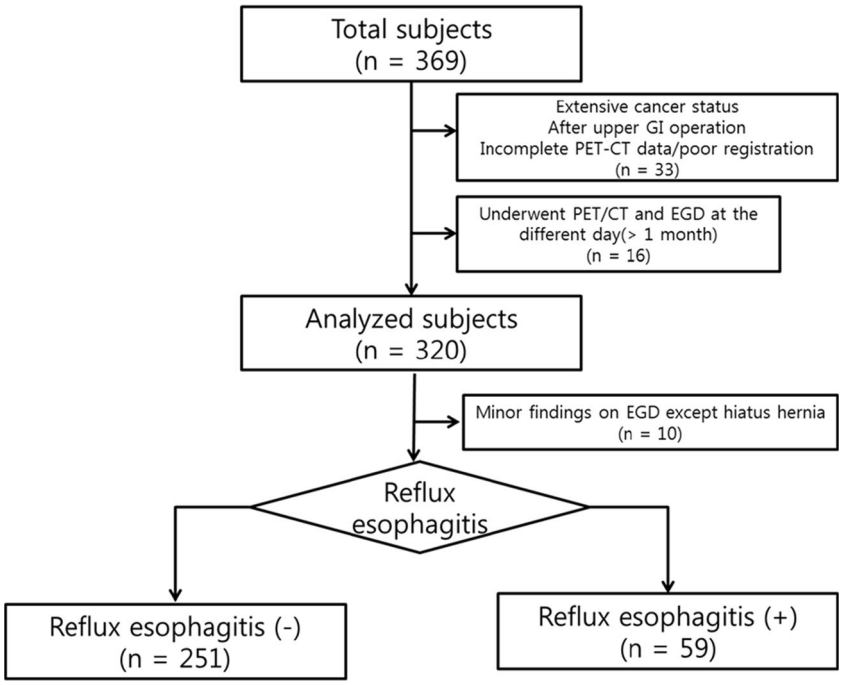

Fig. 1 Flowchart of inclusion and exclusion of the study population

Table 1 EGD effect of esophageal uptake on ^{18}F-FDG PET/CT; range/intensity (no reflux subjects on EGD)

	Degree	Same day (n=212)	Different day (n=39)	p-value
Range	0	138 (65.10 %)	35 (89.74 %)	0.002
	1	33 (15.57 %)	2 (5.13 %)	
	2	27 (12.74 %)	2 (5.13 %)	
	3	14 (6.60 %)	0 (0.00 %)	
Intensity	0	132 (62.26 %)	32 (82.05 %)	0.016
	1	38 (17.92 %)	4 (10.26 %)	
	2	39 (18.40 %)	3 (7.69 %)	
	3	3 (1.42 %)	0 (0.00 %)	

Range: 0=no discernible or focal uptake; 1=less than one-third of the esophagus; 2=more than one-third of the esophagus; 3=nearly or entire esophagus/intensity: 0=no discernible uptake; 1=minimal uptake; 2=similar to liver uptake; 3=higher than liver uptake

$SUV_{EG\ junction}$ was set at 2.99, the sensitivity and specificity for the detection of esophagitis were 81.5 and 78.8 %, respectively, and when the cutoff for SUV_{max} was set at 3.32, they were 81.5 and 83.4 %, respectively (Fig. 5 and Table 3).

Other EGD Findings Affecting Esophageal Uptake on ^{18}F-FDG PET/CT

Fifteen (4.84 %) subjects were diagnosed with hiatus hernia (SUV_{max}, 3.67±1.41; $SUV_{EG\ junction}$, 3.27±1.02), and 8 of these had reflux esophagitis. Only two subjects were diagnosed with Barrett's esophagus (SUV_{max}, 3.28±0.48; $SUV_{EG\ junction}$, 3.53±0.86).

Discussion

The prevalence of GERD in Korea has been rapidly increasing in recent years and has been reported as 3.4–7.9 % [22]. The prevalence of reflux esophagitis in our study was relatively higher than that reported previously; one of the reasons could be that our study population included subjects from Western countries, where the prevalence of GERD is relatively higher.

In several subjects who underwent ^{18}F-FDG PET/CT and EGD on the same day, visual analysis of the range and intensity showed diffuse and discernible ^{18}F-FDG uptake in the esophagus. The influence of EGD, including mechanical irritation by endoscopy, is suggested as the main factor responsible for this diffuse ^{18}F-FDG uptake. However, there were no significant statistical differences in SUV values between the subjects who underwent ^{18}F-FDG PET/CT and EGD on the same day and on different days. It is supposed that the influence of EGD causing ^{18}F-FDG uptake is not more powerful than normal physiologic muscle uptakes. Owing to its linear property of FDG uptake on the same day, esophageal uptake by EGD was easily found on visual analysis, but the intensity of FDG uptake was not higher than focal physiologic uptake.

Early esophageal cancers, including superficial esophageal squamous cell carcinoma, may show low-grade FDG uptake. It is difficult to evaluate the T-stage of early esophageal cancers on ^{18}F-FDG PET/CT [23, 24]. Sherard et al. showed that ^{18}F-FDG PET/CT is not indicated while staging superficial

Table 2 SUV analysis by the Los Angeles classification

Degree of esophagitis N=total number (%) (same day/different day)	Average SUV_{max} (range)			p-value*
	Total	Same day	Different day	
No reflux				
N=251 (81.0 %) (212/39)	2.74±0.62 (1.56–6.39)	2.74±0.60	2.72±0.69	0.822
Minimal				
N=32 (10.3 %) (26/6)	3.02±0.98 (1.63–6.00)	3.00±1.02	3.16±0.80	0.720
LA class A				
N=20 (6.5 %) (18/2)	3.85±0.99 (2.33–6.16)	3.77±1.00	4.59±0.52	0.272
LA class B				
N=5 (1.6 %) (4/1)	4.98±1.53 (3.55–7.56)	5.16±1.71	4.28	0.677
LA class C & D				
N=2 (0.6 %) (2/0)	8.01±0.38 (7.63–8.39)	8.01±0.38	–	

*Statistical difference between 'same day' and 'different day'

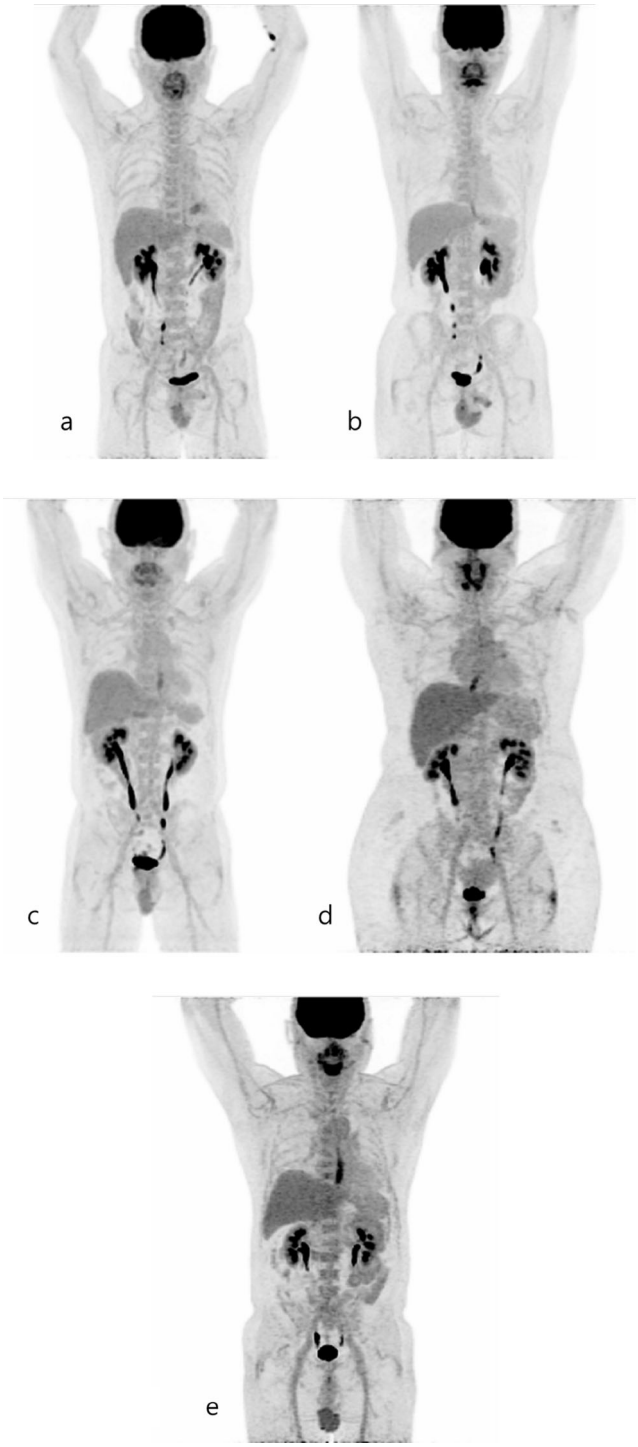

Fig. 3 The correlation between SUV and esophagitis by the Los Angeles classification. As the degree of reflux esophagitis observed on EGD increased, a greater value of the SUV_{max} in the esophagus and around the EG junction was observed. **a** Minimal reflux esophagitis (SUVmax 2.42); **b** Los Angeles classification A (SUVmax 3.51), **c** Los Angeles classification B (SUVmax 4.52), **d** Los Angeles classification C (SUVmax 7.63), and **e** Los Angeles classification D (SUVmax 8.39)

esophageal cancers [25]. Moreover, Johannes et al. reported that focality and eccentricity in visual analysis of ^{18}F-FDG uptake could help differentiate early malignant esophageal lesions from benign ones [12]. This research is focused on the pattern of ^{18}F-FDG uptake because the SUV parameters did not show satisfactory results. Generally, in the 1-day protocol, EGD is performed first, followed by ^{18}F-FDG PET/CT for radiation safety. However, according to our results, EGD performed before ^{18}F-FDG PET/CT on the same day may mask the malignant lesions or misinterpret the extent of malignancy. Compared to operation or biopsy, the effect of noninvasive procedures such as EGD is ignored. However, to overcome this limitation, performing EGD and ^{18}F-FDG PET/CT on the same day should be avoided.

As the degree of reflux esophagitis observed on EGD increased, the SUV_{max} in the esophagus and around the EG junction were also increased. Despite the overlap, these findings were clearly observed. Moreover, the cutoff values for SUV for detecting reflux esophagitis, derived from the ROC analysis, showed acceptable results in the present study (Table 3 and Fig. 5). The SUV parameters presented in previous studies suggested the possibility of FDG PET/CT to detect GERD or esophagitis [26, 27], which was also observed in our study. On the other hand, Barrett's esophagus is a consequence of gastroesophageal reflux disease. The risk of esophageal adenocarcinoma is greater in cases diagnosed with esophagitis; most of this malignancy seems to be related to Barrett's esophagus [20]. In our study, few cases were diagnosed with Barrett's esophagus and showed relatively high-grade FDG uptake, but the degree of FDG uptake was lower than that in cases of severe esophagitis. This can be explained because Barrett's esophagus is not always associated with the active inflammatory process [28, 29].

GERD can be caused by hiatus hernia [30–32]. According to Yeom et al., among patients with reflux esophagitis, hiatal hernia was found in 31.5 % in Korea [33]. Eight of 15 cases with hiatus hernia were diagnosed as having reflux esophagitis in our study. The subjects with hiatus hernia showed relatively high prevalence of reflux esophagitis, and the SUV parameters were statistically significant.

Our study had several limitations. Our findings proposed that subjects undergoing PET-CT and EGD on the same day show more diffuse and discernible FDG uptake along the esophagus on PET-CT. However, the most influential factor causing these findings is not clear. The factors related to EGD, such as inspection time, preconditioning, difficulty of the procedure, or skill of the gastroenterologist, may affect this uptake, but these factors were not evaluated. Moreover, making a

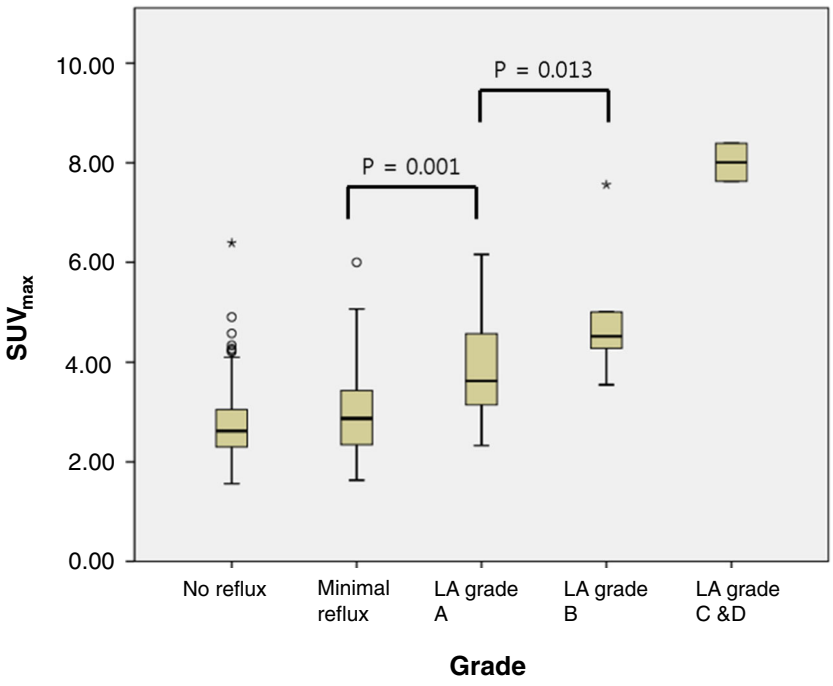

Fig. 4 ^{18}F-FDG uptake and the grades of esophagitis; the degree of reflux esophagitis observed on EGD was increased, and the SUV_{max} in the esophagus and around the EG junction was also increased. It shows the statistical significance in SUV parameters according to the severity of esophagitis

correlation between FDG uptake and symptoms of reflux esophagitis was not possible in this study, because symptoms such as heartburn or regurgitation were not recorded.

Some cases showed typical findings of severe reflux esophagitis on ^{18}F-FDG PET/CT, without notable findings on EGD, possibly because of nonerosive reflux disease (NERD) [34]; however, the exact cause of this finding remains unclear. Another limitation of this study is that it had a retrospective design. Although the total number of subjects in this study was not small, not enough cases had esophagitis graded as greater than Los Angeles classification B, possibly because this study was performed at a single institution in Korea, a country with a relatively low prevalence of GERD.

It is not likely that PET-CT will be used as the diagnostic modality for GERD, and EGD will remain the gold standard for diagnosing diseases of the esophagus, including esophagitis; however, our results will be helpful for interpreting esophageal uptake on ^{18}F-FDG PET/CT.

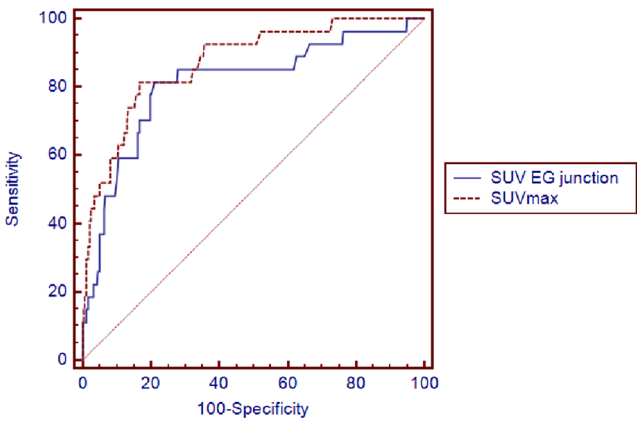

Fig. 5 Receiver-operator characteristic (ROC) curves of the $SUV_{EG\ junction}$ and SUV_{max} in differentiating esophagitis

Conclusion

Our study showed that FDG uptake at the esophagus or at the EG junction might be related to clinically significant esophagitis. However, EGD performed shortly before ^{18}F-FDG PET/CT on the same day may affect the esophageal ^{18}F-FDG uptake. If diffuse and discernible ^{18}F-FDG uptake is observed at the esophagus on ^{18}F-FDG PET/CT, physicians should determine if the subject has undergone prior EGD.

Table 3 Diagnostic performance in the differentiation of no reflux and minimal reflux from cases more severe than Los Angeles classification A

Parameter	$SUV_{EG\ junction}$	SUV_{max}
Threshold	>2.99	>3.32
Area under the curve	0.806	0.866
Sensitivity (%)	81.5	81.5
Specificity (%)	78.8	83.4

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Compliance with ethical standards

Conflict of Interest KwanHyeong Jo, Soyoung Kim, Jongtae Cha, Sang Hyun Hwang, Narae Lee, Mijin Yun and Won Jun Kang declare that they have no conflict of interest.

Ethical Statement This study was approved by the ethics committee in our institution and was performed in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was waived because of the retrospective design of this study.

This manuscript has not been published before and is not under consideration for publication anywhere else, and it has been approved by all co-authors.

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