

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 April 21; 23(15): 2635-2818



**EDITORIAL**

- 2635 Dietary compliance in celiac disease

*Freeman HJ*

- 2640 Is there still a role for the hepatic locoregional treatment of metastatic neuroendocrine tumors in the era of systemic targeted therapies?

*Cavalcoli F, Rausa E, Conte D, Nicolini AF, Massironi S*

**REVIEW**

- 2651 Hepatitis B virus infection and alcohol consumption

*Iida-Ueno A, Enomoto M, Tamori A, Kawada N*

- 2660 Endoscopic management of pancreatic fluid collections-revisited

*Nabi Z, Basha J, Reddy DN*

**ORIGINAL ARTICLE****Basic Study**

- 2673 Overexpression of fibrinogen-like protein 2 protects against T cell-induced colitis

*Bartczak A, Zhang J, Adeyi O, Amir A, Grant D, Gorczynski R, Selzner N, Chruscinski A, Levy GA*

- 2685 Changes in human hepatic metabolism in steatosis and cirrhosis

*Schofield Z, Reed MAC, Newsome PN, Adams DH, Günther UL, Lalor PF*

- 2696 Effect of *Lactobacillus rhamnosus* HN001 and *Bifidobacterium longum* BB536 on the healthy gut microbiota composition at phyla and species level: A preliminary study

*Toscano M, De Grandi R, Stronati L, De Vecchi E, Drago L*

- 2705 Effects of Hwangryunhaedok-tang on gastrointestinal motility function in mice

*Kim H, Kim I, Lee MC, Kim HJ, Lee GS, Kim H, Kim BJ*

- 2716 Role of  $\Delta 133p53$  isoform in NF- $\kappa$ B inhibitor PDTC-mediated growth inhibition of MKN45 gastric cancer cells

*Zhang HM, Sang XG, Wang YZ, Cui C, Zhang L, Ji WS*

**Retrospective Cohort Study**

- 2723 Optimal treatment for Siewert type II and III adenocarcinoma of the esophagogastric junction: A retrospective cohort study with long-term follow-up

*Hosoda K, Yamashita K, Moriya H, Mieno H, Watanabe M*

## Retrospective Study

- 2731 Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain)

*Portillo I, Arana-Arri E, Idigoras I, Bilbao I, Martínez-Indart L, Bujanda L, Gutierrez-Ibarluzea I*

- 2743 Performance of 18-fluoro-2-deoxyglucose positron emission tomography for esophageal cancer screening

*Sekiguchi M, Terauchi T, Kakugawa Y, Shimada N, Saito Y, Matsuda T*

- 2750 Association of obesity with
- Helicobacter pylori*
- infection: A retrospective study

*Xu MY, Liu L, Yuan BS, Yin J, Lu QB*

- 2757 Outcomes and prognostic factors of patients with stage IB and II A pancreatic cancer according to the 8
- <sup>th</sup>
- edition American Joint Committee on Cancer criteria

*Li Y, Tang CG, Zhao Y, Cao WY, Qu GF*

## Clinical Trials Study

- 2763 Patients with non-viral liver disease have a greater tumor burden and less curative treatment options when diagnosed with hepatocellular carcinoma

*Mohsen W, Rodov M, Prakoso E, Charlton B, Bowen DG, Koorey DJ, Shackel NA, McCaughan GW, Strasser SI*

- 2771 Urinary metabolomics analysis identifies key biomarkers of different stages of nonalcoholic fatty liver disease

*Dong S, Zhan ZY, Cao HY, Wu C, Bian YQ, Li JY, Cheng GH, Liu P, Sun MY*

## Observational Study

- 2785 Age-related impairment of esophagogastric junction relaxation and bolus flow time

*Cock C, Besanko LK, Burgstad CM, Thompson A, Kritas S, Heddle R, Fraser RJL, Omari TI*

- 2795 Endoscopic ultrasound-guided cutting of holes and deep biopsy for diagnosis of gastric infiltrative tumors and gastrointestinal submucosal tumors using a novel vertical diathermic loop

*Liu YM, Yang XJ*

- 2802 Non-ALT biomarkers for markedly abnormal liver histology among Chinese persistently normal alanine aminotransferase-chronic hepatitis B patients

*Cheng JL, Wang XL, Yang SG, Zhao H, Wu JJ, Li LJ*

## CASE REPORT

- 2811 One step minilaparotomy-assisted transmesenteric portal vein recanalization combined with transjugular intrahepatic portosystemic shunt placement: A novel surgical proposal in pediatrics

*Pelizzo G, Quaretti P, Moramarco LP, Corti R, Maestri M, Iacob G, Calcaterra V*

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NAME OF JOURNAL  
*World Journal of Gastroenterology*

ISSN  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

LAUNCH DATE  
October 1, 1995

FREQUENCY  
Weekly

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7901 Stoneridge Drive, Suite 501,  
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Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

### PUBLISHER

Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpoffice@wjgnet.com](mailto:bpoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE  
April 21, 2017

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## Retrospective Study

# Performance of 18-fluoro-2-deoxyglucose positron emission tomography for esophageal cancer screening

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**Supported by** (in part) the National Cancer Center Research and Development Fund, No. 27-A-5.

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee for Clinical Research of the National Cancer Center.

**Informed consent statement:** All study participants provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** None of the authors report a conflict of interest.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Invited manuscript

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**Telephone:** +81-3-35422511  
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**Received:** January 6, 2017

**Peer-review started:** January 9, 2017

**First decision:** February 9, 2017

**Revised:** February 23, 2017

**Accepted:** March 20, 2017

**Article in press:** March 20, 2017

**Published online:** April 21, 2017

## Abstract

### AIM

To evaluate the performance of 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) for esophageal cancer (EC) screening.

### METHODS

We retrospectively analyzed the data of consecutive asymptomatic individuals who underwent FDG-PET and esophagogastroduodenoscopy (EGD) simultaneously for cancer screening at our institution from February 2004 to March 2013. In total, 14790 FDG-PET and EGD procedures performed for 8468 individuals were included in this study, and the performance of FDG-PET for EC screening was assessed by comparing the



results of FDG-PET and EGD, considering the latter as the reference.

## RESULTS

Thirty-two EC lesions were detected in 28 individuals (31 squamous cell carcinomas and 1 adenocarcinoma). The median tumor size was 12.5 mm, and the depths of the lesions were as follows: Tis ( $n = 12$ ), T1a ( $n = 15$ ), and T1b ( $n = 5$ ). Among the 14790 FDG-PET procedures, 51 examinations (0.3%) showed positive findings in the esophagus; only 1 was a true-positive finding. The screen sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET for ECs were 3.6% (95%CI: 0.1-18.3), 99.7% (95%CI: 99.6-99.7), 2.0% (95%CI: 0.0-10.4), and 99.8% (95%CI: 99.7-99.9), respectively. Of the 50 FDG-PET false-positive cases, 31 were observed in the lower esophagus, and gastroesophageal reflux disease was observed in 17 of these 31 cases.

## CONCLUSION

This study is the first to clarify the FDG-PET performance for EC screening. Based on the low screen sensitivity, FDG-PET is considered to be difficult to use as a screening modality for ECs.

**Key words:** Cancer screening; Esophageal cancer; Esophagogastroduodenoscopy; Positron emission tomography; Screen sensitivity

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**Core tip:** The present study first clarified the performance of 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) for esophageal cancer screening by adopting an appropriate study method. A large number of asymptomatic screened individuals who underwent both FDG-PET and esophagogastroduodenoscopy were included in the study, and the performance of FDG-PET was assessed by comparing the results of FDG-PET and esophagogastroduodenoscopy, considering the latter as the reference. As a result, the low screen sensitivity (3.6%) and positive predictive value (2.0%) of FDG-PET for esophageal cancer were clearly shown. Based on the results, FDG-PET is considered to be difficult to use as a screening modality for esophageal cancer.

Sekiguchi M, Terauchi T, Kakugawa Y, Shimada N, Saito Y, Matsuda T. Performance of 18-fluoro-2-deoxyglucose positron emission tomography for esophageal cancer screening. *World J Gastroenterol* 2017; 23(15): 2743-2749 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i15/2743.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i15.2743>

## INTRODUCTION

Esophageal cancer (EC) is the eighth most common

cancer worldwide and is reportedly associated with high mortality<sup>[1]</sup>. The high mortality of EC remains problematic also in Japan<sup>[2,3]</sup>. Notably, however, the prognosis of asymptomatic superficial ECs treated by endoscopic resection is reportedly favorable<sup>[3]</sup>. We can therefore postulate that early detection of ECs in the screening setting before the occurrence of symptoms is essential.

Endoscopy, particularly image-enhanced endoscopy, is accepted as the most useful EC screening modality<sup>[4-9]</sup>; others include whole-body cancer screening modalities. 18-Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) is one modality being increasingly used to screen for whole-body cancers, including EC, in the opportunistic screening setting<sup>[10]</sup>. Although the usefulness of FDG-PET for the assessment of EC extension and metastasis, detection of EC recurrence after treatment, and evaluation of the response to therapy for EC has been well examined<sup>[11-17]</sup>, only limited data are available on the performance of FDG-PET for EC screening. With respect to the diagnostic ability of FDG-PET for primary EC lesions, EC that invades the submucosal layer or deeper can reportedly be detected, but more superficial ECs are difficult to detect<sup>[11,13,14,18]</sup>. Based on this finding, it can be hypothesized that FDG-PET is not suitable for EC screening. To the best of our knowledge, however, no study has evaluated the true screen sensitivity of FDG-PET for EC. Asymptomatic individuals instead of patients with clinically diagnosed cancers must be evaluated to clarify the true screen sensitivity<sup>[19,20]</sup>. Furthermore, it is best to analyze screened individuals undergoing both FDG-PET and endoscopy simultaneously because this allows for the most accurate calculations based on the endoscopy findings as the reference<sup>[19,20]</sup>.

In the present study, therefore, we examined the performance of FDG-PET for EC screening, including its screen sensitivity for EC, by analyzing large-scale data of asymptomatic screened individuals who underwent both FDG-PET and endoscopy.

## MATERIALS AND METHODS

### Study design and subjects

This single-center retrospective study was approved by the Ethics Committee for Clinical Research of the National Cancer Center. We retrospectively analyzed the data of consecutive asymptomatic individuals who underwent opportunistic cancer screening at the cancer screening division of the National Cancer Center, Tokyo from February 2004 to March 2013.

During the study period, 25120 screening esophagogastroduodenoscopies (EGDs) were performed for 13128 individuals, including those who underwent more than one EGD in different years. Among them, 14883 EGDs were performed simultaneously (on the previous day) with FDG-PET examinations in 8468 individuals. Excluding 6 individuals who refused to

participate in the study and 24 individuals with a history of esophageal treatment, 14790 EGDs and FDG-PETs performed for 8438 individuals were included and retrospectively analyzed in this study.

To evaluate the performance of FDG-PET for EC screening, we compared the results of FDG-PET and EGD, considering the latter as the reference, and then calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FDG-PET for EC lesions. If multiple ECs were detected in one patient, the most advanced lesion in terms of tumor depth and size was analyzed as the representative one.

ECs were defined as malignant epithelial tumors originating in the esophagus, including squamous cell carcinoma (SCC) and adenocarcinoma<sup>[21]</sup>. According to the Vienna classification, both invasive and noninvasive carcinoma (carcinoma *in situ*) were included in ECs<sup>[22]</sup>.

FDG-PET and EGD were performed on two consecutive days. FDG-PET was performed on the first day and EGD on the second day. Each test was performed and diagnosed in a blinded fashion with no knowledge of the findings of the other test by different doctors<sup>[19,20]</sup>.

#### **FDG-PET examination**

FDG-PET was conducted according to the Japanese FDG-PET guidelines published by the Japanese Society of Nuclear Medicine ([http://www.jsnm.org/fdg\\_pet/](http://www.jsnm.org/fdg_pet/)), as previously described<sup>[20]</sup>. PET and PET/CT were used during the study period. For the first 2 years (February 2004 to December 2005), only PET was used (ECAT Accel; Siemens, Washington DC, United States); this was gradually replaced by PET/CT (Aquiduo PCA-7000B; Toshiba, Tokyo, Japan, or Discovery-600; GEMS, Milwaukee, WI, United States). The findings and diagnoses of FDG-PET examinations were evaluated by a single expert radiologist specializing in nuclear medicine who was blinded to the endoscopic findings. A positive FDG-PET finding was defined as significantly higher round or oval focal accumulation of FDG in the esophagus compared with background levels. Segmental uptake, *i.e.*, FDG accumulation in the shape of the part of the esophagus in which it was present was diagnosed as a negative FDG-PET finding. The maximum standardized uptake value (SUVmax) was evaluated in cases of positive FDG-PET findings.

#### **EGD examination**

EGD examinations were performed by endoscopists certified by the Japanese Gastrointestinal Endoscopy Society as previously described<sup>[19]</sup>. Transoral (GIF H-260, GIF-Q260; Olympus Co., Tokyo, Japan) or transnasal endoscopy (EG 530-NW, EG 580-NW; Fujifilm Co., Tokyo, Japan) was performed according to each screenee's request. The image-enhanced function (narrow band imaging or flexible spectral imaging color enhancement) was routinely used. If necessary, 2% Lugol solution was sprayed on the esophageal mucosa.

Biopsies were taken for histopathological examination of all lesions that appeared potentially malignant. When an EC lesion was detected, the patient was recommended to receive treatment at the National Cancer Center Hospital or any other hospital. The results of the treatment, including the histopathological findings of the resected specimens, were reviewed and recorded.

#### **Evaluation of screenee characteristics**

All screened individuals at our institution are required to complete a self-administered questionnaire on lifestyle, demographic characteristics, and medical history at the time of their first screening and 5 years later<sup>[23]</sup>. In the present study, information about cigarette smoking (nonsmoker, ex-smoker, or current smoker) and alcohol drinking (nondrinker, ex-drinker, or current drinker) were extracted from these questionnaires. Age, sex, height, and weight were also evaluated.

#### **Evaluation of EC characteristics**

The macroscopic type of EC was determined endoscopically in accordance with the Paris classification<sup>[24]</sup>. The tumor location was also determined endoscopically and classified as cervical esophagus, upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus, or abdominal esophagus<sup>[25]</sup>. The size of the EC lesions was measured based on the pathological evaluation of each surgically or endoscopically resected specimen; when a specimen was not resected, its size was determined endoscopically. Tumor depth was also pathologically determined except when EC lesions were not resected. The depth of EC lesions that were not resected was evaluated using EGD and endoscopic ultrasonography. The histopathological type of EC was determined by the evaluation of each endoscopically or surgically resected specimen; the type was determined based on examination of the biopsy specimen only when it was not resected. The staging of EC lesions was based on the TNM classification<sup>[26]</sup>. The presence of lymph node and distant metastasis was evaluated based on radiological imaging (in all patients) and pathological evaluation of resected lymph nodes (only in patients undergoing surgery with lymphadenectomy).

#### **Statistical analysis**

Statistical analyses were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, United States) and the statistical program R, version 3.2.4 (<http://cran.r-project.org>). For evaluation of the sensitivity, specificity, PPV, and NPV of FDG-PET for ECs, 95%CI were also calculated for these estimates. The  $\chi^2$  test or Fisher's exact test was used for categorical variables, and the Mann-Whitney *U* test was used for continuous variables to compare the screenee characteristics between cases with and without ECs. A *P* value of < 0.05 was considered statistically significant.

**Table 1** Screenee characteristics in the cases with and without esophageal cancer *n* (%)

Characteristics	Total ( <i>n</i> = 14790)	Esophageal cancer(+) ( <i>n</i> = 28)	Esophageal cancer(-) ( <i>n</i> = 14762)	<i>P</i> value
Age (yr), median (range)	61.0 (40-92)	67.5 (55-76)	61.0 (40-92)	< 0.001 <sup>1</sup>
Gender				0.002 <sup>2</sup>
Male	9699 (65.6)	26 (92.9)	9673 (65.5)	
Female	5091 (34.4)	2 (7.1)	5089 (34.5)	
Body mass index, median (range)	23.3 (13.3-44.7)	23.6 (17.6-31.3)	23.3 (13.3-44.7)	0.885 <sup>1</sup>
Smoker				0.136 <sup>2</sup>
Current smoker	1310 (12.9)	4 (18.2)	1306 (12.9)	
Former smoker	3921 (38.6)	12 (54.5)	3909 (38.5)	
Non-smoker	4936 (48.5)	6 (27.3)	4930 (48.6)	
Alcohol				0.171 <sup>2</sup>
Current drinker	7479 (73.6)	20 (90.9)	7459 (73.5)	
Former drinker	391 (3.8)	0 (0.0)	391 (3.9)	
Non-drinker	2297 (22.6)	2 (9.1)	2295 (22.6)	

<sup>1</sup>*P* values were calculated using the Mann-Whitney *U* test; <sup>2</sup>*P* values were calculated using the  $\chi^2$  test.

**Table 2** Clinicopathologic findings of esophageal cancers detected in this study

Size (mm), median (range)	12.5 (5-60)
Depth <sup>1</sup>	
Tis/T1a/T1b	12/15/5
Location	
Ce/Ut/Mt/Lt/Mt-Lt/Ae	0/1/20/8/2/1
Macroscopic type	
0-II c/0-II c + II a/0-I + II b	30/1/1
Histopathological type	
SCC/ adenocarcinoma	31/1
Treatment <sup>2</sup> , endoscopic treatment/ surgery/ chemoradiotherapy/ radiation/ unknown	28/1/3/1/1
Lymph node metastasis	
Positive/negative	1/31
Distant metastasis	
Positive/negative	0/32

<sup>1</sup>The depth of four lesions that were not resected (*n* = 3) or had an unknown treatment result (*n* = 1) were determined clinically: T1a (*n* = 2) and T1b (*n* = 2); <sup>2</sup>Two cases overlapped: surgery following noncurative endoscopic resection (*n* = 1) and chemoradiotherapy following noncurative endoscopic resection (*n* = 1). Ae: Abdominal esophagus; Ce: Cervical esophagus; Lt: Lower thoracic esophagus; Mt: Middle thoracic esophagus; SCC: Squamous cell carcinoma; Ut: Upper thoracic esophagus.

## RESULTS

### Screenee characteristics

The screenee characteristics in the cases with and without ECs are summarized in Table 1. As a whole, the median age was 61 years (range, 40-92), and the male:female ratio was 1.9 (9699:5091). The age of those with ECs (median, 67.5 years; range, 55-76 years) was higher than that of those without ECs (median, 61.0 years; range, 40-92 years) (*P* < 0.001). The male:female ratio was also higher in cases with than without ECs (13.0 vs 1.9, respectively; *P* = 0.002).

Information on smoking and alcohol was available for 10167 of 14790 cases (68.7%). Although the proportion of current smokers and drinkers seemed higher in those with than without ECs, no significant difference was observed.

### Clinicopathologic findings of detected ECs

Thirty-two EC lesions, all of which were histologically proven, were detected in 28 individuals; 25 individuals had 1 lesion, 2 individuals had 2 lesions, and 1 individual had 3 lesions. Clinicopathologic characteristics of the 32 EC lesions are summarized in Table 2. The first treatment was endoscopic resection for 28 lesions, chemoradiotherapy for 2 lesions, and radiation for 1 lesion (the treatment for 1 lesion was unknown). Among the 28 endoscopically resected lesions, resection was noncurative in 2 because of submucosal invasion; 1 underwent subsequent esophagectomy with lymphadenectomy, and the other received subsequent chemoradiation therapy. The pathological evaluation of the 28 resected lesions showed that the depth of invasion was pTis in 12 lesions, pT1a in 13 lesions, and pT1b in 3 lesions. The depth of the other four lesions was estimated to be cT1a (*n* = 2) and cT1b (*n* = 2) based on the clinical examination findings. The median lesion size was 12.5 mm (range, 5-60 mm). With the exception of 1 adenocarcinoma lesion, the other 31 lesions were histologically diagnosed as SCC. With respect to lymph node metastasis, one lesion treated with additional esophagectomy with lymphadenectomy following endoscopic resection showed pN0. Among the other 31 lesions that were not treated with surgery, only 1 cT1b case showed cN1; the others showed cN0. No distant metastasis was observed in any patients in this study.

### Sensitivity, specificity, PPV, and NPV of FDG-PET for ECs

The results of the performance of FDG-PET for screening of ECs are shown in Table 3. The sensitivity, specificity, PPV, and NPV of FDG-PET for ECs were 3.6% (95%CI: 0.1-18.3), 99.7% (95%CI: 99.6-99.7), 2.0% (95%CI: 0.0-10.4), and 99.8% (95%CI: 99.7-99.9), respectively. Excluding the cases between 2004 and 2005 during which only PET alone was performed (*n* = 3808), these four values were 5.3% (95%CI: 0.1-26.0),



**Table 3 Performance of 18-fluoro-2-deoxyglucose positron emission tomography for esophageal cancer screening**

	Esophageal cancer(+) ( <i>n</i> = 28)	Esophageal cancer(-) ( <i>n</i> = 14762)	PPV, NPV
FDG-PET positive ( <i>n</i> = 51)	1	50	PPV 2.0% (95%CI: 0.0-10.4)
FDG-PET negative ( <i>n</i> = 14739)	27	14712	NPV 99.8% (95%CI: 99.7-99.9)
Sensitivity, specificity	Sensitivity 3.6% (95%CI: 0.1-18.3)	Specificity 99.7% (95%CI: 99.6-99.7)	

FDG-PET: 18-fluoro-2-deoxyglucose positron emission tomography; NPV: Negative predictive value; PPV: Positive predictive value.

99.6% (95%CI: 99.4-99.7), 2.1% (95%CI: 0.1-11.1), and 99.8% (95%CI: 99.7-99.9), respectively.

### Evaluation of FDG-PET-positive cases and SUVmax

Among the 14790 FDG-PET examinations, 51 (0.3%) showed positive findings in the esophagus; only 1 was a true-positive finding. The true-positive case was a 60-mm 0-II a + II c EC lesion located in the lower thoracic esophagus with a histological diagnosis of SCC and estimated invasion depth of the superficial submucosa; it was detected as a positive FDG-PET finding with an SUVmax of 4.7. The other 50 FDG-PET-positive cases were false-positive, and the median SUVmax in these cases was 3.3 (range, 2.0-5.2). The SUVmax (4.7) of the one true-positive case was higher than that of all but one of the false-positive cases (*n* = 49). Of all 50 false-positive cases, 31 showed a positive FDG-PET finding in the lower part of the esophagus, and gastroesophageal reflux disease (GERD) was observed in 17 of these 31 patients (54.8%; grade A/B of the Los Angeles classification, *n* = 13/4). GERD was not observed in the other 19 false-positive cases.

## DISCUSSION

The present study is the first to evaluate the performance of FDG-PET for ECs in the screening setting. The results clarified the very low screen sensitivity of FDG-PET for ECs. The population comprised asymptomatic individuals, and all detected ECs were superficial and did not invade beyond the submucosal layer. In this situation, the sensitivity of FDG-PET for ECs was very low. Even after excluding old cases using PET alone, the sensitivity was still very low. The difference from several previous studies showing a relatively high sensitivity of FDG-PET for ECs (69%-100%) is considered to be mainly due to the differences in study populations<sup>[11,13,14]</sup>. While the study population of those previous studies was patients with previously known ECs that mostly comprised advanced ECs, the present study population was asymptomatic individuals being screened for cancer. Some previous studies showed low sensitivity of FDG-PET for superficial ECs. The results of our study are consistent with these, and our study is highly important because it confirms the low sensitivity of FDG-PET for ECs in the screening setting<sup>[11,13,14,18]</sup>. Because of the very low

sensitivity, it is believed that FDG-PET is difficult to use as a screening modality for ECs.

The very low PPV with many false-positive cases is also a problem for FDG-PET as a screening modality of ECs. The false-positive results of FDG-PET reportedly may be associated with esophageal inflammation<sup>[27,28]</sup>. In this study, many false-positive cases showed GERD, indicating a possible relationship between false-positive FDG-PET findings and GERD. This raises the question of whether the SUVmax is helpful in differentiating true-positive from false-positive cases, such as those with GERD. In this study, the SUVmax was evaluated in every FDG-PET-positive case, which is a strength of this study. Considering that the SUVmax (4.7) of the one true-positive case was higher than that of almost all false-positive cases (49 of 50), it is possible that the SUVmax may be useful for this differentiation. However, because of the small number of true-positive cases (*n* = 1), it was difficult to draw a clear conclusion regarding this issue. In addition, even if the SUVmax is useful, there must be a limit on the increase in the PPV from the very low value gained in this study.

There were several limitations in this study. First, although this study adopted the results of EGD examinations, the most reliable and accepted modality for detecting ECs, as the reference for the analyses of the performance of FDG-PET, it remains possible that some EC lesions were overlooked by EGD<sup>[4-9]</sup>. However, considering that EGD examinations were performed by experienced endoscopists certified by the Japanese Gastrointestinal Endoscopy Society and that image-enhanced endoscopy was routinely used, the risk of overlooking EC lesions was presumably low, and its effect on the results of the performance of FDG-PET for EC screening was small.

Second, the number of detected ECs was relatively small, and no ECs invading the muscularis propria were included in this study. If ECs invading the muscularis propria had been included, the sensitivity may have increased. Importantly, however, the prevalence of advanced ECs is not expected to be high in the screening setting as shown in this study, and the target lesions to be screened should be early-stage lesions. Thus, the low sensitivity of FDG-PET for ECs in the present study, which analyzed large-scale data of the screening population, is believed to reflect the actual performance of FDG-PET for ECs in the screening

setting.

Third, this study included four ECs in which the clinicopathologic features (tumor depth, *etc.*) were determined not by the pathological evaluation of the whole lesions but by the findings of clinical examinations such as EGD and endoscopic ultrasonography; thus, the accuracy may not have been perfect. However, the diagnostic accuracy of these examinations for ECs is reportedly high, and the effect of this issue on the results of the present study is considered small<sup>[4-9,29]</sup>.

Fourth, the histological type of all ECs except one was SCC in this study, reflecting the predominance of SCC in Japanese ECs and showing that the screening performance of FDG-PET for esophageal adenocarcinomas is difficult to judge from the findings of this study<sup>[3]</sup>. Although the results of FDG-PET performance in EC screening may depend on the histological type of ECs, no high-quality data have shown the difference in FDG-PET visualization between adenocarcinoma and SCC. In addition, considering that the screen sensitivity of FDG-PET for early gastric cancer and early colorectal cancer, both mostly comprising adenocarcinoma, is reportedly low, FDG-PET may still be difficult to use for EC screening even when adenocarcinoma is the predominant histological type of ECs<sup>[19,20]</sup>.

Fifth, data regarding screenee characteristics were missing in a part of cases of this study. However, only individuals considered to be at average risk undergo screening at our institution; thus, the study population as a whole was believed to be at average risk for ECs. The available data on the screenee characteristics showed that the study population did not include many high-risk individuals.

Finally, the FDG-PET findings in this study were evaluated by a single expert radiologist specializing in nuclear medicine. Although this led to reduced interobserver variability, representing a strength of this study, further studies involving multiple radiologists are warranted<sup>[20]</sup>.

In conclusion, this study is the first to examine the performance of FDG-PET for EC screening using a large number of asymptomatic individuals and clearly showed the low sensitivity and PPV of FDG-PET for ECs in the screening setting. Based on these results, FDG-PET is considered to be difficult to use as a screening modality for primary ECs.

## COMMENTS

### Background

The high mortality of esophageal cancer (EC) is problematic worldwide and early detection of ECs in the screening setting is essential. Although 18-Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) is used for cancer screening, only limited data are available on the performance of FDG-PET for EC screening. In this study, the authors examined the performance of FDG-PET for EC screening by analyzing large-scale data of asymptomatic screened individuals who underwent both FDG-PET and endoscopy at the cancer screening division of the National Cancer Center, Tokyo.

### Research frontiers

The usefulness of FDG-PET for the assessment of EC extension and metastasis, detection of EC recurrence after treatment, and evaluation of the response to therapy for EC has been well examined in previous studies. However, there have been few studies evaluating the true performance of FDG-PET for EC screening.

### Innovations and breakthroughs

The present study clarified the FDG-PET performance for EC screening by adopting an appropriate study method. Asymptomatic screened individuals undergoing both FDG-PET and endoscopy simultaneously instead of patients with clinically diagnosed cancers were assessed in this study. The low sensitivity (3.6%) and low positive predictive value (2.0%) of FDG-PET for EC in the screening setting were clearly shown.

### Applications

Based on the results of this study, FDG-PET is considered to be difficult to use as a screening modality for primary ECs.

### Terminology

FDG-PET is a noninvasive nuclear imaging technique (positron emission tomography) using 18-Fluoro-2-deoxyglucose. This modality is increasingly used to screen for whole-body cancers in opportunistic screening.

### Peer-review

Although it is known that PET-CT is not used for EC screening, there have been only limited data available on the performance of FDG-PET for EC screening. Based on the retrospective analysis involving 8438 subjects, this study clarified the very low sensitivity and PPV for detecting EC in an asymptomatic population. This study is well conducted and well thought through. The results are clearly presented and the conclusions are sensible and useful.

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**P- Reviewer:** Deans C, Surucu E **S- Editor:** Yu J **L- Editor:** A  
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ISSN 1007-9327

