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ORIGINAL ARTICLE

Diagnostic value of surveillance ^{18}F-fluorodeoxyglucose PET/CT for detecting recurrent esophageal carcinoma after curative treatment

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Abstract

Purpose Esophageal carcinoma recurs within two years in approximately half of patients who receive curative treatment and is associated with poor survival. While ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a reliable method of detecting recurrent esophageal carcinoma, in most previous studies FDG PET/CT scans were performed when recurrence was suspected. The aim of this study was to evaluate FDG PET/CT as a surveillance modality to detect recurrence of esophageal carcinoma after curative treatment where clinical indications of recurrent disease are absent.

Methods A total of 782 consecutive FDG PET/CT studies from 375 patients with esophageal carcinoma after definitive treatment were reviewed. Abnormal lesions suggestive of recurrence on PET/CT scans were then evaluated. Recurrence was determined by pathologic confirmation or other clinical evidence within two months of the scan. If no clinical evidence for recurrence was found at least 6 months after the scan, the case was considered a true negative for recurrence.

Results The diagnostic sensitivity and specificity of PET/CT for detecting recurrent esophageal carcinomas were 100% (64/64) and 94.0% (675/718), respectively. There were no significant differences in the diagnostic performance of PET/CT for detecting recurrence according to initial stage or time between PET/CT and curative treatments. Unexpected second primary cancers were detected by FDG PET/CT in seven patients.

Conclusions Surveillance FDG PET/CT is a useful imaging tool for detection of early recurrence or clinically unsuspected early second primary cancer in patients with curatively treated esophageal carcinoma but without clinical suspicion of recurrence.

Keywords Esophageal cancer · Surveillance · Nuclear medicine · ^{18}F-fluorodeoxyglucose · PET/CT

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Introduction

Approximately half of esophageal carcinoma patients suffer recurrence within two years of curative treatment [1]. The prognosis for recurrent esophageal carcinomas is poor [2]. However, single or oligo-recurrence and curative treatment have been reported to be associated with prolonged survival after recurrence of esophageal carcinomas [3, 4] and several researchers have studied the impact of salvage treatment for recurrent esophageal carcinomas [5, 6]. It is important to detect recurrent esophageal carcinoma at an early stage in order to maximize opportunities for the patient to obtain such salvage treatment.

In addition to clinical follow-up, upper gastrointestinal endoscopy with biopsy or imaging studies, such as contrast-enhanced chest computed tomography (CT), is recommended for surveillance of recurrent esophageal cancer [7]. However, conventional imaging is sometimes insufficient: as a result, approximately half of recurrent esophageal carcinomas are diagnosed as distant metastases, despite regular surveillance [4, 8]. Furthermore, metastatic lymph nodes are usually identified with conventional CT only when they are greater than 10 mm in diameter, leading to false-negative results when screening for early recurrence in small lymph nodes [9].

In contrast, positron emission tomography/computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (FDG) is able to image the whole body and can detect early functional changes before morphologic changes are evident. A meta-analysis reported that FDG PET/CT can detect recurrent esophageal carcinoma with a pooled sensitivity of 96% and specificity of 78% [10]. However, in most of the studies included in the meta-analysis, FDG PET/CT scans were performed in response to clinical suspicion of recurrence. The utility of regular use of surveillance FDG PET/CT to detect recurrent esophageal carcinoma in esophageal cancer patients without any clinical symptoms or other abnormal imaging findings has not yet been clearly established.

Several studies have reported that post-treatment surveillance protocols that include FDG PET/CT can detect early recurrence in patients with other malignancies. Surveillance with annual FDG PET/CT scans detects more recurrent non-small cell lung cancer than chest CT regardless of whether the lesions are intra- or extra-thoracic [11]. The use of surveillance FDG PET/CT for lung cancer patients also demonstrated added value with respect to selection of management methods [12]. Surveillance FDG PET/CT after treatment of head and neck cancer has been shown to detect not only early recurrence, but also second primary lesions [13]. The value of surveillance FDG PET/CT in cervical cancer, melanoma, and gastric cancer has also been assessed [14–16]. However, to the best of our knowledge, the clinical value of surveillance FDG PET/CT in esophageal carcinoma has not been studied previously.

The purpose of this retrospective study was to evaluate the diagnostic performance of surveillance FDG PET/CT for detection of recurrent esophageal carcinoma and to identify patient subgroups for which surveillance FDG PET/CT may be of the greatest benefit.

Materials and methods

Study subjects

The study population was selected from esophageal cancer patients who underwent curative treatment and on whom surveillance FDG PET/CT was performed at least 3 months after treatment between 2006 and 2015 at our institute. We excluded 11 patients who had a tumor pathology other than carcinoma. Another three patients who had tumors at the esophagogastric junction centered at the cardia (Siewert II) were also excluded because definitive identification of such tumors as either esophageal cancers or gastric cancer remains controversial, and that controversy could have affected the treatment policy in this study [17]. Among 828 FDG PET/CT scans, 46 were excluded for the following reasons: (i) the scans were performed on patients who were diagnosed with recurrence within 2 to 5 months after the scan ($n = 15$), and it was therefore uncertain whether recurrent esophageal carcinoma was absent at the time of the surveillance FDG PET/CT scan (i.e., true negative), or recurrent esophageal carcinoma was present at the time of the surveillance FDG PET/CT scan, but was not detected (i.e., false negative); or (ii) the follow-up duration without recurrence was less than six months and it was not clear whether the negative surveillance FDG PET/CT was a true negative ($n = 31$). Consequently, a total of 782 FDG PET/CT scans of 375 patients were included in this study. This retrospective observational study was approved by our institutional review board with an exemption for written consent from the study subjects.

Medical record review

Medical records were reviewed for clinical characteristics, initial stage, treatment method, clinical follow-up, and diagnosis of recurrence. Cancer stage was based on the American Joint Committee on Cancer Staging Manual, 7th edition. No FDG PET/CT scans were preceded by clinical symptoms or other abnormal findings suggesting recurrent esophageal carcinoma.

Clinical follow-up for surveillance of recurrent esophageal carcinoma after definitive treatment was performed according to our institution's protocol, as previously published [18], and was performed every 2 to 4 months during the first year after definitive treatment, every 4 to 6 months during the next 2 years, and annually thereafter. Surveillance included a physical examination, laboratory test including complete blood count and chemistry, and chest X-ray. CT scans of the chest were performed every 6 to 12 months or more frequently if

clinically indicated. The attending clinician determined whether to perform an FDG PET/CT scan rather than a chest CT. Other tests, including barium contrast esophagography, esophagogastroduodenoscopy, and ultrasonography or CT of neck and abdomen were also performed if clinically indicated.

Recurrence of esophageal cancer was diagnosed by pathologic confirmation or a clinical decision based on imaging. When recurrence was diagnosed within two months of a positive PET/CT scan, it was designated a true positive scan (n = 64). When recurrence was not diagnosed for six months after negative PET/CT scans, it was designated a true negative (n = 675). PET/CT scans in which recurrence was diagnosed within 2 months after the negative PET/CT scan (n = 0) and those in which recurrence was not diagnosed for 6 months after the positive PET/CT scan (n = 43) were considered false negatives and false positives, respectively. Diagnoses of second primary malignancies were also evaluated.

FDG PET/CT imaging

Patients fasted for at least 6 h prior to FDG PET/CT imaging, and blood glucose concentration was confirmed to be <200 mg/dL at the time of FDG injection. Imaging was performed 60 min after injection of 5 MBq/kg of FDG using a Discovery LS (GE Healthcare; n = 115) or an STe PET/CT scanner (GE Healthcare; n = 713) without intravenous or oral contrast medium. A whole-body CT was performed with a continuous spiral technique with an 8-slice helical CT (140 keV; 40–120 mA; section width, 5 mm; Discovery LS) or a continuous spiral technique with a 16-slice helical CT (140 keV; 30–170 mA; section width, 3.75 mm; STe).

The CT scan was followed by a PET scan from head to thigh. Scanning was performed at 4 min per bed position in 2-D mode with attenuation-corrected images (4.3 × 4.3 × 3.9 mm) reconstructed using an ordered-subset expectation maximization algorithm (28 subsets, two iterations; Discovery LS) or 2.5 min per bed position in 3-D mode with attenuation-corrected images (3.9 × 3.9 × 3.3 mm) reconstructed using a 3-D ordered-subset expectation maximization algorithm (20 subsets, two iterations; Discovery STe).

Image analyses

The FDG PET/CT images were reviewed by a nuclear medicine physician. All FDG-avid lesions that showed FDG uptake greater than the mediastinal blood pool activity (for lymph nodes) or background activity (for other recurrent lesions) and could not be explained by physiologic FDG uptake were considered possible recurrent lesions. Each FDG lesion was measured for maximal standard uptake value (SUV_{max}) by manually placing a circular region of interest.

Statistical analyses

The diagnostic performance of PET/CT scans for recurrent esophageal carcinoma was evaluated by calculating the sensitivity, specificity, positive predictive value (PPV), positive likelihood ratio, negative predictive value (NPV), and negative likelihood ratio. Subgroup analyses based upon initial stage and follow-up duration were also performed. A Chi-square test or Fisher's exact test was used for comparisons. All statistical analyses were performed with SPSS® version 24.0 for Windows (Chicago, IL), and P values <0.05 were considered significant.

Results

Characteristics of study subjects

The characteristics of the 375 study subjects are summarized in Table 1. The mean age was 62.5 years, and there were 342 (91.2%) males. The most frequent primary tumor locations were the middle thoracic esophagus (n = 148) and lower thoracic esophagus (n = 139). The histological findings were mostly identification of squamous cell carcinoma (n = 360, 96.0%). The initial tumor stage was 0 or I in 126 subjects, II in 104, and III in 145. Curative treatment options selected were surgery (n = 329), concurrent chemoradiotherapy (CCRT, n = 21), radiotherapy (RT, n = 23), endoscopic submucosal dissection (n = 1), or argon plasma coagulation (n = 1). Neoadjuvant treatment was performed in 85 patients (CCRT 70, RT 2, chemotherapy 13), and adjuvant treatment was used in 101 patients (CCRT 3, RT 13, chemotherapy 85). The number of surveillance PET/CT scans was one in 165 (44.0%), and two in 96 (25.6%) patients.

Surveillance FDG PET/CT for detection of recurrent esophageal carcinoma

Abnormal lesions that suggested recurrent esophageal carcinomas were observed in 107 of 782 scans. Among these, 64 scans were true positive scans and 43 were false positive scans. No abnormal lesions suggestive of recurrent esophageal carcinomas were identified in 675 of 782 scans, with no false negatives. Recurrence was found in 100 patients diagnosed by pathologic confirmation (n = 47) or a clinical decision based on imaging (n = 53) during follow-up. The sensitivity and specificity for detecting recurrent esophageal carcinomas were 100% (64/64) and 94.0% (675/718), respectively (Table 2). The PPV was 59.8% (64/107), and the positive likelihood ratio was 16.7. NPV was 100% (675/675), and the negative likelihood ratio was 0. The accuracy of FDG PET/CT for detecting recurrent esophageal carcinoma was 94.5% (739/782). The sensitivity and specificity of the two

Table 1 Characteristics of 375 subjects who underwent 782 surveillance ^{18}F-FDG PET/CT scans after curative treatment for esophageal carcinoma

Variable		Number (%)
Age	Mean ± SD; years	62.5 ± 8.2
Sex	Male	342 (91.2%)
Location	Cervical	17 (4.5%)
	Upper thoracic	58 (15.5%)
	Middle thoracic	148 (39.5%)
	Lower thoracic	139 (37.1%)
	Esophagogastric junction	13 (3.5%)
Histology	Squamous cell carcinoma	360 (96.0%)
	Adenocarcinoma	8 (2.1%)
	Poorly differentiated carcinoma	5 (1.3%)
	Poorly differentiated neuroendocrine carcinoma	2 (0.5%)
T stage	T0–1	163 (43.5%)
	T2	59 (15.7%)
	T3	147 (39.2%)
	T4	6 (1.6%)
N stage	N0	175 (46.7%)
	N1	137 (36.5%)
	N2	54 (14.4%)
	N3	9 (2.4%)
Stage	0-I	126 (33.6%)
	II	104 (27.7%)
	III	145 (38.7%)
Treatment modality	Surgery	329 (87.7%)
	CCRT	21 (5.6%)
	RT	23 (6.1%)
	Endoscopic submucosal dissection	1 (0.3%)
	Argon plasma coagulation	1 (0.3%)
Neoadjuvant treatment	No	290 (77.3%)
	CCRT	70 (18.7%)
	RT	2 (0.5%)
	CTx	13 (3.5%)
Adjuvant treatment	No	274 (73.1%)
	CCRT	3 (0.8%)
	RT	13 (3.5%)
	CTx	85 (22.7%)
Number of surveillance PET/CT scans for each patient	1	165 (44.0%)
	2	96 (25.6%)
	3	51 (13.6%)
	4	46 (12.3%)
	5	14 (3.7%)
	6	3 (0.8%)

For multiple tumors, the location indicates the most proximal site; stage was based on the American Joint Committee on Cancer (AJCC) Staging Manual 7th edition; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; CTx. chemotherapy

different kinds of PET/CT scanners used for detecting recurrent esophageal carcinoma in this study were not statistically different (100% vs. 100%; 97.9% vs 93.4%, $p = 0.087$; Discovery LS vs. STe). There were also no significant differences in the diagnostic performance of FDG PET/CT with respect to differentiation of squamous cell carcinoma and other types of recurrent esophageal carcinomas (sensitivity 100% vs. 100%; specificity 93.8% vs. 100%, $p = 0.390$).

Table 2 Diagnostic performance of surveillance ^{18}F-FDG PET/CT scans for detection of recurrent esophageal carcinoma

Parameter		Number of scans	Number of positive scans for possible recurrence	Sensitivity (%)	Specificity (%)	PPV (%)	PLR	NPV (%)	NLR	Accuracy (%)
Initial stage (AJCC 7th)	I	280	28	100	93.7	39.3	15.8	100	0	93.9
	II	232	32	100	94.3	62.5	17.7	100	0	94.8
	III	270	47	100	94.1	70.2	16.9	100	0	94.8
PET/CT timing after definitive therapy (months)	<12	218	49	100	92.3	71.4	13.1	100	0	93.6
	12–36	344	38	100	94.7	55.3	19.0	100	0	95.1
	≥36	220	20	100	94.3	40.0	17.7	100	0	94.5
Overall		782	107	100	94.0	59.8	16.7	100	0	94.5

PPV, positive predictive value; PLR, positive likelihood ratio; NPV, negative predictive value; NLR, negative likelihood ratio

Diagnostic performance of surveillance FDG PET/CT according to initial stage

The 782 scans were grouped according to initial cancer stage (Table 2). A total of 280 PET/CT scans indicated initial Stage I cancer, while 232 were Stage II and 270 were Stage III. The incidence of positive PET/CT scans was 10.0% (28/280) for Stage I, 13.8% (32/232) for Stage II, and 17.4% (47/270) for Stage III ($p = 0.041$) esophageal cancers.

The sensitivity, specificity, PPV, and positive likelihood ratio of scans for stage I were 100% (11/11), 93.7% (252/269), 39.3% (11/28), and 15.8, respectively. The NPV and negative likelihood ratio were 100% (252/252) and 0, respectively. The sensitivity, specificity, PPV, and positive likelihood ratio of scans of Stage II esophageal cancers were 100% (20/20), 94.3% (200/212), 62.5% (20/32) and 17.7%, respectively. The NPV and negative likelihood ratio were 100% (200/200) and 0, respectively. For Stage III cancers, the sensitivity, specificity, PPV, and positive likelihood ratio were 100% (33/33), 94.1% (223/237), 70.2% (33/47), and 16.9, respectively, while the NPV and negative likelihood ratio were 100% (223/223) and 0, respectively. The accuracy of each group according to initial stage was 93.9% (263/280), 94.8% (220/232), and 94.8% (256/270). No significant differences between groups were found with respect to sensitivity, specificity, or accuracy. However, the PPV of for Stage II or III (67.1%, 53/79) cancers was significantly higher than for Stage I cancers ($p = 0.010$).

Diagnostic performance of surveillance FDG PET/CT according to timing of PET/CT scan after definitive therapy

The 782 scans were grouped according to the timing of the PET/CT scan after definitive therapy (Table 2). The number of PET/CT scans performed within 12 months of curative treatment was 218. The numbers of scans performed within 12 to 36 months and after 36 months were 344 and 220, respectively.

The sensitivity, specificity, PPV and positive likelihood ratio of scans performed within 12 months of treatment were 100% (35/35), 92.3% (169/183), 71.4% (35/49), and 13.1, respectively, and the NPV and negative likelihood ratio were 100% (169/169) and 0. Diagnostic efficacies for PET/CT scans performed within 12 to 36 months of curative treatment were 100% (21/21), 94.7% (306/323), 55.3% (21/38), and 19.0, respectively. The NPV and negative likelihood ratio were 100% (306/306) and 0, respectively. Diagnostic results for scans performed greater than 36 months after treatment were 100% (8/8), 94.3% (200/212), 40.0% (8/20), and 17.7. The NPV and negative likelihood ratio were 100% (200/200) and 0, respectively. The accuracies of <12-month, 12–24-month and > 36-month groups according to PET/CT timing after definitive treatment were 93.6% (204/218), 95.1% (327/344), and 94.5% (208/220), respectively. The sensitivities, specificities and accuracies of the groups were not significantly different according to PET/CT timing. However, the PPV of the groups were significantly different ($p = 0.042$), such that PET/CT scans performed within 12 months of treatment showed a significantly higher PPV than scans performed more than 12 months after treatment (71.4% vs. 50%, $p = 0.024$). The PPVs of scans performed within 36 months of treatment were also greater than those of scans performed 36 months or more after treatment (64.4% vs. 40%, $p = 0.045$). The incidence of positive PET/CT scans was significantly higher in those performed within 12 months than in those performed after 12 months (22.5% vs. 10.3%, $p < 0.001$).

Intrathoracic recurrent lesions detected by PET/CT

The number of PET/CT scans with an abnormal intrathoracic lesion, including loco-regional, pulmonary or pleural lesions, was 89 out of 782 (11.4%) scans. Among these, 81 showed only intrathoracic lesions, and eight showed both intra and extrathoracic FDG lesions. Recurrent esophageal carcinomas were diagnosed in 56 out of 89 scans (62.9%).

In addition, some patients with abnormal intrathoracic lesions who were diagnosed with true recurrence had only small intrathoracic lesions that might have been undetectable by other imaging methods/tools. Recurrence was identified in three patients in which regional lymph nodes smaller than 10 mm in size were detected in PET/CT scans. The SUV_{max} of those lesions ranged between 3.2 and 6.7, and all recurrences were confirmed by fine-needle aspiration. A representative case of small regional lymph node recurrence detected by PET/CT is shown in Fig. 1. Further, a PET/CT scan demonstrated small pulmonary nodules that were clinically diagnosed as recurrence by a clinician based on multiple imaging modalities. The pulmonary nodules ranged in size up to 8 mm, and SUV_{max} was up to 1.5.

Extrathoracic recurrent lesions or second primary cancers detected by PET/CT

Among 782 PET/CT scans, 50 (6.4%) indicated the possible presence of distant extrathoracic metastases ($n = 24$), second primary cancers (n = 24), or both (n = 2). Among these 50 positive scans, one scan suggestive of colon cancer was excluded from further analysis due to the patient's refusal to undergo further evaluation.

Among the 781 remaining PET/CT scans, 26 (3.3%) indicated the possible presence of distant extrathoracic metastasis. The final results were determined by clinical follow-up ($n = 1$) and/or other imaging techniques, including endoscopy, chest CT, abdomen CT, X-ray, bone scan, liver MRI, by serum

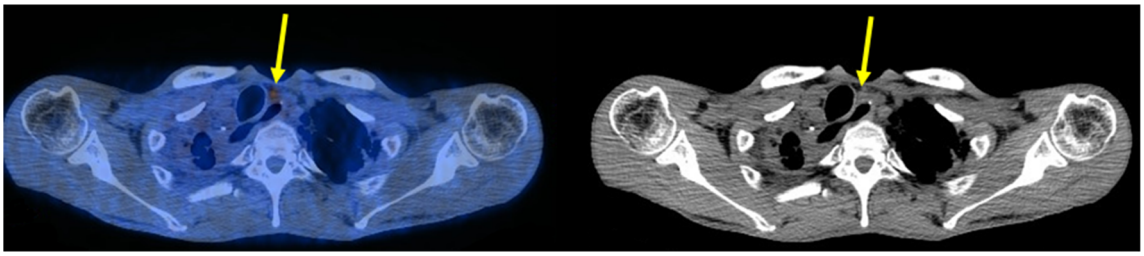

Fig. 1 A 48-year-old man underwent surveillance FDG PET/CT 11 months after curative surgery for esophageal carcinoma (pT1bN1, AJCC 7th). A small hypermetabolic lymph node was demonstrated in the left highest mediastinal area (arrow, size = 8 mm, SUV_{max} = 3.2). Metastatic carcinoma was histologically confirmed by fine-needle aspiration

prostate-specific antigen (PSA) concentration, or using follow-up FDG PET/CT (n = 23). In the remaining two patients with esophageal carcinoma, recurrence was determined by FDG PET/CT alone, because the PET/CT scans had typical multiple hypermetabolic extrathoracic metastases, and the attending physician decided not to perform further diagnostic work-up. In this study, the final incidence of extrathoracic metastasis after surveillance FDG PET/CT in patients with esophageal carcinoma after definitive treatment was 1.7% (13/781), of which 13 cases (100%) were detected by FDG PET/CT. Thirteen of 26 (50%) scans were confirmed to be true extrathoracic metastases. The location of distant extrathoracic metastatic lesions (n = 30) suggested by PET/CT included liver (n = 4), bone (n = 9), non-regional lymph nodes (n = 12), duodenum (n = 1), adrenal gland (n = 1), soft tissue (n = 2), and ascites (n = 1). Clinically true extrathoracic lesions (n = 17) detected by PET/CT were located in the liver (n = 1), bone (n = 7), non-regional lymph nodes (n = 8), and adrenal gland (n = 1). Thirteen of 17 (76.5%) clinically true extrathoracic lesions detected by PET/CT were located at sites that are not within the areas covered by conventional chest CT. Therefore, PET/CT was able to detect extrathoracic recurrent lesions with a sensitivity of 100% (13/13), specificity of 98.4% (756/768), PPV of 50% (13/26), NPV of 100% (755/755), and accuracy of 98.5% (769/781).

Among 781 PET/CT scans, 25 (3.2%) suggested the possible presence of second primary cancers. The final diagnoses were determined by pathological confirmation (n = 12), clinical follow-up (n = 5), and/or other imaging modalities (n = 8). The final incidence of second primary cancers in patients with definitively treated esophageal carcinoma after surveillance FDG PET/CT was 1.5% (12/781), of which seven cases (58.3%) were detected by FDG PET/CT. Among 25 PET/CT scans suggesting second primary malignancy, 7 (28.0%) were true second primary cancers. Lesions were located in the hypopharynx (including pyriform sinus; n = 4), tonsils (n = 1), lung (n = 1) or rectum (n = 1). Six (85.7%) of the seven true second primary cancers detected by PET/CT were located at sites not covered by conventional chest CT. Among seven second primary cancers detected by PET/CT, five were Stage I (three hypopharyngeal cancer, one lung cancer, one rectal cancer) according to the AJCC (7th edition), and the remaining two patients had locally treated Stage III hypopharyngeal cancer or Stage IVa tonsil cancer. A representative case of second primary malignancy detected by PET/CT is demonstrated in Fig. 2. Five patients were diagnosed with another malignancy within six months of the PET/CT scan, although those cancers had not been detected by the previous PET/CT. Early gastric cancer was detected by endoscopy in four cases, and small cell lung cancer was detected by contrast-enhanced chest CT followed by bronchoscopic biopsy in the remaining case. Overall, PET/CT detected an additional primary malignancy with a sensitivity of 58.3% (7/12), specificity of 97.7% (751/769), PPV of 28% (7/25), NPV of 99.3% (751/756), and accuracy of 97.1% (758/781).

Discussion

In this study, FDG PET/CT successfully detected clinically unexpected recurrent esophageal carcinoma with 100% sensitivity and 94% specificity. In addition, FDG PET/CT was able to reliably detect clinically unexpected extrathoracic metastases and second primary cancers, the lesions of which would not be found by conventional surveillance methods in most cases. There were no significant differences in sensitivities and specificities between subgroups according to initial cancer stage or time course of follow-up. Our results justify inclusion of FDG PET/CT in routine surveillance of recurrent esophageal carcinoma after curative treatment.

The diagnostic performance of FDG PET/CT for detection of recurrent esophageal carcinoma demonstrated high sensitivity and specificity. It closely matched the pooled sensitivity of 96% reported in a previous meta-analysis and was superior to the meta-analysis' pooled specificity of 78% [10]. The presence or absence of suspicion of recurrence before the FDG PET/CT scan was not a significant factor influencing specificity for detection of recurrent esophageal carcinoma in that meta-analysis [10]. Another recent study of the sensitivity and specificity of FDG PET/CT for detection of recurrent esophageal adenocarcinoma reported results in the 77–97% and 76–96% ranges, respectively [19]. This study analyzed

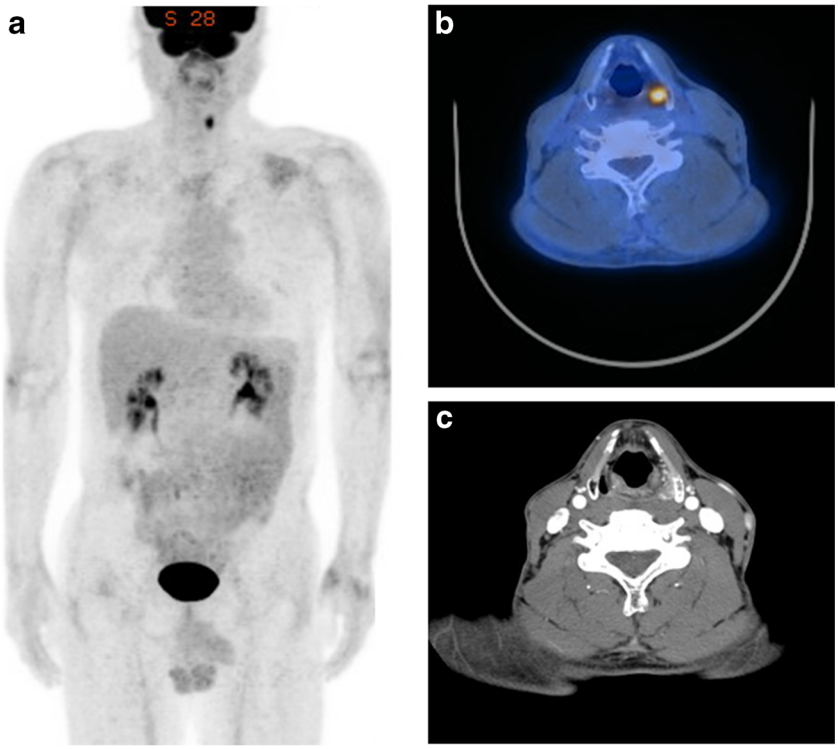

Fig. 2 A 50-year-old man underwent surveillance FDG PET/CT 29 months after curative surgery for esophageal carcinoma (pT1aN0, AJCC 7th). A hypermetabolic lesion was noted in the left pyriform sinus (**a, b**, $SUV_{max} = 5.8$). Contrast-enhanced chest CT performed three months before the PET/CT did not indicate an abnormal lesion in the left pyriform sinus (**c**). A second primary pyriform sinus cancer was diagnosed by laryngomicroscope surgery biopsy after the PET/CT scan

data from FDG PET/CT scans after curative treatment for esophageal carcinoma regardless of whether patients were symptomatic. Our results suggested that FDG PET/CT is an effective method for detecting recurrent esophageal carcinoma irrespective of clinical suspicion of recurrence. However, no studies have been conducted to investigate the diagnostic performance of FDG PET/CT with respect to detection of recurrent esophageal carcinoma in asymptomatic patients only.

The sensitivity and specificity of FDG PET/CT for detection of recurrent esophageal carcinoma were not influenced by initial stage or PET/CT timing after definitive treatment. However, the PPV of FDG PET/CT scans of patients with initial Stage II or III cancers were significantly greater than those of scans of patients with initial Stage I cancers. The PPV of FDG PET/CT scans performed within 12 months of initial treatment was greater than for scans performed after 12 months. The same result was found using 36 months as the cut-off value. Initial tumor stage is a determinant for esophageal carcinoma recurrence [1, 8, 20]. In addition, recurrences are frequent in the early course of follow-up after curative treatment of esophageal cancer, and most recurrences are seen within two years of treatment [1, 21, 22]. In our study, the incidence of recurrence increased according to initial tumor stage (I vs. II vs. III; 3.9% vs. 8.6% vs. 12.2%) and decreased with increasing interval between curative treatment and completion of the scan (16.1% vs. 6.1% vs. 3.6% at <12 months vs. 12–36 months. vs ≥ 36 months, respectively). The incidence of recurrence was greatest in patients with an advanced initial stage of esophageal carcinoma and a PET/CT scan performed early in the time course after curative treatment (2.5% vs. 4.5% vs. 4.3% vs. 13.0% in patients at Stage I and scanned after ≥36 months vs. Stage I patients scanned at <36 months vs. Stage II/III patients scanned at ≥36 months vs. Stage II/III patients scanned at <36 months, respectively). These results correspond with those of previous studies and led to differences in PPVs between subgroups. A PPV is dependent on incidence regardless of intrinsic diagnostic performance of the test. However, FDG PET/CT showed good diagnostic efficacy irrespective of initial cancer stage or PET/CT timing. In terms of cost-effectiveness, FDG PET/CT may be more valuable for surveillance of esophageal carcinoma patients with Stage II or III cancer and within 36 months of treatment.

When the range of scans and size of lesions are taken into account, FDG PET/CT may offer added value when compared with conventional surveillance, including chest CT, for detection of recurrent esophageal carcinoma. Approximately 3.3% of surveillance FDG PET/CT scans detected abnormal FDG uptake lesions in extrathoracic areas; half of those were later determined to be true metastatic lesions. Additionally, three cases of small regional lymph node recurrence and one small pulmonary nodule were revealed by FDG PET/CT. These findings suggest that FDG PET/CT could improve diagnosis of recurrence in some patients, and may affect treatment and management strategy for recurrent esophageal carcinoma. FDG PET/CT therefore warrants inclusion in routine surveillance work-ups for recurrence of esophageal carcinoma.

FDG PET/CT detected unexpected additional primary malignancies in seven patients. On the other hand, five patients were diagnosed with second primary malignancies after an FDG PET/CT scan, but there were no definite abnormalities in corresponding sites. The overall sensitivity and specificity for diagnosis of second primary malignancy in this study were 58.3% and 97.7%, respectively. Moreover, 85.7% of the second primary malignancies would not be detected by conventional chest CT. It was recently reported that the 5-year cumulative risk of second primary malignancy in patients with esophageal squamous cell carcinoma was 19.3% [23]. FDG PET/CT may be valuable for diagnosing head and neck cancers, which are common second primary malignancies in esophageal cancer patients [23] and can be sensitively evaluated by FDG [24]. Five out of seven (71.4%) second primary malignancies detected by surveillance FDG PET/CT were Stage I, and the remaining two malignancies were also locally treated on curative intent. Thus, FDG PET/CT could improve the long-term survival of patients who might otherwise be diagnosed with another malignancy at an advanced stage. This conclusion corresponds closely with the results of a previous study that showed most (83.3%, 20 of 24) second primary malignancies detected by FDG PET/CT were early stage [25].

Among 107 PET/CT scans suggesting recurrence, 67 demonstrated only possible loco-regional recurrent lesions, and 26 showed only possible distant recurrent lesions. The remaining 14 scans showed both loco-regional and distant lesions. Clinically diagnosed recurrences were in a loco-regional area only in 45 patients, in a distant area only in nine patients, and in both in ten patients. The proportion of distant recurrent lesions (29.7%, 19/64) in our study was lower than that of a previous study (45.9%) [3], indicating that surveillance FDG PET/CT could detect earlier recurrent esophageal carcinomas. Earlier detection may give patients an opportunity to receive salvage curative treatment, which can improve long-term survival.

This retrospective study has several limitations. First, a specific follow-up period after definitive treatment of esophageal carcinoma was not strictly designated. As a result, the interval between treatment and surveillance FDG PET/CT varied according to the preference of the clinicians. Second, not all recurrent lesions were confirmed if multiple recurrent lesions were suspicious. Third, 46 of 828 PET/CT scans (5.6%) in which recurrences were diagnosed 2–5 months after the PET/CT scan or the follow-up duration without recurrence was less than 6 months were designated as indeterminate and excluded for analysis, because the final diagnosis was not clear. However, this cut-off was set in accordance with the surveillance schedule for recurrent esophageal carcinoma, because there were no alleged cut-offs in those situations, which was another limitation in this study. On the other hand, any negative FDG PET/CT scan that will be negative also after six months could be regarded as a negative one. Therefore, our sensitivity of 100% for detecting recurrent esophageal carcinomas might be exaggerated against that in a real clinical situation. Fourth, two different kinds of PET/CT scanners were used in this study; however, the sensitivities and specificities of the PET/CT scanners for detection of recurrent esophageal carcinomas were not significantly different. Fifth, this study was based in a single center, and the histologic type of most of patients was squamous cell carcinoma; nonetheless, the diagnostic performance of FDG PET/CT for detection of recurrent esophageal carcinomas was not significantly different between subjects with squamous cell carcinoma and those with other types of esophageal cancer. A prospective multi-center study is needed to confirm the clinical impact of surveillance FDG PET/CT in esophageal carcinoma patients.

Our results indicated surveillance FDG PET/CT is a useful imaging modality to detect early recurrence or clinically unexpected early-stage second primary cancer in patients with esophageal carcinoma after curative treatment and without clinical suspicion of recurrence. The use of FDG PET/CT may improve long-term survival of patients given subsequent salvage therapy or curative therapy. Inclusion of FDG PET/CT in routine surveillance of esophageal carcinoma may therefore be warranted, and may be particularly cost-effective in patients with advanced initial stage cancer or when performed within short follow-up periods after curative treatment.

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Compliance with ethical standards

Conflict of interest All authors declare they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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