Effectiveness of FDG-PET in Screening of Synchronous Cancer of Other Organs in Patients with Esophageal Cancer

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Abstract. *Aim: We investigated the significance of pre-treatment screening by ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) in patients with esophageal cancer. Patients and Methods: We retrospectively evaluated the clinical significance of screening in 200 patients with primary esophageal cancer using FDG-PET. Results: Out of 200 patients, 34 (17%) had synchronous multiple primary tumors; 31 patients had two types of cancers (15.5%) and three patients had three types (1.5%). The 37 second and third primary tumors were 13 stomach cancers (35.1%), 13 head and neck cancers (35.1%), seven colon (18.9%) and two lung (5.4%) cancers. When PET was performed at initial treatment for esophageal cancer, the diagnostic sensitivity of FDG-PET/Computed tomography (CT) for the second and third synchronous primary cancer were 53.8% (7/13) for the stomach; head and neck, 61.5% (8/13); colon, 42.9% (3/7); and lung, 50% (1/2), for an overall sensitivity of 54.1% (20/37 sites). Conclusion: FDG-PET/CT for patients with esophageal cancer may find both metastases from the primary esophageal cancer and other types of synchronous primary cancers.*

The incidence of double primary cancer is reported by the Japan Esophageal Society to be 8.3% for synchronous lesions and 12.4% for metachronous lesions in patients with esophageal cancer (1). Accurate diagnosis and treatment of multiorgan cancer is critical for patients with esophageal cancer. Gastric, and head and neck cancer are not uncommon in the presence of esophageal cancer (2, 3). Several risk factors, including smoking and alcohol, have been strongly associated with esophageal cancer (4-6), and lead to cancer of the upper aerodigestive tract, such as cancer of the oral cavity, oropharynx and larynx (7). The concept that common carcinogenic agents can lead to multiple types of cancer in adjacent regions is known as field cancerization (8). Preoperative screening of the stomach and head and neck regions is, therefore, essential before treatment for esophageal carcinoma.

^{18}F-Fluorodeoxyglucose positron-emission tomography (FDG-PET) is useful in managing various cancer types because glucose metabolism is generally activated in malignancy (9, 10). This imaging technique facilitates for definitive diagnoses in patients with malignant disease by differentiating between benign and malignant tumors, assessing the extent of disease, detecting tumor recurrence, and monitoring response-to-therapy (11-13). We have previously reported on FDG-PET and PET/computed tomography (CT) in diagnosis and treatment of esophageal cancer (12, 14-17).

Although detection of synchronous multiple primary carcinomas by FDG-PET is not uncommon in several types of malignancies (18-20), few reports have investigated the use of FDG-PET/CT in screening for synchronous cancers in other organs in patients with esophageal cancer (21). We investigated the efficacy of FDG-PET/CT in diagnosing multiple-organ neoplasms in patients with esophageal cancer.

Patients and Methods

Patients. We defined multiple primary cancer using the definition of Warren and Gates: each tumor must present a definite picture of malignancy, each must be distinct and the probability of one being a metastasis of the other must be excluded (22). Tumors found simultaneously or within six months from the diagnosis of the first malignancy are classified as synchronous cancer. Tumors found more than six months later were considered metachronous cancer.

We studied 200 patients with esophageal cancer who were treated at the Department of General Surgical Science at the Graduate School of Medicine of Gunma University between January 2006 and

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April 2012. Patients with histologically-confirmed primary esophageal carcinoma were eligible for this retrospective study of clinical data from a consecutive series of patients. None of the patients had received prior treatment for esophageal cancer. All patients underwent FDG-PET/CT for screening before esophageal cancer treatment. The mean age of the patients was 65.9 years (range=42-86 years). Pre-treatment clinical tumor stage was classified using the sixth edition of International Union Against Cancer (UICC)'s TNM classification. We determined tumor stage using CT scans of the neck, chest, and abdomen; bone scans; endoscopic ultrasound (EUS); endoscopy; FDG-PET/CT; and esophagography. Final diagnoses of multiple primary cancer were confirmed by surgical procedures and biopsy. All patients provided informed consent before undergoing examinations. Two experienced nuclear medicine physicians evaluated all PET images qualitatively.

FDG-PET/CT studies. We have described the FDG-PET/CT procedure previously (23).18F-FDG was produced at our cyclotron facility using the method developed by Tomiyoshi *et al*. and the modified method of Hamacher *et al*. (24, 25). PET/CT studies were performed after injection with 5-6 MBq/kg of 18F-FDG after patients fasted for more than 6 h. Sixty minutes after administration of tracer, whole-body images were obtained with PET/CT scanners (Discovery STE; GE Healthcare; Biograph 16; Siemens Medical Solutions, Waukesha, WI, United States). Patients were scanned from the thigh to the head in the arms-down position. X-Ray CT was acquired to perform transmission correction for PET; the following parameters were used: 140 kV and 120-240 mAs (varying according to somatometry). No intravenous contrast material was provided for CT scanning. Patients held their breath briefly at normal expiration to avoid motion-induced artifacts and to match co-registration of CT and PET images in the area of the diaphragm. At completion of CT, the PET data (3 min per bed position) was acquired in 3-D mode. CT images were reconstructed by means of the conventional filtered back-projection method. Attenuation-corrected PET images were reconstructed from an ordered-subset expectation–maximization algorithm into 128×128 matrices.

For the semiquantitative analysis, functional images of standard uptake value (SUV) were produced by attenuation-corrected transaxial image, injected dose of ^{18}F-FDG, patient's body weight, and the cross-calibration factor between PET and dose calibrator. SUV was defined as the concentration of radioactivity in the tissue or lesion (MBq/ml) × patient body weight (g)/injected dose (MBq). Maximum SUV (SUV_{max}) was used to represent the uptake of ^{18}F-FDG in the tumor.

Interpretation. ^{18}F-FDG PET findings were interpreted on computer monitors independently by one of two nuclear medicine physicians. Final diagnoses were made by consensus. ^{18}F-FDG accumulation in regions not likely to be sites of metastatic spread from esophageal cancer was reported as suggestive of synchronous tumor, depending on intensity and pattern. All PET reports were retrospectively analyzed.

Results

There were synchronous multiple primary carcinomas in 34 patients (17%) (Table I), including two in 31 patients (15.5%) and three in three patients (1.5%), out of 200 patients (Table II). The sensitivity of FDG-PET CT for the second and third synchronous primary cancer, when PET was performed as the first treatment for esophageal cancer, is shown in Table III. The sensitivity for primary cancer overall was 54.1% (20/37 sites) (Table III). In 39 areas (19.5%) in 17 sites, we detected non-specific ^{18}F-FDG accumulation (Table IV). In 15 cases these areas of accumulation were diagnosed as inflammation, and one case was a benign tumor. The reason for accumulation in the other 20 cases is unknown, but the lesions were diagnosed with no malignancy by other examinations and follow-up.

Table I. *Characteristics of patients with esophageal cancer.*

	n=200	
Age (years)		
Mean (range)	65.9	(42-86)
Gender		
Male	174	87.0%
Female	26	13.0%
Location		
Cervical	11	5.5%
Upper	23	11.5%
Middle	95	47.5%
Lower	71	35.5%
Histological subtype		
Squamous cell carcinoma	186	93.0%
Adenocarcinoma	11	5.5%
Other	3	1.5%
Clinical stage		
I	55	27.5%
II	53	26.5%
III	51	25.5%
IV	41	20.5%
Treatment of esophageal cancer		
Surgery	103	51.5%
Radiation/chemoradiation	68	34.0%
Endoscopic treatment	29	14.5%
Multiple cancer		
Overall	34	17.0%
2 Types	31	15.5%
3 Types	3	1.5%

Discussion

The occurrence of multiple primary carcinomas in patients with primary esophageal cancer is a well-known phenomenon. It is very important to detect synchronous multiple primary cancer in patients with esophageal cancer, because treatment policy is affected by cancer location and stage. Oncologists can thus design comprehensive, individualized treatment strategies for plural cancer with the condition and situation of patients in mind.

In the present study, we investigated the utility of FDG-PET/CT to diagnose multiple-organ neoplasms in patients

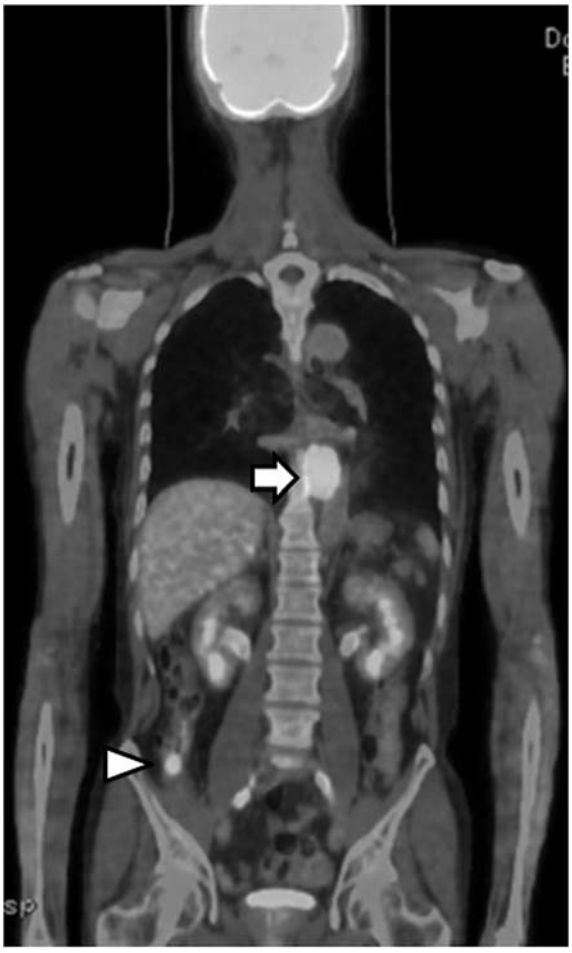

Figure 1. *A 59-year-old man with synchronous colon cancer and esophageal cancer. Positron-emission tomography/computed tomographic images revealed hypermetabolic lesions of the ascending colon (arrow head) and esophagus (arrow).*

Table II. *Localization and the number of second and third synchronous primary cancers.*

Site	Number of patients	%
Stomach	13	35.1
Head and neck	13	35.1
Colon	7	18.9
Lung	2	5.4
Bladder	1	2.7
Breast	1	2.7
Total	37	100

Table III. *Localization and diagnostic sensitivity of positron-emission tomography (PET) for the second, third syncronous primary cancer, when PET was performed at the first treatment for esophageal cancer*

Site	Number of sites	Number of PET-positive patients	Sensitivity (%)
Stomach	13	7	53.8
Head and neck	13	8	61.5
Colon	7	3	42.9
Lung	2	1	50.0
Bladder	1	0	0.0
Breast	1	1	100.0
Total	37	20	54.1

Table IV. *Localization and organ non-specific 18F-fluorodeoxyglucose (^{18}F-FDG) accumulation.*

Site	Number of sites
Colon and rectum	5
Stomach	5
Teeth	4
Small intestine	3
Maxillary sinus	3
Prostate	3
Thyroid	3
Larynx	3
Bone	2
Liver	1
Pelvic area	1
Lung	1
Parotid gland	1
Uterus	1
Adrenal gland	1
Pharynx	1
Subcutaneous area	1
Total	39

with esophageal cancer. Synchronous multiple primary cancer was found in 34 patients (17%). FDG-PET/CT detected 20/37 sites; sensitivity was 54.1%. However, most lesions were also detected by other examination tools. We performed variable examination for screening synchronous multiple cancer in patients with esophageal cancer, including upper GI, esophagogastroduodenoscopy, total colonoscopy, CT (from neck to abdomen), FDG-PET/CT (whole body), and nasopharyngoscope by otolaryngologist. Reportedly, FDG-PET detected unexpected synchronous primary neoplasms in 5.5% of patients with esophageal cancer (21), most of which were in the colon or rectum. Their screening examinations included ^{18}F-FDG-PET, endoscopic sonography, CT of the thorax and abdomen, and external sonography of the cervical region for initial staging (21). In our study, PET/CT detected synchronous primary neoplasms in 10% of patients with esophageal cancer. Head and neck cancer and gastric cancer were detected as major lesions; colon lesions were seen in three cases. A case example is presented in Figure 1. Because

our patients underwent total colonoscopies, with CT (from neck to abdomen), and nasopharyngoscopies by an otolaryngologist, our diagnostic ability might be high. As the rate of squamous cell carcinoma of esophageal cancer in Japan is higher than in Europe and the United States histologically, synchronous head and neck cancer and gastric cancer may be common as field cancerization. Most lesions were also detected by esophagogastroduodenoscopy, nasopharyngoscopy, total colonoscopy and CT in our study. There are some reports that diagnostic sensitivity of PET for synchronous esophageal cancer was low in patients with head and neck cancer (26-27), possibly because when these patients were assessed, their esophageal cancer was at an early stage. Himeno *et al*. reported that PET imaging detected primary esophageal tumors with an invasion status of T1b or greater (*i.e*. tumors involving the submucosa), whereas T1a tumors (*i.e*. tumors invading the muscularis mucosae) were undetectable (28). False-negative PET findings were always related to small (Tis or T1) tumors, suggesting limitations in the spatial resolution of the PET scanner (16). FDG-PET/CT does not replace endoscopy for detecting synchronous upper-GI cancer in high-risk populations. Shim *et al*. have reported that among the 557 patients managed at their institution, 40 (7.2%) were identified as having incidental thyroid carcinomas (29), 22 of which were detected by FDG-PET/CT. Truijers *et al*. reported that besides information on aneurysm wall pathology, PET/CT identified six patients with concomitant malignancies (30). When patients undergo FDG-PET/CT, regardless of benign or malignant disease, we should always consider incidental malignancy.

Detection sensitivity of FDG-PET by type of malignancy has been reported as follows: malignant lymphoma, 93.1%; head and neck cancer, 96.2%; esophageal cancer, 65.7%; hepatobiliary and gallbladder cancer, 78.4%; pancreatic cancer, 97.4%; renal cell cancer, 69.4%; cervical and uterine cancer, 84.2%; ovarian cancer, 96.0%; and bladder cancer, 27.6% (9). Reportedly, sensitivities were very high for some types of cancer. They recommended a combination of screening modalities to redeem FDG-PET and PET/CT, because despite the advantages of FDG-PET in detecting various malignancy types, it is not perfect.

Thirty-nine areas (19.5%) of non-specific ^{18}F-FDG accumulation were detected in the present study. Fifteen areas of accumulation were diagnosed as inflammation, and one was a benign tumor. This rate was higher than in other reports (31, 32), possibly because the SUV cut-off value had not been defined in our study. ^{18}F-FDG is not a tumor-specific substance, so false-positive findings may arise from increased glucose metabolism in benign lesions. Positive findings on ^{18}F-FDG/PET must therefore be confirmed by additional investigation.

FDG-PET/CT can be used to screen for other primary cancers in the course of esophageal cancer staging, especially in facilities that do not usually screen for multiple primary cancers.

In conclusion, FDG-PET/CT for patients with esophageal cancer may lead to important findings not only in seeking metastases from primary esophageal cancer but also in screening of synchronous multiple cancers.

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