

# Pancreatic FDG uptake on follow-up PET/CT in patients with cancer

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**Abstract.** To evaluate the breakdown of unexpected pancreatic <sup>18</sup>F-fluorodeoxyglucose (FDG) uptake and the proportion of secondary primary pancreatic cancer on follow-up, patients with cancer underwent positron emission tomography/computed tomography (PET/CT). The participants consisted of 4,473 consecutive patients with cancer who underwent follow-up PET/CT between January 2015 and March 2019 at Kochi Medical School. Among the participants, 225 with a history of pancreatic cancer were excluded from the present study. Retrospective and blinded PET/CT evaluations of 4,248 patients were performed. In patients with pancreatic FDG uptake, the distribution of FDG uptake in the pancreas was evaluated. The final diagnosis was determined pathologically. A total of 14 (0.3%) of the 4,248 patients exhibited FDG uptake in the pancreatic area. Pancreatic abnormalities were detected in 14 patients, and included five cases of pancreatic metastases (36%), four cases of secondary primary pancreatic cancer (29%), two cases of lymph node metastases (14%), one case of malignant lymphoma (7%), one case of autoimmune pancreatitis (7%) and one case of pseudolesion (7%). One patient with early-stage secondary primary pancreatic cancer had a maximum standardized uptake value ( $SUV_{max}$ ) <3.0. The remaining 13 patients had a  $SUV_{max}$  >3.0 in the pancreas. Of the 14 patients, two had multiple foci of FDG uptake in the pancreas. Patients with multiple foci of FDG uptake exhibited pancreatic metastasis from renal cell carcinoma and malignant lymphoma. In conclusion, the majority of patients with unexpected pancreatic FDG uptake on follow-up PET/CT exhibited malignancies; furthermore, ~30% of the malignancies detected

in patients with pancreatic FDG uptake were secondary primary pancreatic cancers. In patients with unexpected pancreatic FDG uptake on follow-up PET/CT, primary cancer should be considered as well as metastatic tumors.

## Introduction

<sup>18</sup>F-fluorodeoxyglucose-positron emission tomography/computed tomography (<sup>18</sup>F-FDG-PET/CT), as a whole-body scan, is powerful for cancer staging. <sup>18</sup>F-FDG-PET/CT has the ability to detect early malignant lesions characterized by an increased rate of glycolysis (1). <sup>18</sup>F-FDG-PET/CT is also useful when identifying local recurrence or metastases when tumor marker levels are elevated after the completion of treatment. However, a region of novel FDG uptake, which usually reflects recurrence or metastases from the known tumor, can also indicate a secondary primary cancer. Because of the nature of patient management and early cancers that require radical treatment, the detection of secondary primary cancer is an important prognostic factor (2).

Secondary primary cancer could occur months or years after the diagnosis and treatment of the original primary cancer (3). Patients who had experienced cancer could be at increased risk of developing secondary primary cancer (3). Even if the progress of the original primary cancer was good, secondary primary cancer might narrow the choice of treatment methods and result in poor prognosis. In particular, pancreatic cancer has a very poor prognosis and progresses quickly (4). The prognosis of pancreatic cancer has not improved despite extensive research and advances in imaging modalities. There are several reasons for the difficulties in the early diagnosis of pancreatic cancer, including the absence of early-stage biomarkers, anatomical location in the retroperitoneum allowing invasion of the surrounding organs and blood vessels, and non-specific symptoms (5).

<sup>18</sup>F-FDG-PET has already been used to diagnose pancreatic cancer (6-11). However, to our knowledge, no study has examined the frequency of new pancreatic FDG uptake and proportion of secondary primary pancreatic cancers after finding unexpected pancreatic FDG uptake on follow-up PET/CT in patients with cancer other than pancreatic cancers.

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**Key words:** FDG-PET/CT, pancreatic cancer, pancreatic metastases, new pancreatic lesion, past history of cancer

Therefore, this study aimed to evaluate the breakdown of unexpected pancreatic FDG uptake and the proportion of secondary primary pancreatic cancer on follow-up PET/CT in patients with cancer.

## Materials and methods

**Ethic statement.** The present study was approved by the Ethical Review Board of Kochi Medical School (Nankoku, Japan). Due to the retrospective nature of the present study, written informed consent was waived.

**Patients.** The participants consisted of 4,473 consecutive patients who underwent  $^{18}\text{F}$ -FDG-PET/CT to exclude metastatic cancers or local recurrence between January 2015 and March 2019 at Kochi Medical School. Of the 4,473 patients, 225 with a past history of pancreatic cancer were excluded. The remaining 4,248 patients who underwent previous imaging scans including  $^{18}\text{F}$ -FDG-PET/CT for the initial cancer staging or follow-up were included in this study. None of them had pancreatic diseases, neither primary cancer nor others.

**Imaging protocol.** PET/CT was performed 50 min after an intravenous injection of 3.5 MBq/kg FDG via an already secured peripheral venous catheter. Images from the head to the mid-thigh were acquired in three-dimensional (3D) mode at 2 min per bed position in the supine position using a PET/CT scanner (Discovery ST Elite, GE Healthcare, Waukesha, WI, USA) with a 16-slice Light-Speed CT component. All participants fasted for 6 h before undergoing PET/CT, and all participants had fasting blood glucose levels of <150 mg/dl before the injection. Non-contrast-enhanced CT images (140 kVp, 100–200 mAs) were acquired in the helical mode using a 3.75-mm slice thickness. The acquired data were reconstructed using a standard vendor-provided ordered subset expectation maximization algorithm (VUE point plus). CT, PET, and PET/CT images were all reviewed.

**Imaging analysis.** FDG uptake in the pancreatic area was retrospectively and blindly evaluated in 4,248 patients. Positive FDG uptake was defined as a maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ )  $\geq 2.5$ . In the presence of pancreatic FDG uptake, FDG uptake distribution and localization in the pancreas and the site of abnormal FDG uptake excluding the pancreas were evaluated. Two radiologists evaluated the results by reaching a consensus.

**Final diagnosis.** The final diagnosis was determined pathologically. Patients who were not diagnosed pathologically were diagnosed clinically using the follow-up imaging or clinical data.

## Results

**Patient clinical data.** FDG uptake in the pancreatic area was detected in 14/4,248 patients [0.3%; 12 men, two women; mean age, 75 years (range: 49–88 years)]. Table I lists the patient characteristics,  $^{18}\text{F}$ -FDG-PET/CT findings, diagnostic procedures, and final diagnoses. Two of the 14 patients already had double cancer (esophageal and oropharyngeal cancer; rectal

and bladder cancer). Pancreatic abnormalities in 14 patients included five cases of pancreatic metastases (36%), four cases of secondary primary pancreatic cancer (29%), two cases of lymph node metastases (14%), one case of malignant lymphoma (7%), one case of autoimmune pancreatitis (7%), and one case of pseudolesion (7%). The breakdown of the original lesions in the five cancers that metastasized to the pancreas are as follows: Two lung cancer cases, one renal cell carcinoma, one malignant melanoma and one laryngeal cancer. The primary cancer in the four patients with secondary primary pancreatic cancer included one rectal, one cecal, one vaginal, and one bile duct cancer.

**$^{18}\text{F}$ -FDG-PET/CT results.** The mean  $\text{SUV}_{\text{max}}$  of pancreatic FDG uptake in the four proven secondary primary pancreatic cancers was 4.8 (range: 2.6–5.8). Three of the four secondary primary pancreatic cancers in patients were advanced cancer (stage III: One patient, stage IV: Two patients), and one of the three had obvious FDG uptake in the liver that was considered to reflect metastasis. One patient with early-stage secondary primary pancreatic cancer had the lowest  $\text{SUV}_{\text{max}}$  among the 14 patients. The mean  $\text{SUV}_{\text{max}}$  of pancreatic FDG uptake in the five patients with pancreatic metastases was 5.8 (range: 3.8–7.1). Four of the five patients with pancreatic metastasis had FDG uptake of multiple lesions, except for the pancreas. The  $\text{SUV}_{\text{max}}$  of the pancreatic abnormal FDG uptake was higher than 10.0 in three patients with two lymph node metastases and one malignant lymphoma.

Of the five patients that had metastasis to the pancreas, four patients had a solitary FDG uptake in the pancreas body, and the remaining patient (renal cell carcinoma) had multiple FDG uptake. Two of four patients with secondary primary pancreatic cancer had a solitary FDG uptake in the pancreatic head, and two patients had a solitary FDG uptake in the pancreatic tail. All patients with lymph node metastases had a solitary FDG uptake in the pancreatic head. The patient with pancreatic infiltration in lymphoma had multiple FDG uptake throughout the pancreas.

After PET/CT, all 14 patients underwent contrast-enhanced CT (CE-CT), which revealed abnormalities in the pancreas, except for lymph node metastasis in two patients and pseudolesion in one. The interval from the previous imaging to the follow-up  $^{18}\text{F}$ -FDG-PET/CT where pancreatic abnormality was found was <8 months (1:4, 3:8 months) in all four patients with secondary primary pancreatic cancer.

**Final diagnosis.** Four of five pancreatic metastases, four secondary primary pancreatic cancers, and one malignant lymphoma were pathologically proven following endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) (Figs. 1–4). The remaining five, i.e., one pancreatic metastasis, two lymph node metastases, one autoimmune pancreatitis, and one pseudolesion, were diagnosed clinically (Figs. 5 and 6).

## Discussion

This study aimed to evaluate the breakdown of unexpected pancreatic FDG uptake on follow-up PET/CT in patients with cancer. The majority of patients with unexpected pancreatic FDG uptake on follow-up PET/CT exhibited malignancies. Furthermore, ~30% of the malignancies detected in patients

Table I. Patient characteristics.

Patient	Age, years	Sex	Primary	<sup>18</sup> F-FDG-PET/CT		Localization	Period from last examination (months)	Diagnostic procedure	Final diagnosis
				FDG uptake	SUV <sub>max</sub>				
1	65	M	Rectal ca.	Solitary	5.1	Tail	4	EUS-FNA	Pancreatic ca.
2	80	F	Malignant melanoma	Solitary	5.1	Body	6	EUS-FNA	Pancreatic metastasis
3	68	M	Esophageal ca., oropharynx ca.	Solitary	10.0	Head	17	Subsequent CT	Lymph node metastasis
4	76	M	Lung ca.	Solitary	6.9	Body	15	EUS-FNA	Pancreatic metastasis
5	80	M	Malignant lymphoma	Multiple	12.5	Head, Body, Tail	29	EUS-FNA	Malignant lymphoma
6	82	F	Vaginal ca.	Solitary	5.7	Head	8	EUS-FNA	Pancreatic ca.
7	49	M	Laryngeal ca.	Solitary	7.1	Body	6	Subsequent CT	Pancreatic metastasis
8	79	M	Esophageal ca.	Solitary	5.1	Body	11	Subsequent CT	Pseudolesion
9	83	M	Renal cell ca.	Multiple	3.8	Head, Body	7	EUS-FNA	Pancreatic metastasis
10	73	M	Rectal ca., bladder ca.	Solitary	5.1	Head	5	Subsequent CT	Autoimmune pancreatitis
11	72	M	Lung ca.	Solitary	6.1	Body	3	EUS-FNA	Pancreatic metastasis
12	85	M	Unknown primary ca.	Solitary	15.1	Head	3	Subsequent CT	Lymph node metastasis
13	88	M	Cecal ca.	Solitary	5.8	Head	8	EUS-FNA	Pancreatic ca.
14	72	M	Bile duct ca.	Solitary	2.6	Tail	8	EUS-FNA	Pancreatic ca.

ca., cancer; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; CT, computed tomography; M, male; F, female.

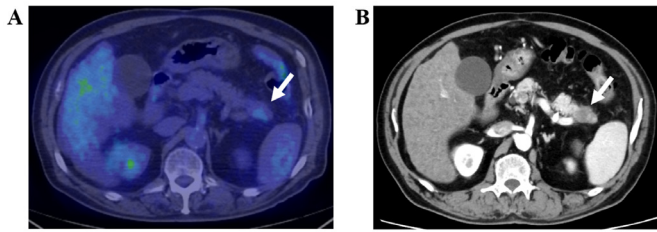


Figure 1. A 72-year-old man with secondary primary pancreatic cancer (Stage Ib), with a past history of bile duct cancer (Patient 14). (A) Positron emission tomography/CT, (B) CE-CT. Fluorodeoxyglucose uptake was detected in the pancreatic tail (maximum standard uptake value: 2.6). On CE-CT, this corresponded to a lesion in the pancreatic tail. Adenocarcinoma different from the tissue type of the bile duct cancer was diagnosed based on endoscopic ultrasound-guided fine needle aspiration results. CT, computed tomography; CE-CT, contrast-enhanced CT.

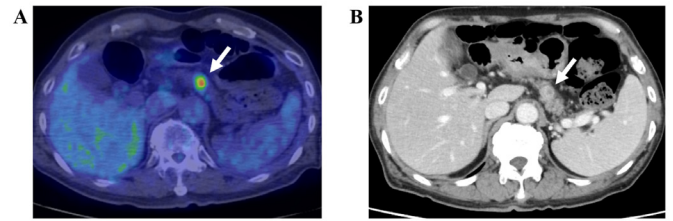


Figure 4. A 72-year-old man with pancreatic metastases from lung cancer (Patient 11). (A) Positron emission tomography/CT, (B) CE-CT. Fluorodeoxyglucose uptake was detected in the pancreatic body (maximum standard uptake value: 6.1). On CE-CT, this corresponded to a lesion in the pancreatic body. Metastatic lung cancer was diagnosed based on endoscopic ultrasound-guided fine needle aspiration results. CT, computed tomography; CE-CT, contrast-enhanced CT.

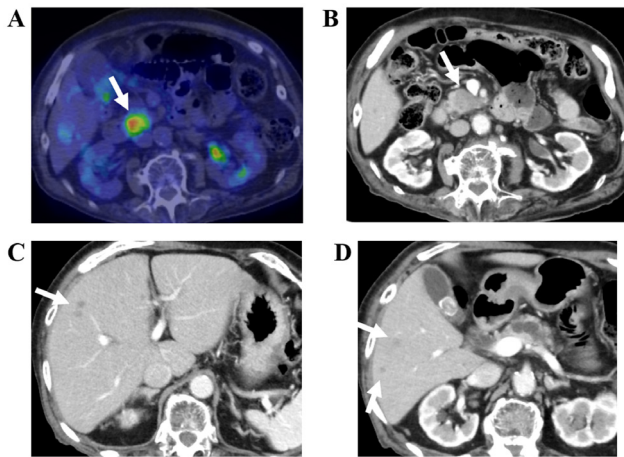


Figure 2. An 82-year-old woman with secondary primary pancreatic cancer (Stage IV), with a past history of vaginal cancer (Patient 6). (A) positron emission tomography/CT, (B-D) CE-CT. FDG uptake was detected in the pancreatic head (maximum standard uptake value: 5.7). On CE-CT, this corresponded to a lesion in the pancreatic head. CE-CT also demonstrated multiple liver metastases without FDG uptake. Adenocarcinoma was diagnosed based on EUS-FNA results. CT, computed tomography; CE-CT, contrast-enhanced CT; FDG, fluorodeoxyglucose.

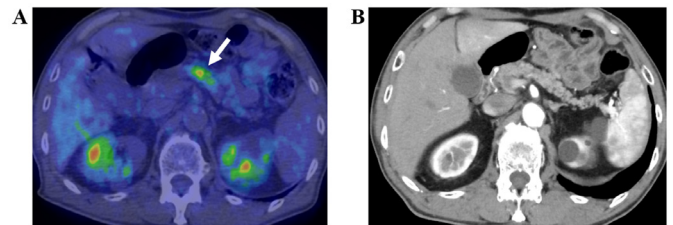


Figure 5. A 79-year-old man with pseudolesion with a past history of esophageal cancer (Patient 8). (A) Positron emission tomography/CT, (B) CE-CT. Fluorodeoxyglucose uptake was detected in the pancreatic body (maximum standard uptake value: 5.1). On CE-CT, no abnormality was detected in the pancreas. CT, computed tomography; CE-CT, contrast-enhanced CT.

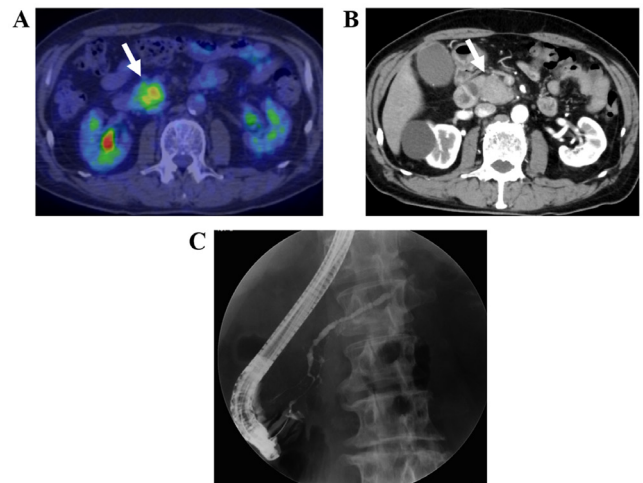


Figure 6. A 73-year-old man with autoimmune pancreatitis, with a past history of rectal cancer and bladder cancer (Patient 10). (A) Positron emission tomography/CT, (B) CE-CT, (C) ERCP. Fluorodeoxyglucose uptake was detected in the pancreatic head (maximum standard uptake value: 5.1). CE-CT demonstrated parenchymal enlargement of the pancreatic head with capsule-like rim enhancement. ERCP demonstrated narrowing of the main pancreatic duct. CT, computed tomography; CE-CT, contrast-enhanced CT; ERCP, endoscopic retrograde cholangiopancreatography.

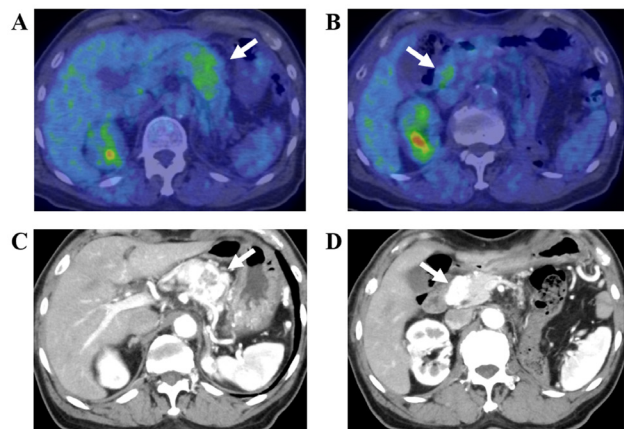


Figure 3. An 83-year-old man with pancreatic metastases from renal cell carcinoma (Patient 9). (A and B) Positron emission tomography/CT, (C and D) CE-CT. Fluorodeoxyglucose uptake was detected in the pancreatic head and body (maximum standard uptake value: 3.8). On CE-CT, this corresponded to a lesion in the pancreatic head and body. Metastatic clear cell carcinoma was diagnosed based on endoscopic ultrasound-guided fine needle aspiration results. CT, computed tomography; CE-CT, contrast-enhanced CT.

with pancreatic FDG uptake were secondary primary pancreatic cancers.

Pancreatic ductal adenocarcinoma, which is by far the most common in various pancreatic neoplasms, is the worst prognosis of all solid cancers (4). It has been reported that 5-year survival rates for patients with completely resected

patients with pancreatic ductal adenocarcinoma are only up to 18.8% (4). Most patients with pancreatic cancer remain asymptomatic until the disease develops to an advanced stage (12). Prognosis could depend on degree of the cancer progression. Therefore, early diagnosis of pancreatic cancer is essential for improved prognosis. Early pancreatic cancers have histopathologic features such as less fibrosis and more remnant pancreatic tissue, which appear isoattenuating in pancreatic phase of dynamic CT (13). The frequency of visually isoattenuating pancreatic adenocarcinomas based on every phase of dynamic CT among pathologically proven pancreatic cancers was 5.4%, particularly 27% of small pancreatic cancers measuring  $\leq 20$  mm has been reported to appear isoattenuating in any phase (14). Although few reports have described the utility of FDG-PET in early pancreatic cancer, FDG uptake had been reportedly observed in 60% of patients with stage I pancreatic cancer (5). In other words, approximately one-half of stage I pancreatic cancers could not be detected with FDG-PET. Therefore, FDG-PET is not suitable for the detection of early pancreatic cancer due to the spatial resolution limit. Three of the four patients had advanced cancer, two of whom had stage IV cancer.

$^{18}\text{F}$ -FDG-PET/CT, as a whole-body scan, is a powerful tool for oncology imaging. In this study, we evaluated the proportion of secondary primary pancreatic cancer in unexpected pancreatic FDG uptake on follow-up PET/CT in patients with cancer. The majority of patients with unexpected pancreatic FDG uptake on follow-up PET/CT had malignancies; furthermore,  $\sim 30\%$  of the malignancies detected in patients with pancreatic FDG uptake were secondary primary pancreatic cancers. The difference between FDG uptake in secondary primary pancreatic cancers and those in pancreatic metastases remains unclear. Therefore, distinguishing secondary primary pancreatic cancers from pancreatic metastases is difficult. According to a previous report, differentiation of secondary primary pancreatic cancers and pancreatic metastases based on their  $\text{SUV}_{\text{max}}$  is difficult (15). Even if the FDG uptake considered to be metastasis with multiple lesions as well as pancreas is recognized, diagnosing pancreatic metastases remains uncertain because pancreatic cancer is advanced quickly. In this study, patients with multiple foci of FDG uptake in the pancreas exhibited pancreatic metastasis from renal cell carcinoma and malignant lymphoma. A diagnosis of pancreatic cancer could be excluded in patients with multiple foci of FDG uptake in the pancreas.

FDG uptake in the lymph nodes or neighboring organs might be confused with that in the pancreas. In fact, in this study, two lymph node metastases and physiological small intestine uptake were initially identified as pancreatic uptake. Lymph node metastasis was identified in two patients because CE-CT revealed enhanced nodes with smooth margins near the pancreas. A pseudolesion was identified in one patient because CE-CT revealed physiological uptake in a portion of the small intestine near the pancreas. When PET/non-CE-CT reveals abnormal FDG uptake in the pancreas, CE-CT may help exclude false-positive FDG uptake around the pancreas. Autoimmune pancreatitis was clinically diagnosed based on capsule-like rim enhancement on CE-CT, the IgG4 level, narrowing of the main

pancreatic duct according to endoscopic retrograde cholangiopancreatography (ERCP), and the efficacy of steroid therapy. Extrapancreatic lesions were not noted in the patient diagnosed with autoimmune pancreatitis.

It may be difficult to narrow the diagnosis of pancreatic lesions on PET/non-CE-CT in patients with subtle or limited uptake in the pancreatic lesion.  $\text{SUV}_{\text{max}} \geq 1.3$  has been used to distinguish malignant from benign Intraductal Papillary Mucinous Neoplasms (IPMNs) in the pancreas (16). Low FDG uptake might cause overestimation. In general,  $\text{SUV}_{\text{max}}$  of 2.5 has been used as a cutoff value for diagnosing malignancies with  $^{18}\text{F}$ -FDG-PET (17,18). Therefore, we used the positive FDG uptake of  $\text{SUV}_{\text{max}} \geq 2.5$ . In this study, one patient with early-stage secondary primary pancreatic cancer had FDG uptake with  $\text{SUV}_{\text{max}}$  of 2.6. The remaining 13 patients including three advanced secondary pancreatic cancer had FDG uptake with  $\text{SUV}_{\text{max}} \geq 3.8$ . FDG uptake in secondary primary pancreatic cancer in early stage could be lower than that in advanced stage. However, FDG uptake could rise with the progression of cancer in a short period. Early detection of secondary primary pancreatic cancer by follow-up PET/CT might be difficult because pancreatic cancer proceeds rapidly.

Some pancreatic cancers are related with inherited predisposition; therefore, three groups have an increased risk of developing pancreatic cancer: i) Hereditary pancreatitis; ii) inherited cancer syndromes including hereditary breast-ovarian cancer, Peutz-Jeghers syndrome, hereditary nonpolyposis colorectal carcinoma, familial adenomatous polyposis, and familial atypical multiple mole melanoma; iii) familial pancreatic cancer (19,20). These three groups (hereditary pancreatitis, inherited cancer syndromes, and familial pancreatic cancer) are considered to be high risk for pancreatic cancer. In particular, pancreatic FDG uptake should be carefully considered in patients with a history of primary breast and/or ovarian cancer. In this study, the primary cancer in two of the three patients with secondary primary pancreatic cancer was colon cancer. However, the genetic background of the two patients was unknown.

A search of the literature performed by the current authors indicates that no previous studies have examined incidental FDG uptake in the pancreas, but studies have reported incidental FDG uptake in the thyroid, the breasts, the colon, and the prostate (1,2,21,22). A study that examined incidental FDG uptake in the thyroid noted FDG uptake in the thyroid in 3.8% of patients with no history of thyroid disease (21). Diffuse uptake was noted in 1.8% of those patients and focal uptake was noted in 2.0%. Of the patients in whom focal uptake was noted and who underwent fine-needle aspiration or surgery, a malignancy was noted in 63.6% (21). In a study that examined incidental FDG uptake in the breasts, focal FDG uptake was noted in the breasts of 0.82% of female patients with a type of cancer other than breast cancer (1). Of those patients who were followed up, a malignancy was noted in 57% (1). In a study that examined incidental FDG uptake in the colon, focal uptake was noted in the colon in 0.94% of patients (22). Of those patients who underwent a colonoscopy, malignancy was noted in 43.4% and precancerous lesions were noted in 26.1% (22). In a study that examined incidental FDG uptake in the prostate,

uptake in the prostate was noted in 1.3% of patients (2). Of those patients who were followed up, malignancy was noted in 12.7% (2).

Recently, the occurrence of second malignant neoplasms has been reportedly influenced by a myriad of factors, including the late effects of cancer therapy (such as chemotherapy and radiotherapy), shared etiological factors with the primary cancer (such as tobacco use, excessive alcohol intake, and obesity), genetic predisposition, environmental determinants, host effects, and combinations of factors (3). <sup>18</sup>F-FDG-PET/CT in patients with a past cancer history should be evaluated in detail, considering the possibility of secondary primary cancers. This study noted unexpected pancreatic FDG uptake in 0.3% of patients with cancer. This frequency is presumably higher than the frequency with which pancreatic FDG uptake is noted on PET/CT in people with no history of cancer, though this has yet to be reported in studies.

Pancreatic metastases are uncommon and account for 2-5% of all pancreatic malignant tumors (23,24). However, the prevalence of pancreatic metastases has been reported to range from 1.6 to 11% by studying a large number of autopsies (25). The original lesions of the five cancers that metastasized to the pancreas were as follows: Two lung cancers, one renal cell carcinoma, one malignant melanoma, and one laryngeal cancer. The majority of metastatic pancreatic cancers had FDG uptake in multiple regions, including the pancreas. The most common primary tumors that more frequently have pancreatic metastases are renal cell carcinoma, lung cancer, breast cancer, and colorectal carcinoma, followed by malignant melanoma and leiomyosarcoma (25,26). In this study, the most common primary malignancy was lung cancer. Pancreatic metastases are less common; however, pancreatic metastases are considered to be common in the terminal stage especially in performing autopsy. Regardless of whether the underlying cause is pancreatic metastases or secondary primary pancreatic cancer, pancreatic FDG uptake could suggest advanced cancer when found on follow-up PET/CT in patients with cancer. However, differentiation of pancreatic metastases and secondary primary pancreatic cancer could be important in determining the treatment strategy.

This study has some limitations. First, this was a retrospective study, and the sample size was relatively small. Second, the aim of the current study was to examine unexpected pancreatic FDG uptake on PET/CT in patients with past history of cancer. This study was unable to examine the effectiveness of subsequent treatment in or the prognosis of these patients. Third, the interval from the previous imaging to the follow-up <sup>18</sup>F-FDG-PET/CT varied. Fourth, all patients in this study were not diagnosed pathologically. Therefore, some early secondary primary pancreatic cancers with FDG uptake lower than  $SUV_{max} < 2.5$  might be overlooked.

In conclusion, the majority of patients with unexpected pancreatic FDG uptake on follow-up PET/CT exhibited malignancies; furthermore, ~30% of the malignancies detected in patients with pancreatic FDG uptake were secondary primary pancreatic cancers. In unexpected pancreatic FDG uptake on follow-up PET/CT, primary cancer should be considered as well as metastatic tumors.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

HI and YM designed the study and wrote the initial draft of the manuscript. MN, KM, and SK contributed to data collection and interpretation. NH and NA performed the imaging examinations. TK, KU and TY participated in the design of the study and provided guidance. HI and YM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by Ethical Review Board of Kochi Medical School (Kochi, Japan). Due to the retrospective nature of the present study, written informed consent was waived. A statement explaining that individuals who did not want to participate in the study could request to opt-out was posted on the bulletin board at Kochi Medical School.

## Patient consent for publication

The patients in our study provided consent for the publication of any associated data and images.

## Competing interests

The authors declare that they have no competing interests.

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