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Diagnosis of pancreatic cancer using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) —Usefulness and limitations in "clinical reality"—

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The present review will provide an overview of the literature concerning the FDG PET diagnosis of pancreatic cancer and a summary from our experience of 231 cases of pancreatic lesions. FDG PET can effectively differentiate pancreatic cancer from benign lesion with high accuracy. Newly-developed PET scanners can detect small pancreatic cancers, up to 7 mm in diameter, by their high resolution, which could make a great contribution to the early detection of resectable and potentially curable pancreatic cancers. FDG PET is useful and cost-beneficial in the pre-operative staging of pancreatic cancer because an unexpected distant metastasis can be detected by whole-body PET in about 40% of the cases, which results in avoidance of unnecessary surgical procedures. FDG PET is also useful in evaluation of the treatment effect, monitoring after the operation and detection of recurrent pancreatic cancers. However, there are some drawbacks in PET diagnosis. A relatively wide overlap has been reported between semiquantitative uptake values obtained in cancers and those in inflammatory lesions. As for false-positive cases, active and chronic pancreatitis and autoimmune pancreatitis sometimes show high FDG accumulation and mimic pancreatic cancer with a shape of focal uptake. There were 8 false negative cases in the detection of pancreatic cancer by FDG PET, up to 33 mm in diameter, mainly because of their poor cellularity in cancer tissues. In addition, there are 19% of cancer cases with a decline in FDG uptake from 1 hr to 2 hr scan. FDG PET was recently applied to and was shown to be feasible in the differential diagnosis of cystic pancreatic lesions, such as intraductal papillary mucinous tumor of the pancreas. Further investigations are required to clarify the clinical value of FDG PET in predicting prognosis of the pancreatic patients.

Key words: positron emission tomography, tumor diagnosis, pancreatic cancer, ^{18}F-fluorodeoxyglucose, glucose transporter, hexokinase, therapy monitoring, prognosis

INTRODUCTION

PANCREATIC CANCER is known for its poor survival and is the cause of death in approximately 16,000 and 24,000 patients each year in Japan and in the United States, respectively.[1,2] Tumor marker, CA19-9 appears to have a relatively high sensitivity in the diagnosis of pancreatic cancer, but the specificity is low because the level of CA19-9 is sometimes high even in chronic pancreatitis or other diseases.[3] There has been no adequate screening test for early diagnosis of the disease, because no significant high-risk group has been identified, except for hereditary pancreatitis patients.[4] At the time of diagnosis after the appearance of symptoms, most patients have an advanced

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stage that is not suitable for curative operation. Although surgical resection in the early stages represents the only possibility for curative treatment, potentially curative surgery is possible only in about 20–30% of patients.[2,5,6] Thus, early detection using effective diagnostic procedures is needed.

Tumor imaging using fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) has been established as a useful clinical tool in a variety of cancers, such as lung cancer, breast cancer, recurrent rectal cancer, and metastatic liver cancer.[7–10] FDG PET imaging was also applied to the diagnosis of pancreatic cancers since the early 1990's and its usefulness has been reported.[11–14] The Japanese Ministry of Health, Welfare and Labour finally approved FDG PET for coverage by public medical insurance in 2002, in which pancreatic cancer is also included in the 10 approved malignant diseases. In contrast, the Medicare reimbursement for PET in the United States, approved in 1998 for several cancers, did not include pancreatic cancer. Recently, some studies have questioned the usefulness of FDG PET in the diagnosis of pancreatic cancer.[15–17]

An important question is whether diagnosis using FDG PET is really useful for patients with pancreatic cancer. Kasperk et al. stated that PET does not reliably prove or exclude malignancy in situations where conventional diagnostic procedures leave doubt as to the nature of a pancreatic mass in the "clinical reality".[16] It was suggested that from a cost-benefit view point pancreatic cancer has too poor a prognosis to be diagnosed with resource-intensive diagnostic tools such as FDG PET if an improved prognosis cannot be expected by PET diagnosis. It has not been established whether FDG PET improves the prognosis of pancreatic cancer patients. It should be noted that this kind of criticism of FDG PET arose from Germany and the United States where many clinical PET centers are already present. As physicians of nuclear medicine and referring surgeons, it is necessary to reconsider the reality of clinical situations.

In the last decade, our group conducted clinical research on pancreatic cancer using FDG PET, with the results suggesting that FDG PET is clearly useful for clinical management in pancreatic cancer patients.[14,18–26] However, evidence-based medicine is currently practiced and it is necessary to observe complete impartiality in the evaluation of the usefulness of FDG PET, not to be biased by prejudice from the standpoint of nuclear medicine, and to show clear clinical evidence. In the present review article, we would like to clarify the usefulness and also the limitations of pancreatic cancer diagnosis using FDG PET from a clinical point of view.

GENERAL ASPECTS IN FDG PET ONCOLOGY

Cellular Mechanism of FDG Uptake

A variety of studies concerning the cellular mechanism of FDG uptake have been published during the last 20 years. A series of studies in this field were well summarized in an excellent review by Kubota et al.[27] FDG or glucose in the vascular space (or in the interstitial space) is transported into cytosol of the cell via a group of glucose transporter proteins (GLUT) located in the cell membrane (Fig. 1).[28] Overexpression of GLUTs was reported in various cancers, including pancreatic cancer.[19,20,29–36] The main subtype expressed in the tumor cells was reported to be GLUT-1.[19,32] This transport mediated by GLUT is called facilitative diffusion, in which glucose or FDG passes through the proteins depending on its concentration gradient without requiring any energy.[28] In usual clinical situations within 1 hour after FDG injection, the glucose or FDG concentration is higher in the intravascular cavity (and in the interstitial space) than in the cellular cytosol, and so glucose and FDG flow mainly from the outside to the inside of the cell (Fig. 2). Inside the cell, glucose and FDG are phosphorylated to glucose-6-phosphate and FDG-6-phosphate (FDG-6-P) by a group of enzymes called hexokinases (HK), respectively.[37,38] The main subtype of HK expressed in the tumor cells was reported as HK-II.[38–40] Glucose-6-phosphate is further metabolized in the glycolytic pathway or in the pentose phosphate pathway or in the glycogen synthesis (in the liver and muscles), while FDG-6-P is not metabolized further in the glycolytic pathway or others. Reverse reaction from FDG-6-P to FDG, mediated by glucose-6-phosphatase (GP), is observed in the normal liver cells, epithelia of the renal tubules and small intestine. This reaction is sometimes observed in tumor cells, such as hepatocellular carcinoma, but is not observed in the vast majority of malignant cell types.[41–43] Thus, FDG is basically trapped in malignant cells (metabolic trapping), which results in clear tumor PET images with a higher tumor-to-normal ratio. Accumulation of FDG in tumor cells is obtained as a result of this multi-step cellular mechanism.

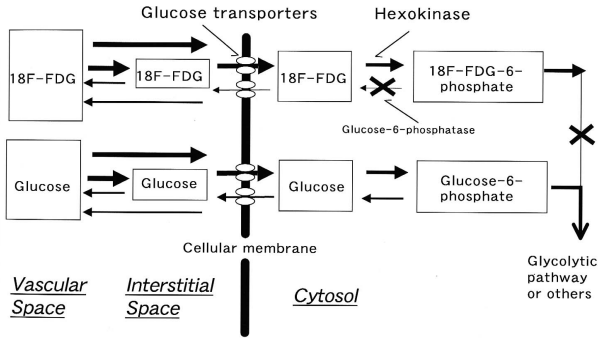

Fig. 1 Schematic figure for the mechanism of FDG uptake. Typically, a three-compartment-model has been applied in the evaluation of FDG uptake in tumor tissue. In this kind of model, however, the presence of heterogeneity of cancer tissue, such as interstitial space has been ignored.

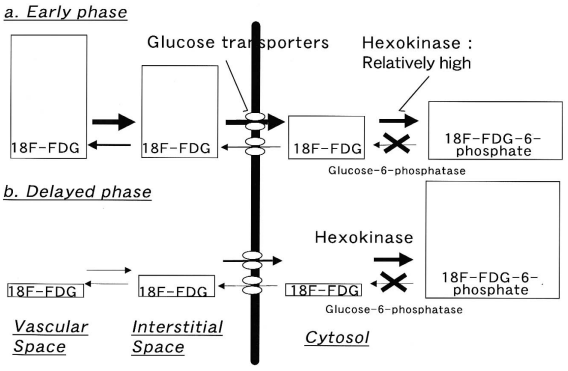

Fig. 2

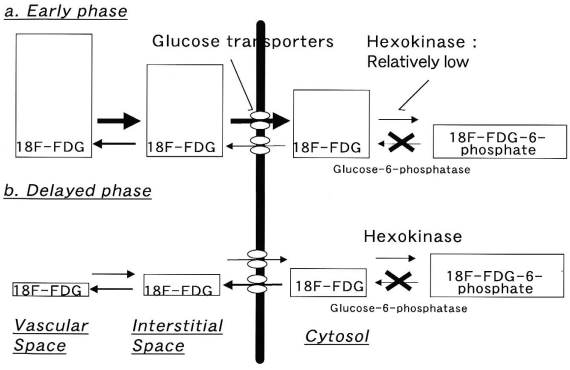

Fig. 3

Figs. 2 & 3 Schematic figures for FDG uptake in early and delayed phases. In these figures, the height of the column indicates the concentration of each substance.

Fig. 2 In a case where the expression of hexokinase is adequate, the reaction of FDG phosphorylation is performed in the cytosol so fast that the intra-cytosol concentration of free FDG is always kept low. During the early phase (0 min–about 60 min after the injection of FDG), FDG flows from the outside to the inside of the cell via glucose transporters according to the concentration gradient. During the delayed phase (about 60–120 min after the injection), the concentration of FDG has already decreased outside the cell, while hexokinase keeps working in the phosphorylation and keep the concentration of free FDG lower in the cytosol. Thus, even during the delayed phase, the concentration of FDG in the interstitial space is higher than that in cytosol, which results in the flow from the outside to the inside and a continuous increase in the total amount of intracellular FDG.

Fig. 3 In a case where the expression of hexokinase is low, the reaction of FDG phosphorylation is performed in the cytosol so slowly that the intra-cytosol concentration of free FDG is not kept low. Thus, during the delayed phase, the concentration of FDG in the vascular and interstitial space is lower than that in cytosol, which results in the flow from inside to outside. Please note that the total amount of intracellular FDG and FDG-6-P in the delayed phase (which means "FDG uptake" clinically) could be higher or lower than that during the early phase, depending on various factors.

A series of studies using immunohistochemistry clarified several aspects of the FDG uptake mechanism in pancreatic cancers.[19,20,29] It appears that the rate-limiting-step of glycolysis in tumor cells sometimes varies even within the pancreatic cancer population. The positive correlations between Standard Uptake Value (SUV) and GLUT-1 expression observed in our previous studies suggested that transport by GLUT is most likely the rate-limiting-step of FDG uptake (Fig. 2).[19] On the other hand, FDG is not always well trapped in tumor cells, and FDG uptake sometimes shows a decrease during the delayed phase, where phosphorylation by HK is clearly the rate-limiting step in the FDG metabolic trap (Fig. 3).[29] These two opposite results for rate-limiting-step may suggest the difficulty in applying a three-compartment model to FDG PET oncology. Sokoloff et al. suggested that their model is only applicable to a localized region of tissue that is homogeneous with respect to the following: rate of blood flow, rate of transport of deoxyglucose and glucose between plasma and tissue, etc.[44] When Sokoloff's three-compartment model is applied to tumor tissue, it is necessary to ignore the interstitial space surrounding the tumor (Fig. 1). In addition, it is necessary to ignore the heterogeneous nature of tumor tissue (including cellularity, vascularity or hypoxia), and the presence of inflammatory cells. Considering these various factors affecting FDG uptake, the mechanism of FDG cannot be over-simplified. An FDG time-activity-curve of an individual tumor does not always follow a similar shape observed in the same type of tumors.[25,29] Only considering the metabolic context of each patient with each individual tumor would be meaningful. Therefore, care should be taken with these factors in FDG uptake, because misdiagnoses could easily be made in everyday clinical practice without knowledge of this complexity.

Appropriate Scan Time and Delayed Scan

With the increasing clinical application of PET using FDG in cancer diagnosis, the scanner time becomes the limiting resource for everyday clinical practice. Thus, obtaining an appropriate scan time for optimal imaging is important in cancer diagnosis.

Several studies revealed that a delayed scan (at 2–3 hours after the injection of FDG) of FDG PET is useful in the differentiation of malignancy in patients with soft tissue tumor, breast cancer, head & neck cancer, lung tumor, liver tumor and pancreatic cancer because of the better Target Non-target Ratio (TNR) obtained in the delayed scan.[25,45–50] These studies are recent important issues in nuclear medicine, because it has been common in many institution to set scan times at 45 minutes to 1 hour after injection of FDG, based on the protocol of brain studies. However, some studies also recommend 2–3 hours as an optimal scan time without the use of an early phase scan (1–1.5 hr).[46,47] We believe, however, that excessive simplification in evaluation of FDG uptake is

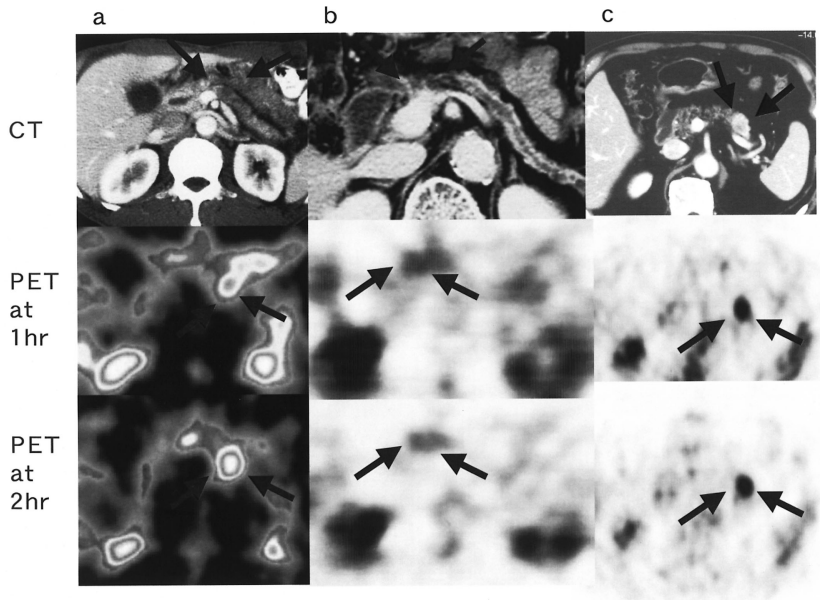

Fig. 4 Various uptake patterns observed in delayed FDG PET scan. Figure a shows a pancreatic cancer case that was unclear at the 1 hr scan, but became clear at the delayed scan (2 hours after FDG injection). Figure b shows a pancreatic cancer case that was relatively clear in the 1 hr scan, but became faint and unclear in the delayed scan. Figure c shows a pancreatic cancer case with the lowest retention index value (–25%) in our institute. The contrast-enhanced CT scan (arterial phase) clearly reveals that this tumor is a hypervascular-type pancreatic cancer. This is the only hypervascular-type case in the PET study in our institution, and is relatively unusual for invasive ductal adenocarcinoma. In this case, FDG PET images show decreased FDG uptake in 2 hr scan, which suggested the possible role of vascularity in the wash-out of FDG in the delayed phase.

risky for everyday practice, especially for pancreatic cancers. Table 1 shows average SUVs of pancreatic cancers in each institution. It should be noted that the value of FDG uptake could be changed by the scan time even using the same quantification method, assuming that pancreatic cancers show similar FDG uptake all over the world. This suggests that accurate diagnosis would not be expected if the scan time was not uniform. Our recent study using immunohistochemistry clarified the cellular mechanism of delayed FDG uptake (Figs. 2 and 3).[25,29] Our recent statistics showed that 19% (13 of 68 cases) of pancreatic cancers showed a decrease in FDG uptake from 1 hr to 2 hr after the injection of FDG, and 3–4.5% (2–3 of 68 cases) could be seen as positive only at the 1 hr scan and could not be seen clearly at 2 hours after the injection of FDG (Fig. 4). This finding cannot be neglected in everyday practice for diagnosis of lethal pancreatic cancers. Considering this fluctuation in FDG uptake, scan timing after FDG injection should be strictly defined to avoid possible false negative cases.

A better diagnostic accuracy could be obtained by the following FDG PET protocol for evaluation of pancreatic cancer according to our previous study,[25]

1) Take a static whole-body scan at 1 hour after injection of FDG,
2) If a positive FDG uptake in the primary site is obtained at 1 hour, it is not necessary to acquire a delayed scan.
3) If an equivocal uptake or no positive FDG uptake at the primary site is detected at 1 hour, it is necessary to perform an additional delayed scan at 2 hr after injection of FDG with a short acquisition time applied only at the level of the pancreas.

Standardized Uptake Value (SUV)

A semiquantitative value for FDG PET studies, such as the standardized uptake value (SUV) or differential uptake ratio (DUR), was once used as a clear cut-off value between malignant and benign lesions. Inokuma et al. reported the cut-off value as 2.2.[14] SUV = 2.2 as a cut-off value between malignant and benign lesions has a reasonable statistical background because that value could be calculated as an average of cancer SUV minus the standard deviation at that time. However, SUVs are known not only as time-dependent values but also as method-dependent ones.[51–53] SUVs can be changed by several factors, such as methods of reconstruction, size and shape of region of interest (ROI), plasma glucose level, and patient body size and shape. Keyes et al. suggested that most of the currently published findings on SUVs in tumors are of little or no value to investigators outside the laboratory where the investigation was conducted, as shown clearly in Table 1.[53]

Table 1 Average standardized uptake value of pancreatic cancers in each institute

Author	Year	Journal	Number of cases	Average SUV of pancreatic cancer	Size of ROI	Shape of ROI	Scan time after FDG injection
Higashi	2003	The present study	90	7.2 ± 3.5	4 × 4 mm	square	60 min
Inokuma	1995	Radiology	35	4.4 ± 2.4	10 × 10 mm	square	60 min
Higashi	1998	J Nucl Med	24	4.3 ± 1.3	10 × 10 mm	square	60 min
Debelke	1999	J Nucl Med	65	5.1 ± 2.6	10 × 10 mm	square	60 min
Nakamoto	2000	Cancer	27	5.0 ± 2.3	10 × 10 mm	square	60 min
Nakamoto*	2000	Cancer	27 (delayed scan)	5.8 ± 3.0	10 × 10 mm	square	120 min
Friess	1995	Gut	34	3.1 ± 2.2	1500 pixels	circular	45 min
Koyama	2001	Ann Nucl Med	86	3.5 ± 1.7	6 mm	circular	40 min
Koyama**	2001	Ann Nucl Med	86 (modified)	3.8 ± 1.7	6 mm	circular	40 min
Frohlich	1999	J Nucl Med	168	4.6 ± 1.4	10 mm	circular	60 min
Stollfuss	1995	Radiology	43	3.2 ± 1.2	20 mm	circular	45 min
Kato	1995	Eur J Nucl Med	15	4.6 ± 1.9	dependent of tumor	circular	50 min
Bares	1994	Radiology	23	6.5 ± 3.4	50–100 pixels	dependent of tumor	45 min
Zimny	1997	Eur J Nucl Med	74 (all)	6.4 ± 3.6	dependent of tumor	dependent of tumor	40 min
Zumny***	1997	Eur J Nucl Med	47 (euglycemia)	6.9 ± 3.7	dependent of tumor	dependent of tumor	40 min
Nakata	2001	Int J Oncol	37	3.0	?	?	55 min
Imdahl	1999	Br J Surg	48	7.3 ± 2.9	?	?	90 min
Sendlar	2000	World J Surg	42	?	15 mm	?	?
Kasperk	2001	World J Surg	124	?	?	?	60–120 min ?

*: same cases studied by delayed scan, **: SUV modified by glycemia, ***: only for patients with euglycemia

Our recent data analysis showed that there was a significant difference between average SUV in pancreatic adenocarcinoma before 2000 (4.68 ± 2.41) (Fig. 5) and that after 2000 in our institute (7.17 ± 3.49) (Table 1). It was suggested that this change in the average SUVs was because of the difference in the ROI size. Before 2000, semiquantitative analysis using SUVs was performed using an old-generation PET machine (PCT3600W, Hitachi Medico, Tokyo, Japan, not for whole-body PET) with the use of filtered-back-projection (FBP) reconstruction methods with 10-mm square ROI size. In 2000, a new-generation whole-body PET machine (GE Advance, General Electric, Milwaukee, WI) was introduced to our hospital, and SUV has been calculated with the use of ordered subsets expectation maximization (OS-EM) reconstruction with smaller ROI size, 4-mm square. ROI size was reduced because of the higher resolution in our new machine. In the former PET machine, the effective resolution after reconstruction was approximately 10 mm, while the latter has a resolution of 4.2 mm. Some studies reported that comparative evaluation between FBP and the OS-EM reconstruction algorithm basically showed a good correlation with each other.[54,55] Therefore, the change in the ROI size affects the average SUVs.

Thus, a SUV can be changeable even in the same institution and it is impossible to compare SUVs as an absolute value between two different institutions with different methods. It is not necessary in usual clinical situation to adhere to the exact value of SUVs.

Other Factors Affecting FDG Uptake

Several factors affecting tumor FDG uptake, other than glucose transporters, hexokinase, are known, such as infiltrating inflammatory cells, tumor cell cellularity, and serum glucose level or insulin level. At first, inflammatory change is discussed. Inflammatory change is one of the most important factors involved in tumor FDG uptake. FDG is not a cancer-specific agent and is known to accumulate in several pancreatic diseases, such as acute pancreatitis, abscess, lesion of massive lymphocyte infiltration, and autoimmune pancreatitis.[15,23,56,57] Recently, whole-body FDG PET has been used also for the purpose of infection imaging.[58] Because of this high accumulation in inflammatory lesions, the wide overlap of SUVs between malignant and benign lesions makes the differential diagnosis difficult. Zimny et al. indicate that only visual qualitative interpretation provides accurate differentiation of pancreatic carcinoma from pancreatitis.[5] In general, diffuse high uptake in the whole pancreas can be diagnosed as an inflammatory lesion, but morphological analysis is not specific and can be misleading, as Strauss et al. reported.[56] Since pancreatic cancer is sometimes accompanied by pancreatitis and because cancer cells can infiltrate diffusely into total pancreatic tissue, a case with pancreatic cancer can represent diffuse high FDG uptake in the whole pancreas (Fig. 6). On the other hand, autoimmune pancreatitis can assume a focal uptake pattern in a FDG PET study (Fig. 6). Furthermore, Kubota et al. showed that even in tumor tissue about 24% of FDG uptake may be related to inflammatory cells, meaning that it is impossible to separate cancer tissue and inflammatory tissue clearly by FDG PET.[59–61] Differentiation between malignancy and benign inflammatory lesions remains an unsolved problem.

Tumor cell cellularity was also reported as an important factor for FDG tumor uptake *in vitro* and *in*

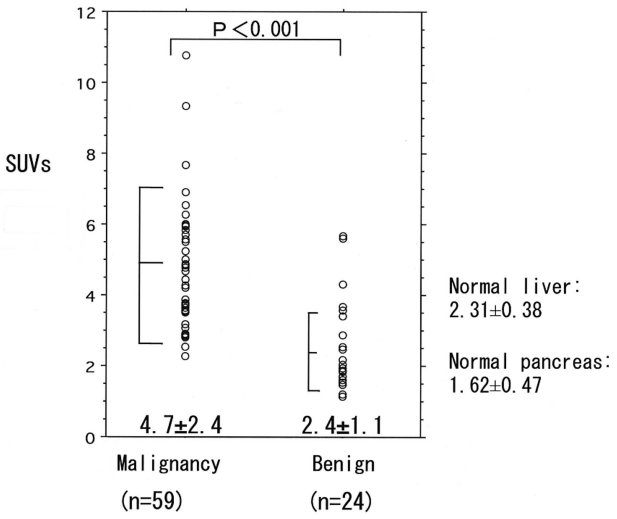

Fig. 5 Comparative scattergram of semiquantitative analysis using SUVs in pancreatic cancer and pancreatitis. There is a wide overlap between pancreatic cancer and pancreatitis. Please note the normal FDG uptake in the normal liver and pancreas.

vivo.[20,57,62–66] Especially in pancreatic cancer, which is known to be rich in dismoplastic reaction, it is necessary to be aware of the possibility of false negative cases due to poor cellularity even when tumor size is fairly large. According to a study from Germany, a pancreatic cancer with a size of 6 cm was missed by FDG PET.[16] In our experience, the largest size of false negative case in pancreatic cancers (invasive ductal adenocarcinoma) was 33 mm in diameter (Fig. 7). This kind of pathological feature (marked desmoplasia, scirrhous type) is not so rare for pancreatic cancers. Cystic type cancers are also known to be poor in cellularity because of the presence of their cystic component.[63] To detect focal uptake corresponding to a cellular-rich mural nodule in the cystic component would be a key point for accurate differential diagnosis of cystic pancreatic lesions, as described in the final chapter.

Blood glucose level should be noted in evaluation of FDG PET. The effect of glucose level in FDG PET oncology is known, but the management of nonfasted

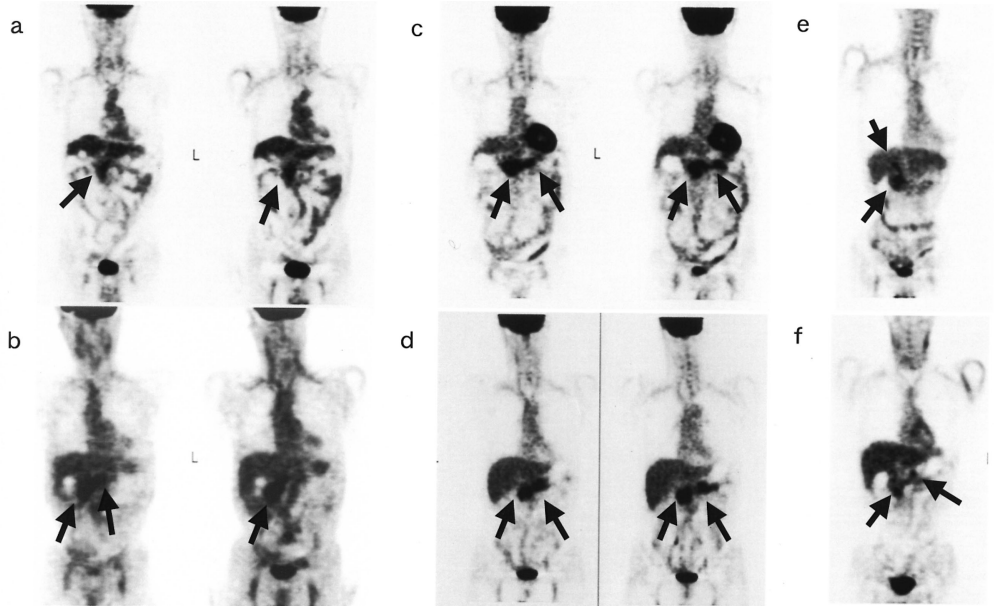

Fig. 6 Focal and diffuse FDG uptake in various pancreatic diseases. a: Autoimmune pancreatitis case. Focal FDG uptake is shown in the pancreatic head. b: Acute pancreatitis case. FDG PET was performed 4 days after ERCP procedure. Diffuse high FDG uptake is shown in the whole pancreas. c: Pancreatic cancer case. Diffuse high FDG uptake is shown in the whole pancreas. Laparotomy showed that invasive adenocarcinoma diffusely infiltrated the entire pancreas. d: Pancreatic cancer and the concomitant pancreatitis case. Diffuse high FDG uptake is shown in the whole pancreas. Resected specimen shows that invasive adenocarcinoma is located in the pancreatic head and concomitant pancreatitis in the body and the tail was confirmed by needle biopsy. e: Pancreatic cancer and the concomitant cholangitis case. Focal FDG uptake is shown in the pancreatic head, combined with a linear high uptake along the common bile duct. Cholangitis due to the PTCD procedure was confirmed at the time of the operation. f: Pancreatic cancer case. Two foci of high FDG uptake are shown in the pancreatic head and body. Other imaging modalities only showed pancreatic head mass. Operation revealed an invasive adenocarcinoma mass in the head, which infiltrated diffusely from the pancreatic head to the pancreatic body along the main pancreatic duct. FDG PET could visualize an area in the body with relatively higher tumor cell density.

Table 2 Diagnostic accuracy of FDG PET in patients with pancreatic cancer in each institute

Author	Year	Journal	Number of cases	FDG PET				CT			Clinical impact & additional information (%)
				sensitivity (%)	specificity (%)	accuracy (%)		sensitivity (%)	specificity (%)	accuracy (%)	
Diagnosis for untreated lesions/cancers											
Differential diagnosis/Pretreatment staging											
Bares	1994	Radiology	85	85	77	82					
Inokuma	1995	Radiology	46	94	82	91	>>	89	73	85	
Kato	1995	Eur J Nucl Med	24	93	78	88					
Friess	1995	Gut	80	94	88	91	>>	79	69	74	
Stollfuss	1995	Radiology	73	95	90	93	>>	80	74	78	
Zumny	1997	Eur J Nucl Med	106	85	84	85					
Zimny*	1997	Eur J Nucl Med	72	98	84	93					
Higashi	1998	J Nucl Med	34	93	67	88					
Debelke	1999	J Nucl Med	65	92	85	91		65	61	65	43%
Imdahl	1999	Br J Surg	48	96	100		>	81	89		
Nakamoto	2000	Cancer	47	96	75	87					
Nakamoto**	2000	Cancer	47	100	80	92					
Diederichs[121]	2000	Pancreas	159			86	=			82	
Diederichs*	2000	Pancreas	123			92	>			82	
Sendlar	2000	World J Surg	42	71	64	69	=	74	46	68	
Kasperk	2001	World J Surg	124	84	66		=	82	61		
Koyama	2002	Ann Nucl Med	86	82	81	81	=	91	62	84	
Koyama***	2002	Ann Nucl Med	86	93	80	90	>	91	62	84	
Papos[122]	2002	Clin Nucl Med	22	100	88	91	>>	100	50	64	
Higashi	2003	The present study	53	65	93	81					60%
Higashi****	2003	The present study	93	100							38%
Differential diagnosis of cystic diseases											
Sperti	2001	Ann Surg	55	94	97	96	>>	65	87	80	
Higashi	2003	This study	39	100							90%
Diagnosis for post-treatment follow-up											
Franke	1999	Anticancer Res	19								53%
Jadvar[123]	1999	Abdominal Imaging	20								14%
Shields[124]	1999	J Nucl Med	19	94							16%
Higashi	1999	J Nucl Med	12								30%
Higashi	2003	This study	46								65%

*: excluding hyperglycemia cases, **: using 1 hr & 2 hr scan, ***: using modified SUV by glycemia, ****: pretreatment staging only

patients or diabetic patients remains controversial. Several studies reported the significant effect of blood glucose level on SUVs.[5,13,67] In contrast, other studies suggested that there was no significant difference between the high blood glucose group and the low one.[68] The influence of hyperglycemia on tumor FDG uptake is explained in two ways: a direct effect on the uptake mechanism in the tumor cell, and an indirect effect via the change in the biodistribution of FDG in the whole body, including fat and muscular tissues. The former was reported by Torizuka et al. using an *in vitro* tumor cell model, in which acute glycemia could decrease tumor FDG uptake.[69] This was explained by the finding that GLUT-1, the main subtype of GLUT in tumor cells, was suggested to be insulin- or hyperglycemia-dependent in normal cells, such as myocardial cells or placental trophoblast cells.[70–72] However, to the best of our knowledge, there has been only one study that reported evidence of GLUT-1 expression mediated by hyperglycemia in tumor cells or transformed cells.[73] Hahn et al. reported that hyperglycemia regulates the glucose transport system of a choriocarcinoma cell line, JAR, but does not influence that of another cell line, JEG-3. In other words, it was not confirmed that regulation of glucose transport by hyperglycemia is always preserved in all transformed cells. Concerning the indirect effect of hyperglycemia, several studies proposed the use of "glycemia-modified SUV" in the diagnosis of pancreatic cancers.[74,75] These values are calculated based on a hypothesis that there is a linear decrease in SUVs according to the increase in the serum glucose level. As far as we know, however, there has been no evidence of this linearity between SUVs and glucose level. With respect to the indirect effect of glucose, the most important factors in the systemic glucose metabolism in the whole body are fat and muscle tissues, and the amount of these tissues is different in each person. In addition, Torizuka et al. revealed that chronic hyperglycemia does not significantly change FDG uptake in their human adenocarcinoma

Table 3 FDG PET studies for pancreatic lesions in our institute (2000. 6–2002. 9)

	Total cases		Clinical impact & additional information	
	231 cases		132 cases	57%
Diagnosis for untreated lesions/cancers	185 cases	80%	102 cases	55%
Differential diagnosis	53 cases	23%	32 cases	60%
Differential diagnosis of cystic disease	39 cases	17%	35 cases	90%
Pretreatment staging	93 cases	40%	35 cases	38%
Diagnosis for post-treatment follow-up	46 cases	20%	30 cases	65%
Ditection of recurrence	21 cases	9%	18 cases	86%
Evaluation of treatment efect	25 cases	11%	12 cases	48%

cell models, while acute hyperglycemia does change it significantly.[69] This means that acute hyperglycemia should be considered different from chronic hyperglycemia. These factors suggest that linearity is not expected in the relation between SUVs and glucose level. As mentioned above, it is not necessary to adhere to the exact value of SUVs. The use of insulin in diabetic animals was not effective for enhancing image quality of tumor FDG accumulation.[76] Thus, there is no easy way to improve image quality of tumor FDG uptake or to correct SUVs by accurate calculation when a patient is diabetic or is not fasted. The only necessity is the instruction to fast to patients and to check the glucose level immediately prior to FDG injection.

DIAGNOSIS OF PANCREATIC DISEASES WITH FDG PET

Table 2 shows the diagnostic accuracy of pancreatic cancers in each institution, including the results of the present study. In many studies, the diagnostic results of FDG PET were better than those of CT. Table 3 shows the number of FDG PET studies performed in our institution between June, 2000 and September, 2002 for patients with pancreatic diseases. Of 231 cases, 185 (80%) were performed for diagnosis of an untreated lesion and 46 cases (20%) were for post-treatment follow-up. Clinical impact and additional information were observed in more than half of the total cases (57%). In the present chapter, the clinical usefulness and the limitations of FDG PET in pancreatic cancer imaging will be discussed.

Differential Diagnosis of Pancreatic Cancer from Pancreatitis

Differential diagnosis between pancreatic cancer and pancreatitis has been one of the biggest problems in the management of pancreatic diseases. Many studies have revealed that FDG PET is the most effective imaging modality (Table 1).[13,14,22,55,77,78] Figure 8 shows four cases of pancreatic head mass, which cannot be clearly diagnosed by CT scan, although FDG PET clearly reveals the presence of cancer tissue with focal accumulation. It was suggested that FDG PET can perform this kind of differential diagnosis with high accuracy, greater than 85% in most of the published data and that this was the main purpose of the FDG PET scan in pancreatic diseases.[18,22,76,77,79] Many studies also used quantitative analysis, such as SUVs, for the purpose of differentiation of pancreatic cancer from benign lesions and some studies showed cut-off values between them.[18,74,79] Recently, however, several studies questioned the effectiveness of FDG PET in the differential diagnosis of pancreatic diseases and the wide overlap of SUVs between malignant and benign lesions has become an important problem in the diagnosis, as mentioned above. Recent advances in CT and MRCP have improved their usefulness in the evaluation of pancreatic lesions, and the percentage of equivocal lesions between malignant and benign diseases has decreased. Therefore, the number of lesions that are equivocal by other imaging modalities and are referred for FDG PET examination are decreasing, and PET diagnosis in such cases is becoming increasingly difficult. Our recent experience of 231 pancreatic cases showed that FDG PET for this purpose was performed only in 23% of cases (53 of 231) in our institution (if "preoperative staging" is considered separately) (Table 3). Among these 53 cases, which were equivocal between malignancy and benign inflammatory lesion in other imaging modalities, FDG PET was useful in 32 cases (60%) but provided equivocal results in 21 cases (40%). Sensitivity, specificity, and accuracy were shown as 65 (15/23 cases), 93, and 81%, respectively. We experienced 8 false negative pancreatic cancer cases. This figure, 65% for sensitivity, is the lowest in the literature, as shown in Table 2. (If we include "preoperative staging" cases, however, the sensitivity will be higher, 93%, 108/116 cases.) "In a clinical reality," the current clinical importance of FDG PET diagnosis for differentiation of "equivocal" pancreatic lesions is becoming relatively low, compared with previous practices. Thus, from a clinical point of view, there is a limitation of FDG PET in the differential diagnosis between pancreatic cancer and mass-forming pancreatitis. SUVs cannot always differentiate malignancy from benign inflammatory lesions because of the wide overlap

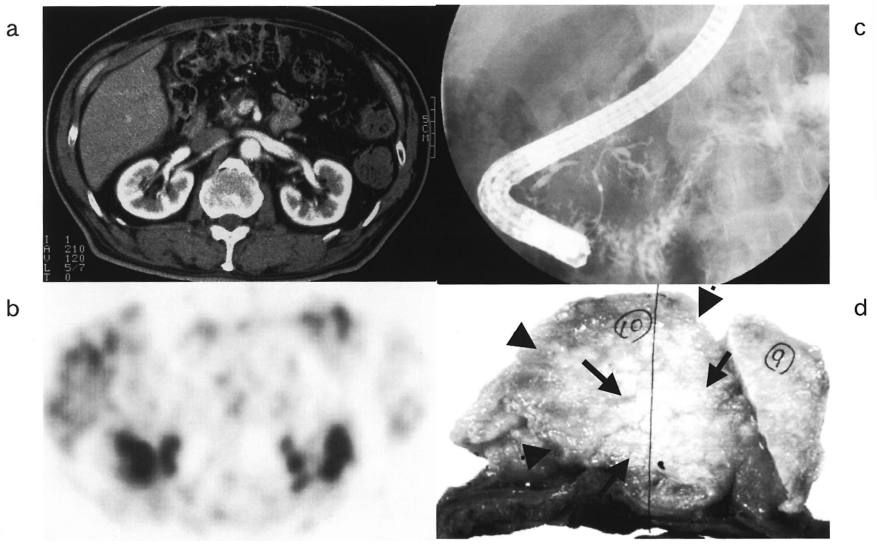

Fig. 7 The largest false negative pancreatic cancer in our FDG-PET cases (33 mm). Screening abdominal US revealed main pancreatic duct dilatation and the 74-year-old male was admitted to our hospital. a: CT scan showed equivocal findings with main pancreatic duct dilatation. b: FDG PET was negative in the 1 hr scan. c: ERCP showed irregular stenosis of MPD in the pancreatic head, and therefore, pancreatic head resection was performed. d: The surgical specimen immediately after the operation showed a small pancreatic mass (18 mm, *arrows*), but macroscopic findings after the fixing procedure using formalin revealed a 33-mm mass (*arrowhead*), and poor tumor cell cellularity was confirmed by microscopic pathological examination.

(Fig. 5). In addition, the shape of the FDG accumulation cannot be used as a differential indicator of malignancy from benign lesions (Fig. 6). Shreve et al. reported that focal FDG uptake can be observed both in the setting of mild acute diffuse pancreatitis and in focal active pancreatitis associated with mass.[15]

In the differentiation of malignancy from benign lesions, delayed or dual-phase scanning is a recent breakthrough in FDG PET oncology, as mentioned above.[25,45–50] In our previous study, Nakamoto et al. reported that improved accuracy can be achieved by the use of an additional delayed scan in the differential diagnosis of pancreatic diseases, because many malignant lesions show a constant increase in FDG uptake, while many benign lesions show a decrease in FDG uptake with a delayed PET scan (Fig. 4).[25] However, there are a number of pancreatic cancer cases that showed a decrease of FDG uptake during the delayed phase, and there are a number of pancreatic benign lesions (including autoimmune pancreatitis) that showed a rise during the delayed phase (Fig. 6). Only a limited number of cases were included in our preliminary study, and so further evaluation using larger numbers of patients is needed to elucidate the best criteria for the differential diagnosis of pancreatic diseases.

As for autoimmune pancreatitis, several studies were reported recently, and the presence of the disease has been widely known.[80–83] Several specific characteristics of CT images, such as "capsule-like rim," were reported, and the CT diagnosis of autoimmune pancreatitis is becoming established.[84,85] History taking and blood data evaluation with a knowledge of the disease is necessary for the diagnosis. Figure 6a shows a case of autoimmune pancreatitis with the shape of the focal uptake pattern. In such a case, the differential diagnosis between malignancy and pancreatitis is almost impossible by FDG PET alone. Delayed PET scanning can differentiate many cases of autoimmune pancreatitis with the evaluation of decreased uptake in the delayed phase, but a few cases in an active phase showed a steep rise of FDG uptake between 1 hr and 2 hr.

We face a similar problem when we perform an FDG PET study immediately following endoscopic retrograde cholangio-pancreatography (ERCP) or percutaneous transhepatic cholangio-drainage (PTCD). Sometimes, ERCP causes fairly severe pancreatitis, which results in high FDG accumulation. It is noted that even in the absence of symptoms high FDG uptake could be observed. Typically, diffuse high uptake may be seen (Fig. 6), but focal uptake could be seen depending on the severity of inflammation and the duration after ERCP. Insertion of a PTCD tube could cause inflammatory FDG uptake in the biliary tract (Fig. 6e). Sometimes, secondary liver abscess due to PTCD-related infection mimics liver metastasis. Appropriate indication-criteria for an FDG PET study would be needed, as Zimny et al. previously reported.[86]

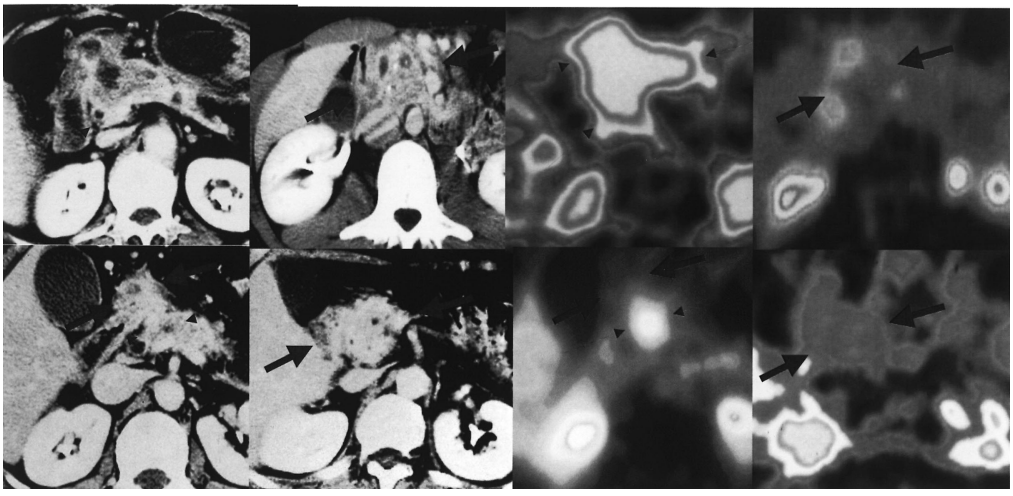

Fig. 8 Differential diagnosis of pancreatic cancer from mass-forming pancreatitis. Heterogeneous mass lesions in the pancreatic head are shown in the CT images (a–d) and PET images (a′–e′), corresponding to each other. Figure a shows a pancreatic cancer case, which was diagnosed using CT as pancreatic cancer with pseudo-cystic change. However, FDG PET revaled a high uptake throughout the lesion (a′). Figure b shows a pancreatic cancer case, which was first diagnosed as acute pancreatitis with pseudo-cysts using a CT scan. However, FDG PET detected a pancreatic cancer in the pancreatic head without any uptake in the cystic portion (b′). In both cases, PET findings were confirmed by operation. Figures c–d show typical mass-forming pancreatitis cases without any focal uptake in the lesions by FDG PET.

Staging of Pancreatic Cancer Using Whole Body PET

About 40% of patients with pancreatic cancer that is diagnosed as resectable by preoperative imaging modalities turned out to be unresectable at the time of operation.[87,88] It is suggested that accurate preoperative staging is one of the most useful and effective applications of FDG PET in the management of patients with pancreatic cancer. Staging using whole body PET was actually the most common purpose of the present pancreatic FDG PET study with 93 cases (40%) of 231 pancreatic PET cases between 2000 and 2002 (Table 3). The capability of whole body scanning with a single examination at one time is clearly an advantage of FDG PET, compared with other imaging modalities. Whole body FDG PET detected distant metastasis or unexpected lesions in 35 cases (38%) in our institution, such as the detection of distant LN metastasis (n = 3), liver metastasis (n = 10), peritoneal dissemination (n = 9), bone and multiple distant metastasis (n = 9), and other coexisting malignancies (n = 4) (Fig. 9). In these cases, the management of the patient was changed, and cost-saving and improved quality of life were expected by avoiding unnecessary surgery. This is the most important role of FDG PET in the diagnosis of pancreatic cancer in our experience. A similar tendency was reported elsewhere as well, with FDG PET providing important additional information and a change in patient management in about 40% of pancreatic cancer cases (Table 2).[74,89–91]

Liver metastasis is usually suggested as a contra-indication of pancreatic cancer resection. Therefore, detection of liver metastasis is really needed in the diagnosis using FDG PET. Several studies revealed excellent diagnostic accuracy of FDG PET in comparison with other modalities, such as CT or US.[13,14,90] In our institution (between June, 2000 and March, 2001), the detectability of liver metastasis by FDG PET (sensitivity: 85%, specificity: 97%, accuracy: 94%) was slightly better than that of CT scan (sensitivity: 67%, specificity: 100%, accuracy: 90%). False positive cases were seen in some inflammatory cases, such as liver abscess or intrahepatic bile duct infection mainly due to PTCD. False negative cases were sometimes observed in cases with small liver metastasis less than 1 cm in size (Fig. 10). Frohlich et al. also reported similar results, in which the detection rate for metastatic liver lesions >1 cm was 97% while that for lesions < or = 1 cm was 43%.[90] On the other hand, FDG PET can often detect a small lesion that CT scan cannot differentiate, because even if a small lesion with a size of 5 mm has strong radioactivity, it can be detected as a relatively larger lesion by FDG PET (Fig. 10b). Nakamoto et al. reported that FDG PET accurately differentiated seven metastatic lesions from cysts when the diagnosis using US or CT was unreliable because of the small size of the lesion (< or = 1 cm).[22] In the detection of such a small metastatic liver nodule by FDG PET, there are two factors that require care; 1) the parenchyma of the liver is not

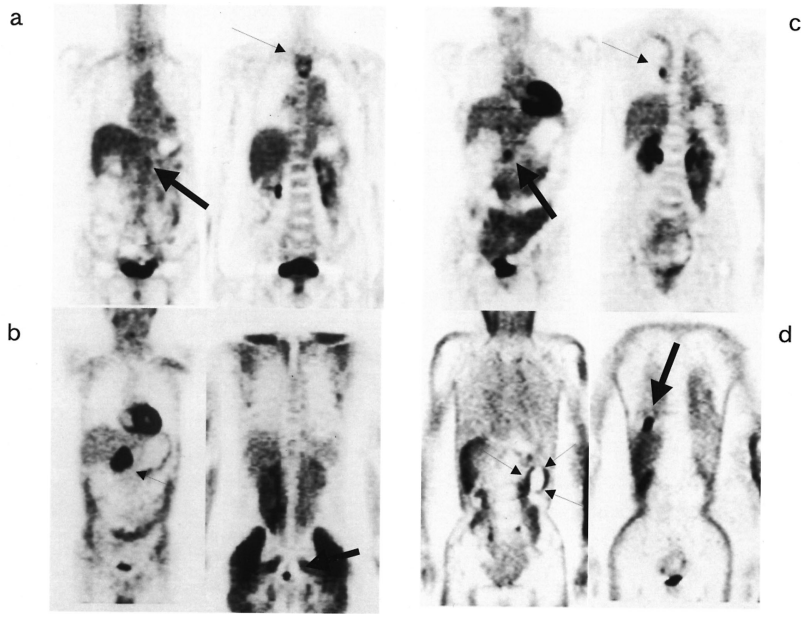

Fig. 9 Detection of distant metastasis or unexpected lesions by FDG PET. FDG PET revealed distant metastases or unexpected lesions in all four cases, which resulted in changes in patient management or clinical impact. Figure a shows a pancreatic cancer case with bone metastasis. This kind of solitary bone metastasis is sometimes observed in the cervical spine. Figure b shows a pancreatic cancer case with incidentally-detected high rectal uptake. Colonoscopy shows the presence of a cancer in the rectum. Figure c shows a pancreatic cancer case with incidentally-detected mediastinal high uptake. Pancreaticoduodenectomy was performed first and then endoscopic examination was performed in the mediastinum, which revealed a metastatic lymph node with histology of squamous cell carcinoma (SCC). The patient had already received a curative operation of lung cancer (SCC) 5 years prior to this PET study. Figure d shows a pancreatic tumor case with incidentally-detected high uptake in the lung field. After the detection of this lung nodule by FDG PET, CT and other imaging modalities confirmed the presence of primary lung cancer. However, the operation revealed that the pancreatic mass was an inflammatory pseudo-tumor (so-called "gazeoma"). In this case, FDG PET and other imaging modalities were false positive for the pancreatic mass, but were true positive for lung cancer. Anyway, FDG PET had a clinical impact for the lung lesion.

homogeneous in terms of FDG uptake and 2) respiratory motion artifacts sometimes cause image-deformity. Figure 10 a′–e′ shows the influence of these two factors, in which normal liver parenchyma itself is observed fairly heterogeneous in terms of FDG uptake. Therefore, sometimes it is impossible to differentiate a faint small tumor uptake from a scattered spotty pattern in the normal liver. Furthermore, respiratory motion causes an artifact on lesions near the diaphragm.

It is also known that LN metastasis is one of the most important aspects of clinical management as an independent prognostic indicator for pancreatic cancer patients.[92–96] Unfortunately, FDG PET is not the best modality to detect LN metastasis in the diagnosis of pancreatic cancer. In our institution between June, 2000 and March, 2001, the detectability of LN metastasis by FDG PET study (sensitivity: 36%, specificity: 93%, accuracy: 56%) was slightly worse than that of CT scan (sensitivity: 46%, specificity: 93%, accuracy: 63%). Bares et al. reported from their study, which was the very first study on the diagnosis of pancreatic cancer using FDG PET, that detectability of LN metastasis was 76%.[13] After that study, however, there has been no study that showed better or similar results in accuracy, except for their second study.[97] Zimny et al. reported an accuracy rate for the detection of LN metastasis of only 46%, similar to our previous results.[5] The reasons for this poor diagnostic result are unknown, but one reason may be the effect of strong radioactive scatter from the main tumor on peripancreatic small LN. FDG uptake in the small LN is masked by strong accumulation in the main tumor. It is suggested that another possible culprit for the poor results is the number of cancer cells in the LN, or tumor cell cellularity. When pathological microscopic analysis is regarded as the gold standard, small numbers of cancer cells in normal sized LN are of course positive. Due to the limitations of resolution, FDG PET has a disadvantage in the detection of microscopic metastasis in normal-sized LN, similar to other imaging modalities.

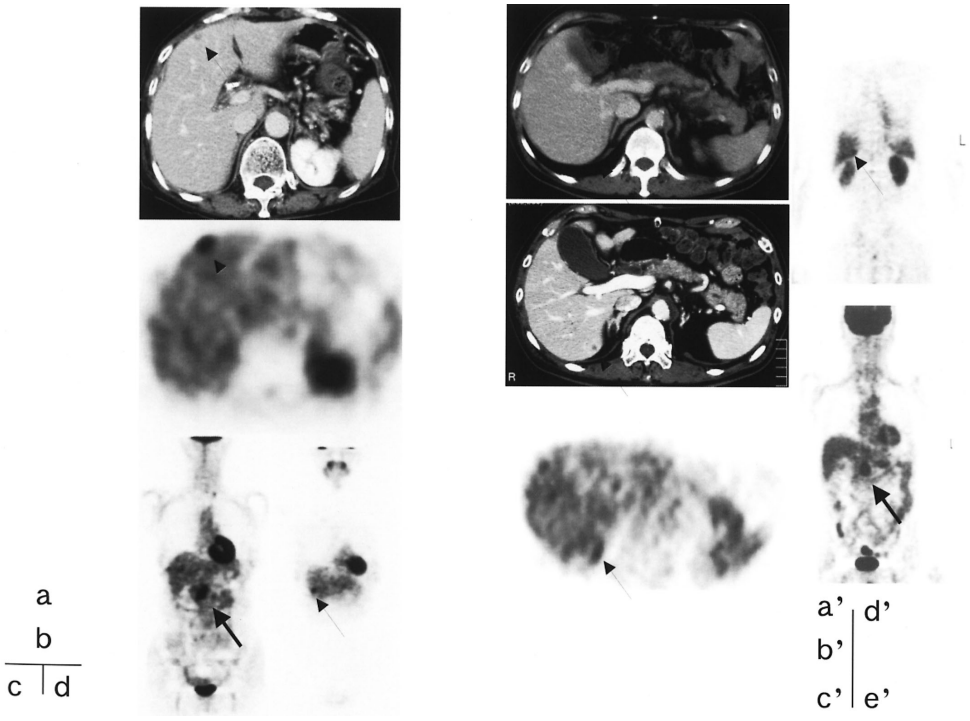

Fig. 10 Detection of liver metastasis by CT and FDG PET. Figures a–d show a case with a small liver nodule (less than 1 cm). Liver metastasis was not detected by the CT scan or by ultrasound, but FDG PET clearly revealed a nodule in the liver. Figures a′–e′ also show a case with a small liver nodule (less than 1 cm). CT scan (a′), performed 16 days before the FDG PET study, could not detect a liver nodule, while CT scan (b′), performed on the same day of FDG PET study, revealed a ring-enhanced liver nodule. Axial and coronal FDG PET showed a faint and irregular focal uptake corresponding to the same nodule, but the PET diagnosis (blind to the CT results) was equivocal for liver metastasis. Normal liver parenchyma itself is fairly heterogeneous in terms of FDG uptake, and therefore, sometimes it is impossible to differentiate a faint small tumor uptake from a scattered spotty pattern in the normal liver uptake. Respiratory motion causes artifacts on the lesions near the diaphragm.

Detection of Small Pancreatic Cancers (T1 or TS1)

The vast majority of pancreatic cancer patients will die within 1–2 years, and the only treatment method for long time survival is resection, which could be achieved by the detection of small sized pancreatic cancers localized in the pancreas. Fortner et al. showed that tumor size is the primary prognosticator for pancreatic cancer, shown as "the smaller, the better."[98] A small cancer less than 20 mm in diameter without LN metastasis is defined as T1 in the UICC classification and as TS-1 in the classification of the Japan Pancreas Society, and has already been confirmed to have better prognosis than the others.[99,100] However, only 8% of all pancreatic carcinomas had a maximal tumor diameter of 2 cm or less.[101] Furthermore, early detection of pancreatic cancer using tumor marker, CA19-9, is not useful because only 50% of small tumors (less than 20 mm) are associated with an increased CA19-9 value.[88] Concerning FDG PET, there has been no study focusing on small pancreatic cancer. Our recent findings in the diagnosis of 16 cases of TS1 pancreatic cancers using FDG PET showed high detectability. Of 16 TS1 cancers, FDG-PET clearly detected 13 cases with a sensitivity of 81%, among which the smallest cancer detected by FDG PET in our institution was 7 mm. Three false negative cases consisted of one cancer with the size of 4 mm (pathology showed that it was a cancer-*in-situ*) and two cancers (18–20 mm) diagnosed by non-attenuation-corrected images. With regard to the resolution (4.2 mm) of the new PET machine, a 4-mm-nodule is close to the minimum size detectable in this PET machine. The lack of attenuation-correction (AC) was the likely culprit for the other two false negative cases, because lack of AC is critical in the diagnosis of deeply seated abdominal tumors.[102] Detectability of FDG-PET in the diagnosis of TS1 pancreatic cancers is basically reliable and satisfactory. In contrast, most cases were without symptoms and were initially detected by screening abdominal ultrasound (US) with dilatation of the main pancreatic duct without visualization of the mass itself. CT scan was also performed in all cases, and showed equivocal findings in the detection of the mass itself in most cases (7 cases, 44%). Thus, it is suggested that FDG-PET is promising

for the detection of TS1 pancreatic cancers.

Therefore, it may be expected that an appropriate use of FDG-PET in a health check-up system could play an important role in the detection of curable pancreatic cancers. However, there has been only one study evaluating the use of FDG-PET for cancer screening.[103] Yasuda et al. reported their results of cancer screening in 3,165 healthy persons (male: 2,017, female: 1,148). According to a statistical report on the Japanese population, the incident rate of newly diagnosed pancreatic cancer is about 0.3%.[1] This figure corresponds to about 3 cases of pancreatic cancer in their 3,165 population, although they could detect 10 lung cancers in their cancer screening, but no pancreatic cancer. The reason for this low detectability is unclear, but one reason may be the difference in the ages between the subjects in their study (40–60 years old) and in the disease-incident peak of pancreatic cancers (50–70 years old). Anyway, from a cost-benefit view point, the use of FDG-PET in this kind of health check-up system may not be effective for the detection of possibly curable pancreatic cancers because of this low incident rate. It is known that pancreatic cancer is slightly more frequent in male patients, and that the incidence of this disease is increased in smokers and patients with chronic pancreatitis.[87] An appropriate health-check-up system for patients at relatively high risk should be established.

Evaluation of the Therapeutic Effect and Recurrent Pancreatic Cancer

To evaluate the therapeutic effect using FDG PET, it is necessary to determine an appropriate time interval between treatment and a follow-up PET study. Tumor metabolism is likely to decrease during the therapy, while secondary inflammatory reaction caused by treatment, especially radiotherapy, may increase FDG uptake with time. An animal study revealed that this inflammatory reaction could affect not only the irradiated organ, but also non-irradiated organs, probably via a cytokine interaction, and total FDG uptake could fluctuate for more than one month.[104] The clinical data of FDG PET evaluation in the therapeutic effect and detection of recurrence are relatively limited in pancreatic cancer due to its poor prognosis with short follow-up period. A previous study reported the usefulness of FDG PET in the evaluation of the therapeutic effect of IORT (intraoperative radiation therapy) in pancreatic cancers, in which FDG PET showed that the metabolic change in irradiated cancer after IORT was significantly earlier than the morphological change detected by CT scan.[21] However, although FDG PET would effectively evaluate the local control of the primary site, there was no relation between FDG PET results and prognosis in that paper. Franke et al. also reported the diagnostic benefit of follow-up of pancreatic cancers, but the benefit was basically limited in the detection of distant metastasis by FDG PET.[89] Our recent experience showed that pancreatic FDG PET studies were performed for the evaluation of post-treated pancreatic cancers in 46 (20%) of 231 cases. Maisey et al. reported in their pilot study that the absence of FDG uptake at 1 month following chemotherapy for pancreatic carcinoma is an indicator of improved overall survival.[105] Evaluation of the therapeutic effect was performed using PET in 25 cases (11%) by us, but the usefulness of FDG PET for this purpose has not been thoroughly evaluated.

In 21 (9%) of 231 pancreatic patients, FDG PET was performed to detect unknown recurrent site(s) after a relatively curative operation for pancreatic cancer. In 12 of these cases, where rising CA19-9 was reported without any evident sign of recurrence by other imaging modalities, FDG PET could detect the recurrent sites clearly, such as local (n = 3), liver (n = 3), peritoneal dissemination (n = 3), lung (n = 2), distant lymph nodes (n = 2), and multiple metastasis (n = 1). FDG PET could also exclude the presence of recurrence in 6 cases diagnosed with indeterminate findings by other imaging modalities. Thus, FDG PET appears feasible for follow-up of pancreatic cancers after treatment. Further evaluation of larger numbers of cancer cases is needed.

Prediction of Survival of Pancreatic Cancer Patients

Recently, the prediction of survival of cancer patients by means of FDG uptake, has become an important topic in the field of PET oncology. Many studies evaluating the relation between FDG PET results and prognosis have been reported for a variety of cancers, including non-small-cell lung cancer, malignant lymphoma, germ cell cancer, head and neck cancer, esophageal cancer, rectal cancer, and breast cancer.[106–113] These studies are impressive and important because this kind of predictability is supposed to be difficult to achieve by anatomical imaging modalities. Most studies suggested a relationship between FDG uptake and prognosis as "the lower, the better." However, the approach in each study differed. Some showed this relation between prognosis and FDG uptake in the primary tumor before treatment.[106–108] In contrast, some showed a relation between prognosis and FDG uptake in the primary tumor after treatment.[109–112] Two studies showed that there was a significant correlation between prognosis and FDG uptake after treatment, but that there was no relationship between prognosis and FDG uptake before treatment.[109,110] One study showed that there was a difference in the prognostic value of FDG uptake between squamous cell carcinoma and adenocarcinoma of the lung.[107] Thus, it seems that there are different tendencies in the prognostic value of FDG uptake between each malignancy or each pathological type or each reporting institute. Or, there may have been statistical inconsistencies.

As for pancreatic cancer, Nakata et al. reported two studies concerning the predictability of SUVs achieved before treatment for the prognosis of pancreatic cancer patients.[114,115] They reported that a group with SUV of 3.0

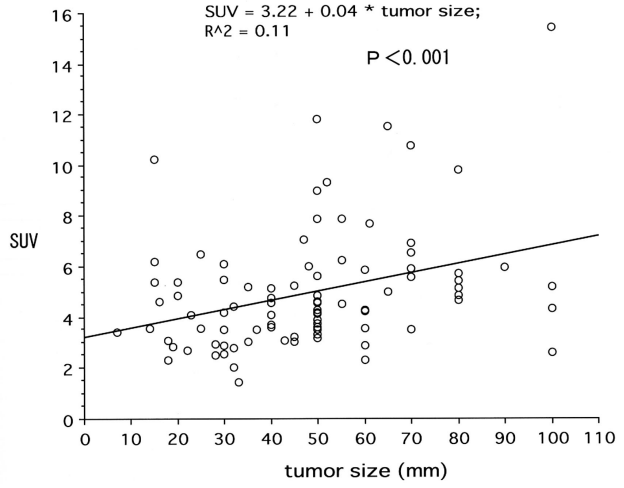

Fig. 11 Relationship between tumor size and SUVs in pancreatic cancer cases. In our institution, there is a tendency that "the larger, the higher."

or smaller had a longer survival period than the other group with SUV of 3.0 or higher. Zimny et al. also reported a similar tendency of prognostic difference, although the cut-off value (SUV = 6.0) was different.[116] We also tried to carry out a similar statistical analysis and found a similar tendency, but no significant difference in prognosis between the higher and lower SUV groups with cut-off line in SUV of 3.0, 7.0 or 4.7 (our average of the total pancreatic cancer cases before 2000). With regard to the prognostic significance, there are two important aspects: 1) cut-off value, and 2) relationship between tumor size and SUVs.

First, cut-off value between group with better prognosis and that with worse prognosis is discussed. Nakata et al. defined the cut-off SUV of 3.0 as the average of the SUVs in total cases. This means that there should be a wide borderline area around the cut-off line if the SUVs showed a normal distribution. SUV itself has a time-dependent nature, as mentioned above. In addition, they included in their analysis all the pancreatic cancers with all the clinical stages. Concerning the positive and negative predictability, this kind of prognostic prediction using SUV of the primary lesion is clinically difficult to apply to all cancer patients with all stages or all sizes in a block. For example, it is unclear which one has a better prognosis, a cancer with SUV of 2.0 and size of 6 cm or a cancer with SUV of 6.0 and size of 1 cm. It is unclear whether a cancer with SUV of 2.0 and liver metastasis or a cancer with SUV of 6.0 without liver metastasis would show better prognosis.

Second, the relationship between tumor size and SUVs is discussed. The relationship between prognosis and tumor size or staging was previously established and is reliable by standard clinical analysis including significantly more patients.[92–95,98,101] Fortner et al. showed that tumor size is the primary prognosticator for pancreatic cancer in a similar manner, shown as "the smaller, the better."[98] According to our findings, SUVs had a tendency to show a positive linear progression with tumor size or tumor staging before treatment (Fig. 11). In our institution, it appeared that the lower half SUV group survives relatively longer than the upper half SUV because of differences in clinical stages or tumor size. Nakata et al. and Zimny et al. also analyzed tumor size of pancreatic tumors or clinical stage as one of the affecting factors in the prognosis in their studies, which showed no significant difference between the higher and lower SUVs groups. The reason for these controversial results should be clarified in larger numbers of patients.

Considering prognostic factor, it would be fair to compare SUVs of tumors only in patients with cancer of a similar size or clinical stage. Recently, Higashi et al. reported a similar positive relation between prognosis and SUVs in lung cancers. In their study, they separated the patients into several groups according to the clinical stages and showed a similar correlation in each group.[106] This kind of approach may be needed in the evaluation of the prognosis in pancreatic cancers. Further investigations in this field are needed for the improvement of prognosis of pancreatic cancer patients, because a prediction of long time survivors is the most desirable aspect in the management of pancreatic cancer patients in "the reality" of clinical practice.

Diagnosis of Cystic Pancreatic Tumors

Diagnosis of cystic pancreatic tumor is sometimes difficult. It was recently reported that intraductal papillary mucinous tumor (IPMT) of the pancreas is a distinct entity of pancreatic cystic neoplasm, which is characterized by diffuse or segmental dilatation of the pancreatic ducts and intraductal papillary growth with thick mucin secretion.[117,118] Concerning the diagnosis in cystic pancreatic diseases using FDG PET, however, only some studies have been reported.[63,119] We reported a clinical value of FDG PET for the diagnosis in the cystic pancreatic tumors including intraductal papillary mucinous tumor of the pancreas.[120] Thirty-nine cases (17%) of 231 pancreatic FDG PET subjects were evaluated for this purpose (Table 3) during the previous two years, and our findings show FDG PET has a reliable diagnostic ability with a sensitivity of 100% in the detection of cystic type cancers, such as intraductal papillary mucinous carcinoma of the pancreas (IPMT carcinoma) or mucinous cystic adenocarcinoma (MCT adenocarcinoma). Semiquantitative analysis using SUV showed a significant difference between IPMT carcinoma, IPMT borderline cases and IPMT adenoma, with an average value of 3.9 ± 1.2, 2.0 ± 0.6 and 1.5 ± 0.1. Further evaluations using larger numbers of patients are needed.

CONCLUSIONS

With the introduction of high-resolution PET machine and also with advances in other imaging modalities, the role of FDG PET in the diagnosis of pancreatic cancer is currently changing. The importance of the differential diagnosis is decreasing, and there are a percentage of false positive and false negative cases. Delayed scanning is promising in the differential diagnosis, but brings with it a new problem, how to clarify the most appropriate scan time or scan protocol for pancreatic cancer diagnosis using FDG PET. Preoperative staging is becoming the main objective of FDG PET, and has been reported as useful for the detection of distant metastasis and unexpected lesions, and to have a clinical impact on patient management in about 40% of cases. Other purposes of PET diagnosis, such as evaluation of therapeutic effect, diagnosis of recurrence, follow-up study, detection of "curable pancreatic cancer," prediction of prognosis, and differential diagnosis of cystic pancreatic cancers are promising, but their evaluations are still on going. With the introduction of PET-CT, the role of FDG PET in the diagnosis of pancreatic cancer will again change.

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