Differentiation of autoimmune pancreatitis from suspected pancreatic cancer by FDG-PET

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Abstract

Purposes: Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been widely used for the diagnosis of pancreatic cancer. Because autoimmune pancreatitis is easily misdiagnosed as pancreatic cancer and can be tested for by FDG-PET analysis based on the presence of suspected pancreatic cancer, we attempted to clarify the differences in FDG-PET findings between the two conditions. **Methods:** We compared the FDG-PET findings between 15 patients with autoimmune pancreatitis and 26 patients with pancreatic cancer. The findings were evaluated visually or semiquantitatively using the maximum standardized uptake value and the accumulation pattern of FDG. **Results**: FDG uptake was found in all 15 patients with autoimmune pancreatitis, whereas it was found in 19 of 26 patients (73.1%) with pancreatic cancer. The accumulation pattern of nodular shape was frequently seen in pancreatic cancer with significance, whereas a longitudinal shape indicated the existence of autoimmune pancreatitis. Heterogeneous accumulation was found in almost all cases of autoimmune pancreatitis, whereas homogeneous accumulation was found in pancreatic cancer. Most cases of pancreatic cancer showed solitary localization with significant difference, whereas multiple localizations in the pancreas favored the existence of autoimmune pancreatitis. FDG uptakes in the hilar lymph node were more frequently seen in autoimmune pancreatitis than in pancreatic cancer with significance, and those in the lachrymal gland, salivary gland, biliary duct, retroperitoneal space, and prostate were only seen in autoimmune pancreatitis. **Conclusions:** FDG-PET provides a useful tool for differentiating autoimmune pancreatitis from suspected pancreatic cancer, if its accumulation pattern and extra-pancreatic involvements are considered. IgG4 measurement and other current image tests will confirm further diagnosis.

Key Words: FDG-PET, autoimmune pancreatitis, pancreatic cancer

Introduction

Adenocarcinoma of the pancreas represents one of the leading causes of death in Japan and Western countries. The poor prognosis is related to the aggressive biology of this tumor and the difficulty in early diagnosis. Current image and laboratory tests have improved the diagnostic efficiency to some extent, but insufficiently. Recently, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been widely used for the diagnosis of pancreatic cancer, and is reported to be a valuable diagnostic modality for differentiating malignant from benign lesions of the pancreas [1, 2, 3, 4, 5, 6, 7]. Therefore, many patients who are suspected of having pancreatic cancer tend to undergo FDG-PET, which is necessary to differentiate between pancreatic cancer and benign pancreatic conditions such as tumor-forming chronic pancreatitis. Among benign pancreatic conditions or tumor-forming chronic pancreatitis, autoimmune pancreatitis now represents a majority of the cases that mimic pancreatic cancer.

Autoimmune pancreatitis is a recently proposed disease concept and shows irregular narrowing of the main pancreatic duct and swelling of the pancreatic parenchyma [8]. This disease is associated with the various autoimmune phenomena of hypergammaglobulinemia, histological evidence of lymphoplasmacytic inflammation, occasional coexistence of other autoimmune diseases, and a favorable response to glucocorticoid treatment [9, 10, 11]. The characteristic clinical features of this disease are an elderly male preponderance and a high occurrence of obstructive jaundice, which, together with the swelling of the pancreatic parenchyma, have sometimes led to the misdiagnosis of pancreatic cancer and unnecessary operations [11, 12, 13, 14]. A previous study has disclosed that 2.6% of patients who have received Whipple resection based on the diagnosis of pancreatic cancer show histological findings of autoimmune pancreatitis, lymphoplasmacytic sclerosing pancreatitis[14]. Accordingly, it is urgent to establish the test for differentiating between the two conditions.

We have previously reported that patients with autoimmune pancreatitis have high serum IgG4 concentrations and abundant IgG4-bearing plasma cell infiltration in the affected organs[15, 16]. IgG4

provides a useful tool for differentiation between autoimmune pancreatitis and pancreatic cancer, to some extent [15]. To differentiate the two conditions more accurately, it is recommended that a combined diagnostic system including new imaging methods and IgG4 be developed.

Many patients with autoimmune pancreatitis could be included in the patients who will receive FDG-PET based on the suspicion of pancreatic cancer. However, FDG-PET cannot always differentiate between such lesions [17, 18], since the inflammatory foci of the pancreas also accumulates FDG [19, 20, 21, 22]. In addition, previous reports have shown that patients with autoimmune pancreatitis also show intense FDG uptake [19, 23, 24]. There have been no convincing reports of systemic studies assessing the difference in FDG-PET findings between autoimmune pancreatitis and pancreatic cancer. Because FDG-PET is recommended for many patients who are suspected of having pancreatic cancer, it is urgently necessary to determine the difference in FDG-PET findings between autoimmune pancreatitis and pancreatic cancer. The aim of the present study was to clarify this issue by comparing a sufficient number of FDG-PET results between autoimmune pancreatitis and pancreatic cancer.

Methods

Study Subjects

Between September 1994 and June 2005, we treated and followed 64 patients with autoimmune pancreatitis, 53 men and 11 women aged 38-79 years (median age 62.4 years). The diagnosis was based on the diagnostic criteria for autoimmune pancreatitis proposed by the Japanese Pancreas Society and the revised proposal [25, 26]. Fifteen of these patients had received FDG-PET between June 2003 and February 2006, 13 men and 2 women, aged 55 - 75 years (median age 63.0 years). During the same period, we treated 26 patients with pancreatic cancer who received FDG-PET. The diagnosis of pancreatic cancer was confirmed on the basis of histological findings in 20 patients and on the basis of both typical findings on imaging procedures and the clinical course in 6 patients.

Laboratory tests

We examined various blood tests which possibly influence the uptake of FDG, including blood sugar[27] and CRP [28], in addition to ordinary blood tests of BUN, creatinine, bilirubin, ALP, amylase, WBC, and CA19-9.

Positron emission tomography

The PET scan was performed using a dedicated PET scanner (Advance Nxi, GE, Milwaukee, U.S.) in a two-dimensional imaging mode. Emission scans were obtained with a 2-3 min acquisition time per table position, requiring 6 or 8 table positions to cover the area from the pelvis floor to the head. After emission scanning, transmission scans of the same area were obtained with a 1-2 min acquisition time per table position. The PET image set was reconstructed by the ordered subset expansion maximization (OSEM) algorithm with segmented attenuation correction (SAC), and the resulting resolution was approximately 4.3 mm full-width at half-maximum (FWHM).

After at least 4 hours of fasting, the patients were injected with 5 MBq/kg (max 370 MBq) of F-18 FDG intravenously. An early whole body scan was performed for all patients at 60 min after FDG injection, and a delayed scan of the upper abdomen at 120 min after injection was added, except in 3 patients.

Data analysis.

Focal FDG accumulation was evaluated visually or semiquantitatively by the maximum standardized uptake value (SUV max) in the regions of interest (ROIs) placed over the accumulation in the pancreas on the MIP (maximum intensity projection) images at the early and delayed period.

FDG accumulation was assessed for pancreatic lesions and extra-pancreatic lesions. For pancreatic lesions, analysis was performed to assess the following points; (1) contour: smooth (Fig. 1A, C,

arrow)/ irregular (Fig. 1B, D, arrow), (2) shape: nodular (Fig. 1A, C, arrow) / longitudinal (Fig. 1B, D, arrow), (3) accumulation pattern: homogeneous (Fig. 1A, C, arrow)/ heterogeneous (Fig. 1B, D, arrow), (4) extent of accumulation: solitary/multiple. For extra-pancreatic lesions, analysis was performed to assess the levels of accumulation in the salivary gland, hilar lymph node, biliary duct, or retroperitoneal space. Two radiologists (O.K., M.M) assessed the FDG-PET findings independently without knowledge of the results of the other imaging procedures. If disagreement occurred, a final decision was made after discussion.

Statistical analysis for differences was performed by Chi-square analysis or Fisher's exact test, and the Mann-Whitney test. A level of corrected $P<0.05$ was accepted as statistically significant. All reported P values are 2-sided.

All participants provided written informed consent for FDG-PET and invasive tests such as the ERCP prior to the taking of serum samples. The institutional ethics committee granted permission for the study.

Results

Comparison of Clinical Characteristics

Table 1 shows the comparison of clinical characteristics between autoimmune pancreatitis and pancreatic cancer. The ratio of men to women was higher significantly in patients with autoimmune pancreatitis than in patients with pancreatic cancer. Age distribution was equivalent for both groups. We found no significant differences in the frequency of hyperglycemia or serum levels of fasting blood sugar and C-reactive protein. In addition, we found no significant differences in the serum levels of blood urea nitrogen, creatinine, total bilirubin, alkaliphosphatase, and amylase, or in the white blood cell count. The serum levels of CA19-9 in pancreatic cancer were higher than those in autoimmune pancreatitis.

Comparison of FDG uptake

Pancreatic lesions

The prevalence and manner of FDG accumulation of the pancreatic lesions showed significant difference between autoimmune pancreatitis and pancreatic cancer. Accumulations were observed in all patients with AIP, whereas in 73.1% of patients with pancreatic cancer (Table 2). The maximum standard uptake value (SUV max) showed no significant differences between autoimmune pancreatitis and pancreatic cancer at both the early and delayed phase. In addition, there was no significant difference in the ratio of the delayed to early SUV max between autoimmune pancreatitis and pancreatic cancer. However, early SUV max more than 6.6 is only found in pancreatic cancer, which consist of 3 patients (Table 2, Fig. 2).

With regard to the accumulation pattern, an irregular contour was more frequently seen in autoimmune pancreatitis compared with pancreatic cancer, but the difference was not significant (Table 3). A nodular shape was frequently seen in pancreatic cancer with significance. A longitudinal shape was frequently found in autoimmune pancreatitis, whereas it can be also found in diffuse type of pancreatic cancer (Table 3). Heterogeneous accumulation was found in almost all cases (14/15) of autoimmune pancreatitis with significance. Homogeneous accumulation is found in pancreatic cancer (Table 3). Most cases of pancreatic cancer showed solitary localization with significant difference. Multiple localizations indicate autoimmune pancreatitis (Table 3).

Extra-pancreatic lesion

FDG uptake in the hilar lymph node was more frequently seen in patients with autoimmune pancreatitis than in those with pancreatic cancer, to a significant difference. FDG uptakes in the lachrymal gland, salivary gland, biliary duct, and retroperitoneal space were only seen in autoimmune pancreatitis, though no significant difference was found between the two groups (Table 4).

Representative cases

Representative cases for pancreatic cancer and autoimmune pancreatitis are shown in Fig. 1. Typical FDG-PET findings for pancreatic cancer are a smooth contour, nodular shape, homogeneous accumulation, and solitary localization (Fig. 1 A, C), whereas those for autoimmune pancreatitis are an irregular contour, longitudinal shape, heterogeneous accumulation, and multiple localizations with extra –pancreatic lesions (Fig. 1 B, D).

Discussion

We examined the clinical utility of FDG-PET for differentiation between autoimmune pancreatitis and pancreatic cancer, and disclosed the following interesting findings. First, FDG-PET uptake was significantly more frequently seen in autoimmune pancreatitis than in pancreatic cancer. Second, the accumulation pattern of FDG-PET images possibly discriminates between the two conditions. Third, FDG uptake in extra-pancreatic organs may assist in differentiation between the two conditions. These results suggest that FDG-PET could select AIP patients among patients with suspected pancreatic cancer; these patients will then undergo IgG4 measurement or other image tests to confirm the diagnosis of autoimmune pancreatitis.

Though FDG-PET is a sensitive diagnostic modality in detecting malignant tumors, inflammation can give rise to FDG uptake in the same intensity range as pancreatic neoplasm [18]. In chronic pancreatitis, tumors detected by FDG-PET consist of degenerative necrosis surrounded by granulation tissue [29]. Autoimmune pancreatitis also causes intense FDG uptake in the pancreas [23, 24]. The present study showed FDG uptake in all 15 patients with autoimmune pancreatitis, whereas it was found in 19 of 26 patients (73.1%) with pancreatic cancer. Contrary to the present results, previous studies have found that the sensitivity of FDG uptake in patients with pancreatic cancer is higher at 96% [2, 30] and 91% [31], and that with autoimmune pancreatitis is lower at 83% [24]. Although the exact reasons for this discrepancy are unknown, FDG-PET is considered to be a sensitive modality for detecting

autoimmune pancreatitis.

Because FDG uptake is influenced by various factors aside from disease state, we checked the differences in these influencing factors between the two conditions. First, patients with high serum glucose levels showed high false-negative results because of decreased FDG-uptake by tumors. [26] Second, an acute exacerbation of chronic pancreatitis may lead to an incorrect result of static FDG-PET imaging, as acute pancreatitis clearly showed an increased SUV with ranges similar to those for pancreatic cancer [2]. Third, FDG-PET may be falsely positive if CRP is elevated [28]. We found no significant differences in the frequency of hyperglycemia or fasting serum levels of glucose, amylase, CRP, and WBC between autoimmune pancreatitis and pancreatic cancer. Furthermore, no significant differences were found in blood tests for renal functions, biliary enzymes, and total bilirubin. Accordingly, the present FDG-PET studies were not influenced by these factors, and represent the disease state of autoimmune pancreatitis or pancreatic cancer.

The next question is how to differentiate between autoimmune pancreatitis and pancreatic cancer by FDG-PET images. Some reports have described that the SUV is higher in malignant tumors than in benign lesions, showing a delayed SUV value greater than 4.0 for pancreatic cancer, that of 3.0-4.0 for chronic pancreatitis, and that of less than 3.0 for the controls [2]. We found that early SUV max more than 6.6 is restricted to pancreatic cancer, which may be helpful in differentiation to some extent. However, the present study showed that any SUV max disclosed no significant difference between the two conditions. The accumulation pattern of FDG possibly discriminates between the two conditions. A nodular shape was frequently seen in pancreatic cancer, whereas a longitudinal shape was frequently seen in autoimmune pancreatitis. Heterogeneous accumulation was found in almost all cases of autoimmune pancreatitis, while homogeneous accumulation was observed in pancreatic cancer. Most cases of pancreatic cancer showed solitary localization, whereas autoimmune pancreatitis showed multiple localizations in pancreas. Accordingly, typical FDG-PET findings for autoimmune pancreatitis are an irregular contour, longitudinal shape, heterogeneous accumulation,

and multiple localizations, whereas those for pancreatic cancer are a smooth contour, nodular shape, homogeneous accumulation, and solitary localization. A previous report also showed that the characteristic FDG accumulation of AIP is diffuse, and if focal, differentiation from pancreatic cancer is difficult [24]. Longitudinal FDG uptake found in autoimmune pancreatitis is due to diffuse distribution of the inflammatory process, and FDG uptake by inflammatory cells possibly results in heterogeneous accumulation because of the scattered distribution of inflammatory cells. However, the diffuse type pancreatic cancer may also show a similar longitudinal shape, though these cases are rare. The nodular and homogeneous accumulation of FDG found in pancreatic cancer is possibly due to restricted and condensed distribution of tumor cells and its active outer growth.

FDG uptake in extra-pancreatic organs may assist in differentiation between the two conditions. The prominent features of autoimmune pancreatitis involve a variety of extra-pancreatic complications seen in sclerosing cholangitis, lachrymal and salivary gland swellings, hypothyroidism, hilar lymphadenopathy, retroperitoneal fibrosis, interstitial pneumonia, and tubulointerstitial nephritis [32]. Some of these extra-pancreatic lesions show pathological findings similar to those of pancreatic lesions, including infiltration of abundant IgG4 bearing plasma cells [7, 9]. The present study showed that FDG uptake in the hilar lymph node is a useful finding for the diagnosis of autoimmune pancreatitis, though extrapancreatic accumulation of FDG in the lymph nodes is difficult to differ from metastasis to lymph nodes of malignancy. In addition, FDG uptake in the lachrymal gland, salivary gland, biliary duct, and retroperitoneal space are found only in autoimmune pancreatitis. Concomitant FDG uptake in these organs supports the diagnosis of autoimmune pancreatitis.

Severe lymphocytic infiltration in the pancreatic tissue suggests the possibility that gallium-67 citrate (Ga-67) accumulates in the pancreas, because gallium-67 concentrates in lymphoid cells. Previously, we performed gallium-67 scintigraphy in 24 patients with autoimmune pancreatitis before and after 4 weeks of corticosteroid therapy, and found marked gallium-67 accumulation in 16 patients (67%) at the pancreas, in 16 patients (67%) at the hilar lymphnode and in 5 patients (21%) at the

salivary gland before corticosteroid therapy. These positive images changed to negative after 4 weeks of therapy [33]. Because we have no data concerning gallium-67 scintigraphy for pancreatic cancer, we did not evaluate its specificity in detecting autoimmune pancreatitis. However, FDG-PET seems to be superior in sensitivity for detection of autoimmune pancreatitis than gallium-67 scintigraphy. In detecting extrapancreatic lesions, such as hilar lymphadenopaty and salivary gland, imagings of FDG-PET were comparable with those of gallium-67 scintigraphy. Though gallium-67 scintigraphy showed negative images after steroid therapy markedly, we could not confirm utility of FDG-PET in follow-up because we had no FDG-PET images after corticosteroid therapy.

The mechanism of accumulation of FDG in autoimmune pancreatitis is thought to be due to massive infiltration of activated lymphocytes. In this meaning, similar pattern of FDG-PET has been reported in malignant lymphoma of the pancreas with extrapancreatic accumulation. [34] Similar to lymphoma, autoimmune pancreas also showed high serum concentration of soluble IL2 receptor and β2-microgloburine. [35] Accordingly, the possible diagnosis of lymphoma should be considered for case with similar FDG-PET pattern to autoimmune pancreatitis.

In conclusion, FDG uptake was found in all patients with autoimmune pancreatitis, suggesting that FDG-PET provides a useful tool for selecting patients with autoimmune pancreatitis among patients with suspected pancreatic cancer, if considering its accumulation pattern and extra-pancreatic involvements. IgG4 measurement and current image tests will confirm the diagnosis of autoimmune pancreatitis for these selected patients.

Acknowledgments

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Table 1. Comparison of clinical characteristics between patients with autoimmune pancreatitis and those with pancreatic cancer

	Autoimmune Pancreatitis n=15 median (range)	Pancreatic Cancer n=26 median (range)	p
Men / Women	13/2	11/15	0.0082
Age (year)	63.0 (55-75)	66.0 (41-81)	0.9568
Fasting blood sugar (mg/dl)	86.0 (73-115)	84.0 (51-257)	0.7700
Hyperglycemia (BS>120mg/dl)	0	5	0.1391
CRP (mg/dl)	0.16 (0.02-0.96)	0.11 (0.01-9.830)	0.5200
White Blood Cell[s] (/μl)	5290 (3080-9110)	5700 (3260-9920)	0.3864
BUN (mg/dl)	14 (10-26)	14 (6-24)	0.9664
Creatinine (mg/dl)	0.76 (0.51-1.14)	0.69 (0.43-1.89)	0.0804
Total bilirubin (mg/dl)	0.91 (0.29-7.56)	0.97 (0.26-10.22)	0.8710
ALP (IU/l)	575 (130-1609)	435.5 (164-3128)	0.4816
Amylase (IU/l)	107.0 (38-331)	69.5 (31-204)	0.1364
CA19-9 (U/l)	15.5 (0.6-474.8)	87.3 (13.7-9464)	0.0005

Table 2. FDG accumulation of pancreatic lesions between autoimmune pancreatitis and pancreatic cancer

		Autoimmune Pancreatitis	Pancreatic Cancer	p
		n = 15	n = 26	
Number of Positive[s] (%)		15 (100.0)	19 (73.1)	0.0353
Max Standardized Uptake Value				
early	median	4.6	5.3	0.2112
	(range)	(3.7 - 6.6)	(3.1 - 11.0)	
delayed	median	5.4	6.5	0.3203
	(range)	(3.2 - 9.1)	(2.8 - 9.9)	
delayed/early	median	1.149	1.222	0.7357
	(range)	(0.842 - 1.492)	(0.636 - 1.544)	

Table 3. FDG accumulation pattern of pancreatic lesions between autoimmune pancreatitis and pancreatic cancer.

	Autoimmune Pancreatitis n = 15	Pancreatic Cancer n = 19	p
Contour			
smooth	**2**	**7**	
irregular	**13**	**12**	**0.2401**
Shape			
nodular	**7**	**16**	
longitudinal	**8**	**3**	**0.0310**
Accumulation			
homogeneous	**1**	**8**	
heterogeneous	**14**	**11**	**0.0468**
Location			
solitary	**7**	**18**	
multiple	**8**	**1**	**0.0042**

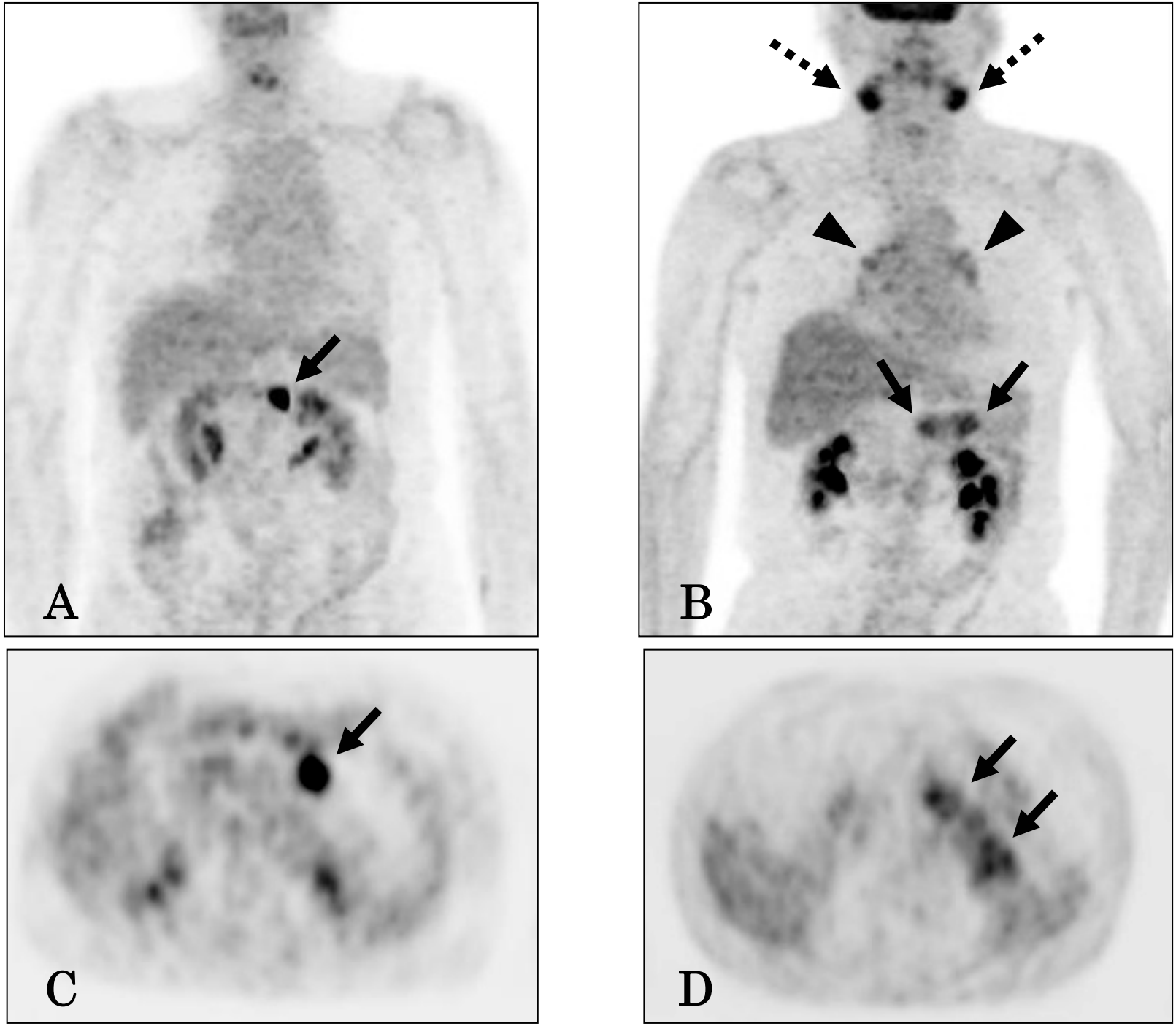
Table 4. FDG accumulation of extrapancreatic lesions between autoimmune pancreatitis and pancreatic cancer.

	Autoimmune Pancreatitis n = 15	Pancreatic Cancer n = 26	p
Lachrymal gland	**1**	**0**	**0.3659**
Salivary gland	**2**	**0**	**0.1280**
Hilar lymphadenopathy	**9**	**3**	**0.0030**
Biliary duct	**1**	**0**	**0.3659**
Retroperitoneal tissue	**1**	**0**	**0.3659**
Prostate	**2**	**0**	**0.1280**
Liver	**0**	**3**	**0.5377**
Bone	**0**	**3**	**0.5377**

Figure Legends

Figure 1. Representative FDG-PET images for pancreatic cancer (A, C) showing smooth, nodular, and homogeneous pattern, and for autoimmune pancreatitis (B, D) showing irregular, longitudinal, and heterogeneous pattern and. Pancreatic cancer; (A) Coronal maximum intensity projection (MIP) image, (C) SPECT image. Autoimmune pancreatitis; (B) MIP image, (D) SPECT image. Arrow: pancreas, dotted arrow: salivary gland, arrow head: hilar lymphnode.

Figure 2. Scattergram of max SUV values. (A) max SUV early, (B) max SUV delayed, and (C) max SUV ratio (delayed/early).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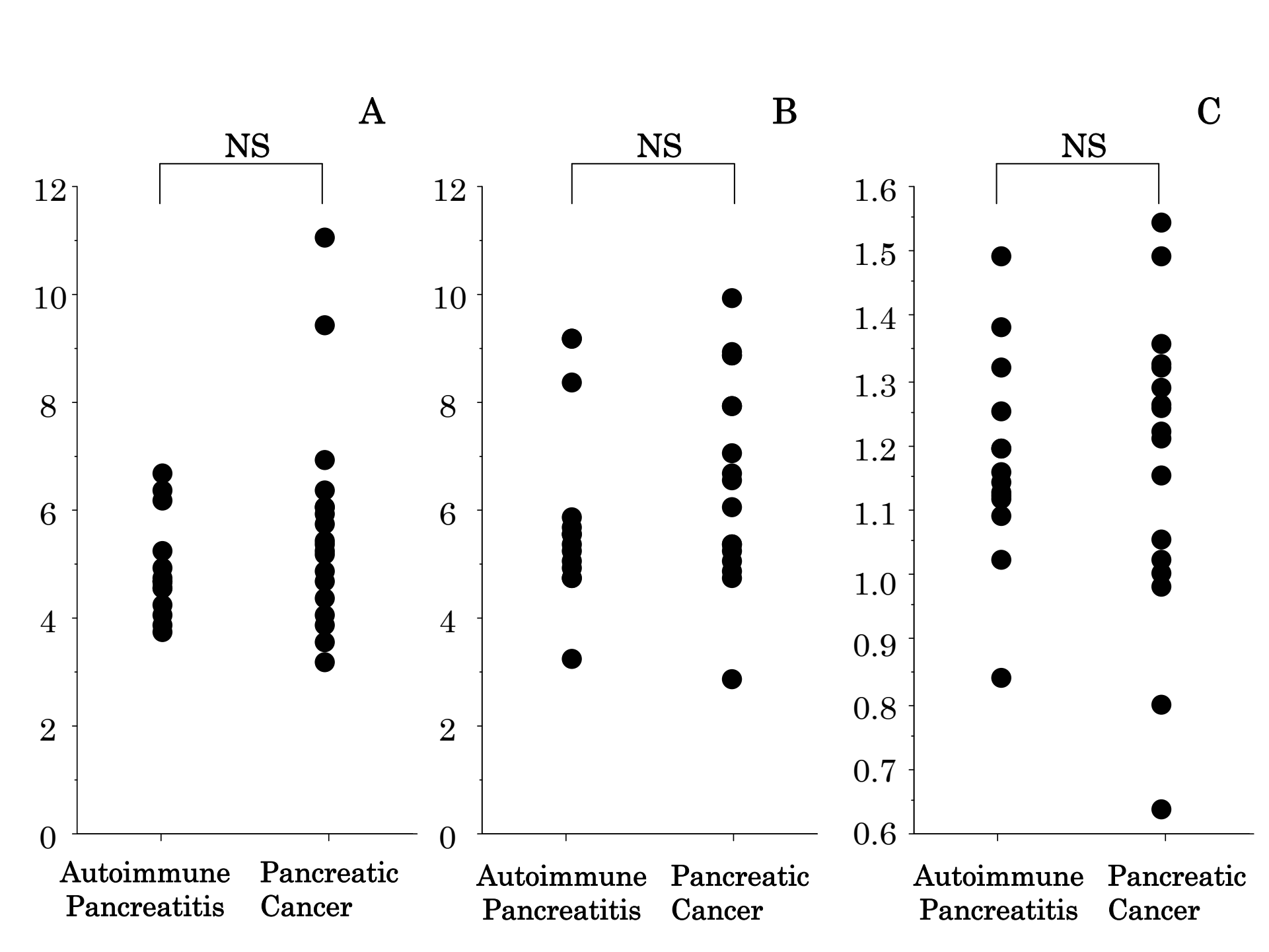
A
NS
12
10
8
6
4
2
0
Autoimmune Pancreatitis
Pancreatic Cancer
B
NS
12
10
8
6
4
2
0
Autoimmune Pancreatitis
Pancreatic Cancer
C
NS
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
Autoimmune Pancreatitis
Pancreatic Cancer