Clinical Utility of FDG PET/CT in Patients with Autoimmune Pancreatitis: a Case-Control Study

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Autoimmune pancreatitis (AIP) shares overlapping clinical features with pancreatic cancer (PC). Importantly, treatment of the two conditions is different. We investigated the clinical usefulness of 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in patients with suspected AIP before treatment. From September 2008 to July 2016, 53 patients with suspected AIP at National Taiwan University Hospital had PET/CT prior to therapy to exclude malignancy and evaluate the extent of inflammation. Their scans were compared with those from 61 PC patients. PET imaging features were analyzed using logistic regression. Significant differences in pancreatic tumor uptake morphology, maximum standardized uptake value, high-order primary tumor texture feature (i.e. high-gray level zone emphasis value), and numbers and location of extrapancreatic foci were found between AIP and PC. Using the prediction model, the area under curve of receiver-operator curve was 0.95 (p < 0.0001) with sensitivity, specificity, positive predictive, and negative predictive values of 90.6%, 84.0%, 87.9%, and 87.5% respectively, in differentiating AIP from PC. FDG PET/CT offers high sensitivity, albeit slightly lower specificity in differentiating AIP from PC. Nonetheless, additional systemic inflammatory foci detected by the whole body PET/CT help confirm diagnosis of AIP in these patients before initiating steroid therapy, especially when biopsy is inconclusive.

Positron emission tomography and computed tomography (PET/CT) using 18F-fluorodeoxyglucose (FDG) has been used in pancreatic cancer (PC) to survey distant metastasis before treatment and to evaluate therapeutic response1,2. Lymphoplasmacytic sclerosing pancreatitis has been unexpectedly identified in pathological specimens of patients initially diagnosed with PC, which was later confirmed to be autoimmune pancreatitis (AIP). AIP is a unique form of pancreatitis recognized in recent years as part of systemic immunoglobulin G4-related disease (IgG4-RD)3. Due to its similar clinical presentation, PC can be difficult to differentiate from AIP clinically. Although characteristic features of “sausage-like” enlargement of the pancreas with a “capsule-like” rim accompanied by narrowing of the main pancreatic duct in contrast-enhanced CT are diagnostic of AIP, many patients present with atypical imaging features making it difficult to differentiate from PC1. This is especially true in patients exhibiting a focal pancreatic mass and dilated pancreatic duct4. Even though an elevated serum IgG4 level can be present in type I AIP patients, type II AIP patients have normal serum IgG4 level, and some PC patients show elevated titers5,6. Biopsy of the pancreatic mass is can be non-diagnostic, especially with insufficient histological samples. Importantly, treatment of the two conditions is different: patients with PC should receive prompt surgery, whereas steroid therapy is the first line treatment for AIP. Moreover, patients with AIP have been reported to have a higher incidence of co-existing malignancy.

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Therefore, this study aimed to determine whether FDG PET/CT could provide clinical useful information in patients with suspected AIP before initiation of steroid therapy.

**Results**

FDG PET/CT confirmed systemic inflammatory lesions in 52 of 53 patients with suspected AIP, in which 2 had IgG4-RD but not AIP. Pancreatic malignancies were subsequently proved in these 3 patients (Fig. 1). All diagnosed AIP patients (a total of 50) fit the 2011 International Consensus Diagnostic Criteria for AIP at the time of this analysis. Among the 50 patients confirmed of AIP after PET scan, 11 (22.0%) had histopathological features of lymphoplasmacytic sclerosing pancreatitis with \( \text{IgG4-positive plasma cells per high power field} > 10 \) and \( \text{IgG4 cell ratio at least 40 \%} \). Thus, 11 subjects were of definitive type I AIP, 37 probable type I AIP, 1 probable type II AIP, and 1 AIP-not otherwise specified. In the 64 PC patients (including 3 patients initially diagnosed of AIP), reference standards were the surgical specimens in 52 (81.3%), biopsies guided by ultrasonography in 11 (17.2%), and CT-guided biopsy in 1 (1.6%). All histopathological confirmations were made within 1 month of FDG PET/CT. At the time of the analysis, 29 of the 114 (25.4%) patients died, all of which were from the PC group. Ulcerative colitis was incidentally found in FDG PET/CT in 2 AIP patients. Two other AIP patients had hepatocellular carcinoma and laryngeal cancer more than 5 years after their initial FDG PET/CT scan. None of the AIP patients developed pancreatic malignancy during the follow-up period and were all regularly followed up at the outpatient clinic at the time of this analysis (median, 36.9 months; range, 6–82.9 months).

The ranges of the examined PET parameters are shown in the Table from Supplementary data. Mean MTV was \( 34.4 \pm 5.6 \text{ mL} \) for PC, and \( 49.1 \pm 5.3 \text{ mL} \) for AIP. Three patients (3/64, 4.7%) from PC group had diffuse pancreatic uptake, and the remaining 58 (58/64, 90.6%) had localized pancreatic morphology. Forty-one of 50 (82.0%) confirmed AIP patients had at least one site of extrapancreatic inflammation. In contrast to 16 (16/64, 25.0%) of the PC patients, half (25/50) of AIP patients had more than 2 sites. AIP and PC patients also differed with respect to sites of extrapancreatic lesions (Table 2). Extra-abdominal lymph nodes, mostly the mediastinum (25/50, 50.0%) and salivary glands (26/50, 52.0%) were the most frequent extrapancreatic lesions in AIP patients; whereas, liver (13/64, 20.3%) and abdominal lymph nodes (9/64, 14.1%) were more frequently seen in PC patients. Moreover, some sites of extrapancreatic uptake were only observed in the AIP group: lacrimal glands (1/50, 2.0%), axillary lymph nodes (7/50, 14.0%), vessel walls (8/50, 16%), and the pituitary gland (3/50, 6.0%).

**Univariate Analysis.** Eleven morphological parameters were statistically significant \( (P < 0.01) \) in differentiating AIP from PC according to univariate analysis (Table from Supplementary data).
Backward Stepwise Logistic Regression Analysis. Further logistic regression analysis yielded diffuse pancreatic tumor morphology, more than two extrapancreatic sites of FDG uptake, primary tumor exhibiting a lower maximum SUV, and lower high gray-level zone emphasis (HGLZE) value most optimal for predicting AIP (Figs 2–4, and Table from Supplementary data). The prediction model formulated from the combination of these four parameters showed an AUC of 0.95 ($P < 0.0001$, Table 3 and Fig. 1 from Supplementary data). The sensitivity, specificity, PPV, NPV, and accuracy of the formulated prediction model were 90.6% (95% CI, 80.7–96.5%), 84.0% (95% CI, 70.9–92.8%), 87.9% (95% CI, 79.3–93.2%), 87.5% (95% CI, 76.4–93.8%), and 87.7% (95% CI, 80.3–93.1%), respectively, for determining AIP from PC in the cohort of 114 patients included in the study (Table 4).

Pancreatic Malignancies Found in Patients Suspected of AIP. Pancreatic malignancies were detected in 3 patients with suspected AIP using FDG PET/CT prior to initiation of steroid therapy. Two subjects have concomitant proven IgG4-RD which both salivary glands and mediastinal lymph nodes involvement were seen in their PET/CT scans (Fig. 2 from Supplementary data). Their pancreatic lesions were of localized morphology with SUVmax and an HGLZE value greater than 5 and 140, respectively. Also, in another patient with suspected
focal type AIP, pancreatic tumor HGLZE value was high (255.2) despite a SUVmax of less than 5, and only one site of extrapancreatic uptake (mediastinal lymphadenitis) was seen in FDG PET/CT. This patient later underwent surgery confirming the presence of a pancreatic tail adenocarcinoma.

Discussion
Therapy for AIP and PC is markedly different. These two entities are at times hard to distinguish due to overlapping clinical features, and difficulty in obtaining adequate biopsy specimens for diagnosis. Herein, this study aims to determine whether addition of FDG PET/CT in the clinical algorithm can provide clinical useful information in patients suspect of AIP before therapy.

The present study showed that (1) AIP usually exhibits diffuse pancreatic uptake, lower SUVmax and HGLZE values than PC; (2) More than 80% of AIP patients had at least one site of extrapancreatic inflammation, and half of them showed least 2 sites of involvement; (3) The location of extrapancreatic lesions also differed between AIP and PC, with preference of salivary glands and mediastinal lymph nodes involvement in AIP. Moreover, lacrimal glands, axillary lymph nodes, vessel walls, and the pituitary gland were only observed in our AIP cohort; (4) PET successfully detected pancreatic malignancy in 3 patients initially suspect of AIP before steroid therapy, 2

| Site                        | Pancreatic cancer (n = 64) | Autoimmune pancreatitis (n = 50) |
|-----------------------------|---------------------------|----------------------------------|
| Lacrimal glands             | 0 (0.0)                   | 1 (2)                            |
| Salivary glands             | 4 (6.3)                   | 26 (52)                          |
| Extra-abdominal LAPs        |                           |                                  |
| Supraclavicular             | 1 (1.6)                   | 3 (6)                            |
| Axillary                    | 0 (0.0)                   | 7 (14)                           |
| Mediastinal                 | 7 (10.9)                  | 25 (50)                          |
| Abdominal LAPs              | 9 (14.1)                  | 2 (4)                            |
| Lung                        | 5 (7.8)                   | 0 (0)                            |
| Biliary tract               | 1 (1.6)                   | 5 (10)                           |
| Liver                       | 13 (20.3)                 | 1 (2)                            |
| Retropertitoneum (including kidneys) | 1 (1.6) | 8 (16) |
| Vessels                     | 0 (0.0)                   | 8 (16)                           |
| Pituitary gland             | 0 (0.0)                   | 3 (6)                            |
| Bone                        | 3 (4.7)                   | 0 (0)                            |

Table 2. Site of Extrapancreatic Lesions in 114 Patients. Note: data in parentheses are percentages; LAPs: lymphadenopathy.

Figure 4. Pancreatic cancer. Axial PET (a) and PET/CT fused (b) images showed intense hypermetabolic areas from pancreatic head to tail (diffuse morphology, arrow), and the most intense focal area at periampullary region (arrowhead). No definite extrapancreatic lesion was found. The pancreatic tumor showed a SUVmax of 8.4, and a high gray-level zone emphasis value of 201.3. The patient underwent Whipple’s surgery confirming the diagnosis of pancreatic cancer. The disease was complicated with ischemic bowel disease and multi-organ failure developed, and the patient died despite intensive care support.
of which also proved to have systemic inflammatory foci owing to underlying IgG4-RD. Hence, FDG PET/CT showed sensitivity, specificity, accuracy of 90.6%, 84.0%, and 87.7% in differentiating PC from AIP.

Extrapancreatic manifestation of AIP has been described since Yoshida et al.8 reported the first case of type I AIP in 1995. Subsequently, an elevated serum level of IgG4 has been linked to the disease, and the disease considered IgG4-related autoimmune disease (IgG4-RD) owing to its systemic multi-organ involvement19–22. Prompt diagnosis of AIP is challenging, and can be hard to distinguish from PC in patients who present with obstructive jaundice, mild abdominal discomfort, and weight loss.20–22. Abdominal CT or magnetic resonance imaging does not provide information specific for AIP, especially in patients with atypical imaging features such as a low-density mass in CT, pancreatic ductal dilatation, or distal atrophy, which can mimic various neoplastic processes. In addition, no standard laboratory parameter, including serum IgG4 concentration, is reliable for diagnosing AIP or illustrating the extent of IgG4-RD. Not all patients with AIP present with an elevated serum IgG4 level, nor is a rising level indicative of the disease.13. Patients with respiratory, biliary, rheumatic, and liver disease, and even those with PC can have an elevated serum IgG4 level.14,15, Moreover, an increased incidence of malignancy in patients with AIP or IgG4-RD pancreatitis has been reported.16–18. Accurate diagnosis is of utmost importance since only surgical resection offers curative treatment for PC, whereas corticosteroid or rituximab treatment are given for patients with AIP.

Published studies have described the usefulness of FDG PET or FDG PET/CT for determining the prevalence and distribution of extrapancreatic lesions in AIP, and systemic manifestations of IgG4-RD.19–23. PET has added advantages of whole-body screening, the ability to highlight unsuspected lesions involving critical organs such as the pericardium, kidneys, aorta, proximal biliary structures, and retroperitoneum, and can help determine the extent of disease.23,24 More than half of AIP patients fail to achieve sustained remission after initial corticosteroid therapy,13 and it has been shown that rituximab might be an effective treatment.25,26 Therefore, whole-body screening provided by FDG PET/CT can be used to assess response to therapy. Consistent with previous work, the current study showed more frequent salivary glands and mediastinal lymph nodes involvement in AIP.21,27. In addition, lacrimal glands, axillary lymph nodes, vessel walls, and pituitary gland activities were only seen AIP patients compared to PC. Similar findings were also reported by the UK, Japanese, Korean, Chinese, and Taiwanese researchers28–31.

FDG PET/CT showed sensitivity, specificity, accuracy of 90.6%, 84.0%, and 87.7% in differentiating PC from AIP. AUC: area under the ROC curve, CI: confidence intervals, ROC: Receiver-operating-characteristic curve.

| Parameter                          | Optimal threshold for diagnosing pancreatic cancer | Odds Ratio | AUC (CI) | P value |
|------------------------------------|--------------------------------------------------|------------|----------|---------|
| Number of extrapancreatic lesions  | <2                                               | 2.9        | 0.60 (0.50–0.70) | 0.009   |
| Pancreatic pattern                 | localized                                        | 10.2       | 0.73 (0.63–0.81) | <0.0001 |
| SUV max                            | >6.8                                             | 2.2        | 0.74 (0.65–0.82) | <0.0001 |
| High gray-level zone emphasis      | ≥131.3                                           | 1.1        | 0.77 (0.68–0.85) | <0.0001 |
| Combined                           |                                                  | 0.95       | 0.88 (0.78–0.98) | <0.0001 |

Table 3. ROC Analysis for Differentiation Between Autoimmune Pancreatititis and Pancreatic Cancer (n = 114). AUC: area under the ROC curve, CI: confidence intervals, ROC: Receiver-operating-characteristic curve.

| Parameter                  | Optimal threshold for diagnosing pancreatic cancer | Odds Ratio | AUC (CI) | P value |
|---------------------------|--------------------------------------------------|------------|----------|---------|
| Number of extrapancreatic lesions | <2                                           | 2.9        | 0.60 (0.50–0.70) | 0.009   |
| Pancreatic pattern        | localized                                       | 10.2       | 0.73 (0.63–0.81) | <0.0001 |
| SUV max                   | >6.8                                            | 2.2        | 0.74 (0.65–0.82) | <0.0001 |
| High gray-level zone emphasis | ≥131.3                                         | 1.1        | 0.77 (0.68–0.85) | <0.0001 |
| Combined                  |                                                  | 0.95       | 0.88 (0.78–0.98) | <0.0001 |

Table 4. Differentiating Pancreatic Cancer from Autoimmune Pancreatitis in the 114 Patients Using FDG-PET Derived Parameters.

Several limitations of this study that could limit the conclusions should be considered. The major limitation is the retrospective nature with relatively small number of patients diagnosed with AIP. Second, more than 90% of the AIP patients presented with elevated serum IgG4 level, hence these patients were probably of a more severe disease phenotype. Nevertheless, these patients were also more likely to require prompt treatment because of...
and followed the same protocol as described in our previous study. A 45-min (early-phase) and 2-hour post-injection (delayed-phase) using the same PET/CT scanner was performed, and visual uptake was resolved by consensus.

We were able to visualize lesions in both early and delayed phases. A pancreatic lesion with diffuse morphology was defined as uptake in more than two or contiguous segments, whereas a lesion with normal structures or artifacts in the FDG PET transaxial slices were analyzed visually for uptake morphology. Therefore a conventional whole body FDG PET/CT can provide useful information in delineating the extent of disease involvement outside the pancreas, which may help to confirm the diagnosis of AIP when biopsy results are inconclusive. Further prospective studies enrolling a larger number of patients with tissue proof are needed to validate and strengthen the study results.

In conclusion, the combination of FDG-PET parameters and texture analysis may provide additional clinical useful information in patients with suspected AIP prior to steroid therapy. Extrapancreatic involvement found by FDG PET/CT can be helpful in supporting the diagnosis of AIP when the pancreatic findings alone are indeterminate. This may be especially useful in clinically difficult cases where coexisting malignancy is highly suspected, but biopsy is inconclusive.

**Methods**

**Patient Selection and Study Criteria.** From September 2008 to July 2016, 53 consecutive patients (Table 1) with suspected AIP according to the 2008 Asian Diagnostic Criteria were enrolled in the present study. The number of extrapancreatic FDG-avid lesions was counted for each patient. Patients were grouped into two categories: those with two or more and those with less than two sites of extrapancreatic FDG-avid lesions.

**FDG PET/CT Imaging.** All patients fasted for at least 4 hours to maintain serum glucose concentrations below 180 mg/dL before intravenous injection with 370 MBq (10 mCi) of FDG. PET/CT image acquisition at 45-min (early-phase) and 2-hour post-injection (delayed-phase) using the same PET/CT scanner was performed, and followed the same protocol as described in our previous study.

**PET/CT Data Analysis.** Two nuclear medicine physicians (MF Cheng and YW Wu) with >10 years of clinical experience, unaware of the results of other diagnostic tests, histology, and final diagnosis, reviewed the images independently using the built-in software (eNTEGRA, GE Medical Systems, WI). Diverging interpretations were resolved by consensus.

Increased FDG activity in the pancreas greater than the surrounding background activity, and not associated with normal structures or artifacts in the FDG PET transaxial slices were analyzed visually for uptake morphology. A pancreatic lesion with diffuse morphology was defined as uptake in more than two or contiguous segments, otherwise the lesion was characterized as having a localized morphology. A pancreatic lesion was classified as AIP if the lesion showed patchy FDG distribution in the pancreas without focal intense activity, and more than 2 sites of extrapancreatic FDG uptake were found. Otherwise, the pancreatic lesion was classified as malignant. The number of extrapancreatic FDG-avid lesions was counted for each patient. Patients were grouped into two categories: those with two or more and those with less than two sites of extrapancreatic FDG-avid lesions.
For semiquantitative evaluation, all foci with abnormally increased FDG uptake were evaluated by placing a volume of interest (VOI) in the suspected pancreatic lesion seen in the co-registered CT images. The standardized uptake values (SUVs) normalized to body weight (SUV – tissue concentration, injected dose –1 body weight –1) were acquired using the attenuation corrected images. For quantitative analysis, metabolic volume (MTV) was automatically selected in the axial PET images with maximum SUV (SUVmax) ≥ 2.5 as the primary pancreatic tumor, as identified by the nuclear medicine physicians. Adjustments were made if non-tumor areas were incorrectly included within the VOI. Only lesions with a MTV > 5 mL (mean 41.1 ± 3.9 mL, range 8.2–295.2 mL) were included in the analysis to avoid the partial volume effect.

In addition to lesion SUVmax, MTV, and SUVmax delayed/early ratio (SUVR), the total lesion glycolysis (TLG) of the lesion were also calculated. For all tumors, the FDG PET data were quantized into 32 bins, followed by textural analysis via first-order and high-order primary tumor texture features, as described in the Supplementary Data. A total of 19 PET texture indices commonly used in medical imaging research were included in the analysis (Supplementary data).

**Statistical Analysis.** All aforementioned parameters were examined for their ability to distinguishing AIP from PC by comparing one morphological parameter and outcome (AIP or PC) one at a time. Parameters with a significant relationship (P < 0.01) were then included in a backward stepwise logistic regression analysis. A prediction model was formulated using significant parameters from the above backward stepwise logistic regression analysis. Only those parameters with predictive probability of 0.35 or higher were included in the final prediction model. The corresponding area under the receiver operating characteristic curve (AUC) was reported. The resulting prediction model was examined to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in differentiating PC from AIP.

Numerical data were expressed as mean ± standard deviation (SD). Quantitative parameters were compared using two-tailed Student t test. Values of P < 0.05 were considered statistically significant. All analyses were conducted with the JMP® version 5 statistical software package (SAS Institute Inc., Cary, NC, USA).

**Data availability.** All data generated or analyzed during this study are included in this article (and its Supplementary Information files).

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Author Contributions
M.F.C., H.P.W., and Y.W.W. were responsible for study conception, design, and grant support. H.P.W., Y.W.T., and W.C.L. contributed to clinical data collection. M.F.C. and Y.W.W. searched the literatures and interpreted PET images. Y.L.G. was responsible for statistical analysis. M.E., Y.W.W., Y.C.C., C.L.K., and C.J.L. performed data analysis. M.F.C. drafted the manuscript and H.P.W., W.Y.W., and R.F.Y. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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