

Evaluation of pancreatic carcinoma with FDG PET

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Abstract

Background: To assess the diagnostic usefulness and clinical impact of positron emission tomography with [F-18]fluorodeoxyglucose (FDG PET) on the management of patients with known or suspected pancreatic carcinoma.

Methods: Attenuation-corrected FDG PET was performed in 20 patients (12 male, eight female) with pancreatic carcinoma at the time of initial diagnosis ($n = 7$), for tumor surveillance after Whipple surgery ($n = 11$), and for reevaluation after chemoradiation therapy ($n = 2$). Visual analysis of PET images were correlated with the results of abdominal computed tomography (CT) and carbohydrate antigen (CA) 19-9 serum tumor marker level that were obtained within 1 month of the PET study. Diagnostic validation was by histology in nine patients and by clinical or radiologic follow-up (5–48 months) in 11 patients. Changes in therapeutic management that were prompted by PET were tabulated.

Results: PET was concordant with the findings of abdominal CT in 14 patients (13 true positive, 1 true negative). PET detected clinically unsuspected lung lesions, confirmed subsequently by a chest CT, in one of these 14 patients. PET was discordant with CT in six patients. PET detected tumor recurrence in three patients in this group (15% of total) with nondiagnostic CT findings and elevated CA 19-9 serology. In two of these three patients, chemotherapy with gemcitabine was initiated based on PET localization of disease. Tumor was confirmed in the remaining one of the three patients at autopsy shortly after the PET study. FDG localization in a displaced loop of bowel resulted in an apparent false-positive hepatic lesion in one of six patients in the discordant group. PET un-

derestimated the extent of metastatic disease in the remaining two of six patients due to hyperglycemia.

Conclusion: In patients with suspected pancreatic carcinoma at the time of initial presentation, PET is complementary to abdominal CT and allows detection of unsuspected distant metastases. In patients with suspected recurrent pancreatic carcinoma, based on elevated or rising CA 19-9 serology, PET can localize the disease when abdominal CT is nondiagnostic as a result of posttherapy anatomic alteration. Imaging evaluation with PET may impact the clinical management of patients with pancreatic carcinoma.

Key words: PET—FDG—CT—CA 19-9—Pancreas—Cancer.

Pancreatic ductal adenocarcinoma is a dreadful disease with a poor prognosis. Diagnosis at an early stage, when the tumor is small and localized, is therefore very important for potential cure with surgery. Unfortunately, the disease commonly presents in the late stages primarily due to nonspecific clinical signs and symptoms [1]. Nevertheless, in patients with unresectable advanced disease, a recently approved chemotherapeutic agent, gemcitabine (2,2'-difluorodeoxycytidine), has been shown to provide alleviation of some disease-specific symptoms and to prolong survival as first-line therapy as well as in the fluorouracil (5-FU) refractory cases [2–5].

Carbohydrate antigen 19-9 (CA 19-9) has been identified as a useful serologic marker for predicting prognosis and relapse in patients with known or suspected recurrent pancreatic carcinoma [6–10]. A level greater than 1000 U/mL (normal level <37 U/mL) suggests unresectability, but normalization after therapy predicts relatively longer survival [11]. However, CA 19-9 is nonspecific and may be elevated in a variety of benign (e.g., pancre-

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atitis, cholangitis, cirrhosis) and malignant (e.g., gastrointestinal cancers, cholangiocarcinoma, hepatocellular cancer) conditions. CA 19-9 is also not suitable for screening because the level is frequently normal in the early stages of pancreatic carcinoma. Furthermore, about 5% of the population cannot synthesize CA 19-9 [11]. Despite these limitations, CA 19-9 is a reliable biological marker for monitoring of patients with known or suspected pancreatic cancer, which can prompt imaging evaluation.

Abdominal ultrasonography (US), computed tomography (CT), and endoscopic retrograde cholangiopancreatography (ERCP) are the most frequent diagnostic methods used for evaluation of patients with clinical suspicion for pancreatic cancer [12–14]. However, these methods have difficulty in distinguishing pancreatic cancer from chronic mass-forming pancreatitis and in differentiating viable tumor from posttherapy changes [15]. Percutaneous biopsy or fine-needle aspiration with CT or US guidance may also be inconclusive because inflammation and fibrosis around the tumor may impede accurate sampling [1, 16]. The exact role of magnetic resonance imaging (MRI) remains unclear, although recent reports have indicated advantages over helical CT [17, 18].

Positron emission tomography with [¹⁸F]fluorodeoxyglucose (FDG PET) has been demonstrated to be useful in the evaluation of indeterminate pancreatic masses, staging of pancreatic cancer, and detection of metastatic disease and in differentiating viable tumor from posttherapy changes [19–31]. The purpose of our retrospective study was to assess the diagnostic usefulness and clinical impact of FDG PET on the management of a group of consecutive patients who presented with clinical suspicion for pancreatic carcinoma.

Materials and methods

Patients

The study population consisted of 20 consecutive patients (12 male, eight female; age range = 40–76 years, mean age = 61 years) who were referred to our PET Imaging Center, between December 1997 and March 1999, with clinical suspicion for pancreatic carcinoma. The patients were referred at the time of initial diagnosis ($n = 7$), for tumor surveillance after Whipple surgery ($n = 11$), and for reevaluation after chemoradiation therapy of unresectable disease ($n = 2$). Two patients had a history of non-insulin-dependent diabetes mellitus.

Diagnostic validation was by histology in nine patients (all seven patients with initial presentation and two patients with recurrent disease) and by clinical or radiologic follow-up (5–48 months) in the remaining 11 patients. Serum CA 19-9 assay was performed in all patients using an immunoradiometric technique (normal level <

37 U/mL) [11]. Both the serum CA 19-9 assay and abdominal CT were obtained within 1 month of the PET study, without intervening therapeutic interventions. Changes in clinical management that were prompted by PET findings were tabulated.

CT

Helical abdominal CT was performed (5-mm collimation, pitch 1.5) after oral contrast administration and 40 s after intravenous administration of 140 mL iodinated contrast material at a rate of 4 mL/s. The images were reconstructed to 5 mm thickness. Either discrete low-attenuation pancreatic mass or diffuse pancreatic enlargement with hepatic or distant metastatic lesions was considered to represent malignancy.

PET

The patients were instructed to fast for at least 4 h before intravenous injection of 10–15 mCi (370–555 MBq) of FDG. Imaging was initiated 45–60 min after radiotracer administration. Transaxial PET images were acquired with a PC-4096 PET camera (Scanditronix AB, Uppsala, Sweden). The primary imaging parameters of the PC-4096 camera are in-plane with an axial spatial resolution of 6.0 mm FWHM (full-width half-maximum), 15 contiguous slices of 6.5-mm separation, and a sensitivity of ~5000 cps/uCi. All images were reconstructed using a conventional filtered back-projection algorithm to an in-plane resolution of 7 mm FWHM. Attenuation correction was performed from transmission images acquired with a rotating pin source containing Ge-68. All projection data were corrected for nonuniformity of detector response, dead time, random coincidence, and scattered radiation. To assure complete anatomic coverage of the areas of interest, imaging was performed at four to eight contiguous bed positions. Transaxial images were reformatted in coronal and sagittal projections using software developed in our laboratory.

Visual interpretation of the images was performed in conjunction with clinical information and close correlation with abdominal CT scans to localize abnormal tracer uptake. Tracer accumulation in the pancreatic bed or by lesions identified on CT greater than background hepatic uptake was considered abnormal.

Results

Table 1 summarizes the patient characteristics and imaging results. PET findings were concordant with the findings of both abdominal CT and CA 19-9 assay in 14 patients (70%). Thirteen patients in this group had ele-

Table 1. Summary of patient characteristics and findings of the study

Patient (presentation)	Age (years)	Sex	CA19-9 (U/mL) ^a	PET	CT	Pathology	Comments
1 (post Whipple)	76	M	203	+	+	None	
2 (post Whipple)	66	M	116	+	-	+	Autopsy
3 (post Whipple)	55	F	32	-	-	None	
4 (post Whipple)	71	M	17	+	-	None	Displaced bowel loop
5 (post Whipple)	62	F	6950	+	-	None	Gemcitabine therapy
6 (initial)	66	F	440	+	+	+	
7 (post Whipple)	61	M	93	+	+	None	
8 (post Whipple)	52	F	355	+	+	None	
9 (initial)	58	F	3520	+	+	+	Unsuspected lung lesions
10 (post ChemoRT)	63	M	43	+	+	None	
11 (post Whipple)	59	F	57	+	-	None	Gemcitabine therapy
12 (post ChemoRT)	40	M	3100	+	+	None	
13 (initial)	68	M	10,400	+	+	+	
14 (initial)	51	M	38,000	+	+	+	
15 (post Whipple)	64	F	590	+	+	None	
16 (initial)	63	M	5200	+	+	+	
17 (initial)	57	M	69,500	+	++	+	Hyperglycemia
18 (post Whipple)	72	M	10,500	+	++	None	Hyperglycemia
19 (post Whipple)	63	F	75	+	+	+	
20 (initial)	57	M	470	+	+	+	

^a Normal level < 37 U/mL

-, no lesion detected; +, positive for lesion; ++, more lesions detected in comparison to the other imaging modality; ChemoRT, chemoradiation therapy

vated CA 19-9 level (range = 43–38,000 U/mL) and abnormal abdominal CT and PET findings. Histology was available in seven of these patients who presented at the time an initial diagnosis of pancreatic ductal adenocarcinoma. PET detected clinically unsuspected lung lesions in one of these patients, which were confirmed subsequently by a chest CT. Both PET and abdominal CT were negative in one of 14 patients in the concordant group who had undergone a Whipple procedure 2 years previously for pancreatic carcinoma. This patient presented with intractable abdominal pain and a CA 19-9 of 32 U/mL, which is at the upper limit of normal.

PET was discordant with CT in six patients. PET detected tumor recurrence in three of these patients (15% of total), with equivocal CT findings and elevated CA 19-9. In two of these three patients, chemotherapy with gemcitabine was initiated based on PET detection of disease and elevated serology. Tumor was confirmed in the remaining one of three patients in this group at autopsy shortly after the PET study.

In one of six patients in the discordant group, an initial PET study was falsely positive, with an apparent hepatic lesion. This patient had a normal serology and a negative CT. A subsequent abdominal MRI study demonstrated no hepatic abnormality. The apparent false-positive PET finding was considered to be due to relatively high focal bowel FDG uptake. A 6-month follow-up PET study in this patient was normal.

In the remaining two of six patients who had a history of diabetes mellitus and difficult glucose control, PET underestimated the extent of hepatic metastases in com-

parison with abdominal CT, which was most likely due to hyperglycemia.

Discussion

Our results indicate that PET and abdominal CT are complementary for the evaluation of patients with suspected pancreatic carcinoma at the time of initial presentation of disease. One advantage of abdominal CT in this clinical setting is delineating the regional anatomy for preoperative evaluation of local tumor extension and vascular tumor involvement and for directing image-guided biopsy [13, 14, 16, 17]. However, PET has been demonstrated to be more accurate than CT in differentiating chronic mass-forming pancreatitis from pancreatic carcinoma [15]. Malignant lesions show high FDG uptake, whereas FDG accumulation in chronic pancreatitis is low. Using a semiquantitative analysis with standardized uptake value (SUV), Delbeke et al. reported an optimal cutoff level of 2.0 for differentiating malignancy from benign lesions [32]. Another advantage of PET in this clinical setting is the ability of PET to detect unsuspected metastases, which can potentially affect clinical management. In one of our patients with initial presentation of unresectable disease based on abdominal CT, PET detected additional unsuspected lung lesions, confirmed subsequently with a chest CT. However, there was no change in medical management in view of unresectability of disease.

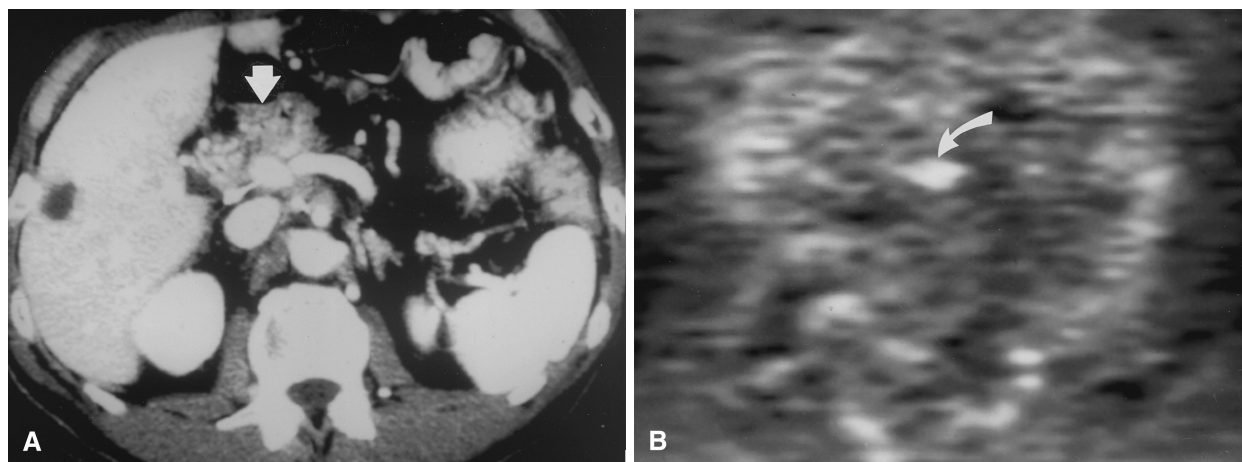


Fig. 1. This patient with an elevated CA 19-9 level of 116 U/mL had undergone a Whipple procedure 10 months before the CT and PET studies shown here. **A** Axial contrast-enhanced abdominal CT shows abnormal heterogeneous soft tissue (*arrow*) in the surgical bed at the level of splenic venous confluence to the portal vein. Post-therapy changes cannot be distinguished from recurrent tumor. Low-attenuation region in the right hepatic lobe corresponds to a cyst. **B** The coronal

attenuation-corrected PET image of the abdomen shows an area of intense tracer accumulation in upper mid-abdomen (*curved arrow*) in the surgical bed region, highly suspicious for recurrent tumor. Moderately high physiologic bowel tracer uptake is also evident. The patient died shortly after the PET study from pneumonia. A limited autopsy was performed and confirmed tumor recurrence in the surgical bed.

In patients who have undergone Whipple surgery or chemoradiation therapy, serial serum CA 19-9 assay is useful as a follow-up clinical parameter for prognosis and in predicting recurrence [6, 10, 11]. Patients who normalize their CA 19-9 postoperatively live longer, although a progressive rise in the level suggests recurrence. PET is advantageous over CT in differentiating viable tumor from posttherapy changes by demonstrating high FDG localization in the tumor [33].

Three patients (15% of total) in our study group with prior Whipple surgery presented with rising serum CA 19-9 level and equivocal CT findings. PET accurately detected recurrence in all three patients. In two of these patients (10% of total), additional chemotherapy with gemcitabine was undertaken based on localization of recurrent disease by PET. During the follow-up period, the disease burden remained stable in one of the two patients by observing no progression of disease on abdominal CT and no change in CA 19-9 level. In the second patient treated with gemcitabine, CA 19-9 level declined to normal range. In the remaining third patient in this group who died from pneumonia shortly after the PET study, a limited autopsy demonstrated recurrent pancreatic carcinoma in the surgical bed (Fig. 1).

Our data, which suggest that PET is more accurate than CT in evaluating patients with suspected pancreatic carcinoma, are in line with the findings of previous reports [20, 34, 35]. In one study of a group of 26 patients with suspected pancreatic carcinoma, PET was superior to CT, US, and ERCP in diagnosing pancreatic carcinoma and in detecting metastatic disease and in the differential diagnosis of pancreatic carcinoma and chronic pancreati-

tis [20]. In another study of 54 patients with suspected pancreatic tumor, PET was more accurate (93%) than CT (80%), conventional US (83%), and endoscopic US (84%) in differentiating malignancy from benign disease, including chronic pancreatitis, mucinous cystadenoma, and pseudocyst [35]. Cumulative analysis of nine studies in 333 patients demonstrated high sensitivity (93%), specificity (88%), and accuracy (92%) for FDG PET in detecting pancreatic carcinoma [36].

PET may also change therapeutic management by demonstrating unsuspected metastatic disease, which avoids the expense, morbidity, and mortality of unnecessary surgical procedures. In one study, PET avoided laparotomies in 17% of patients who were originally regarded as candidates for curative surgery based on preoperative CT and angiography [24]. In another recent study, addition of PET to CT evaluation altered the surgical management in 43% of patients with suspected pancreatic carcinoma [32]. PET localization of disease in two patients (15% of total) in our study also prompted additional chemotherapy with gemcitabine, which resulted in stability of disease in one patient and clinical improvement in the other patient. Our lower figure is probably a result of pretest selection bias. Nevertheless, the information provided by PET, which was not available by abdominal CT, was significant for the individual patients and helped in medical decision making to employ additional chemotherapy despite the associated adverse therapy side effects.

PET may have limitations in specific clinical situations. FDG PET may be falsely positive in patients with inflammatory pancreatic disease [37]. The focal FDG

uptake can be similar, both qualitatively and quantitatively, to neoplasm even in the setting of absent or equivocal clinical, laboratory, and CT findings for pancreatitis [37]. Nevertheless, in view of cumulative experience with FDG PET in the evaluation of indeterminate pancreatic masses, PET will be useful for differentiating cancer from low-grade inflammatory condition.

In one of our patients, a displaced loop of bowel resulted in an apparent right hepatic lobe lesion. High FDG uptake by normal bowel may make evaluation of the abdomen and pelvis difficult because high uptake can mimic a lesion, whereas diffuse uptake can hide a lesion [38]. Miraldi et al. used bowel cleansing with a laxative to reduce artifacts [39]. We do not ordinarily employ bowel cleansing before a PET study. A subsequent PET scan in our patient was negative, and he has remained free of demonstrable disease on follow-up clinical and imaging evaluations.

Hyperglycemia can mask detection of malignancy because glucose competes with FDG for cellular uptake. In a study of 171 patients with pancreatic disease, both the sensitivity for detection of malignancy and mean tumor SUV were lower in patients with fasted plasma glucose level above 130 mg/dL than in those patients with glucose level below 130 mg/dL (sensitivity 69% vs. 83% and SUV 2.5 vs. 3.5, respectively) [40]. In our study, two patients with diabetes mellitus and difficult glucose control had elevated plasma glucose levels (172 and 234 mg/dL) at the time of the PET study. Hyperglycemia is the likely explanation for the underestimation of metastatic disease by FDG PET in comparison with abdominal CT in these patients. Therefore, as has been suggested by other investigators, in patients with diabetes mellitus, FDG PET should preferably be performed when the fasting blood glucose level is within or close to normal range [40]. Our study also reemphasizes the importance of euglycemia at the time of FDG administration and that hyperglycemia can hinder lesion detection.

Our study is limited with regard to heterogeneous patient population, patient selection bias, post-PET evaluation bias, and lack of histologic confirmation for all PET-detected lesions to allow calculation of sensitivity, specificity, and negative and positive predictive values. Correlation of PET and CT findings was done only to determine the relative concordance between the two studies in an individual patient. Further, although the changes in the therapeutic management in two of our patients, which were prompted by PET, resulted in an apparent relative short-term benefit during the follow-up period, we could not determine whether these changes actually resulted in improved long-term clinical outcome.

Conclusions

Our results are in line with those of previous studies in demonstrating the diagnostic value of PET in patients

with suspected pancreatic carcinoma. Specifically, in patients with suspected recurrent pancreatic carcinoma based on elevated or rising CA 19-9 serum tumor marker level, PET is useful in detecting and localizing the tumor when abdominal CT is nondiagnostic in view of post-therapy anatomic alterations. Moreover, demonstration of tumor by PET can impact the therapeutic management of patients with recurrent pancreatic carcinoma. Additional studies are necessary to assess whether such changes in therapy prompted by PET actually result in improved clinical outcome.

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