18F-FDG Positron Emission Tomography CT (FDG PET-CT) in the Management of Pancreatic Cancer: Initial Experience in 12 Patients

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Abstract

Introduction. Staging and restaging of pancreatic malignancy can be demanding. Often, there are liver lesions seen on diagnostic CT suspicious for secondary deposits. Positron emission tomography (PET)-CT may have a great potential in confirming or ruling out actual malignancy in those areas. **Methods** We prospectively studied 12 pancreatic adenocarcinoma patients, who had undergone PET-CT imaging as part of their staging or restaging process. Imaging was performed after intravenous administration of 10 mCi F-18 FDG. Results were compared with CT, histopathological findings and/or clinical follow up. **Results.** PET-CT correctly identified 11 lesions and ruled the absence of disease in 4 out of 4 patients (PPV 92%, NPV of 100%, and accuracy 94%), compared to CT which had (PPV 79%, NPV 50% and accuracy 75%). CT identified 4 metastatic liver lesions in 12 patients of which 3 were actually benign processes. **Conclusion**. FDG-PET detects pancreatic malignancy and metastatic disease with higher accuracy than conventional CT. The ability of PET-CT to rule out or correctly identify metastases greatly enhances the physician's decision-making process to choose the right therapeutic intervention.

Key words

PET scan – pancreatic cancer – CT scan – PET-CT scan – liver metastases

Introduction

Adenocarcinoma of the pancreas accounts for approximately 30,000 deaths each year in the United States [1]. Although surgery offers a potential cure, as many as 70% develop early recurrence within 6–12 months following surgery. The dismal outcome is secondary to the aggressive biology of this tumor, the presence of undetected extrapancreatic tumor spread at the time of surgery, and resistance to current chemotherapeutic agents. Accurate staging, particularly identification of distant metastases, is of paramount importance to decide the best treatment options, such as selection of patients for surgery.

Current standard staging includes contrast-enhanced helical computed tomography (CT) of the abdomen with chest x-ray/CT to detect involvement of adjacent structures such as the superior mesenteric artery (SMA) and distant metastases [2]. Endoscopic ultrasonography (EUS) is increasingly employed to detect vascular encasement and to perform an ultrasound-guided fine-needle aspiration cytology (FNA) to obtain histologic confirmation of malignancy [3]. In some specialized centers, exploratory laparotomy is also performed prior to definitive surgical treatment. Despite extensive preoperative staging, previously undetected metastases are found during laparotomy or laparoscopy in up to 30% of patients with pancreatic cancer [4–6].

Positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG), a noninvasive imaging technique, can be used to image the entire body in a single session. PET has been shown to be the most accurate examination for the detection of local recurrences and distant metastases in patients with gastrointestinal malignancies, especially colorectal cancer [7, 8]. In patients with suspected pancreatic cancer, PET not only has a high sensitivity for liver metastases but also can help to differentiate between malignant and benign lesions [9-11]. However, the precise anatomic delineation of PET-positive findings is hindered by the limited anatomic information of PET images [12,13].

To overcome this limitation, simultaneous examination by PET-CT has been developed with the aim of coregistering functional (PET) and anatomic information (CT) by the same scanner (PET-CT) [12]. This is with the objective of providing better detection rates with additional information of unclear lesions that may be missed on either helical CT or PET alone. These theoretical advantages have recently

been confirmed for colorectal and lung cancer, where PET-CT was significantly more accurate in predicting the tumor stage than PET or CT alone [7,8,14].

The main objective of this study was to evaluate the impact of PET-CT on the management of patients with pancreatic cancer. Secondary study objectives were the ability of PET-CT to differentiate benign and malignant pancreatic lesions and to detect distant metastases. We prospectively studied 12 patients with pancreatic cancer to evaluate the impact of PET-CT on the management of patients who had underwent a standardized conventional diagnostic work-up.

Methods

A pilot prospective study on patients being evaluated for pancreatic cancer was conducted between May 2003 and March 2004. Tumor staging included standard CT (1-3 mm slices) of abdomen, pelvis and chest, PET-CT, EUS with FNA of the primary tumor, and serum CA 19-9 levels. The staging was performed in a stepwise manner, so that all patients had helical CT and PET-CT. EUS was performed in all patients to perform fine needle aspiration (FNA) and CA 19-9 was measured.

All laboratory, radiological, and histological data were entered into a prospective database and, after definition of inclusion criteria and study end points, the data of eligible patients were analyzed in May 2004. Each patient with a focal lesion in the pancreas or with clinical suspicion of pancreatic cancer was eligible for this analysis. Follow-up was performed by personal contact with the attending or general physician. Data analysis was done in accordance with the guidelines of the local Ethics Committee, and written informed consent for PET-CT scanning was available for each patient.

All patients had fasted for at least 4 hours (4 to 6 hours) and received an injection of 10 mCI F-18 FDG intravenously 60 minutes prior to the PET-CT examination. In addition, patients received oral contrast (gastrograffin, but not barium) to improve delineation of abdominal structures on CT (15). Intravenous contrast medium was not given because all patients underwent an additional helical CT scan to avoid artifacts on PET scan.

A combined in-line PET-CT scanner (GEMS Discovery LS, Waukesha, WI) was used for all examinations. Helical non-enhanced CT scan was acquired from the top of the head to the pelvic floor using a standardized low-dose protocol of 140 kV, 110 mA, and a tube-rotation time of 0.75 second per rotation in normal breathing. Immediately after CT, PET was performed covering the same axial fields of view of the body. PET emission data were obtained using an acquisition time of 5 minutes per table position, and the section thickness of CT and PET studies were adapted to each other (4.25-mm contiguous slices). Because the CT data were used for transmission correction, additional transmission scanning was not necessary and imaging of the entire examination was completed in 30 minutes [16].

The attenuation corrected PET images, the CT images and the integrated PET-CT images were viewed simultaneously by nuclear medicine physicians as well as radiologists using *eNtegra* software (GE Medical Systems). Image interpretation was based on the identification of regions with increased FDG uptake on the PET images, and the anatomic delineation of all FDG-positive lesions on the integrated PET-CT images. Furthermore, all CT images were viewed separately to identify additional lesions without FDG uptake using soft tissue, lung and bone window leveling. Clinical data including CA 19-9, pathology and follow-up was provided by the medical oncologist.

Findings on PET-CT were compared with CT and validated by intra-operative findings and histology of the resected specimen or biopsies. For patients who were diagnosed to have a benign pancreatic lesion by PET/CT, and did not undergo resection, clinical follow up was assessed to confirm the diagnosis made by PET/CT.

Informed consent was obtained from each patient and the study protocol confirmed to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2000, reflected in a priori approval by the University of Alabama Institutional Review Board.

Results

PET-CT was performed in 12 patients with suspected pancreatic cancer. Male:female ratio was 9:3 with median age of 61 years. Patient characteristics are given in Table I. The median time interval between helical CT and PET-CT was 10-21 days. The follow-up findings on the patients are detailed in Table II.

Table I. Characteristics of study of patients

Total		12
	Men	9
	female	9
Age (Median)	61 years	
Range	43-74	
Tumor location		
	Head	10
	Body	1
	Tail	1
Histology		
	Malignant	11
	Benign	1
FDG uptake		
	FDG positive	11
	FDG negative	0

Sites of metastases included liver, lymph nodes, adrenal gland and mesentery. CT identified 4 metastatic liver lesions in 12 patients of which 3 were actually benign processes, both confirmed by PET as well as other modalities (MRI or ultrasound). Pre-operative imaging was done in 4 patients with localized pancreatic disease, among whom only one

Table II. Summary of findings and outcome in patients staged with PET-CT

Patient	CT scan findings	PET	PET max	PET mean	Pathology	Follow-up
1	Left paraaortic LN +; inferior tip posterior segment liver +	left paraaortic LN +; inferior tip posterior segment liver –	10.2	7.1	-	Liver lesions – on F/U CT scan
2	Infiltration but no definite mass in pancreas	PET confirmed pancreatic neoplasm	11.8	7.1	Malignant	Chemotherapy resulted in response and decrease in uptake on PET and decrease in CA19-9
3	No residual or distant disease s/p Whipple's surgery	residual disease in pancreatic bed and liver mets detected	7.4	5.1	-	Post-chemo uptake in anterior right lobe of liver and lateral segment of the left lobe of liver Max SUVs 5.8 and 4.9 respectively.
4	Small pancreatic head lesion; sub-cm suspicious liver met	pancreatic head -, liver –	2.3	1.8	Benign	F/U at 1 year, patient alive with no malignancy
5	Negative	negative	4.3	2.8	Benign	Pancreatitis
6	Pancreatic body mass with peripancreatic lymph node, 1 liver met	pancreatic body lesion, 1 liver met	3.3	2.6	Malignant	Patient treated for metastatic disease
7	Mesenteric mets, left adrenal adenoma	local recurrence +, right and left adrenal mets +, splenic mets +	6.4	3.6	-	Post-op recurrent disease. Patient treated with systemic therapy
8	Pancreatic head +; peripancreatic LN left hepatic and gastroduodenal arteries involvement ; two 2 mm nodules in the right lung	malignancy involving the head and proximal body of pancreas but no evidence of metastasis	1.9	1.1	-	Patient underwent Whipple's procedure
9	Body of the pancreas mass, mediastinal LN +, liver +	body of the pancreas +; No metastatic lesions are identified in the liver. There is no abnormal activity in the chest or mediastinum.	6.4	4.1		Treated for locally advanced disease with neoadjuvant therapy
10	Head of pancreas +; peripancreatic nodes +	head of the pancreas +	2.8	2.2	Chronic pancreatitis	Inflammatory LN
11	Unresectable infiltrative mass; mesentery mets	neck and body mass +; no mets	2.2	1.7	-	Treated for locally advanced disease with chemoradiotherapy
12	Unresectable locally invasive pancreatic mass; small solid renal tumor / renal cell carcinoma	head mass; hyperglycemia/ suboptimal scan	6.8	3.1	Mucinous neoplasm (questionable colloid carcinoma).	Patient was found to have two primaries: pancreas and renal cell carcinoma

LN: lymph nodes; F/U: follow-up; met: metastase

underwent Whipple's surgery due to the presence of distant metastases or benign cytology as described below. Two patients had benign lesions and were alive at the end of the study time. One underwent EUS-guided biopsy two times and laparoscopic evaluation with biopsy, all showing no malignant cells despite very suggestive findings on CT of abdomen and the second patient was found to have pancreatitis.

The utilization of PET-CT among this group helped not only to confirm staging, but also prevented unnecessary surgery, thereby preventing related complications and expenditures. Two patients who had abnormal findings on the CT scan but no uptake on PET scan was confirmed to have

benign etiology on FNA biopsy (Table II). CA19-9 was not helpful as the levels were elevated in benign cases too.

One patient had a good response to chemotherapy and CT scan was not able to show a pancreatic abnormality. However, PET was able to decide about continuing therapy in that patient in the presence of uptake.

PET-CT correctly identified 11 lesions (sensitivity 100% and specificity 80%) and ruled the absence of disease in 4 out of 4 patients (PPV 92%, NPV of 100%, and accuracy 94%), compared to CT which had a sensitivity of 92%, specificity of 25%, PPV79%, NPV 50% and accuracy 75%.

One such example is shown in Figs 1-3. In this patient, in addition to a rising CEA level, PET-CT scan showed

an interval increase in the intensity and the extent of FDG activity at periportal surgical bed measuring SUVm 6.0 at image 116 (previous SUVm 4.2) (Fig. 1). On the contrary, no evidence of disease recurrence was seen on the CT scan (Fig. 2). Given these results, it was likely that the patient had recurrent disease and a biopsy was planned. It should be noted that she will proceed without confirmation of disease by biopsy. Interventional radiology was recommended
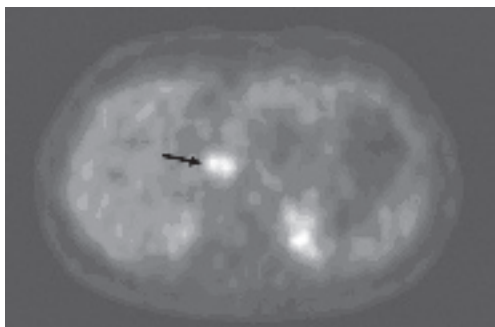

Fig 1. Axial attenuation PET image from PET-CT scan performed October 23, 2007. The image is at the same level as in 1a and 1b. There is FDG uptake in the surgical bed (black arrow) concerning for local recurrence.

Fig 2. Axial contrast enhanced CT scan performed at the same level as in 1. There is a small amount of non-enhancing soft tissue in the surgical bed (black arrow) but no enhancing mass to indicate local recurrence.
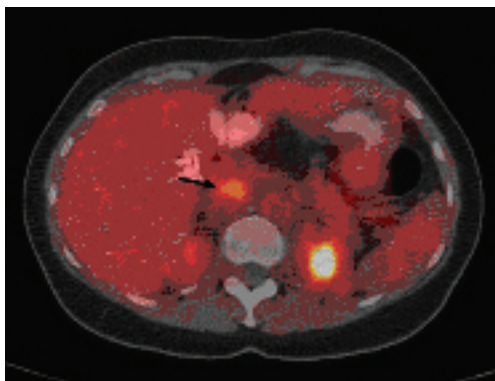

Fig 3. Axial fused image from a PET-CT scan performed following chemotherapy. The image is at the same level as Figures 1 and 2. There is FDG uptake in the surgical bed confirming for local recurrence (black arrow).

against biopsy due to risk and possibility of not obtaining the appropriate tissue. Therefore, the patient proceeded with systemic chemotherapy. Repeat PET-CT after two months of chemotherapy showed a response by a decrease in SUVm 5.2, from, previous SUVm 6 (Fig. 3).

Discussion

This was a pilot study and although the number of patients was small, it provides important information in the field of oncology and radiology. The study suggests that the use of PET-CT has an impact on the oncologic management of patients with pancreatic cancer in two ways; (i) unnecessary surgery and further staging examinations could be avoided by reliably excluding cancer; and (ii) by detecting additional metastases. In other words, PET-CT can help to differentiate benign from malignant pancreatic lesions as well as to detect distant metastases.

Surgery remains the only curative therapy of non-metastatic pancreatic cancer.

Although perioperative mortality has markedly decreased during the past two decades, complication rates remain high [17]. The long-term outcome is dismal with 5-year survival rates of 10–25% [18]. Novel and sensitive staging methods are required to improve preoperative patient selection to offer potential care by surgery to the right patients.

Data on the use of PET-CT in the staging of patients with pancreatic cancer are scarce. The sensitivity and specificity of PET-CT for the diagnosis of pancreatic cancer in our study was similar to PET alone and consistent with previous figures available in the literature [19]. The results of our study indicate that PET-CT correctly identified pancreatic lesions with a very high sensitivity (100%) and specificity (80%) for malignancy compared to helical CT with sensitivity of 92% and specificity of 25%. Our study also showed a high NPV (100%), suggesting that cancer could be excluded based on PET-CT findings alone. The specificity of PET is limited regarding the exclusion of pancreatic cancer, and PET should always be combined with a simultaneous CT with intravenous contrast.

However, PET and PET-CT are not used for screening asymptomatic patients, but for assessing malignancy in patients with suspected pancreatic cancer. For this reason, the PPV and NPV are much more relevant, since they describe the probabilities of FDG-positive lesions to be malignant, and of FDG-negative lesions not to be malignant, respectively.

The routine use of PET is generally not considered to be cost-effective, hence it has not been accepted as standard staging for pancreatic cancer at many centers. However, our data suggest that in patients with suspected pancreatic cancer, PET-CT was saving costs by excluding patients from resection because of metastasis. An estimated cost for a Whipple procedure is in the range of $35,000-40,000 in the USA [19]. The expenses related to hospital stay for 12-20 days in USA are approximately $34,35 [19, 20]. Neither shortening the length of hospital stay nor the use of

CT guided FNA and surgical assessment of metastasis (by a thoracoscopic or laparoscopic approach) can reverse the cost-effectiveness of PET-CT.

Though there is little data regarding costs, it is clear that improved patient selection by PET-CT may increase survival after surgery, which might reduce overall costs. Because PET-CT is the combination of PET and CT, the detection rate of the PET and CT portions of PET-CT are the same as for either examination alone. The major advantages of PET-CT are the simultaneous availability of both functional and anatomic information which facilitates an optimal fusion of both imaging techniques. Only by this improved imaging fusion, FDG-positive findings, e.g. lymph node metastases can be exactly identified.

It is important to bear in mind that FDG uptake is not specific for malignancy [21] and that FDG-positive lesions always require histologic confirmation before a patient is denied surgery. Local resectability is still best assessed by helical CT, especially the evaluation of vascular encasement of the SMA and celiac axis. In this study, only a low-dose CT without intravenous contrast medium was used for the image fusion of PET-CT. Regular helical CT using intravenous contrast with arterial and porto-venous phases can be performed by the PET-CT scanner. Whether PET-CT with intravenous contrast (helical PET-CT) may replace helical CT as an "all-in-one" staging procedure for pancreatic cancer, needs to be evaluated in future studies. This technique will not only increase specificity but also improve cost-effectiveness of PET-CT.

18F-FDG PET can effectively differentiate pancreatic cancer from benign lesions involving both primary and secondary sites with high accuracy. Liver is a common site for metastasis from the pancreas. The physician can rightly choose the appropriate course of therapeutic intervention, whether it be a radical resection or chemo radiation [22].

Schmidt et al. compared the accuracy in staging of various malignant tumors in 41 patients with whole-body magnetic resonance imaging (WB-MRI) using parallel imaging (PAT) and PET-CT [23]. Coronal T1w and STIR sequences at 5 body levels, axial HASTE imaging of the lung, and contrast-enhanced T1w sequences of the liver, brain, and abdomen were performed. TNM stage was assessed for both modalities in a separate consensus reading using histological results and radiological follow up within 6 months as the standard of reference. Three primary and 4 recurrent tumors were detected; one recurrent tumor was missed with WB-MRI. On the other hand, 60 benign and 60 malignant lymph nodes were detected with a sensitivity of 98% and specificity of 83% for PET-CT and 80%/75% for WB-MRI, respectively. For distant metastases, sensitivity/ specificity was 82% for PET-CT and 96%/82% for WB-MRI. This study suggests that WB-MRI and PET-CT both are reliable imaging modalities for tumor staging. WB-MRI is highly sensitive in detecting distant metastases and PET-CT is superior in lymph node staging.

In **conclusion**, staging and restaging of pancreatic malignancy can be very demanding due to the low specificity of CT. Also, imaging of the pancreatic bed region is difficult by PET due to the relatively low tumor to background ratio. The normal physiological 18F-FDG distribution in the upper abdomen is relatively high, unlike in the lungs. Therefore, addition of CT makes the findings significantly more specific and thereby accurate. 18F-FDG PET-CT can therefore effectively differentiate pancreatic cancer from benign lesions involving both primary and secondary sites with high accuracy than conventional CT or FDG PET alone. Liver is a common site for metastasis from pancreas. Often, there are liver lesions seen on diagnostic CT suspicious for secondary deposits. PET-CT may have a great potential in confirming or ruling out actual malignancy in those areas. The physician can rightly choose the appropriate course of therapeutic intervention.

Conflicts of interest

None to declare.

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