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Contribution of whole body FDG-PET to the detection of distant metastasis in pancreatic cancer

Yoshihiro NISHIYAMA,* Yuka YAMAMOTO,* Koiku YOKOE,* Toshihide MONDEN,* Yasuhiro SASAKAWA,* Kunihiko TSUTSUI,** Katashi SATOH* and Motoomi OHKAWA*

*Departments of *Radiology and **Clinical Laboratory, Faculty of Medicine, Kagawa University*

Objective: Accurate baseline staging is necessary to appropriately treat pancreatic cancer. The present study was undertaken to evaluate the clinical contribution of whole body FDG-PET to the detection of distant metastasis in pancreatic cancer. ***Methods:*** A total of consecutive 42 patients with previously untreated pancreatic cancer were examined. Whole body FDG-PET imaging for initial staging was performed with a 3D acquisition and iterative reconstruction on Siemens ECAT HR+ scanner at 1 hour post 185–200 MBq ^{18}F-FDG injection. PET findings were correlated with clinical and radiological data to determine the impact of PET on staging. ***Results:*** In 16 patients, there were one or more sites of metastasis based on clinical data. FDG-PET correctly identified the presence of metastasis in 13 of 16 patients and its absence in 23 of the remaining 26 patients. Thus, FDG-PET missed 4 metastatic sites in 4 patients (liver and lung metastasis). FDG-PET correctly identified 8 metastatic sites in 7 patients (peritoneal dissemination and liver, bone and supraclavicular lymph node metastasis), which were missed on CT imaging. Based on whole body FDG-PET, the clinical stage was changed in 5 of 42 patients (11.9%). ***Conclusions:*** These results suggest that FDG-PET and CT appear to have a complementary role in the detection of distant metastasis in patients with pancreatic cancer.

Key words: FDG-PET, pancreatic cancer, distant metastasis

INTRODUCTION

PANCREATIC CANCER is a malignancy with an extremely poor prognosis.[1] Resection has so far been the optimal treatment for patients with clinically localized pancreatic cancer, providing the only chance of a cure. However, the pancreatic tumor is characterized by early spread to lymph nodes, peritoneum, and liver. Therefore, the aim of preoperative evaluation should be not only to assess the resectability of the primary tumor but also to search for metastasis. Thus accurate staging is important for planning appropriate therapy and to avoid unnecessary laparotomy in patients with unresectable disease.

Preoperative imaging studies should be able to detect distant metastasis and the presence of vascular invasion. Morphologic imaging modalities such as computed tomography (CT), ultrasonography and magnetic resonance imaging (MRI) are the best imaging modalities to evaluate the local extent of disease as well as the relationship with vascular structures.[2,3] However, liver or peritoneal metastases are not always suspected or detected using these conventional preoperative examinations and the patient ends up undergoing laparotomy. To overcome this situation, some preoperative diagnostic procedures have been attempted.[4,5]

Positron emission tomography (PET) with the metabolic tracer F-18-fluorodeoxyglucose (FDG) allows functional characterization of tissues. Because malignant tissue, particularly pancreatic cancer, is characterized by increased glucose metabolism, PET permits the visualization not only of the primary tumor but also of its metabolic spread.[6–10] Furthermore, PET machines can image the whole body and detect unexpected lesions.[11] Whole body FDG-PET has been proven to be a very effective imaging

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For reprint contact: Yoshihiro Nishiyama, M.D., Department of Radiology, Faculty of Medicine, Kagawa University, 1750–1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761–0793, JAPAN.

E-mail: nisiyosi@kms.ac.jp

modality for initial staging and restaging of many malignant tumors.[12] However, whether FDG-PET is useful to detect the spread of cancer and to help determine the staging of pancreatic cancer is unknown. The objective of the present study was to evaluate the clinical contribution of whole body FDG-PET to the detection of distant metastasis in pancreatic cancer.

MATERIALS AND METHODS

Patients

The study population consisted of consecutive 42 patients (26 males, 16 females; age range 33–93 years, mean age 65.8 years) who were histologically diagnosed with pancreatic cancer between June 2002 and February 2004 at our institution. None of them had received any treatment previously. All patients underwent conventional radiological staging studies and FDG-PET for evaluation of the primary tumor and metastatic work-up. Conventional radiological staging by means of CT scan was done in all patients. CT and FDG-PET scans were performed within 2 weeks of each other. All available clinical information was reviewed.

The study was approved by the local ethics committee of our institution, and all patients provided written or oral informed consent.

CT

CT studies were performed with a multidetector-row (4-slice) scanner (Aquilion; Toshiba, Tokyo, Japan) or with a single scanner (HiSpeed Advantage, model 9800; General Electric Medical Systems, Milwaukee, WI). According to the standard imaging protocol at our hospital, both unenhanced upper abdomen and contrast enhanced scans of chest and abdomen were performed. When necessary, thin slice chest CT scanning was carried out. With the Aquilion CT scanner, contrast-enhanced CT provides three set of scanning sequences of the upper abdomen, initiated 20 sec (arterial phase), 50 sec (portal venous phase) and 180 sec (equilibrium phase) after the start of the intravenous injection of 100 m*l* of contrast material via a power injector at a rate 3m*l*/sec. With the HiSpeed Advantage CT scanner, only equilibrium phase imaging was performed at 180 sec after the start of the intravenous injection of 100 m*l* of contrast material via a power injector at a rate 1 m*l*/sec. One-centimeter thick contiguous image sections were obtained.

CT study findings including bony windows were interpreted by experienced radiologists blinded to the diagnostic findings from other modalities. Based on written clinical report of the CT scan, each patient was assigned a stage of pancreatic cancer.

FDG-PET

Patients were instructed to fast for at least 5 h prior to FDG administration. None of the patients had a history of diabetes. Accordingly, no intravenous insulin was administered.

All FDG-PET examinations were performed with an ECAT EXACT HR+ camera (Siemens/CTI Inc., Knoxville, TN). This camera acquires 63 planes simultaneously over 15.5 cm field of view. In-plane resolution was approximately 4.6 mm, with an axial resolution of approximately 3.5 mm full width at half maximum. Images were acquired in 3D mode. Radiochemical purity, sterility and pyrogenicity of FDG were tested for each sample at our cyclotron unit. Transmission scan was obtained using a ^{68}Ge rod source for the purpose of attenuation correction. Emission scan for the whole-body imaging started at 60 min after injection of 3 MBq/kg FDG. Six or seven bed positions were used to scan from the skull base to the upper thighs. Reconstruction of both transmission and emission scans used accelerated maximum likelihood reconstruction and ordered-subset expectation maximization, which reduces image noise and avoids reconstruction artifacts resulting from filtered backprojection reconstruction of data with low count densities.

FDG-PET image analysis

The PET images were evaluated qualitatively (visual inspection). Evaluation was performed separately and independently by two nuclear medicine specialists (Y.N., Y.Y.) blinded to the diagnostic findings from other modalities in three orthogonal planes on the computer monitor. In case of disagreement, the final decision was made by consensus. If regions of FDG accumulation were manifest on the FDG-PET image, the site of each region was evaluated. Hypermetabolic areas, which were more intense than physiologic liver uptake and could not be attributed to structures such as the bladder, ureters, or gastrointestinal tract (which physiologically accumulate FDG), were considered positive for malignancy. For analysis of metastatic tumor, whole-body was divided into 5 regions: liver, lung, bone, peritoneum and distant lymph node.

Final diagnosis

If there was an area with increased FDG accumulation other than that of the known primary lesion, further diagnostic procedures, including MRI, bone scintigraphy, and ultrasonography, were performed. The final diagnosis of FDG-PET findings was made by histological and/or cytological analysis and/or clinical-radiological follow-up. A hypermetabolic FDG lesion was considered true-positive for malignant involvement if proven by histological and/or cytological analysis or if resolved after therapy or progressed on follow-up FDG-PET or other imaging. An FDG-negative CT lesion was considered true-negative if it showed stability in size on conventional imaging follow-up for least 6 months or remained negative on repeated FDG-PET.

Table 1 Details of the clinical data and FDG-PET findings for eighteen patients with distant metastasis in pancreatic cancer

Patient	Age (y)/ Sex	Glucose (mg/dl)	Primary tumor			Metastatic tumor			
			Diagnosis	Tumor diameter (cm)	PET	Site	Method of diagnosis	PET	CT
1	68/M	100	ductal adenocarcinoma	4	TP	Liver	Cl	TP	TP
2	66/F	113	ductal adenocarcinoma	2	TP	Liver	Cl	TP	TP
3	67/M	93	ductal adenocarcinoma	3	TP	Liver	Cl	TP	TP
4	93/F	99	ductal adenocarcinoma	3	TP	Liver	Cl	TP	TP
5	52/M	126	ductal adenocarcinoma	3	TP	Liver	Cl	TP	TP
6	76/M	142	ductal adenocarcinoma	2	TP	Liver	Cl	TP	FN
7	55/M	131	ductal adenocarcinoma	3	TP	Liver	Cl	TP	TP
						Bone	Cl	TP	FN
8	74/M	125	ductal adenocarcinoma	3	TP	Liver	Cl	TP	TP
						Lung	Cl	FN	TP
9	60/F	93	ductal adenocarcinoma	4	TP	Liver	Cl	TP	TP
						Peritoneum	Cl	TP	FN
10	67/M	122	ductal adenocarcinoma	3	TP	Liver	Cl	TP	TP
						Bone	Cl	TP	FN
						Peritoneum	Cl	TP	FN
11	68/F	94	ductal adenocarcinoma	4	TP	Lung	Cl	TP	TP
						Peritoneum	Cl	TP	FN
12	55/M	82	ductal adenocarcinoma	3	TP	Bone	Cl	TP	FN
13	69/M	140	ductal adenocarcinoma	3	TP	Neck lymph node	Cl	TP	FN
14	60/M	137	ductal adenocarcinoma	4	TP	Liver	Cl	FN	TP
15	55/M	142	ductal adenocarcinoma	3	TP	Liver	Cl	FN	TP
16	33/M	120	ductal adenocarcinoma	3	TP	Liver	Cl	FN	TP

TP: true-positive, FN: false-negative, Cy: cytology, Cl: clinical and radiologic follow-up

Table 2 Comparison of FDG-PET and CT for the detection of distant metastasis to 5 sites (liver, lung, bone, peritoneum and distant lymph node) in 42 patients with pancreatic cancer

Parameter	Imaging Method		
	FDG-PET	CT	Chi-square test
Sensitivity	81.8% (18/22)	63.6% (14/22)	$p < 0.05$
Specificity	98.4% (185/188)	97.9% (184/188)	NS
Accuracy	96.7% (203/210)	94.3% (198/210)	NS

NS = Not statistically significant

Numbers in parentheses indicate numbers of patients showing:
true-positive over total (sensitivity);
true-negative over total (specificity);
true-positive plus true-negative over total of both group (accuracy).

Analysis

The results of FDG-PET and CT with respect to the distant metastasis using site by site analysis were compared with the final diagnosis based on findings of histopathology and/or clinical follow-up. The results of FDG-PET and CT for distant metastasis were classified into true positive, true negative, false positive or false negative with respect to the final diagnosis. From these data, the sensitivity, specificity and accuracy of the two methods were calculated. The differences in the results were statistically analyzed using the chi-square test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The mean follow-up time for patients without distant metastases was 249 (range 185–826) days. For the primary pancreatic lesions, the positive rate was 85.7% (36/42) on FDG-PET. Of the 6 negative FDG-PET patients concerning the primary pancreatic cancer, 3 patients had mucinous cystadenocarcinoma (3 cm, 4 cm and 4.5 cm in diameter) and remaining 3 patients had ductal adenocarcinoma (2 cm, 3 cm and 4.5 cm in diameter). The glucose blood levels of these 6 patients were within the normal range (mean 106 mg/dl, range 96–128 mg/dl).

In 16 of the 42 patients with pancreatic cancer, distant metastasis was detected by radiological findings (n = 14) or cytological verification (n = 2). All these 16 patients were positive on FDG-PET for primary pancreatic cancer. The details of clinical data and FDG-PET findings for these patients are listed in Table 1. FDG-PET correctly identified the presence of metastasis in 13 of 16 patients (81.3%) and its absence in 23 of the remaining 26 patients (88.5%). FDG-PET missed 3 liver metastases and 1 lung metastasis. CT imaging missed 8 metastatic sites of 7 patients (peritoneal dissemination and liver, bone and supraclavicular lymph node metastasis), all of which were

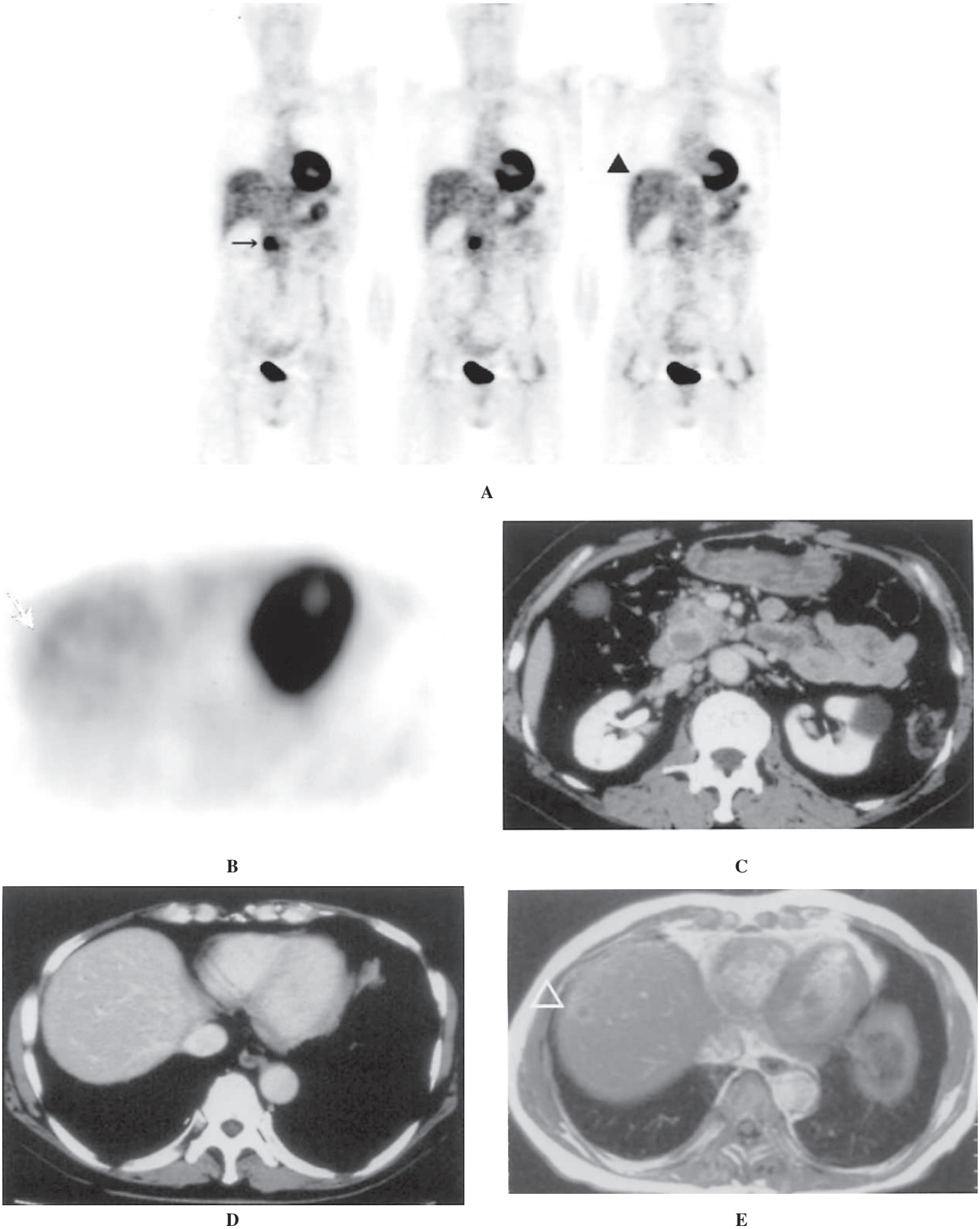
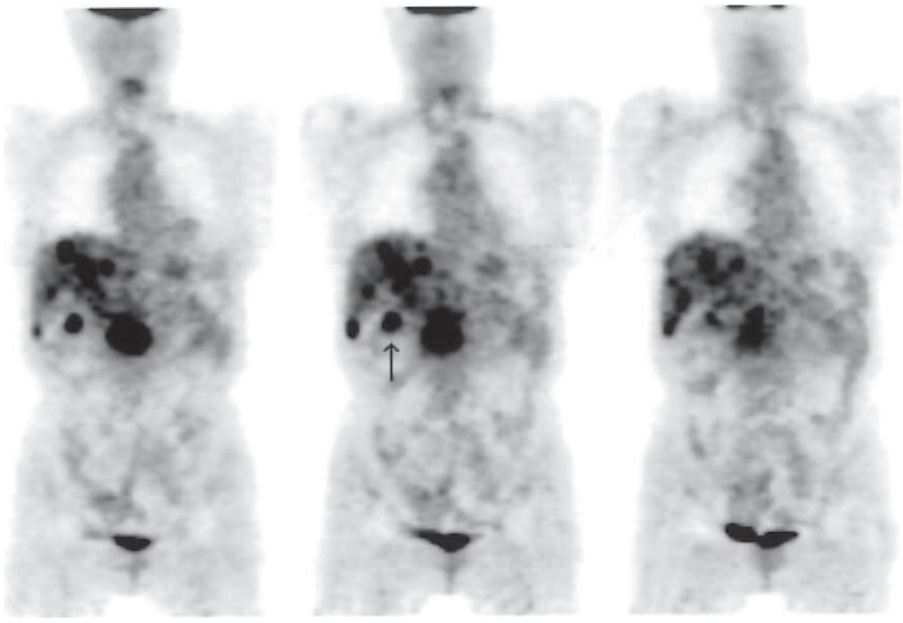


Fig. 1 Coronal (A) and axial (B) FDG-PET, CT (C, D) and MR (E) scans of a 76-year-old male with pancreatic cancer (Patient no. 6 from Table 1). Focal, intense uptake of FDG was found in the pancreatic head portion (*arrow* in A). Small, focal uptake of FDG was found in the liver (*arrowhead* in A, *white arrow* in B). CT image shows the mass shadow at the pancreatic head (C). CT image missed the liver metastasis (D). Postcontrast MR image shows a small metastasis (*white arrowhead*) at the S8 segment of the liver (E).



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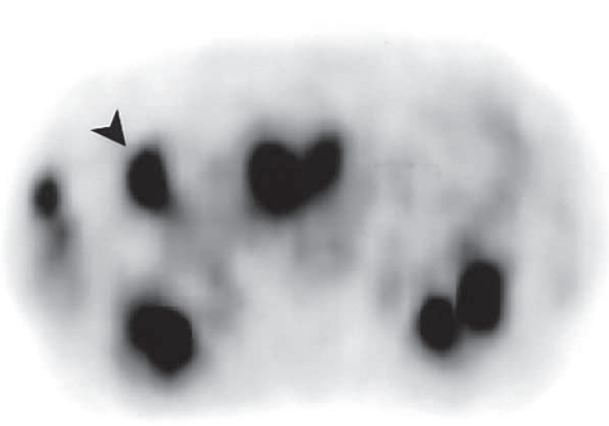

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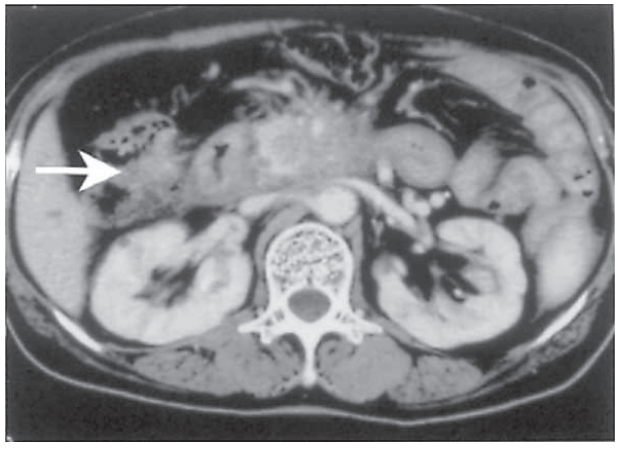

C

Fig. 2 Coronal (A) and axial (B) FDG-PET and CT (C) scans of a 60-year-old female with pancreatic cancer (Patient no. 9 from Table 1). Focal, intense uptake of FDG was found in the pancreatic head portion and multiple focal uptake of FDG was found in the liver (A, B). CT image shows a large mass in the pancreatic head engulfing the celiac axis (C). Focal uptake of FDG was found in the peritoneum (*arrow* in A, *arrowhead* in B), but had been missed on the CT image (*white arrow* in C).

detected by FDG-PET. With a combination of FDG-PET and CT, all metastatic sites were detected. The results of evaluation of the diagnostic value of FDG-PET and CT with respect to distant metastasis to five sites including liver, lung, bone, peritoneum and distant node are shown in Table 2. The sensitivity of FDG-PET was significantly higher than that of CT ($p < 0.05$).

Thirteen of the 16 patients with distant metastasis had liver metastasis and were found to have 39 liver metastatic lesions. Of the lesions 25 were larger than 1 cm, and of these 22 (88%) were positive on FDG-PET. Of the 14 lesions smaller than 1 cm, 7 (50%) were detected by FDG-PET. However, one metastatic liver lesion smaller than 1 cm was positive on FDG-PET but negative on CT in 1 patient. Figure 1 illustrates a small liver metastasis that clearly showed focally increased FDG accumulation. Three lesions of two patients suggested liver metastasis on CT but were true-negative on FDG-PET.

Three patients were found to have bone metastasis and 3 patients peritoneal dissemination. FDG-PET correctly identified the presence of metastasis in all these 6 patients. However, CT imaging failed to show metastatic disease in all these 6 patients. Figure 2 illustrates a patient with liver metastasis and peritoneal dissemination that shows focally increased FDG accumulation at the liver and peritoneum.

Two patients were found to have lung metastasis. FDG-PET results were true-positive in one and false-negative in the other. This false-negative FDG-PET result, which showed true-positive CT result, was a small lung lesion less than 1 cm.

FDG-PET showed false-positive results in 3 patients. Two of these had been suspected to have lung metastasis on FDG-PET, but were confirmed to have pneumonia. In one patient, foci of multiple spotty FDG accumulation were visualized in the abdomen and confirmed to be physiologic intestinal accumulation by clinical follow-up.

Three patients were overstaged and 2 patients were understaged with FDG-PET. Compared with CT, FDG-PET had an impact on patient management in 5 patients. Patient management was altered from curative to palliative in 3 patients (6, 12 and 13 in Table 1) and palliative to curative in 2.

DISCUSSION

Although there are several reports indicating the value of FDG-PET in the diagnosis of pancreatic cancer,[13–15] the diagnostic role of FDG-PET for the detection of distant metastasis in this disease has not been fully evaluated in comparison with CT. The present study indicated that FDG-PET has an additional value, in relation to CT, for evaluation of distant metastasis of pancreatic cancer. FDG-PET could detect the metastatic tumor in 7 patients not found to have malignant tumors on CT and changed the clinical stage in 5 patients (12%). Therefore, patients with proven metastasis after positive PET findings were switched to therapies for disseminated disease. In the detection of distant metastasis, the sensitivity of FDG-PET was significantly higher than that of CT. Because whole body FDG-PET has a high capability to detect most malignancies at any site in the body, it can be used as a reliable diagnostic modality of the staging in patients with pancreatic cancer.

A major problem in the management of pancreatic cancer is that a high proportion of patients are already in an advanced stage of the disease at the time of diagnosis. In a multicenter trial including 330 patients suffering from pancreatic cancer, only 29% of cases were still resectable.[16] In the present study, the accuracy of 94.3% for detecting metastatic disease with CT increased to 96.7% with FDG-PET. To identify unsuspected metastatic lesions, FDG-PET performed better than CT. Routinely performed FDG-PET in the preoperative work-up of these tumors may reduce the number of unnecessary surgical procedures. Furthermore, a combination of FDG-PET and CT increased the accuracy for detecting metastatic disease up to 100% suggesting it to be a more sensitive detection modality.

In the present study, the detection of extrapancreatic spread by FDG-PET showed high sensitivity (81.8%) and specificity (98.4%). One reason for false-negative results on FDG-PET may be lesion size. Three cases of liver metastasis which were not detected by FDG-PET were less than 1 cm in diameter. However, one case of liver metastasis which was also smaller than 1 cm was missed by CT but detected by FDG-PET (Fig. 1). FDG-PET and CT appear to have a complementary role in the detection of liver metastasis. However, there were variations in the contrast-enhanced CT imaging protocol in the present study. The CT examinations were performed using multidetector-row or single scanner. Some patients had portal venous phase contrast-enhanced CT images for detecting liver metastases and others had only equilibrium phase contrast-enhanced CT images. This needs further studies, including systematic method.

On the other hand, FDG-PET could detect peritoneal dissemination which is difficult to detect on anatomic imaging such as CT. Furthermore, initial CT failed to detect bone metastases shown by PET that were later verified by radiological follow-up.

One of the problems encountered in whole body FDG-PET study is nonspecific uptake in the alimentary and urinary tracts.[17] Physiologic colon and ureter uptake is sometimes difficult to differentiate from that observed in pathologic lesions. In the present study, one false-positive case was of physiologic colon uptake. Two other cases were of inflammatory lung uptake. It is well known that FDG accumulates in infectious processes and activated inflammatory cells.[18] Therefore, positive PET findings in patients with concomitant infectious disease and physiologic intestinal uptake should be interpreted with caution.

The liver metastasis of pancreatic cancer with FDG-PET has been discussed in several reports.[6,9] 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. A whole body PET machine may detect unexpected metastasis in the lymph node, lung or bone as well as liver metastasis from pancreatic cancer. Higashi et al.[19] reported that whole body FDG-PET detected distant metastasis or unexpected lesions in about 40% of studied cases.

Despite its high sensitivity and specificity for detection of metastasis, however, FDG-PET as a single modality does not provide sufficient information for cancer staging. Both PET and CT play a complementary role for identification and delineation of metastasis. The recent development of a hybrid PET/CT scanner for the simultaneous acquisition of anatomic (CT) and functional (PET) data may overcome the problems in separate PET and CT imaging for the detection, localization, and characterization of malignant sites in cancer patients.[20]

Based on the results of this study, comparing the results of FDG-PET with CT, we recommend the routine addition of FDG-PET to the preoperative staging of potentially resectable pancreatic cancer. This combined

approach may lead to a marked increase in the detection of distant metastasis. The benefit seems to be even greater for locally advanced tumors, which are more likely to lead to metastasis.

CONCLUSION

Whole body FDG-PET can provide relevant additional information for the detection of distant metastasis in patients with pancreatic cancer although there are false-negative results on FDG-PET. These results suggest that FDG-PET and CT have a complementary role in the detection of distant metastasis in patients with pancreatic cancer.

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