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Optimal scan time for evaluating pancreatic disease with positron emission tomography using F-18-fluorodeoxyglucose

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Objective: Image interpretation in positron emission tomography (PET) using F-18-fluoro-2-deoxy-D-glucose (FDG) is usually performed for images obtained at 1 h postinjection (PI) of FDG, but it remains unknown whether this is the optimal time for imaging patients with pancreatic disease. The aim of this study was to assess the optimal scan time for FDG-PET for patients suspected of having pancreatic cancer. ***Patients and Methods:*** Forty-four patients with suspected pancreatic cancer underwent FDG-PET scans at both 1 h and 2 h PI. Tracer uptake in the pancreatic lesions and possible liver metastasis was interpreted qualitatively, using a 5-point grading system (0 = normal, 1 = probably normal, 2 = equivocal, 3 = probably abnormal, and 4 = definitely abnormal) by 4 nuclear medicine physicians independently, who were blind to all clinical information. Detection performance with each image was compared using receiver operating characteristic (ROC) analysis. An average score of the 4 readers for each patient was also defined as consensus average index (CAI) and compared between the two images. ***Results:*** ROC results indicated no significant differences in detection performance (Averaged areas under ROC curves of 1 h vs. 2 h were 0.92 vs. 0.90 for primary tumor, and 0.81 vs. 0.85 for liver metastases). There were no significant differences in CAIs between 1 h and 2 h PI images in interpreting primary tumor and positive liver metastases, but a significant difference was observed for cases without liver metastases ($p < 0.05$). ***Conclusions:*** The certainty of excluding liver metastases was increased when the 2h image was used, although ROC analysis did not establish a difference between 1 h and 2 h imaging for differentiating malignant and benign lesions in primary pancreatic cancer or its liver metastases.

Key words: FDG, PET, pancreatic cancer, optimal scan time

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) using ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is widely used to evaluate various neoplastic diseases.[1] It is also applicable for pancreatic cancer because of highly expressed glucose transporter-1 in pancreatic cancer cells,[2,3] and there have been many reports describing the feasibility of FDG-PET for patients with pancreatic cancer.[4–7] It is reported to be useful not only in differentiation between pancreatic cancer and mass-forming pancreatitis, but also in the diagnosis of recurrence,[8] monitoring therapeutic effects[9] and predicting prognosis.[10] Although tracer uptake is generally higher in malignant lesions than in benign conditions, it is sometimes difficult to differentiate between them only by the degree of uptake, because some benign conditions like inflammation actively take up

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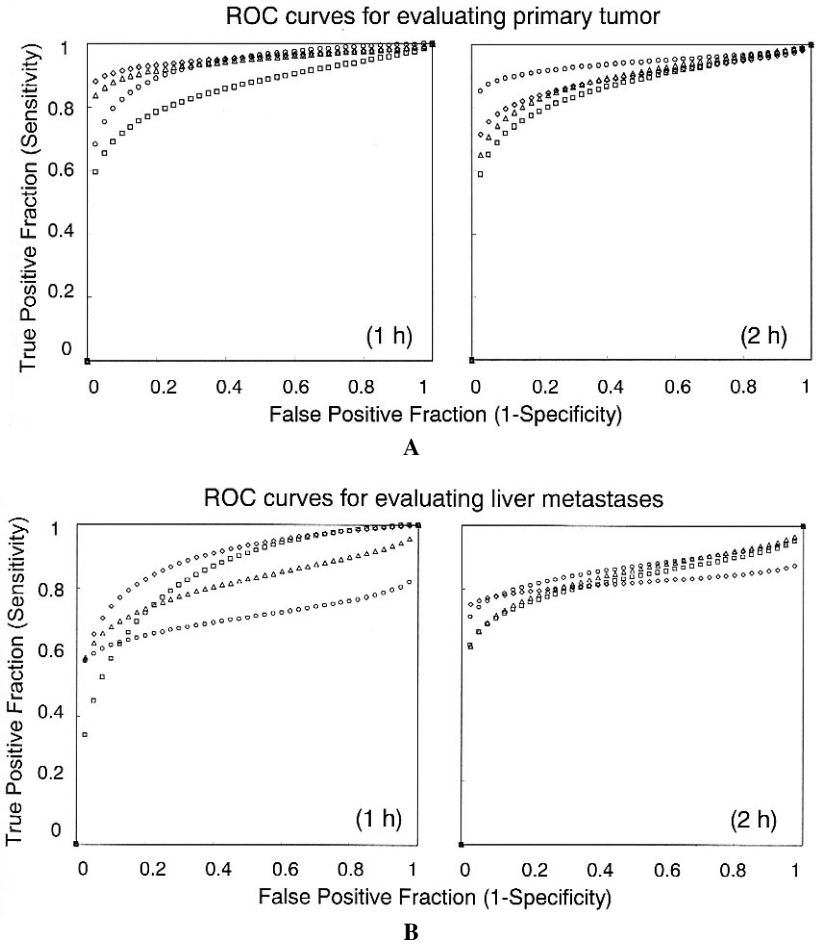

Fig. 1 ROC curves for primary tumor (A) and liver metastases (B) measured for 2 images by four nuclear medicine physicians. There were no significant differences between using 1 h and 2 h postinjection images for diagnosis of primary or metastatic liver tumors. The patterns of the ROC curves from each reader were rather similar to each other in interpreting primary tumor, but there was more variability for images obtained at 1 h than those obtained at 2 h in evaluating liver metastases.

FDG.[11,12]

To date, emission scans have usually been performed approximately 1 h after FDG administration. It remains unclear if this is the optimal timing to image patients. It is known that FDG uptake in most malignant tissues increases with time even after 1 h postinjection (PI), while that in benign lesions decreases with time. We have previously shown the possible usefulness of additional delayed scanning and semiquantitative analysis using a retention index.[13] Other groups have also reported the contribution of delayed scanning in soft tissue tumors, breast cancer, head and neck cancer and lung cancer.[14–17] Most series show that higher tumor-to-background ratios are obtained at scanning times longer than 1 h PI. Although acquisition of delayed images in addition to conventional scanning at 1 h can be helpful to obtain the correct diagnosis, dual time acquisition may be difficult to perform in routine clinical settings because it is a time-consuming procedure. Higher tumor to normal tissue ratios have been shown to give better results with delayed images when quantitative analysis is applied, but little is known about whether or not this would really affect the diagnostic accuracy of visual interpretation, which has been widely performed in many institutes. Our interest was whether a single acquisition of a delayed image at 2 h PI might make visual diagnoses more accurate compared to conventional acquisition at 1 h PI.

The aim of this study was to evaluate the single optimal scanning time for pancreatic disease based on the diagnostic accuracy of visual interpretation of images obtained at 1 h and 2 h PI.

PATIENTS AND METHODS

Patients

The study group comprised 44 patients (28 men and 16 women; mean age, 59.9 yr; age range, 37–81 yr) with suspected malignant tumors in the pancreas. Diagnosis

Table 1 ROC results for four nuclear medicine physicians

	Area under fitted binormal ROC curve (A_z)				
	Observer 1	Observer 2	Observer 3	Observer 4	Mean ± S.D.
For primary tumor					
1 h	0.95 (0.03)	0.94 (0.04)	0.93 (0.04)	0.86 (0.06)	0.92 ± 0.04
2 h	0.89 (0.05)	0.89 (0.05)	0.94 (0.04)	0.86 (0.06)	0.89 ± 0.03
For liver metastasis					
1 h	0.90 (0.06)	0.81 (0.11)	0.71 (0.13)	0.84 (0.71)	0.81 ± 0.08
2 h	0.82 (0.12)	0.84 (0.09)	0.86 (0.11)	0.83 (0.10)	0.84 ± 0.02

ROC: receiver operating characteristic. Values in parentheses are estimates of SE.

Table 2 Jackknife analysis of pooled, multireader ROC results

	A_z (1 h PI)	A_z (2 h PI)	95% CI
Primary tumor	0.92 (0.04)	0.90 (0.05)	[–0.05, 0.10]
Liver metastasis	0.81 (0.08)	0.85 (0.10)	[–0.20, 0.13]

ROC: receiver operating characteristic; A_z: area under ROC crurve of jackknife analysis; PI: postinjection; 95% CI: 95% confidence interval. A_z is reported for each image obtained at 1 h PI and 2 h PI. Values in parentheses are estimates of SE. The 95% CIs are given for estimated difference in A_z (A_z of 1 h PI – A_z of 2 h PI).

Table 3 Consensus average index for each image (Mean ± S.D.)

	1 h PI	2 h PI	p value
For primary tumor			
Malignant cases	3.42 ± 0.97	3.50 ± 1.05	0.230
Benign cases	1.05 ± 1.05	1.39 ± 1.18	0.163
For liver metastasis			
Positive cases	2.93 ± 1.30	2.96 ± 1.46	0.685
Negative cases	1.31 ± 0.83	0.87 ± 0.75	0.012

was confirmed by surgery (n = 32), and clinical follow-up including radiological findings (n = 12). The diseases were as follows: pancreatic cancer (n = 33), including 3 cases of pancreatic mucinous cystadenocarcinoma and 1 case of osteoclast-like giant cell tumor, and chronic pancreatitis (n = 11). Patients with autoimmune-related pancreatitis were excluded from this study, because their diagnosis could be suspected based on clinical data.[18] Before being enrolled in this study, each patient gave written informed consent, as required by the Kyoto University Human Study Committee.

PET imaging

PET was performed with a whole-body PET camera (PCT3600W, Hitachi Medico, Tokyo, Japan) that has 8 rings, which provide 15 tomographic sections at 7-mm intervals. The intrinsic resolution was 4.6 mm full width at half maximum at the center, and the axial resolution was 7 mm at half maximum. The effective resolution after reconstruction was approximately 10 mm. The patients fasted for at least 5 hrs before the FDG injection. The exact position of the pancreatic lesion was determined and marked using ultrasonography prior to PET examination. Each patient was positioned on the PET camera bed and underwent transmission scanning for attenuation correction for about 11 minutes. After the transmission scan was obtained, approximately 370 MBq (10 mCi) of FDG was administered intravenously, and static scanning was performed 1 and 2 hrs later for 12 minutes. Plasma glucose concentration was monitored just before the FDG injection. Image reconstruction was performed by means of a filtered back projection (FBP) algorithm.

Image analysis

Interpretation was performed in random order by 4 experienced nuclear medicine physicians, who were not aware of any of the clinical data. FDG uptake in the pancreas was assessed visually, and the degree of abnormality of FDG accumulation was classified into five grades: 0 = normal, 1 = probably normal, 2 = equivocal, 3 = probably abnormal, and 4 = definitely abnormal. The positivity of a metastasis in the liver was graded using the same 5-point grading scale. The average of the scores of the four nuclear medicine physicians was calculated and was defined as the "consensus average index" (CAI) for each image. Receiver operating characteristic (ROC) analysis was performed in order to compare the difference in the performance of the two images. The ratings for each observer were analyzed using the binormal curve-fitting routine of the CORROC2 program developed at the University of Chicago by Metz et al.[19] The CORROC2 analysis calculated a binormal curve fit, the area under the fitted ROC curve (A_z) and the standard error (SE) of the estimate of A_z for the two images being compared. Jackknife analysis was also used to show reduced bias associated with between-case and between-reader correlations and a reduction in SE of the estimated A_z.[20]

For a semiquantitative index of FDG uptake in tumors, standardized uptake value (SUV), which is decay-corrected tissue activity divided by the injected dose per patient body weight, was calculated. No correction was applied for partial volume effects. The region of interest

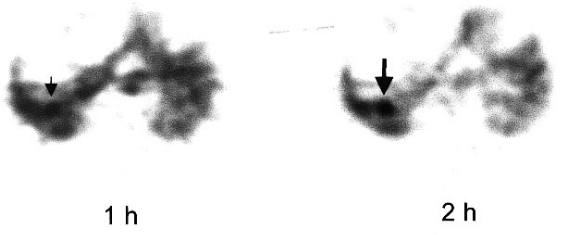

Fig. 2 No readers suspected liver metastasis when they evaluated 1 h images (*left*, CAI = 0.75), but three readers considered the 2 h images positive (*right*, CAI = 3.00). Liver metastasis was confirmed by surgery.

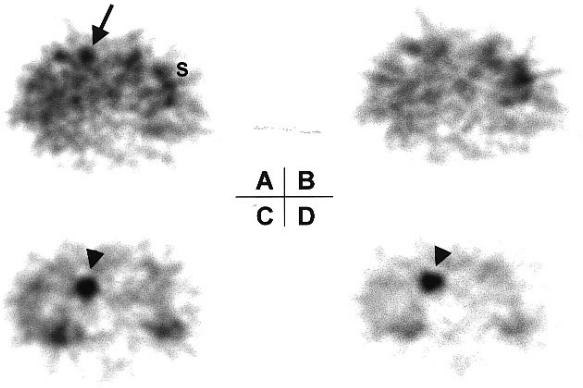

Fig. 3 Two slices of the same level of PET images obtained at 1 h (A, C) and 2 h (B, D) postinjection. For some focal intense uptake, two of the readers suspected liver metastases while the remaining two readers considered the findings equivocal (A, *arrow*, CAI = 2.75). On the other hand, no readers suspected liver metastases in delayed image (B, CAI = 0.75). Main primary tumor located in the pancreatic head was apparent in both images, which were correctly diagnosed by all readers (C, D, *arrowhead*, CAI = 4.0). "S" demonstrates accumulation in the stomach.

(ROI) placed over the tumor was 10 × 10 mm (independent of tumor size) and was placed in tumor areas that showed the highest FDG activity. The SUV of the normal liver was also calculated using a 25 × 25 mm ROI.

RESULTS

Of 44 patients, 33 were diagnosed as having a malignant pancreatic tumor, including 11 with positive metastatic liver diseases. The remaining 11 patients had chronic pancreatitis. The average SUVs of the malignant primary tumors obtained at 1 h and 2 h PI were 5.60 and 6.36, respectively, with this difference statistically significant ($p < 0.001$). In addition, there was no significant difference in average SUVs of the liver metastases between 1 h and 2 h PI (5.42 vs. 5.52), but average tumor-to-normal liver ratios were 2.11 and 2.56, respectively, with this difference statistically significant ($p = 0.015$). The results of the CORROC2 analysis are shown in Table 1, and the fitted curves for each image are illustrated in Figure 1. The average value of area under the curve of the 1 h PI images was higher (0.92) than that of the 2 h PI images (0.89) for evaluating primary tumor, and vice versa (0.81 at 1 h vs. 0.84 at 2 h) for liver metastases. No significant differences between the two images were observed using Jackknife analysis (Table 2). The CAIs for the two images are summarized in Table 3. There were no significant differences between the 1 h and 2 h PI images in interpreting primary tumor and positive liver metastases, but a statistically significant difference was observed for cases without liver metastases ($p < 0.05$).

DISCUSSION

The usefulness of delayed scanning with FDG-PET has been reported for several tumors. In evaluating soft tissue tumors, an SUV measured 4 h PI was reported to be useful as an index of tumor malignancy.[14] In breast cancer, lesion detectability was improved by starting the PET acquisition at 3 h PI.[15] In addition, dual-time point images obtained at 70 min and 98 min were helpful in differentiating malignant lesions from inflammation and normal tissues in head and neck tumors.[16] Recently, Kubota et al. reported that lesion-based sensitivity and patient-based sensitivity in lung cancer were both improved by evaluating delayed images obtained at 2 h PI, compared to 1 h PI.[17] We also reported that additional delayed acquisition at 2 h PI may help to reduce false positive results in evaluating patients with suspected pancreatic cancer.[13] With improved PET devices, the whole body is usually imaged, and qualitative analysis is done in most cases. Scanning the same patient twice may not be always desirable in routine clinical settings. Thus, we compared the diagnostic accuracy of delayed images obtained at 2 h PI with those obtained at 1 h PI to determine which time point is more suitable for examining patients suspected of having pancreatic cancer. An objective index, which we defined as consensus average index (CAI) by calculating a mean value for each image, was used.

The ROC analysis showed that there was no significant difference between 1 h and 2 h images for visually evaluating primary pancreatic tumors and liver metastases, although there was a significant difference in SUVs for both primary tumors and the metastases-to-normal liver ratios. This indicates that pancreatic cancers and their metastatic tumors in the liver have high glucose metabolism, and that it is at 1 h PI that they can be recognized as malignant tumors. However, comparison of the CAIs between the two images showed that we can diagnose negative liver metastasis with more confidence by inter-

preting 2 h PI images. Moreover, the patterns of the ROC curves from each reader were rather similar to each other in interpreting primary tumor, but there was more variability for images obtained at 1 h than those obtained at 2 h in interpreting liver metastases. This finding indicates that the readers tended to interpret primary tumors similarly using either image and also in assessing liver metastases using 2 h images. The expected results could be different if the readers evaluated liver metastases with images obtained at 1 h. In other words, various degrees of physiological uptake in the liver may affect the readers' interpretation.

When we determined a CAI > 2 as being positive, a discrepancy between the two images occurred in 3 cases for primary tumor and 5 cases for liver metastases. There were three cases where a false negative reading was changed to true positive with the 2 h image, with one of these cases shown in Figure 2. These three cases that were correctly diagnosed as positive only with the 2 h PI can probably be explained by reduction of physiological uptake resulting in increased tumor-to-surrounding tissue ratios in the delayed images. Four cases in which true negative metastases were accurately diagnosed only at 2 h were based on reduction of noisy physiological uptake in the liver at 2 h PI. One of these cases is shown in Figure 3. In summary, in these cases, correct diagnoses were made by decreasing FDG uptake in the normal tissue, rather than by increasing activity in the tumors.

There was one case in which accurate diagnosis (chronic pancreatitis) was possible only at 1 h PI. In this case, endoscopic-retrograde pancreatography was performed just 3 days before the PET examination and the serum level of amylase was high. As was previously discussed,[13] severe inflammatory processes can cause more intense uptake in delayed images than in the usual images obtained at 1 h PI. This mechanism resulted in a false positive interpretation of the delayed images in our study.

In this study we evaluated images reconstructed with filtered back projection (FBP). Reconstruction with ordered subsets expectation maximization (OS-EM) has recently become popular as well as other algebraic reconstruction methods, and segmented-attenuation-corrected PET images reconstructed by OS-EM are generally interpreted. Using such techniques, we are able to obtain high quality images with fewer streak artifacts than are frequently seen using reconstructions with FBP. Elimination of these artifacts may reduce the false positive and false negative results of liver metastases in 1 hr PI that were observed in our study. If we had evaluated images reconstructed with OS-EM, the results might have been different.

In conclusion, ROC analysis showed no statistically significant differences in diagnostic accuracy when either 1 h PI or 2 h PI images were interpreted. However, there was a tendency to interpret negative liver metastases with more confidence using delayed images. The sensitivity for diagnosing liver metastases was slightly higher in evaluating 2 h PI images in diabetic patients. If the purpose of the PET scan is to differentiate between malignant and benign tumors, the expected results would not be different. If the purpose is staging, especially evaluating whether or not patients have metastatic disease in the liver, images obtained at 2 h PI would be more easily interpreted.

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