Diagnostic usefulness of FDG PET for pancreatic mass lesions

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The purpose of this study was to investigate the feasibility of $[^{18}F]$2-deoxy-2-fluoro-D-glucose (FDG) positron emission tomography (PET) in patients with a pancreatic mass by comparing the results with those of X-ray computed tomography (CT) and magnetic resonance (MR) imaging. *Methods:* Eighty-six patients with pancreatic lesions, included 65 malignant tumors and 21 benign masses (55 masses were proven histologically and the others were diagnosed clinically), were studied. The diagnostic factors of CT and MR imaging were evaluated, and those of FDG PET were also evaluated for malignant and benign masses by visual interpretation and quantitative interpretation with the standardized uptake value (SUV) and SUVgluc which was designed to reduce the effects of a high blood sugar level. Visual interpretations were evaluated only in FDG PET images, and quantitative interpretations were evaluated by referring to CT and/or MR imaging. The correlation between SUV and the degree of histological differentiation in pancreatic ductal adenocarcinoma was investigated. *Results:* Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for CT imaging were 91, 62, 88, 68 and 84%, and for MR imaging 78, 70, 88, 54 and 76%, respectively. In visual interpretation of FDG PET images, the sensitivity, specificity, PPV, NPV and accuracy were 82, 81, 93, 59 and 81%, respectively. Significant differences between malignant and benign lesions existed in SUV and SUVgluc ($p < 0.0001$, each). With the cutoff value of SUV as 2.1 and SUVgluc as 2.2, the accuracy of diagnosis was maximal. With that cutoff value, the sensitivity, specificity, PPV, NPV and accuracy for SUV were 89, 76, 92, 70 and 86%, and for SUVgluc 91, 76, 92, 73 and 87%, respectively. The sensitivity and NPV of SUVgluc were higher than those of SUV, which suggests that SUVgluc may be more useful in reducing the number of overlooked malignant tumors. The specificity and PPV of FDG PET were superior to those of CT and MR imaging. There were no significant differences between the SUVs of moderately differentiated adenocarcinomas and those of well differentiated adenocarcinomas. *Conclusion:* To improve the diagnostic procedure for classifying masses, FDG PET with not only SUV but also SUV corrected by the blood sugar level is required in addition to morphological diagnosis by CT and/or MR imaging.

Key words: pancreas, FDG PET, blood sugar level, CT, MRI

INTRODUCTION

PANCREATIC CANCERS SHOWING HIGH DEGREES of malignancy have the poorest prognosis, and the rate of death from pancreatic cancer is on the increase in several countries including Japan.[1]

At first, tumor markers and ultrasonography (US) were usually used to detect pancreatic masses, but pancreatic cancers are difficult to diagnose correctly. Recently, imaging methods such as X-ray computed tomography (CT) and magnetic resonance imaging (MRI) are generally used for more detailed examination. But these diagnostic imaging methods cannot always distinguish pancreatic cancers from benign pancreatic masses.

[^{18}F]2-deoxy-2-fluoro-D-glucose (FDG) positron emission tomography (PET) is a new alternative nuclear imaging for the diagnosis of malignant tumors. FDG PET studies can assess glucose metabolic activity in tumors noninvasively. This imaging method is based on the observation that malignant tumors have a higher uptake than the surrounding normal tissue.[2,3] Quantitative measurements in addition to visual interpretations are often performed to obtain objective evaluation. The usefulness of quantitative analysis of FDG PET has been reported in various kinds of tumors including pancreatic cancers.[4]

Patients with pancreatic cancers frequently have hyperglycemia due to pancreatic dysfunction. Because hyperglycemia reduces FDG uptake in malignant lesions, detectability of malignant tumors decreases as a result.[5] For accurate quantitative analysis, it is important to eliminate the influence of hyperglycemia. Diederichs et al. reported that the rate of detection of pancreatic malignancies in patients with blood sugar (BS) levels above 130 mg/dl was lower than that in patients with a BS level below 130 mg/dl.[6]

The purpose of this study was to assess the feasibility of FDG PET in patients with a pancreatic mass by comparing the results with CT and MR images. For clinical diagnosis, determining the most suitable cutoff value that picks up any malignancy was attempted. With this cutoff value, diagnostic factors such as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of FDG PET were investigated. We also investigated the effect of the BS level on FDG accumulation in a pancreatic mass and attempted to correct the underestimation of FDG uptake in patients with BS levels above 130 mg/dl.

MATERIALS AND METHODS

Patients

From October 1993 to July 1999, eighty-six patients (50 males and 36 females; age, 64.0 ± 9.6 years) diagnosed with pancreatic masses by US, CT and/or MR imaging underwent FDG PET prior to treatment. The final diagnosis was 65 pancreatic malignancies and 21 benign pancreatic masses.

Forty-four of the 65 pancreatic malignancies that were histologically proven by open surgery (37 cases) and cytologically proven by ascites or pancreatic juice (7 cases) comprised 39 tubular ductal adenocarcinomas, 4 mucinous cystadenocarcinomas and 1 malignant small round cell tumor. The remaining 21 patients with malignant tumors were diagnosed clinically.

Of the 21 benign pancreatic masses, 11 proven histologically by surgery comprised 4 tumor-forming pancreatitis, 3 pseudocysts, 1 adenoma, 1 serous cystadenoma, 1 mucinous cystadenoma and 1 insulinoma. The ten remaining benign masses were diagnosed clinically as tumor-forming pancreatitis, because there was no change

in mass size, their good clinical course or follow up until at least 12 months later.

Prior to FDG PET studies, all patients were had their BS level measured (normal range: 70–105 mg/dl).

CT Imaging

Dynamic CT scans of the abdomen were performed with a Somatom Plus-S scanner (Siemens, Erlangen, Germany), an X-vigor scanner (Toshiba Medical Systems, Tokyo, Japan), or a High Speed Advantage scanner (General Electric Medical Systems, Milwaukee, WI, U.S.A.). The patients were bolus-administered 80–100 ml of iodinated contrast media intravenously at the rate of 2.5–3.0 ml/sec. Scanning for dynamic study was started at 35–40 sec (early phase), and then 100–120 sec (late phase) after the start of contrast material injection. CT images were judged separately by 3 experienced radiologists blinded to the clinical data, and judgements were decided by the majority. Findings of malignant pancreatic tumors on CT images were as follows: low-attenuating regions on dynamic contrast images and vascular invasion or invasion of contiguous organs.[7] The overall finding on the CT image was judged as a malignancy when the pancreatic mass had more than one of the above findings.

MR Imaging

Thirty-seven of 86 patients that were recent cases underwent MRI of the abdomen by means of a 1.5-T MRI system, a Signa Horizon scanner (General Electric Medical Systems, Milwaukee, WI, U.S.A.), or a Vision scanner (Siemens, Erlangen, Germany). Twenty-seven pancreatic malignant cases detected by MRI comprised 17 tubular ductal adenocarcinomas, 1 mucinous cystadenocarcinoma and 9 clinically diagnosed pancreatic malignancies. Ten benign cases comprised 3 tumor-forming pancreatitis, 1 pseudocyst, 1 adenoma, 1 mucinous cystadenoma and 4 clinically diagnosed benign masses. T1-weighted gradient-echo images (T1WI), fat-suppressed T1-weighted gradient-echo images (T1WI fs), and/or dynamic contrast-enhanced T1-weighted gradient-echo images (dynamic T1WI) were evaluated (TR/TE/flip angle/imaging matrix/field of view: 180/4.2/90°/256 × 192 pixels/340 mm for Signa Horizon and 149/4.1/90°/ 256 × 169/320 mm for Vision). For dynamic study, 8–14 ml of Gadolinium-DTPA as contrast material was injected as a bolus via the cubital vein. MR images were judged separately by 3 experienced radiologists blinded to the clinical data, and judgements were decided by the majority. Findings of malignant pancreatic tumors on MR imaging were indicated as follows: low signal intensity tumor on T1WI (T1WI fs), or dynamic T1WI and vascular invasion or infiltration of peripancreatic tissues.[8] Overall finding on MR imaging was judged as a malignancy when the pancreatic mass had more than one of the above findings.

Table 1 Diagnostic factors of each and overall findings of CT and MR imaging

Diagnostic criteria	CT (n = 86)			MRI (n = 37)			
	low	invasion	overall	low in T1 (fs)	low in dyn.	invasion	overall
Sensitivity (%)	82	68	91	59	80	44	78
Specificity (%)	62	90	62	78	50	90	70
PPV (%)	87	96	88	89	89	92	88
NPV (%)	52	48	68	44	33	38	54
Accuracy (%)	77	73	84	64	75	57	76

PPV: positive predictive value, NPV: negative predictive value, low: low-attenuating regions on dynamic contrast images, invasion: vascular invasion or invasion of contiguous organ, low in T1 (fs): low signal intensity tumor on T1WI or fat-suppressed T1WI, low in dyn.: low signal intensity tumor on dynamic T1WI (Dynamic MR studies were done in 14 patients)

Table 2 Diagnostic factors of FDG PET by visual and quantitative interpretation

Interpretation Judgement of FDG PET	visual (n = 86)	quantitative			
		SUV (n = 86)	SUV (BS ≤ 130) (n = 57)	SUV (BS > 130) (n = 29)	SUVgluc (n = 86)
cutoff value	—	2.1	2.1	2.1	2.2
Sensitivity (%)	82	89	93	81	91
Specificity (%)	81	76	80	67	76
PPV (%)	93	92	93	90	92
NPV (%)	59	70	80	50	73
Accuracy (%)	81	86	90	79	87

PPV: positive predictive value, NPV: negative predictive value, BS: blood sugar level (mg/dl)

FDG PET

FDG was produced with the NKK-Oxford superconducting cyclotron and NKK synthesis system. A HEADTOME IV SET-1400W-10 (Shimadzu Corp., Kyoto, Japan), which has 4 detector rings providing 7 contiguous slices at 13 mm intervals, was employed for the PET studies. The effective spatial resolution was 14 mm in FWHM. The mark for positioning reference to start the scans was primarily set by US on the surface of the body. With this mark, transmission scans were performed for 15 minutes with a ^{68}Ge/^{68}Ga ring source for attenuation correction. Patients were under continual intravenous administration of 185~370 MBq FDG in the fasting condition for at least 4 hours. Emission scans were performed at 40 minutes to 55 minutes after intravenous injection. Reconstruction was done by a filtered-back projection method.

FDG PET Analysis

• Visual Interpretation of FDG PET image

FDG PET images were estimated by visual interpretation without information on CT and/or MR imaging. A region of FDG accumulation that was stronger than the background accumulation was considered to be a malignant pancreatic tumor.

• Quantitative Interpretation of FDG PET image

Regions of interest (ROIs: circles 6 mm in diameter) were placed in the highest FDG accumulation area among suspected pancreatic mass lesions, referring to the CT and/or MR images, and mean standardized uptake values (SUVs) were determined as follows:

$$SUV = \frac{\text{tissue concentration (mCi/g)}}{\text{injected activity (mCi) per body weight (g)}}.$$

"SUVgluc," was corrected by the following method: [SUVgluc = SUV·130/BS (BS > 130 mg/dl), SUVgluc = SUV (BS ≤ 130 mg/dl)].

The nonparametric Mann-Whitney U-test was used to analyze data. A two-tailed p value of less than 0.05 was considered significant.

Histological Analysis of Pancreatic Ductal Adenocarcinoma

In the cases of ductal adenocarcinoma whose degree of differentiation was proven with the "Classification of Pancreatic Carcinoma Japan Pancreatic Society First English Edition (1996)" as a criterion, the correlation between SUV and the degree of histological differentiation in pancreatic carcinoma was investigated.

RESULTS

Diagnostic Factors of CT and MR Imaging

The diagnostic factor of each finding and that of the overall findings on CT images are summarized in Table 1. The finding of "low-attenuating regions on dynamic contrast images" showed higher diagnostic factors than

Table 3 False cases in condition that cutoff value of SUV was set at 2.1

No.	disease	location	SIZE	BS	SUV	SUVgluc	CT	MRI
1	PC	H	40	149	1.30	1.49	M	M
2	PC	BT	25	379	1.47	4.29*	M	M
3	PC	H	20	93	1.74	1.74	M	ND
4	PC	PD	10	101	1.78	1.78	B	B
5	MCAC	B	10	123	1.87	1.87	B	B
6	PC	B	40	201	2.05	3.17*	M	M
7	PC	H	35	236	2.09	3.80*	M	M
8	MCA	H	29	79	2.13	2.13*	M	B
9	TFP	H	20	101	2.14	2.14*	B	B
10	TFP	H	30	361	2.92	8.11	B	B
11	AP + Cy	BT	70	159	3.37	4.12	M	M
12	TFP	H	25	107	3.70	3.70	B	M

(case 1–7, false-negative cases; case 8–12, false-positive cases)

SIZE: tumor size (mm), BS: blood sugar level (mg/d*l*), PC: pancreatic adenocarcinoma, MCAC: mucinous cystadenocarcinoma, MCA: mucinous cystadenoma, TFP: tumor-forming pancreatitis, AP + Cy: acute pancreatitis + pseudocyst, H: pancreatic head, B: pancreatic body, BT: pancreatic body to tail, PD: pancreatic duct, M: malignant, B: benign, ND: not done, *: diagnosed correctly by SUV gluc
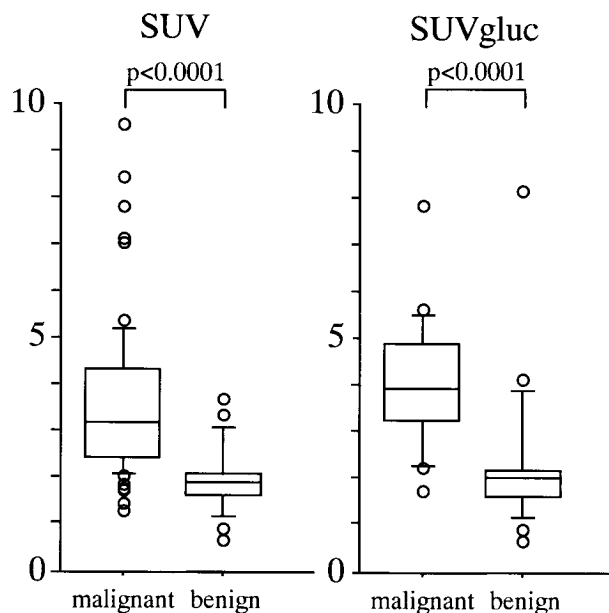

Fig. 1 The distribution of SUVs and SUVglucs of malignant and benign pancreatic lesions. The mean SUV ± S.D. of malignant pancreatic masses was 3.50 ± 1.66, and that of benign ones was 1.91 ± 0.65. And the mean SUVgluc ± S.D. of malignant pancreatic masses was 3.84 ± 1.71, and that of benign ones was 2.27 ± 0.83. Significant statistical differences between SUV and SUVgluc of malignant and benign lesions were seen (p < 0.0001, Mann-Whitney U-test).

Fig. 2 Correlation between SUVs and histological differentiations of tubular ductal adenocarcinoma. P/D: poorly differentiated adenocarcinoma, M/D: moderately differentiated adenocarcinoma, W/D: well differentiated adenocarcinoma. There is no significant difference between SUVs of M/D and those of W/D.

the other CT findings. The sensitivity, specificity, PPV, NPV and accuracy of the overall findings were 91, 62, 88, 68 and 84%, respectively.

The diagnostic factor of each finding and that of the overall findings on MR imaging are summarized in Table 1. The finding of "low signal intensity tumor on dynamic
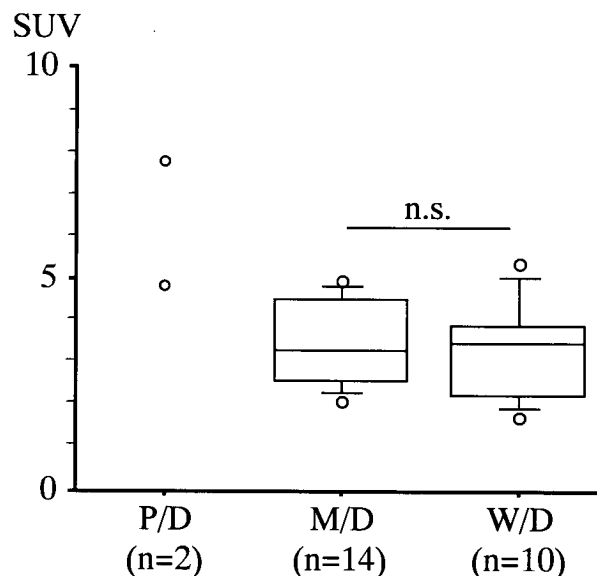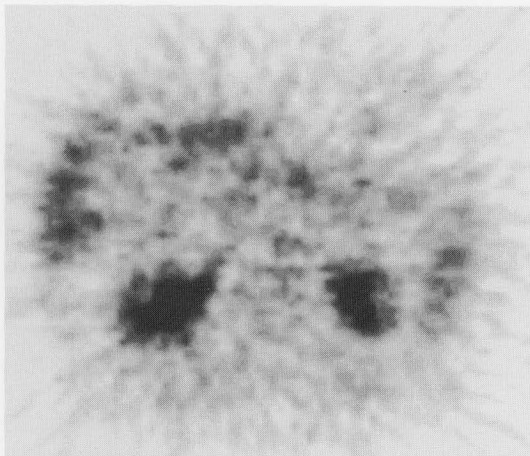
T1WI" showed the highest diagnostic factors among findings in MR imaging. The sensitivity, specificity, PPV, NPV and accuracy of the overall findings were 78, 70, 88, 54 and 76%, respectively.

Visual and Quantitative Interpretation of FDG PET Images

By visual interpretation of FDG PET images, 43 of 65 malignant pancreatic tumors and 17 of 21 benign pancre-
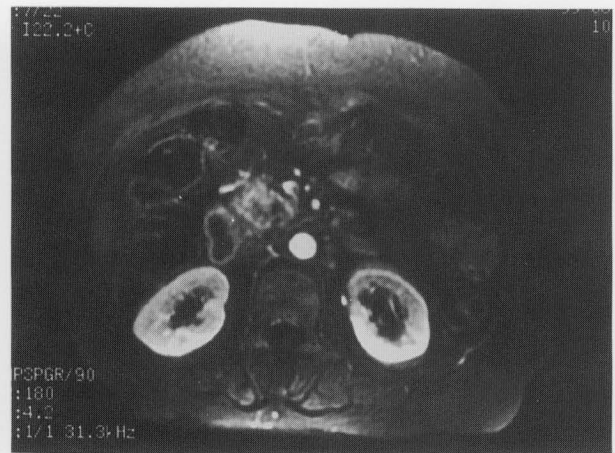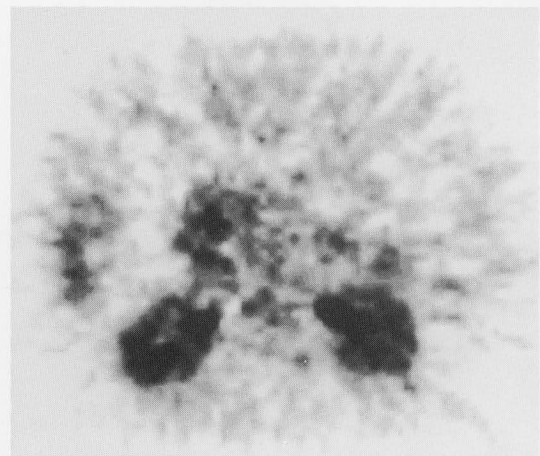
A

A

B

B

Fig. 3 A 69-year-old woman with a pancreatic mass. Dynamic enhanced CT of the abdomen shows the mass lesion in the pancreatic head that shows low density in the early phase (A). On CT imaging the mass is considered to be malignant tumor. However, there is no abnormal high FDG accumulation on FDG PET image, and SUV of that lesion is 1.97, so the mass lesion is considered to be benign mass on FDG PET (B). Histopathological examination by open surgery shows the inflammatory tissue, the mass is finally diagnosed to be tumor-forming pancreatitis.

Fig. 4 A 70-year-old woman with a pancreatic mass. Dynamic contrast-enhanced fat-suppressed T1-weighted spin-echo image of the abdomen shows the mass lesion in the pancreatic head that demonstrates enhanced mass lesion in the early phase (A). On MR imaging the mass is considered to be a benign tumor such as a tumor-forming pancreatitis. However, there is the abnormal high FDG accumulation on FDG PET image, and SUV of that lesion is 2.78, so the mass lesion is considered to be malignant on FDG PET (B). The mass is finally diagnosed to be a pancreatic adenocarcinoma by the cytology of the pancreatic juice.

atic masses were correctly diagnosed. The sensitivity, specificity, PPV, NPV and accuracy of diagnosis with visual analysis of FDG PET images were 82, 81, 93, 59 and 81%, respectively (Table 2).

The distribution of SUV and SUVgluc of pancreatic lesions are shown in Figure 1 as quantitative results. The mean SUV ± S.D. of malignant pancreatic masses was 3.50 ± 1.66, and that of benign pancreatic masses was 1.91 ± 0.65. There was a significant difference between the SUVs of malignant tumors and those of benign masses ($p < 0.0001$). The mean SUVgluc ± S.D. of malignant pancreatic masses was 3.84 ± 1.71, and that of benign pancreatic masses was 2.27 ± 0.83. There was a signifi-

cant difference between SUVglucs of malignant tumors and those of benign masses ($p < 0.0001$). With the cutoff value of SUV at 2.1, the accuracy of diagnosis was maximal at 86%, and the sensitivity, specificity, PPV and NPV were 89, 76, 92 and 70%, respectively (Table 2). With the cutoff value of SUVgluc as 2.2, the accuracy of diagnosis was maximal at 87%, and the sensitivity, specificity, PPV and NPV were 91, 76, 92 and 73%, respectively (Table 2). The sensitivity and NPV of SUVgluc were higher than those of SUV. The diagnostic value of SUV was higher in the patient group with a BS level below 130 mg/dl than

in the all patients, and was lower in the group with a BS level above 130 mg/d*l* than in the all patients (Table 2). The diagnostic value of FDG PET was higher than those of CT and MR imaging.

With the cutoff value of SUV set at 2.1, there were seven false-negative cases and 5 false-positive cases (Table 3). The BS levels of 6 cases (4 false-positive cases and 2 false-negative cases) were above 130 mg/d*l*. In these 12 false cases, SUVgluc diagnosed 5 cases accurately (3 false-positive cases and 2 false-negative cases).

Histological Analysis of Pancreatic Ductal Adenocarcinoma

Twenty-six pancreatic ductal adenocarcinomas whose tissue differentiations were identified comprised 2 cases of poorly differentiated adenocarcinoma, 14 cases of moderately differentiated (m/d) adenocarcinoma and 10 cases of well differentiated (w/d) adenocarcinoma. The mean SUV ± S.D. of m/d adenocarcinoma was 3.40 ± 1.14, and that of w/d adenocarcinoma was 3.49 ± 1.01. No significant difference was observed between SUVs of m/d adenocarcinoma and those of w/d adenocarcinoma (Fig. 2). The mean SUVgluc ± S.D. of m/d adenocarcinoma was 3.55 ± 0.97, and that of w/d adenocarcinoma was 4.20 ± 2.17. And no significant difference was observed between SUVglucs of m/d and w/d adenocarcinoma.

Case Presentation

Two cases in which FDG PET was useful in diagnosis are shown in Figures 3 and 4. Figure 3 shows a case of tumor-forming pancreatitis that was not correctly diagnosed on CT. The case shown in Figure 4 was pancreatic adenocarcinoma that was not correctly diagnosed on MRI.

DISCUSSION

It is considered important to distinguish benign pancreatic lesions from malignant tumors, and the early detection of pancreatic cancers is very important for the improvement of prognosis. Distinction between benign and malignant tumors seems to be possible to some extent with other imaging methods such as CT and MR imaging, but it is difficult to distinguish in some cases, for instance, between tumor-forming pancreatitis and cystic pancreatic masses.[9,10]

There are great variations in the effects on diagnosis reported in the literature on CT and MR imaging: accuracy of findings on CT imaging ranges from 67 to 77%, and that of findings on MR imaging ranges from 70 to 87%.[7,11,12] In this study, the accuracy on CT imaging was slightly higher, and that on MR imaging was comparable. The sensitivity, NPV and accuracy of MRI were lower than those of CT in our cases, which may reflect differences between the cases judged by CT and MR imaging in the population and characteristics.

In the field of nuclear medicine, the diagnosis of pancreatic tumors with a variety of radionuclide pharmaceuticals has already been evaluated, it is reported that FDG PET is more useful in diagnosis than other radioisotopic pharmaceuticals thus far employed.[13–16]

In this study, visual interpretation of FDG PET images had lower sensitivity, NPV and accuracy than those of CT images. Actually, CT and/or MR imaging were performed prior to FDG PET, so that only the visual interpretation of FDG PET images was not suitable for clinical use. For that reason, other imaging methods such as CT should be referred to in evaluating FDG PET images.

The cutoff value of SUV was determined to be 2.1 because the accuracy of SUV was the highest. When the cutoff value of SUV was set at 2.1, accuracy was highest at 86% and sensitivity and specificity were 89, 76%, respectively. In other studies, accuracy with SUV was reported to be 82% to 93%.[17–19] Our accuracy is comparable to those reported by others. The cutoff value reported in other studies ranged widely from 1.53 to 3.5, although it is around 2 in many studies.[17–19] This wide distribution may be related to the type of instrument adopted, the waiting time between intravenous injection and emission scan and how ROI was placed, as well as whether the values employed were the mean or maximal SUV of the ROI. Specificity, PPV, NPV and accuracy with SUV are higher than those with CT and MR imaging, especially regarding PPV and NPV. We recommend that the tumor site should be identified first with CT and/or MR imaging, followed by FDG PET to distinguish between benign and malignant tumors.

Diagnostic effects with the SUV decreased in the patient group with a BS level above 130 mg/d*l*; in the patient group with a BS level under 130 mg/d*l*, in contrast, they were better than those of the SUV in all patients. Diederichs et al. reported that high plasma glucose reduced FDG uptake and the rate of detection of pancreatic malignancies.[6] It was also confirmed in our results that the diagnostic factors of FDG PET were less satisfactory for patients with hyperglycemia.

Langen et al. designed "Modified SUV" to reduce the effect of the BS level, but, there are no reports indicating that the diagnostic effects of "modified SUV" exceed those obtained with SUV.[20,21] The "modified SUV" was adapted for all patients, so that the SUV of malignant tumors in the patient group with a normal BS level decreased, and the number of false negative cases increased. Diederichs et al. reported that the detection rate of pancreatic malignancies in patients with BS levels above 130 mg/d*l* was lower than that in patients with BS levels below 130 mg/d*l*.[6] Based on this report, the standard BS level of 130 mg/d*l* was employed for correcting SUV in our study. We designed SUVgluc, which was modified from an equation for their "modified SUV," to reduce the effect of the BS level further. When the cutoff value of SUVgluc was 2.2, the sensitivity, NPV and

accuracy with SUVgluc were better than with SUV, which suggests that SUVgluc may be more useful in regard to reducing overlooked malignant tumors. We therefore considered the adjustment by the BS level with SUVgluc to be useful.

With a cutoff value of SUV as 2.1, there were 12 false cases, comprising 7 false negative cases and 5 false positive cases. Most false negative cases were composed of pancreatic carcinomas with hyperglycemia and most false positive cases were tumor-forming pancreatitis. Such false cases have been mentioned in other reports.[17,18,21] Four of the false negative cases presented hyperglycemia, and SUVgluc correctly diagnosed three of them, but SUVgluc did not correctly diagnose other false negative cases, and it was necessary to discuss a more suitable method to correct the SUV. Furthermore, many small masses should be false negative because of lower FDG accumulations conducted by partial volume effects.[22] Indeed, tumor size was under 10 mm in diameter in 2 false-negative cases. The diagnostic effects are expected to be improved by excluding partial volume effects from FDG accumulation in small masses. Three false-positive cases cannot be correctly diagnosed by SUVgluc, and those SUVs were above 2.9. False-positive cases may have been caused by increased FDG accumulation in the presence of localized inflammation within the pancreas.[9] It is necessary to consider symptoms and the clinical course in distinguishing benign pancreatic lesions from malignant tumors.

Our examination of the degree of histological differentiation revealed no difference between w/d adenocarcinoma and m/d adenocarcinoma in the SUV. A correlation has been reported between the proliferative index and FDG uptake in head and neck tumors, even though there is no relationship between the degree of histological differentiation and the SUV.[23]

Recently, the delayed image which was obtained during the glycolysis plateau phase 90–120 min after injection of the tracer was reported to be useful for the differentiation between malignant and benign pancreatic masses.[24] Glucose transporter-1 (GLUT-1) was also reported to be related closely to FDG accumulation in pancreatic tumor FDG PET.[25] A further increase in diagnostic effects in distinguishing benign from malignant lesions is expected with the use of new methods and appropriate pharmaceuticals.

In this study, diagnosis by means of FDG PET was superior to that using CT or MR imaging. In conclusion, FDG PET with not only SUV but also SUV corrected by the BS level should be required in cases in which it is difficult to diagnose between benign and malignant lesions by comparing CT and/or MR images.

ACKNOWLEDGMENT

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