to the data from each observer and to compare Az for each pair using a univariate z-score test (14).

RESULTS

Diagnostic Accuracy of Each Observer

A summary of ROC curves obtained from interpretation in Step 1 using PET alone is shown in Fig. 1. Az values did not differ significantly between the six observers for each step. The means and dispersion of sensitivity, specificity, PPV and Az are shown in Table 1. Although Az values did not differ significantly, sensitivity, specificity and PPV varied widely between the observers.

Effect of Reference to CT on Diagnostic Accuracy

The mean specificity increased significantly when observers referred to CT ($P < 0.05$), although sensitivity, PPV and Az did not change significantly (Table 1).

Variability in Interpretation

The mean κ value and the strength of inter-observer agreement for each step are shown in Table 2. Inter-observer agreement for all lesions in each step was moderate ($\kappa = 0.58$ for Step 1; $\kappa = 0.55$ for Step 2; and $\kappa = 0.53$ for Step 3).

Inter-observer agreement was higher for 'Cancer' and 'Not malignant' lesions than for 'Normal' lesions for each step (moderate versus fair).

Although the κ values for each group in Step 1 were higher than those in Steps 2 and 3, the differences were not statistically significant. The κ values of 'Cancer' and 'Not malignant' lesions in Step 2 were higher than those in Step 3; however, the differences were not statistically significant.

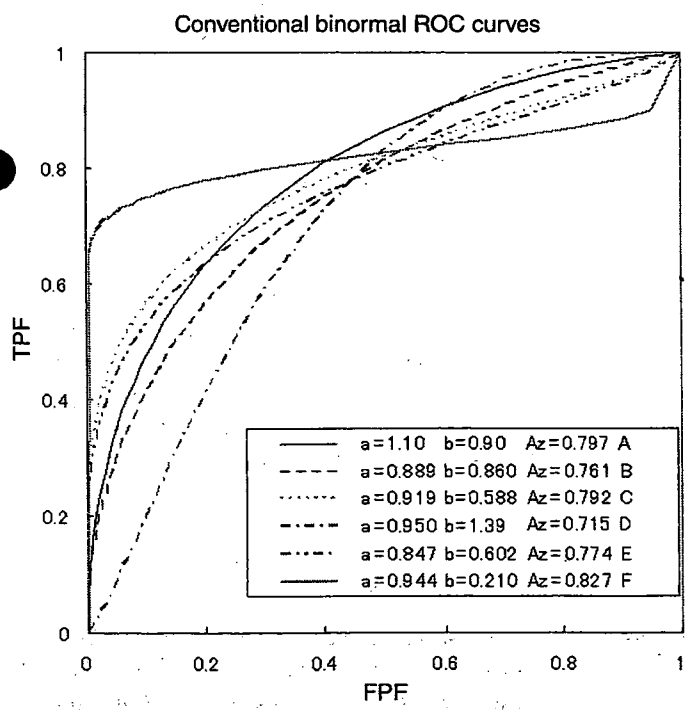

Figure 1. Summary receiver-operating characteristic curves obtained from interpretation in Step 1 of evaluations with positron emission tomography alone (please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org). TPF, true positive fraction; FPF, false positive fraction.

Patterns of FDG Uptake with Poor Agreement

In assessing inter-observer agreement for each organ, we determined the organs that were interpreted with difficultly by PET alone. The numbers of sites presenting poor or good agreement in each organ for the 68 lesions in Step 1 using PET alone are shown in Tables 3–5. Lesions for which fewer than five observers agreed in diagnosis were considered as poor agreement, while lesions for which five or six observers agreed in diagnosis were considered as good agreement.

FDG uptakes in the 'Normal' 32 true negative lesions that presented poor agreement included nine physiological uptakes in the larynx, mediastinum, intestine and ovary, and four benign lesions in the thyroid, neck, lung and uterus (Table 3). The case with physiological FDG uptake in the ascending colon is shown in Fig. 2.

FDG uptakes in the 18 'Cancer' true positive lesions that presented poor agreement included 10 malignant lesions in the thyroid, hilum, breast, colon and stomach (Table 4).

FDG uptakes in the 18 'Not malignant' false negative lesions that presented poor agreement included eight benign lesions in the thyroid, lung, colon and joint, and four physiological uptakes in the hilum, intestine and ovary (Table 5).

DISCUSSION

Diagnostic Accuracy of Each Observer

We assessed observer accuracy using the scores representing a rating on the likelihood of malignancy for 68 lesions by each observer. No significant differences were identified for any step in Az of the six observers. Wide variation in sensitivity, specificity and PPV detected between observers was caused by differing decision thresholds during interpretation. Selection of different thresholds does not cause Az to vary, as an ROC curve depicts all of the tradeoffs available as the threshold is varied. Therefore, variability of the decision threshold between observers exists where no significant differences were identified in diagnostic accuracy as quantified with Az. That is, the scores given for each lesion could vary between the six observers even though there were no significant differences in diagnostic accuracy indicated by Az.

Table 1. Mean (range of six observers) sensitivity, specificity, PPV and Az of FDG-PET cancer screening based on lesions

	Step 1	Step 2	Step 3
	PET alone	PET + CT	PET + CT + Other information
Sensitivity	78.7 (72.2–83.3)	75.9 (66.7–83.3)	72.2 (61.1–83.3)
Specificity	64.7* (58.0–74.0)	71.3* (64.0–78.0)	74.0* (66.0–82.0)
PPV	44.9 (41.7–51.9)	49.2 (41.9–57.7)	50.6 (39.3–60.9)
Az**	0.778 (0.715–0.827)	0.788 (0.718–0.851)	0.794 (0.704–0.848)

PET, positron emission tomography; CT, computed tomography; PPV, positive predictive value.
*Mean specificity of PET + CT and PET + CT + Other information was higher than that of PET alone (Wilcoxon matched pairs signed rank sum test, $P < 0.05$).
**Az, area under curve in ROC.

Table 2. Mean κ value and strength of inter-observer agreement for the likelihood of malignancy of 68 FDG-avid lesions in 40 cases

		Step 1	Step 2	Step 3
		PET alone	PET + CT	PET + CT + Other information
Total lesions ($n = 68$)	κ	0.58	0.55	0.53
	Agreement	Moderate	Moderate	Moderate
'Normal' ($n = 32$)	κ	0.30	0.28	0.28
	Agreement	Fair	Fair	Fair
'Cancer' ($n = 18$)	κ	0.57	0.44	0.42
	Agreement	Moderate	Moderate	Moderate
'Not malignant' ($n = 18$)	κ	0.51	0.46	0.41
	Agreement	Moderate	Moderate	Moderate

FDG, 2-(fluorine 18) fluoro-2 deoxy-D-glucose.
κ value <0, poor; 0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect.
'Normal': 32 true negative lesions that were not suspected malignant in FDG-PET cancer screening and were confirmed as physiological uptakes or benign lesions after 1 year.
'Cancer': 18 true positive lesions that were suspected malignant in FDG-PET screening and were later diagnosed as malignant lesions.
'Not malignant': 18 false positive lesions that were suspected malignant in FDG-PET screening and were later diagnosed as benign lesions or physiological uptakes.

Effect of Reference to CT on Diagnostic Accuracy

We defined sensitivity as the proportion of malignancies given a rating of 3–5 and specificity as the fraction of benign lesions or physiological FDG uptakes given a rating of 1–2. This classification has critical meaning, therefore, Az has less value when comparing test performance between Steps 1 to 3. The mean specificity increased significantly in this study when observers referred to CT. Chen et al. also reported that additional CT for localization and lesion characterization showed an increased specificity of PET for cancer screening in asymptomatic individuals (4). In the present study, however, mean sensitivity and PPV did not change significantly when observers referred to CT. Several investigators report that the combination of FDG-PET and CT significantly improves diagnostic accuracy in the diagnosis of malignancy (15–17). The fact that the present results demonstrate no improvement in sensitivity and PPV may be due to selection bias: the present study did not include false negative lesions of PET that are recognized in CT. Sensitivity on general FDG-PET screening may be improved when observers refer to CT, given the inclusion of CT positive lesions that are without remarkable FDG uptakes such as bronchioloalveolar lung carcinoma (18).

Variability in Interpretation

We assessed inter-observer agreement on the scores for likelihood of malignancy (1–5 points) in 68 lesions. The 68 lesions that presented varying intensities of FDG uptake were founded in whole-body FDG-PET performed for cancer screening of 40 asymptomatic individuals.

Inter-observer agreement for all lesions in each step was moderate. Berg et al. reported that inter-observer agreement

Table 3. Agreement in each site of 'Normal' 32 true negative lesions in Step 1 using PET alone

Sites	Diagnosis	No. of sites	No. of each agreement	
			Poor**	Good***
Larynx	Physiological*	2	2	0
Oral cavity	Physiological	4	0	4
Mediustinum	Physiological	2	1	1
Epigastrium	Physiological	5	0	5
Intestine	Physiological	6	4	2
Ovary	Physiological	1	1	0
Uterus	Physiological	1	0	1
Prostate	Physiological	2	0	2
Ureter	Physiological	1	0	1
Thyroid	Thyroadenitis	1	1	0
Neck	Lymphadenopathy	1	1	0
Lung	Pneumonia	2	1	1
Rib	Fracture	1	0	1
Shoulder	Arthritis	1	0	1
Liver	Cyst	1	0	1
Uterus	Myoma	1	1	0
Total		32	12	20

*Physiological: physiological FDG uptake.
**Poor: fewer than five observers agreed in diagnosis.
***Good: five or six observers agreed in diagnosis.

Table 4. Agreement in each site of the 18 'Cancer' true positive lesions in Step 1 using PET alone

Sites	Diagnosis	No. of sites	No. of each agreement	
			Poor	Good
Thyroid	Thyroid Cancer	3	3	0
Lung	Lung Cancer	2	0	2
Hilum	LN metastasis or lung cancer	2	2	0
Breast	Breast cancer	2	1	1
Colon	Colon cancer	2	2	0
Stomach	Gastric cancer	2	2	0
Pancreas	Pancreas cancer	1	0	1
Subclavicular	Lymphoma	1	0	1
Mediustinum	Lymphoma	1	0	1
Paraaorta	Lymphoma	1	0	1
Mesenterium	Lymphoma	1	0	1
Total		18	10	8

LN metastasis, lymph node metastasis.

among radiologists on mammogram screening after training in Breast Imaging Reporting and Data System was moderate (9). Our results suggest that interpretation of FDG-PET in cancer screening is adequately reproducible as a whole.

Inter-observer agreement for all lesions at each step was moderate, compared to fair agreement for 'Normal' subjects. The higher prevalence of malignant lesions (18/68) means that the set used in this study was not strictly representative of FDG-PET within the general screening population. Inter-observer agreement on general FDG-PET screening might normally be lower, given the inclusion of a larger number of normal healthy subjects. Low inter-observer agreement may cause the marked variability in recall rate among the institutions that perform screening FDG-PET.

Inter-observer agreement was lower for 'Normal' lesions than for 'Cancer' and 'Not malignant' lesions for each step (fair versus moderate). Since sensitivity are calculated based on the data for 'Cancer' and specificity are based on those for 'Not malignant' and 'Normal', inter-observer variation observed for 'Cancer' and 'Not malignant and Normal' are corresponding to variability in sensitivity and specificity between observers (58.0–74.0, 72.2–83.3 in Step 1, respectively).

Inter-observer agreement decreased when observers referred to CT, however, the differences were not statistically

Table 5. Agreement in each site of the 18 'Not malignant' false positive lesions in Step 1 using PET alone

Sites	Diagnosis	No. of sites	No. of each agreement	
			Poor	Good
Thyroid	Goiter or thyroadenitis	3	2	1
Parotid gland	Warthin tumor	1	0	1
Lung	Pneumonia or pleural tumor	4	2	2
Sternoclavicular joint	Arthritis	1	1	0
Colon	Adenoma or polyp	4	3	1
Hilum	Physiological	1	1	0
Intestine	Physiological	1	1	0
Stomach	Physiological	1	0	1
Ovary	Physiological	2	2	0
Total		18	12	6

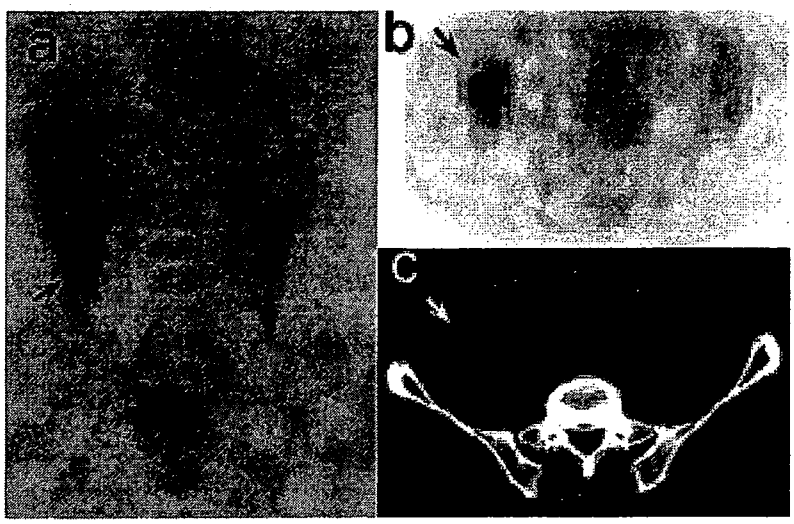

Figure 2. Physiological 2-(fluorine 18) fluoro-2 deoxy-D-glucose uptake in the intestine of 'Normal' subjects that presented poor agreement: a 54-year-old male. (a) Coronal and (b) transaxial FDG-PET image revealed focal uptake in the ascending colon (arrow). (c) The corresponding lesion was not demonstrated on CT. CT, computed tomography.

significant. Although side-by-side reading of PET and CT improves lesion localization and supports lesion characterization, correlative interpretation of PET and CT differed between observers. Metser et al. concluded that in-line PET/CT offers better lesion localization relative to visual fusion of PET and CT, especially for small lymph nodes, lesions adjacent to mobile organs and lesions adjacent to the chest or abdominal wall (19). Syed et al. reported that PET/CT increases inter-observer agreement and confidence in disease localization of FDG-avid lesions in patients with head and neck cancers (20). By precisely localizing FDG uptakes, interpretation of image fusion by integrated PET/CT might offer higher inter-observer agreement in comparison to interpretation of PET images alone or side-by-side interpretation of PET and CT images.

Although inter-observer agreement of 'Cancer' and 'Not malignant' lesions decreased when observers referred to other information, the differences were not statistically significant. In cancer screening, positive lesions are eventually recommended for diagnostic work-up or observation with close follow-up. The clinical recommendation is determined by evaluation of the PET and CT findings with reference to past history, smoking and drinking habits, and results of other screening tests. Correlative interpretation of PET, CT and other information may need to be standardized to achieve greater agreement in subjects with suspected cancer by FDG-PET.

Patterns of FDG Uptake with Poor Agreement

We evaluated the organs that were most difficult to interpret by PET alone. Some observers tended to over-diagnose FDG uptake to avoid potential false negative outcome, while others did not pick up suspected lesions in 'Normal' subjects. Physiological FDG uptake is recognized at various sites in various degrees. A focal intense uptake in intestine mimics FDG uptake of colon tumor as shown in Fig. 1. Reporting criteria for various patterns of FDG uptakes in intestine differed between observers. For higher agreement on results for the 'Normal' 32 true negative lesions in FDG-PET, interpretation of physiological FDG uptake for the larynx, mediastinum, intestine and ovary should be standardized.

Various FDG uptakes in goiter, pneumonia, colon adenoma and arthritis confound image interpretation of FDG-PET and act to reduce inter-observer agreement. Interpretation of FDG-avid lesions in the thyroid, lung, hilum, breast, colon, stomach and ovary may require standardization for higher agreement in 'Cancer' and 'Not malignant' subjects.

CONCLUSIONS

Our results suggest that interpretation of FDG-PET in cancer screening is adequately reproducible, whereas interpretation of physiological FDG uptake in 'Normal' subjects is less reproducible. Improvement of inter-observer variability in assessing physiological FDG uptakes requires universal reporting criteria in FDG-PET. Furthermore, correlative interpretation of PET, CT and other information may require standardization in subjects with suspected cancer by FDG-PET.

Acknowledgments

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Conflict of interest statement

None declared.

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SHORT COMMUNICATION

FDG-PET of patients with suspected renal failure: standardized uptake values in normal tissues

Ryogo Minamimoto · Nobukazu Takahashi · Tomio Inoue

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Abstract
Objective This study aims to clarify the effect of renal function on 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging and determine the clinical significance of renal function in this setting. We compared FDG distribution between normal volunteers and patients with suspected renal failure.
Methods Twenty healthy volunteers and 20 patients with suspected renal failure who underwent FDG-PET between November 2002 and May 2005 were selected for this study. We define "patients with suspected renal failure" as having a blood serum creatinine level in excess of 1.1 mg/dl. The serum creatinine level was examined once in 2 weeks of the FDG-PET study. Regions of interest were placed over 15 regions for semi-quantitative analysis: the white matter, cortex, both upper lung fields, both middle lung fields, both lower lung fields, mediastinum, myocardium of the left ventricle, the left atrium as a cardiac blood pool, central region of the right lobe of the liver, left kidney, and both femoris muscles.
Results The mean standardized uptake values (SUVs) of brain cortex and white matter were higher in healthy volunteers than in renal patients. The mean SUVs of the mediastinum at the level of the aortic arch and left atrium as a cardiac blood pool were lower in healthy volunteers than in patients with suspected renal failure. These regions differed between healthy volunteers and patients with suspected renal failure ($P < 0.05$).
Conclusions We found decreasing brain accumulation and increasing blood pool accumulation of FDG in patients with high plasma creatinine. Although the difference is small, this phenomenon will not have a huge effect on the assessment of FDG-PET imaging in patients with suspected renal failure.

Keywords FDG-PET · Renal failure · Serum creatinine · Standardized uptake value

Introduction

2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scanning is used in the evaluation of patients with tumors and with brain disease [1]. FDG is the most common radiopharmaceutical material in clinical use because of its high sensitivity and specificity. FDG is an analog of glucose in which the hydroxyl group in the 2 position has been replaced with a fluorine atom. Glucose is almost completely reabsorbed from the tubules [2]. Unlike glucose, FDG is excreted through the urine. It is unknown whether the distribution of FDG in a patient with suspected renal failure differs from that of healthy volunteers. The purpose of this study is to clarify the effect of renal function on FDG-PET imaging and to determine the clinical significance of renal function in this setting. We compare distributions and consider whether the distribution of FDG in normal tissue indicates a change in the state of renal dysfunction, and whether information regarding renal function is necessary for diagnosis using FDG-PET.

R. Minamimoto (✉) · N. Takahashi · T. Inoue
Department of Radiology, Graduate School of Medicine, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan
e-mail: t046047b@yokohama-cu.ac.jp

Materials and methods

The preparation of radiopharmaceuticals and whole-body PET study of FDG uptake were carried out using a modified method based on that of Hamacher et al. [3]. PET images were gained by a SET 2400 W machine (Shimadzu, Kyoto, Japan) equipped with 59.5 cm and 20.0 cm transverse fields of view; 63 image planes were produced with a 3.125-mm interval between images. Transverse resolution at the center of the field of view was 4.2 mm, and the full width at half-maximum was 5.0 mm. A whole-body image was obtained 60 min after the injection of 210–360 MBq of FDG using the multiple-bed position technique. Attenuation-corrected transverse images were reconstructed with the ordered-subsets expectation maximization algorithm into 128 × 128 matrices with pixel dimensions of 4.0 mm in plane and 3.125 mm axially. Coronal images with 9.8-mm section thickness were also reconstructed from attenuation-corrected transverse images or visual interpretation.

Patients and healthy volunteers

Twenty healthy volunteers and the 20 patients with suspected renal failure who underwent FDG-PET between November 2002 and May 2005 were selected for this study. We define "patients with suspected renal failure" as those patients having a blood serum creatinine level in excess of 1.1 mg/dl. The serum creatinine was measured using the Roche enzymatic method. The normal range for serum creatinine in our facility is 0.36–1.04 mg/dl. The serum creatinine level was examined once within 2 weeks of the FDG-PET study. All patients had stable renal function for at least 6 months, were not undergoing dialysis, and were without a history of muscle disease, collagen disease, or diabetes mellitus. Serum electrolytes were within the respective normal ranges. The 20 patients with suspected renal failure consisted of 16 men and 4 women; their mean age was 69.3 ± 9.4, average body weight was 57.0 ± 8.0 kg, average height was 162.9 ± 7.4 cm, and average glucose level was 91.8 ± 15.8 mg/dl. The patients were suspected of having malignancy: pancreas cancer (n = 4), cancer of unknown origin (n = 4), colon cancer (n = 3), laryngeal cancer (n = 3), malignant lymphoma (n = 2), lung cancer (n = 1), esophagus cancer (n = 1), bile duct cancer (n = 1), and renal cell cancer (n = 1). Of the 20 patients with suspected renal failure, ten patients showed abnormal uptakes of FDG on malignancy, whereas the other ten did not show abnormal uptake. The 20 healthy volunteers consisted of 12 men and 8 women; their mean age was 58.2 ± 4.8, average body weight was 62.0 kg ± 10.7 kg, average height was 164.8 cm ± 10.1 cm, and average glucose level was 91.9 mg/dl ± 17.4 mg/dl. Blood glucose level was tested immediately prior to injection of FDG; all volunteers and patients had levels <136 mg/dl, which had no effect on the distribution of FDG-PET imaging [4]. The 20 healthy volunteers were assessed to produce baseline data that were compared with the FDG-PET results of the patients with high serum creatinine levels who were suspected of having renal failure. All healthy volunteers were confirmed to have no disease 2 years following FDG-PET. Informed consent was obtained from all patients.

Semi-quantitative analysis

We produced standardized uptake value (SUV) functional images using attenuation-corrected transverse images, injected doses of FDG, body weight, and cross-calibration factors between the PET scanner and the dose calibrator. Mean SUV was defined as follows: SUV = conc/dose/wt. "Conc" is the radioactive concentration in tissue or a lesion in MBq per gram, "dose" is the injected dose in MBq, and "wt" is the patient's body weight in grams. For semi-quantitative analysis, regions of interest (ROIs) were placed over 15 regions: the white matter (70 pixels) and cortex (190–301 pixels) at the level of the centrum semiovale, both upper lung fields at the aortic arch level (111 pixels), both middle lung fields at the carinal level (111 pixels), both lower lung fields (111 pixels), mediastinum at the aortic arch level (70 pixels), myocardium of the left ventricle (22 pixels), left atrium as a cardiac blood pool (70 pixels), central region of the right lobe of the liver (111 pixels), left kidney (79–195 pixels), and both femoris muscles (111 pixels). ROIs for the left kidney were placed on the coronal image showing the maximal kidney size. ROIs for other organs were placed on transverse PET images. We used the ROI placement method for white matter and cortex reported by Delbeke et al. [5]. The ROI placement method for other organs was that used by Paquet et al. [6]. We excluded organ regions from the study if we considered that the ROIs could be influenced by abnormal FDG uptake by suspected cancer or by physiological accumulation; when organs were not detected even with reference to another modality, such as computed tomography, we excluded them from this examination.

Statistical analysis

We evaluated statistically significant differences in the mean SUV between healthy volunteers and patients with suspected renal failure using a non-parametric Mann–Whitney U test. $P < 0.05$ was considered to represent a statistically significant difference.

Results

The SUVs of patients with suspected renal failure are presented in Table 1. The mean SUVs of ROIs of healthy volunteers and patients with suspected renal failure are also shown in Table 1. Two patients demonstrated abnormal accumulations of FDG in the right lower lung field. We excluded these two lower lung fields and also excluded the left atrium that was thought to be influenced by these two accumulations. The region of the myocardium at the left ventricle was not detected in one patient; the region of the kidney was not detected in two patients. The mean SUVs of brain cortex, white matter, and left kidney was higher in the healthy volunteers than in patients. The mean SUVs of all the other regions were higher in the patients than in healthy volunteers. Of the 15 regions, differences ($P < 0.05$) were found between the healthy volunteers and patients in the mean SUV of the white matter and the cortex at the level of centrum semiovale, the mean SUV of the mediastinum at the aortic arch level, and the mean SUV of the left atrium as a cardiac blood pool. The FDG-PET images of healthy volunteers and patients with suspected renal failure are presented in Fig. 1. Of the 20 patients with suspected renal failure, no differences in the mean SUVs were found between patients with abnormal uptake on malignancy and others.

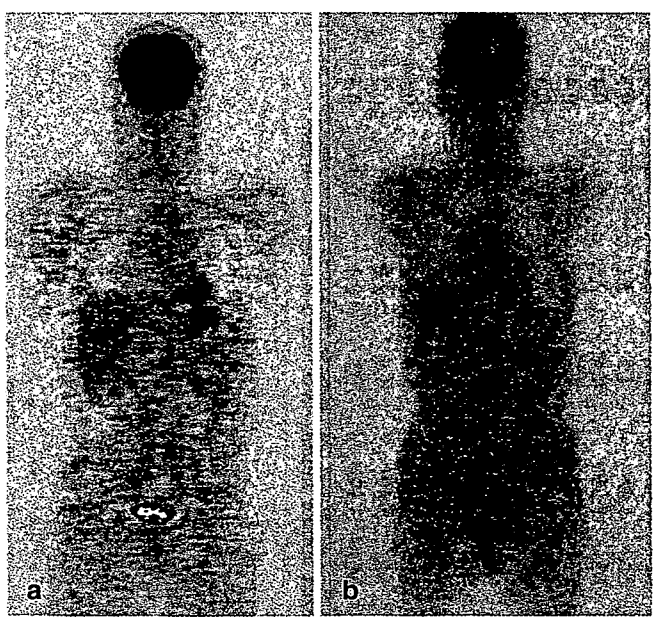

Fig. 1 FDG-PET images of healthy volunteer (**a**) and patient with suspected renal failure (**b**) are shown. These images, especially of the brain cortex, are different between the healthy volunteers and patients with suspected renal failure

Discussion

2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) is an analog of glucose in which the hydroxyl group in the 2 position has been replaced with a fluorine atom [2]. FDG is excreted through the urine but glucose is almost completely reabsorbed from the renal tubules. FDG accumulates in the kidneys and is filtered through the glomerulus as glucose. Deoxyglucose is known to be reabsorbed from the glomerular filtrate in the proximal segment of the renal tubule in two stages. The first stage is related to the uphill transport across the brush border membrane by Na^+–glucose cotransport and the second stage is related to the downhill transport across the basolateral membrane by facilitated diffusion [7]. Unlike glucose, FDG is excreted through the urine. FDG is known to be incompletely reabsorbed by the tubules, unlike glucose, which is completely reabsorbed in the proximal tubules of the kidney [8–10]. In dogs, the excretion rate of FDG through the urine is 16% and 50% per injected dose, respectively, at 60 min and 135 min after intravenous injection [11]; the precise mechanism and ratio of tubular reabsorption of FDG in humans are not known. Creatinine measurements in serum and urine are commonly used as an indication of renal function and the rate of progression. Urine creatinine measurements are considered to be more accurate than those in serum for the evaluation of renal function. Creatinine clearance has a close relationship with glomerular filtration rate (GFR), but sometimes fails to detect a reduction in GFR and fails to estimate renal function because GFR may be reduced with the creatinine measurement still in the normal range [12]. Laboratory assessment of the serum creatinine level is, however, a relatively low-cost test and is available in any standard hospital laboratory. An increased plasma creatinine level is usually the first step in diagnosing renal failure [13]. We did not determine whether the distribution of FDG in patients with high plasma creatinine differs from that in healthy volunteers. We found that the mean SUVs of brain cortex and white matter were higher in healthy volunteers than in patients with suspected renal failure. The mean SUVs of the mediastinum at the aortic arch level and of the left atrium were lower in healthy volunteers than in patients with suspected renal failure. We propose that the differences in SUV in the mediastinum and left atrium were caused by blood concentration of FDG, and that the differences of SUV in the brain cortex and white matter were caused by a decreased intake rate of FDG by the tissues. In animal studies, administration of saline alone or saline plus furosemide was unable to lower the %kg injected dose per gram of FDG in blood. In contrast, furosemide increased the %kg injected dose per gram

Table 1 Mean SUVs of FDG in normal tissue of patients with suspected renal failure

Patient no.	Age	Sex	Serum creatinine (mg/dl)	Brain cortex	White matter	Right upper lung	Left upper lung	Right middle lung	Left middle lung	Medias-tinum	Right lower lung	Left lower lung	Left atrium	Heart wall	Liver	Left kidney	Right femoris muscle	Left femoris muscle
1	76	M	1.11	4.4	2.6	0.5	0.5	0.4	0.6	1.6	0.7	0.8	2.0	2.8	2.3	2.3	0.5	0.7
2	56	F	1.12	4.6	2.6	0.3	0.4	0.3	0.5	1.2	0.5	0.5	–	1.2	2.0	1.9	0.6	0.6
3	77	M	1.13	5.5	2.4	0.5	0.5	0.5	0.5	1.3	0.8	0.6	1.2	–	2.1	2.1	0.4	0.4
4	63	M	1.19	4.8	2.4	0.4	0.4	0.6	0.4	1.4	0.6	0.4	1.5	2.7	1.4	–	0.5	0.7
5	65	M	1.20	5.5	2.2	0.4	0.3	0.3	0.6	1.0	0.5	0.6	1.3	4.5	1.2	1.7	0.5	0.5
6	76	M	1.26	4.5	1.8	0.3	0.3	0.2	0.3	1.5	0.3	0.3	1.4	1.0	1.5	2.3	0.8	0.7
7	68	M	1.28	4.7	2.4	0.4	0.5	0.3	0.6	1.8	0.7	0.8	1.9	4.0	2.2	2.6	0.7	0.6
8	77	M	1.29	5.5	3.0	0.5	0.6	0.7	0.6	1.8	0.7	0.7	1.8	2.2	2.3	2.8	0.6	0.5
9	63	M	1.42	4.9	2.2	0.6	0.6	0.6	0.8	1.4	0.8	0.8	1.6	4.3	1.3	0.8	0.6	0.7
10	66	M	1.48	4.5	2.1	0.3	0.5	0.3	0.5	1.5	0.6	0.5	1.6	5.3	1.9	1.9	0.8	0.8
11	80	M	1.56	4.5	2.5	0.4	0.4	0.5	0.8	1.8	–	1.0	1.8	5.1	2.4	2.4	0.8	0.8
12	65	F	1.61	3.3	1.5	0.4	0.4	0.3	0.3	1.5	0.6	0.5	1.7	2.0	1.8	1.8	1.1	0.9
13	65	M	1.76	3.5	1.2	0.3	0.3	0.3	0.4	1.3	0.4	0.4	–	1.4	1.3	1.1	0.7	0.8
14	60	F	1.95	5.2	2.5	0.3	0.5	0.6	0.4	1.4	–	0.5	1.5	4.8	1.8	2.2	0.3	0.3
15	65	M	1.98	4.4	2.0	0.7	0.6	0.5	0.6	1.5	0.7	0.5	1.1	1.9	1.6	2.9	0.7	0.5
16	74	M	2.02	4.1	2.2	0.3	0.3	0.3	0.3	1.1	0.5	0.2	1.1	0.9	1.6	–	0.8	0.7
17	47	F	2.17	4.6	2.1	0.6	0.8	0.7	1.1	1.1	1.0	1.0	1.3	2.0	1.5	1.6	0.6	0.7
18	80	M	2.75	5.4	2.2	0.4	0.5	0.6	0.5	1.6	0.5	0.6	1.5	2.6	1.7	2.1	0.6	0.7
19	82	M	2.89	4.5	2.0	0.3	0.4	0.3	0.5	1.6	0.5	0.7	1.4	4.8	2.2	2.1	0.7	0.5
20	81	M	3.39	5.1	2.1	0.3	0.5	0.4	0.5	1.7	0.5	0.6	1.7	3.9	1.7	2.0	0.9	0.6

SUVs standardized uptake values, *FDG* fluoro-2-deoxy-D-glucose

Table 2 Mean SUVs of ROIs of healthy volunteers and patients with suspected renal failure

	Brain cortex	White matter	Right upper lung	Left upper lung	Right middle lung	Left middle lung	Mediastinum	Right lower lung	Left lower lung	Left atrium	Heart wall	Liver	Left kidney	Right femoris muscle	Left femoris muscle
Healthy volunteers	5.3 ± 0.9	2.7 ± 0.4	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	1.3 ± 0.2	0.9 ± 0.1	0.5 ± 0.1	1.3 ± 0.1	2.9 ± 2.2	1.7 ± 0.3	2.5 ± 1.1	0.6 ± 0.1	0.6 ± 0.1
Patients with suspected renal failure	4.7 ± 0.6*	2.2 ± 0.4*	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.6 ± 0.2	1.5 ± 0.2*	0.6 ± 0.2	0.6 ± 0.2	1.5 ± 0.2*	3.0 ± 1.5	1.8 ± 0.4	2.0 ± 0.5	0.7 ± 0.2	0.6 ± 0.1

ROIs regions of interest
* $P < 0.05$ compared with healthy volunteers

of FDG in blood. The excretion of FDG through the urine was unaffected by an excessive load of water, and the uptake of FDG in blood did not change. The hydrated group had a higher excretion of FDG in the urine than the dehydrated group, but the difference was not as great as seen in animals. Excretion control in humans may differ from that in animals [14, 15]. To our knowledge, no articles have focused on FDG excretion with low GFR. Glucose metabolism in patients with chronic renal failure differs from that of healthy volunteers. Insulin-mediated glucose metabolism of patients with renal failure is reduced by 47% when compared with that of normal volunteers. Patients with renal failure suffer from inhibited glucose utilization [16]. Insulin acts to stimulate glucose uptake, oxidation, and storage [17, 18]. Patients with kidney disease and renal dysfunction are said to be insulin resistant. The kidney has an important role in glucose homeostasis. Decreasing insulin-stimulated glucose uptake has revealed uremic patients. Insulin resistance in renal patients is accompanied by hyperinsulinemia, glucose intolerance, and derangements in insulin secretion. Recent clinical studies report pre-existing insulin resistance in patients with mild degrees of renal dysfunction and even in patients with near-normal renal function. Homeostasis model assessment of insulin resistance (HOMA-IR), serum insulin concentration, and serum glucose concentration were investigated in healthy subjects and renal patients. These three parameters have almost no relationship with GFR, but this study demonstrated significant differences between healthy subjects and renal patients [19]. Bingham et al. [20] reported that insulin has a significant effect on brain glucose metabolism and that it affects mainly the cerebral cortex. Hasselbalch et al. [21] reported that the effect of insulin on the brain is little or nonexistent. The relationship between kidney disease and insulin resistance of the brain is not known, but the two may be linked. We found decreasing brain accumulation and increasing blood pool accumulation of FDG in patients with high plasma creatinine. Differences of the mean SUVs were small. Our results tend to support the report of Hasselbalch et al. [21].

Conclusions

The current study revealed decreasing brain accumulation and increasing blood pool accumulation of FDG in patients with high plasma creatinine measurements. Although the difference is small, this phenomenon will not have a huge effect on the assessment of FDG-PET imaging in patients with suspected renal failure.

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ORIGINAL ARTICLE

Performance profile of FDG-PET and PET/CT for cancer screening on the basis of a Japanese Nationwide Survey

**Ryogo Minamimoto · Michio Senda · Kimiichi Uno
Seishi Jinnouchi · Takeshi Iinuma · Kengo Ito
Chio Okuyama · Kazuhiro Oguchi · Masami Kawamoto
Yutaka Suzuki · Eriko Tsukamoto · Takashi Terauchi
Rumi Nakashima · Masami Nishio · Sadahiko Nishizawa
Hiroshi Fukuda · Tsuyoshi Yoshida · Tomio Inoue**

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Abstract
Objective The aim of this study is to survey the situation of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) cancer screening in Japan and to describe its performance profile.

Methods "FDG-PET for cancer screening" was defined as FDG-PET or positron emission tomography and computed tomography (PET/CT) scan with or without other tests performed for cancer screening of healthy subjects. We sent questionnaires regarding FDG-PET

R. Minamimoto (✉) · T. Inoue
Department of Radiology, Yokohama City University, Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan
e-mail: t046047b@yokohama-cu.ac.jp

M. Senda
Division of Molecular Imaging, Institute of Biomedical Research and Innovation, Kobe, Japan

K. Uno
Nishidai Clinic Diagnostic Imaging Center, Tokyo, Japan

S. Jinnouchi
Atsuchi Memorial Institute of Radiology, Atsuchi Memorial Clinic PET Center, Kagoshima, Japan

T. Iinuma
National Institute of Radiological Sciences, Chiba, Japan

K. Ito
Department of Brain Science and Molecular Imaging, National Institute for Longevity Sciences, National Center for Geriatrics and Gerontology, Ohbu, Japan

C. Okuyama
Department of Radiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Koyto, Japan

K. Oguchi
Positron Imaging Center, Aizawa Hospital, Matsumoto, Japan

M. Kawamoto
Yuai Clinic, Diagnostic Imaging Center, Radiology, Yokohama, Japan

Y. Suzuki
HIMEDIC Imaging Center at Lake Yamanaka, Yamanashi, Japan

E. Tsukamoto
Medical Cooperation Teishinkai Central CI Clinic, Sapporo, Japan

T. Terauchi
Cancer Screening Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

R. Nakashima
Japanese Red Cross Kumamoto Health Care Center, Kumamoto, Japan

M. Nishio
Department of Radiology, Nagoya PET Imaging Center, Nagoya, Japan

S. Nishizawa
Hamamatsu Medical Imaging Center, Hamamatsu Medical Photonics Foundation, Hamamatsu, Japan

H. Fukuda
Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

T. Yoshida
Department of Radiology, Koga Hospital 21 PET Center, Kurume, Japan

cancer screening to 99 facilities in which FDG-PET tests were performed during the fiscal year 2005. Replies were obtained from 68 of the 99 facilities, of which 46 facilities performed FDG-PET cancer screening. The total number of subjects who underwent FDG-PET cancer screening was 50558. From 38 of 46 facilities, reliable results of thorough examinations were obtained for the subjects who were positive by FDG-PET and/or one or more of the combined screening tests was performed and were referred for further evaluation. The total number of subjects in these 38 facilities amounted to 43996.

Results A total of 50558 healthy subjects underwent FDG-PET (including PET/CT) scanning with or without other tests for cancer screening in 46 PET centers during the fiscal year of 2005 in Japan. Thorough examination was indicated for 9.8% of the cases as a result of positive findings suggesting possible cancer. On analyzing 43996 cases from 38 PET centers from which detailed information was obtained, 500 cases of cancers (1.14%) were found, of which 0.90% were PET positive and 0.24% were PET negative, resulting in the relative sensitivity of PET being 79.0%. Cancers of the thyroid, colon/rectum, lung, and breast were most frequently found (107, 102, 79, and 35 cases, respectively) with high PET sensitivity (88%, 90%, 80%, and 92%). PET showed an overall positive predictive value of 29.0%. PET/CT had a better detection rate, sensitivity, and positive predictive value than dedicated PET ($P < 0.01$).

Conclusions We were able to clarify the performance profile of "FDG-PET for cancer screening" on the basis of a Japanese nationwide survey. The number of facilities possessing PET is increasing steadily, highlighting the necessity of evaluating the usefulness of "FDG-PET cancer screening" as soon as possible by undertaking long-term investigations of large series of subjects.

Keywords FDG · PET · PET/CT · Cancer screening

Introduction

The aim of this study was to survey the situation of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) cancer screening in Japan and to describe its performance profile.

In Japan, FDG-PET for cancer screening has become widespread. "FDG-PET for cancer screening" was defined as FDG-PET or positron emission tomography and computed tomography (PET/CT) scan with or without other tests performed for cancer screening of healthy subjects. The Japanese Society of Nuclear Medicine and The Clinical PET Promoting Committee published "The Guidelines of FDG-PET Cancer Screening" [1] in 2004, with the aim of improving the quality of FDG-PET cancer screening. Each PET center was asked to regularly report the number of FDG-PET cancer screening procedures performed and provide detailed information on screened cancers.

Materials and methods

Subject for investigation

Questionnaires regarding FDG-PET cancer screening were sent to 99 facilities in which FDG-PET tests were performed during the fiscal year 2005. Replies were obtained from 68 of the 99 facilities, of which 46 facilities performed FDG-PET cancer screening. Between April 2005 and March 2006, the total number of subjects who underwent FDG-PET cancer screening was 50558 (27862 men, 20740 women, 1956 undefined). From 38 of 46 facilities, reliable results of thorough examinations were obtained for the subjects who were positive by FDG-PET and/or one or more of the combined screening tests was performed and were referred for further evaluation. The total number of subjects in these 38 facilities amounted to 43996 (25193 men, 18803 women).

Contents of the investigation

The questionnaire regarding FDG-PET cancer screening consists of an "Investigation of facilities" part that describes the inspective situation of each facility, and "Investigation of suspected cancer cases" part that describes the inspection situation of suspected cancer cases. The "Investigation of facilities" part asked about the following: (1) the number of PET centers conducting FDG-PET screening or not; (2) the method of FDG-PET procedure (FDG-PET machines, injected volume of FDG, presence of absorption revision and the method, time to obtain imaging of FDG-PET, screening range, performance of delayed scanning and its time to start; (3) the character of CT scanners integrated in PET/CT system (mAs, CT image reconstruction interval); (4) the kinds of fixed combined screening tests; (5) the total number, sex, and age group of subjects undergoing FDG-PET cancer screening; (6) the number of repeated FDG-PET cancer screening tests in 2005; (7) the number, sex, age group of subjects with positive findings suggesting possible cancer; (8) the number of positive/negative findings suggesting possible cancer; (9) the number of excluded cancer cases with combined screening tests after cancer was suspected by FDG-PET; and (10) the number of obtained results suggesting possible cancer cases.

Detailed information was required regarding all possible cancer cases in the part of "investigation of suspected cancer cases." We provided five types of investigation sheets, "lung cancer," "colon/rectum cancer," "thyroid cancer," and "breast cancer," which are frequently detected by FDG-PET, and "other cancers" for cancers other than these four. The "Investigation of suspected cancer cases" part asked about the following: (1) the month that FDG-PET cancer screening was performed; (2) sex; (3) age group; (4) past history of cancer; (5) repeated FDG-PET cancer screening or not, other suspected cancers by FDG-PET screening; (7) FDG-PET (including FDG-PET/CT) imaging findings, and delayed imaging findings; (8) results of combined cancer screening tests; and (9) final results of further examination.

"Investigation of suspected cancer cases" consisted of three categories, namely, "proved cancer," "excluded cancer," and "strict follow-up because of excluded cancer." In the case of categorization to "finally excluded cancer," the final result of further examination was required.

"Clinical stage" and "pathological stage" of each cancer, "the degree of differentiation of cancer," "the degree of macroscopic depth," and "the degree of microscopic depth" of colon/rectum cancer were on the basis of the respective latest general rules of each cancer published up to 2005 [2–5]. In the "investigation of suspected cancer cases" of lung cancer, the Noguchi classification and ground glass opacity (GGO) classification were required [6, 7].

Definition of terms

^{18}F-fluorodeoxyglucose-positron emission tomography cancer screening is defined as a cancer screening program using FDG-PET (including FDG-PET/CT) aimed at the detection of cancer at an early stage. Any PET or PET/CT cameras, method of FDG-PET test, combined screening tests, and method of further examination are allowed. Any way to select patients and any way to handle the expense burden are allowed.

In the case of a past history of cancer, screening for recurrence requested by the attending physician or by the patient is excluded from the definition of "FDG-PET cancer screening." But when the cancer was considered to have been cured, and FDG-PET was performed to screen other sites for cancer, FDG-PET test was included in the definition of "FDG-PET cancer screening."

"Combined screening tests," defined for each PET center, are those undergone by more than half of the subjects who undergo FDG-PET cancer screening in each PET center. If a screening test was performed at another facility in the same period, and its result provided to the PET center, it was defined as "combined screening test." If further examination is judged necessary on the basis of the obtained PET information, any additional test other than the screening program fixed in each PET center is not considered to be a "combined screening test." If a cancer screening test was performed using a PET/CT scanner, regardless of the method used or way of interpretation, the information obtained from the CT integrated in the PET/CT system was regarded not as a combined screening test but as PET/CT modality itself. In our analysis, the positive rate of PET findings was distinguished from that of the combined screening test findings, because the CT findings could not be ignored when using PET/CT. "PET positive" is defined as positive findings on PET or PET/CT. Accordingly, the cases with PET/negative and CT/positive findings on screening tests performed by PET/CT were included in "PET/positive," and the number of such cases was determined as needed.

"Required further examination" is defined as cases for which a thorough examination was recommended on the basis of the comprehensive results of FDG-PET and/or any combined screening tests.

Cases for which reexamination was recommended are not included in "required further examination." "Obtained result of further examination" is defined as being clearly categorized as "proved cancer," or "excluded cancer," or "strict follow-up because of disproved cancer" by the result of additional examination, further examination and treatment.

Facilities cooperating with the questionnaire survey

The facilities cooperating with the questionnaire survey are listed in Table 1.

Statistical analysis

The chi-square test for independence was performed to compare the detection rate, sensitivity, and positive predictive between PET and PET-CT, and a P value of less than 0.05 was considered to be significant. The McNemmer test was performed to compare the detected number of cancers on the screening program that were positive/negative by screening FDG-PET and by one or more of the combined screening tests, with a P value of less than 0.05 considered to be significant.

Table 1 Positron emission tomography (PET) centers that responded to the survey

PET centers conducting FDG-PET cancer screening		
Nikko Memorial Hospital	Fukuiken Saiseikai Hospital	
Sapporo Minamisanjo Hospital	Oumikusatsu Tokushukai Hospital	
Central CI Clinic	Nishijin Hospital	
Aomori PET Diagnostic Imaging Center	Takeda Oncologic Positron Imaging Center	
Dokkyo Medical University Hospital	Sakazaki Clinic	
Utsunomiya Central Clinic	Saiseikai Nakatsu Hospital, Osaka	
Kenoh Iruma Clinic	MI Clinic	
Tokorozawa PET Diagnostic Imaging Clinic	Higashitemma Clinic	
Asahi General Hospital	Tsukazaki Clinic	
Nishidai Clinic	Himeji Central Hospital	
Musashimurayama Hospital	Institute of Biomedical Research and Innovation	
Yuai Clinic	Takai Hospital	
Shonan Atsugi Clinic	Okayama Kyokuto Hospital	
HIMEDIC Imaging Center at Lake Yamanaka	Chuden Hospital	
Shizuoka Tokushukai Hospital	Hiroshima Heiwa Clinic	
Shizuoka Cancer Center Hospital	Kagawa University Hospital	
Hamamatsu Medical Imaging Center	Takinomiya General Hospital	
Daiyukai Daiichi Hospital	Koga Hospital 21	
Nagoya PET Imaging Center	Kitakyushu Medical Checkup Clinic	
Aizawa Hospital	Uozumi Clinic	
Kizawa Memorial Hospital	Japanese Red Cross Kumamoto Health Care Center	
Saiseikai Matsusaka General Hospital	Medical Imaging Centre	
University of Fukui	Atsuchi Memorial Clinic	
PET centers not conducting FDG-PET cancer screening		
Hokkaido University Hospital	Tokyo Metropolitan Institute of Gerontology	Shiga Medical Center for Adults
Nishina Memorial Cyclotron Center	Musashi Hospital, National Center of Neurology and Psychiatry	The Medical and Pharmacological Research Center Foundation
Tohoku University Hospital	Yokohama Stroke and Brain Center	Mitsubishi Kyoto Hospital
Cyclotron Radioisotope Center, Tohoku University	Yokohama City University Hospital	Osaka City University Hospital
Gunma University Hospital	Hamamatsu Medical Center	Osaka University Hospital
National Institute of Radiological Sciences	National Center for Geriatrics and Gerontology	National Cardiovascular Center
National Cancer Center Hospital East	Nagoya City Rehabilitation and Sports Center	
The University of Tokyo Hospital	Nagoya University Hospital	

Results

The results of "investigation for facilities"

The number of PET centers conducting or not conducting FDG-PET screening

We sent questionnaires regarding FDG-PET cancer screening to 99 facilities. Answers were obtained from 68 of these facilities, of which 46 facilities performed FDG-PET cancer screening.

Method of FDG-PET test

"Method of FDG-PET test" is understood to mean type of PET or PET/CT scanner, injected volume of FDG, presence of absorption revision and its method, imaging time for a FDG-PET test, imaging range, use of delayed scan, and its starting time.

The FDG-PET screening test method was analyzed in 45 facilities, with no reply being obtained from the remaining one facility. Seventy-four imaging machines consisted of 35 PET scanners and 39 PET/CT scanners that were used for FDG-PET cancer screening. Injection volume of FDG was consistent in 7 facilities (range 130–296 MBq, average 200.1 MBq), and variable in 37 facilities. The facilities with variable injection volumes of FDG frequently used 222 MBq for subjects 165 cm tall weighing 60 kg, with the range per facility varying widely from 134 MBq to 309 MBq. Average FDG injection volume was 231.9 MBq in the fixed two-dimensional (2D) acquisition mode, and 210.2 MBq in the fixed three-dimensional (3D) acquisition mode. Maximum injection volume of FDG ranged widely from 148 MBq

to 500 MBq (average 321.8 MBq). Attenuation correction is performed in 44 of the 45 facilities. All the attenuation correction with PET scanner was performed by conventional transmission scanning, and all the attenuation correction of PET/CT cameras was performed by CT scanning. Fixed emission correction was 2D in 18 facilities, 3D in 27 facilities, and depending on PET or PET/CT in 1 facility. The start time of emission scan was frequently 60 min after injection of FDG (average 58.6 min). Total required scanning time (including the scanning time of CT and transmission scan) varied widely from 15 min to 45 min, which was considered to depend on the properties and specifications of each PET or PET/CT scanner. The scanned range was most frequently the "parietal to femur region" regardless of whether a PET scanner or PET/CT scanner was used. In two facilities, the scanned range varied according to the machine used. In a few facilities an orbit was fixed for the top position of screening and the pubic bone or inguinal region for the bottom position. Delayed scanning was performed regularly at 6 facilities, as needed at 27, and never at 11. The start time of delayed scanning was frequently 120 min after the injection of FDG (average: 120.5 min).

Character of CT scanners integrated in PET/CT system

The "mAs" value (the product of X-ray tube current and exposure time) fixed to CT scanners integrated in the PET/CT system was consistent in 13 facilities and variable in 15 facilities. Although the displayed mAs value on the machine and its definition differ according to the manufacturer, the average displayed mAs value on the machine itself in every facility applying a consistent mAs value to CT scanning was 44.8 mAs, whereas in facilities applying variable mAs values it was 78.6 mAs on chest scanning and 88.7 mAs on abdominal scanning. CT image reconstruction interval was most frequently 3.75 mm (range 2.5 mm–7.5 mm, average 4.0 mm).

Combined screening tests

The combined screening tests in the various facilities are listed in Table 2. Thirty-six facilities performed one or more combined screening tests in addition to FDG-PET, while eight facilities did not. The number and type of combined screening tests differed according to facility or individual subjects in the same facility. No correlation was found between the number of combined screening tests and the rate of detected possible cancers. A large number of combined screening tests are not the cause of the increase in the number of detected possible cancers.

The total number, sex, and age group of subjects who underwent FDG-PET cancer screening

The total number of subjects who underwent FDG-PET cancer screening in the 46 facilities was 50558 (27862 men 20740 women, 1956 unidentified). The number of

Table 2 Combined screening tests and number of PET centers performing each test

Modalities	Number	Modalities	Number
Brain MRI	14	Cervical cytology	4
Otolaryngologic examination	1	Pelvic ultrasonography	9
Head and neck CT	10	Pelvic CT	11
Head and neck MRI	0	Pelvic MRI	14
Thyroid ultrasonography	14	Prostate ultrasonography	6
Inspection and palpation of breast	4	Prostate MRI	11
Breast ultrasonography	9	Prostate specific antigen (PSA)	35
Mammography	6	Carcinoembryonic antigen (CEA)	34
Sputum cytology	5	Cancer antigen 19-9 (CA19-9)	34
Chest X-ray	8	Cancer antigen 125 (CA125)	31
Chest CT	24	α-fetoproteins (AFP)	28
Gastric fluoroscopy	2	Pepsinogen	19
Gastric endoscopy	8	Squamous cell carcinoma antigen (SCC)	14
Abdominal ultrasonography	24	Cytokeratin-19 fragment (CYFRA)	7
Abdominal CT	18	Pro-gastrin releasing peptide (Pro-GRP)	6
Abdominal MRI	5	Cancer antigen 15-3 (CA15-3)	3
FOBT (one time screening)	8	Neuron specific enolase (NSE)	3
FOBT(two times screening)	23	Thyroglobulin	3
FOBT (three times screening)	2	Sialyl Lewis X-i antigen (SLX)	1
Barium enema	0	Nuclear matrix protein-22 (NMP-22)	1
Colonoscopy	1		

Combined screening tests, defined for each PET center, are those taken by more than half of the subjects who underwent FDG-PET cancer screening in the center. Of the 44 PET centers which performed FDG-PET for cancer screening
FOBT fecal occult blood test, *MRI* magnetic resonance imaging, *CT* computed tomography

Table 3 Number of subjects who underwent FDG-PET cancer screening during the 1-year period in a total of 46 PET centers

Age group	Number	Rate (%)	Male	Female
10–19	14 (10)	0.03	4 (3)	10 (7)
20–29	391 (354)	0.77	163 (144)	228 (210)
30–39	3377 (3096)	6.7	1829 (1669)	1548 (1427)
40–49	9009 (8191)	17.8	5168 (4698)	3841 (3493)
50–59	17190 (15514)	34.0	9786 (8801)	7404 (6713)
60–69	13495 (12209)	26.7	7986 (7244)	5509 (4965)
70–79	4604 (4148)	9.1	2645 (2384)	1959 (1764)
80–	522 (474)	1.0	281 (250)	241 (224)
Unknown	1956	3.7	–	–
Total	50558 (43996)	100.0	27862 (25193)	20740 (18803)

The numbers in parentheses represent those examined in 38 "qualified" centers, in which reliable results of the thorough examinations were obtained for the subjects who were positive by FDG-PET and/or one or more of the combined screening tests if any and were referred for further evaluation

subjects in each age group is listed in Table 3. Cancers were most frequently found in the age groups of 50–59 years and 60–69 years, which together make up 61% of the total subjects. PET machines were used in 32970 cases and PET/CT machines in 17588. Eight facilities were excluded from the analysis of "investigation of suspected cancer cases" because of unreliable results. The total number of subjects in these 38 facilities amounted to 43996 (25193 men, 18803 women). The average number of FDG-PET screening tests performed in the 30 facilities that opened prior to March 2005 was 1368 (total 41033; range 52–5179).

The number of repeated FDG-PET cancer screening tests in 2005

The number of repeated FDG-PET cancer screening tests was determined in 18 facilities that had opened by April 1, 2004. The total number of repeated FDG-PET cancer screening tests in 2005 was 5688, and the average repeated rate of FDG-PET cancer screening was 26.2% (range 2.9%–55.0%). The average repeated rate of FDG-PET cancer screening was slightly higher in the Tokai area than in other areas.

The number, sex, and age group of subjects with positive findings suggesting possible cancer

The results of subjects with positive findings suggesting possible cancer were obtained from 40 facilities. The number, sex, and age group of subjects with positive findings suggesting possible cancer are listed in Table 4. Positive findings in the 40 facilities were noted in 4428 cases (2209 men, 2049 women, 170 unidentified). Cancers were most frequently found in the age groups of 50–59 years and 60–69 years, which make up 62%

Table 4 Number of subjects who were positive by screening FDG-PET and/or one or more of the combined screening tests if any

Age group	Number	Male	Female
10–19	0	0	0
20–29	22	10	12
30–39	184	69	115
40–49	602	252	350
50–59	1362	654	708
60–69	1390	775	615
70–79	615	395	220
80–	83	54	29
Unknown	170	–	–
Total	4428	2209	2049

of the total subjects with positive findings. Cancers were most frequently found in the age group of 60–69 years in men and 50–59 years in women. The average suggested possible cancer rate was 9.8% in the 40 facilities (range 1.7%–24.6%). The rate of suggested possible cancer tended to increase with increasing age. The rate of suggested possible cancers was 9.0% when a PET scanner was used (range 2.8%–23.8%) and 11.0% when a PET/CT scanner was used (range 1.7%–24.6%), and thus the rate was higher with PET/CT than PET ($P < 0.01$).

The number of positive/negative findings in suggested possible cancer cases

Of the suggested possible cancer cases, the number of positive findings in PET (including PET/CT) but negative in combined screening tests or no combined screening tests amounted to 1747 (PET 872 cases, PET/CT 875 cases), positive in PET and positive in one or more combined screening tests 1235 (PET 697 cases, PET/CT 538 cases), and negative in PET and positive in com-

bined screening tests 1537 (PET 865 cases, PET/CT 672 cases). The rate of PET positivity in the cases with suspected cancer was 66.0% (6.1% of total cases undergoing cancer screening, range of suggested possible cancer rate in individual facilities 1.4%–25.7%), and 64.5% with PET scanners, and 67.5% with PET/CT scanners, and thus the PET positive rate was slightly higher in screening tests performed using PET/CT scanners ($P < 0.02$).

The number of cases in which cancer was excluded with combined screening tests despite suspicious findings on FDG-PET

Replies regarding this item were obtained from 26 facilities. Cancer was excluded by combined screening tests in 255 cases (67 cases with suspicious findings with PET scanners, 188 cases with PET/CT scanners). Replies to both this question and the number of positive findings suggested that possible cancer were obtained from 25 facilities with regard to 2143 cases (PET positive in 1507 cases). In 14% of the PET positive cases cancer was excluded with the combined screening tests, and in this way further examinations could be avoided.

The number of cases requiring further examination in which clear results were obtained

Of the 4428 cases 2071 reliable results were obtained suggesting possible cancer from 40 facilities. The percentage of such results was 46.8%. The number of obtained responses to the "investigation of suspected cancer cases" part referred to 1937 cases in 38 facilities (response rate 43.7%). There were no correlations between "the number of performed FDG-PET cancer screenings," "the number of suggested possible cancers," and the "response rate of investigations about suspected cancer cases."

Analysis of detected cancers

From 38 of 46 facilities, reliable results of thorough examinations were obtained for the subjects who were positive by FDG-PET and/or one or more of the combined screening tests if any, and who were referred for further evaluation. Of 46 facilities from which final results were obtained, 8 facilities were excluded because of unreliable results, and so the results of detected cancer from 38 facilities were finally analyzed. The number of performed PET screenings was 43996 cases in 38 PET centers, where 1937 cases were reported to manifest positive findings suggesting possible cancer, and 500 cancers were found. Finally, cancer was detected in 1.14% of the tests performed. The number, sex, and age group of the subjects in whom cancer was detected are listed in Table 5, and the kinds of cancer in Table 6. The total number of detected cancers was 531, but 31 results (colon/rectal cancer: 10 cases, thyroid cancer: 10 cases, lung cancer: 2 cases, uterine cancer: 2 cases, pancreatic cancer: 2 cases, gastric cancer: 2 cases, gastrointestinal stromal tumor [GIST]: 1 case) obtained from facilities other than the 38 mentioned earlier were excluded from the analysis because of incomplete results. Of the 500 cases (1.14% of the total screened number) of detected cancer, 395 cases had positive findings on PET (including PET/CT) amounting to 0.90% of the total screening number (0.85% excluding the case of PET/negative and CT/positive with screening test performed by PET/CT), and PET negative findings in 0.24%. As a result, 79.0% of detected cancers were positive on PET. Of the 395 cases, 209 were found by screening performed with PET scanners (detection rate of cancers was 0.78% in screening tests performed with PET scanners), whereas 186 cancers were detected by screening tests performed with PET/CT scanners (detection rate of cancer was 1.09% in screening tests performed by PET/CT scanners). Detection rate of cancer was higher with PET/CT than PET ($P < 0.01$).

Table 5 Number of subjects with cancer detected by the screening program and the rate of detection of the total of 43996 subjects in 38 centers

Age group	Number Total	Male	Female	Rate Total	Male	Female
10–19	0	0	0	0	0	0
20–29	1	1	0	0.28	0.69	0
30–39	8	4	4	0.26	0.24	0.28
40–49	54	20	34	0.66	0.43	0.97
50–59	151	73	78	0.97	0.83	1.16
60–69	175	111	64	1.43	1.53	1.29
70–79	96	66	30	2.31	2.77	1.70
80–	13	8	5	2.74	3.20	2.23
Unknown	2	–	–	–	–	–
Total	500	283	215	1.14	0.64	0.49

Table 6 Number of cancers detected by the screening program

Disease	Number	Disease	Number
Thyroid cancer	107	Head and neck cancer	6
Colorectal cancer	102	Bladder cancer	4
Lung cancer	79	Origin unknown cancer	4
Prostate cancer	47	Ureter cancer	3
Breast cancer	35	GIST[a]	3
Gastric cancer	30	Thymic cancer	2
Malignant lymphoma	19	Gallbladder cancer	2
Renal cancer	13	Cholangiocellular cancer	2
Esophagus cancer	8	Brain tumor	1
Uterine cancer	8	Testicular cancer	1
Liver cancer	7	Bone tumor	1
Pancreas cancer	7	Multiple myeloma	1
Ovarian cancer	7	Chronic myelogenous leukemia	1

Total 500 cases
[a] Gastrointestinal stromal tumor

When excluding PET/negative and CT/positive findings with screening tests performed with PET/CT scanners, the detection rate of cancer was 0.97% of all the screening tests, which was higher than that achieved with PET scanners ($P < 0.05$). Of cancers detected with PET/CT, the rate of PET positivity (relative sensitivity) was higher with PET/CT scanners (85.3%) than with PET scanners (74.5%) ($P < 0.01$). When excluding PET/negative and CT/positive findings with screening tests performed by PET/CT, the relative sensitivity of PET/CT was 76.1%, which was not significantly different from that of screening tests performed with PET scanners. According to the results of further examinations, the true positive rate for subjects with suggested possible cancer (positive predictive value) was higher with PET/CT (37.3%) than PET (24.5%) ($P < 0.01$). When excluding PET/negative and CT/positive findings with screening tests performed with PET/CT, the positive predictive value was higher with PET/CT (36.9%) than PET ($P < 0.01$). Of the 1937 cases in which a final result was obtained, repeated FDG-PET cancer screening tests in the fiscal year of 2005 were performed in 232 cases, with cancer found in 27. The cancer detection rate was 0.47% in the repeated FDG-PET cancer screening tests in which the PET positive rate was 0.26% (15 cases), of which cancer was found in 55.6%. The number of each type of cancer detected and the number of positive/negative cases by FDG-PET (including PET/CT) and by one or more of the combined screening tests are shown in Table 7. The number of cancers found was considered to be 504 detected lesions in 500 cases here because breast cancer was found in the bilateral breasts in four subjects. The number of cancers detected was higher with FDG-PET than with the combined screening tests ($P < 0.01$). The most frequently detected cancers with high PET positive rates were thyroid cancer, colon/rectum cancer, lung cancer, and breast cancer, whereas prostate cancer and gastric cancer showed low PET positive rates. Thyroid cancer, colon/rectum cancer, breast cancer, and malignant lymphoma were frequently detected by FDG-PET ($P < 0.01$), whereas gastric cancer and prostate cancer were frequently detected by combined screening tests($P < 0.01$). The number of lung cancers detected by FDG-PET and by combined screening tests was almost equal. Of the 186 cases of detected cancer with positive findings on PET/CT, PET/negative and CT/positive findings were noted in 20 cases (11%) including 8 cases of lung cancer (40 cases of positive findings on PET/CT), 5 cases of renal cancer (6 cases of positive findings on PET/CT), and 2 cases of breast cancer (14 cases of positive findings on PET/CT). The detection rate of cancer in PET positive cases found by PET scanners or PET/CT scanners, which were considered to depend on the results of the combined screening tests or screened population, did not differ significantly in thyroid cancer, colon/rectal cancer, or breast cancer, whereas lung cancer and other cancers were found more frequently with PET/CT scanners (detection rates being 0.19% and 0.37%, respectively) than with PET scanners (detection rates being 0.09% and 0.23%, respectively). When excluding PET/negative and CT/positive findings with screening tests performed by PET/CT, the detection rates of lung cancer and other cancers were 0.18% and 0.31%, respectively, so the detection rate of PET/CT scanners was significantly higher than that of PET scanners ($P < 0.01$). The most frequently found "other cancers" by PET/CT scanner were 16 cases of prostate cancer and 9 cases of malignant lymphoma.

Analysis of detected major cancers

Thyroid cancer

Four-hundred subjects (121 men, 279 women) were suspected of having thyroid cancer. One-hundred and seven cases (38 men, 69 women) of thyroid cancer, and 242