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The detection rates and tumor clinical/pathological stages of whole-body FDG-PET cancer screening

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Objective: FDG-PET has been used for cancer screening, mainly in East-Asia, and cancers are found not infrequently. However, their stages have not been clarified. We examined the detection rates of various cancers using whole-body PET for the screening of cancers in asymptomatic individuals, focusing on their clinical and pathological stages. ***Methods:*** Whole-body PET was obtained as a part of our cancer screening program among 3,426 healthy subjects. All subjects participated in a course of PET examination in conjunction with conventional examinations including a medical questionnaire, tumor markers, immunological fecal occult blood test, neck and abdominal ultrasonography and whole body computed tomography. A diagnosis and staging was obtained by an analysis of the pathological findings or by an analysis of the clinical follow-up data. ***Results:*** Malignant tumors were discovered in 65 lesions found in 3,426 participants (1.90%). The PET findings were true-positive in 46 of the 65 cancer cases. The cancers were found in the following organs: the colon 14; thyroid gland 10; stomach 7; lung 5; liver 3; breast 2; and one each in the kidney, gallbladder, esophagus, pancreas and retroperitoneum. The stages were as follows: stage 0 5, stage I 17, stage II 10, stage III 7, and stage IV 6. One was an unknown primary. There were 19 false-negative findings (0.6%) on PET. Six cancers (0.18%) were missed in our screening program. ***Conclusions:*** PET imaging has the potential to detect a wide variety of cancers at potentially curative stages. Most PET-negative cancers are early stage cancers, and thus can be detected using other conventional examinations such as endoscopy.

Key words: FDG-PET, cancer screening, detection rate, stage

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) with ^{18}F-fluorodeoxy-glucose (FDG) has been developed to quantitatively assess local glucose metabolism. Because malignant tumors exhibit an increased glucose metabolism, the FDG uptake by PET helps us to differentiate between benign and malignant tumors,[1] determine the degree of malignancy,[2] evaluate the effectiveness of chemotherapy or radiotherapy[3] and predict the prognosis.[4–6] Since the invention of the whole-body imaging technique,[7] PET has also been used to depict hypermetabolic cancers and the whole-body PET technique developed over the last few years has now surpassed most expectations regarding its utility in the field of clinical oncology. PET imaging has been shown to be sufficiently sensitive to detect various cancers.[1,8,9] It can also be used successfully in patients with unknown primary tumors.[10] As a result, PET imaging has the potential to detect cancers of many types with a single study. It also provides information on the extension of the cancer, because the primary tumor and

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metastatic foci can both be detected simultaneously. Recently, FDG-PET has been used for cancer screening mainly in East-Asia.[11–16] The detection rate has thus been reported to be ten to twenty times higher than for conventional screening.[17] The most important aspect of cancer screening is to detect cancer in its early stage. To our knowledge, however, there have been very few reports evaluating whether PET cancer screening can accurately detect early stage cancer. In this study, we examined the detection rates of various cancers by using whole-body PET for the screening of cancers in asymptomatic individuals, especially focusing on their clinical and pathological stages.

SUBJECTS AND METHODS

Patients

Between April 21, 2003 December 31, 2004, whole-body FDG PET was performed as a part of our cancer screening program among 3,426 healthy subjects. The subjects consisted of 2,014 men and 1,412 women, with a mean age of 56.4 years (range 22–87 years). All participants were recruited from the general population who agreed to participate in our cancer program. None of them had previously received PET examination. The program consisted of a course of PET examination in conjunction with conventional examinations including a medical questionnaire, tumor markers, immunological fecal occult blood test (FOBT), neck and abdominal ultrasonography and whole body computed tomography (CT) (Table 1). The participants were also asked to undergo gastrointestinal endoscopy at our institute or other affiliated hospitals, and their results were thereafter incorporated into our analysis. Abnormal results were compared with the subsequent operative or endoscopic histopathological results.

Our screening protocols were approved by the ethics committee of our institutional review board, and written informed consent was obtained from all of the cancer screening participants.

PET imaging protocol

The average injection dose of FDG was 180 MBq (3.7 MBq/kg weight, [maximum 259 MBq]). The whole body PET scan was started at one-hour after injection of FDG to obtain both the transmission and emission data using a PET camera (Advance Nxi, GE Medical Systems, Waukesha, WI, USA). All participants fasted for at least 5 hours prior to the injection of the tracer. All studies were performed with the patient in the supine position. A 2-minute emission study was performed for each bed position, including the pelvis, abdomen and chest to the level of the head. Immediately after the emission studies, a 1-minute transmission scan for each bed position was performed. Images were acquired in the 2-D mode. Attenuation-corrected transaxial images were reconstructed by the ordered subset expectation maximization (OS-EM) algorithm and segmented attenuation correction (SAC) into 128 × 128 matrices. The delayed FDG PET (2 hours) images were obtained in case abnormal uptake was suspected or findings were equivocal on one-hour FDG PET image, which was performed in 30% of the subjects.

Table 1 Number of subjects examined

	No. of subjects
PET	3426
medical questionnaire	3426
tumor markers	3426
neck and abdominal US	3426
whole body CT	3426
FOBT	3423
GF	799
CF	57

CT imaging protocol

Before the FDG-PET study, CT images were acquired, typically from the external auditory meatus to the upper thigh without using intravenous contrast medium during breath-hold. The scanner used was multislice computed tomography unit (Robusto, Hitachi Medico, Tokyo, Japan). The technical parameters for the CT portion of the examination were as follows: a detector-row configuration of 4 × 5mm, a pitch of 7:1 (high-speed mode), a gantry rotation time of 0.8 s, a table speed of 35 mm per gantry rotation, 120 kVp, and 100–160 mA. The 10-mm-thick transaxial CT images were reconstructed at 10-mm intervals.

Ultrasonographic examination protocol

Ultrasonography (US) of the thyroid gland, abdomen and pelvis were performed by using a EUB-8500 (Hitachi Medico, Tokyo, Japan) and Acuson Sequoia 512 (Mochida-Siemens Medical Systems, Tokyo, Japan) with a 5 or 7.5-MHz linear transducer and a 5-MHz Doppler frequency. All sonographic imaging was performed by two experienced sonographers.

Endoscopic examination

After the FDG-PET study, the endoscopic examination of the upper abdomen was done at the request of the patients (n = 799) and endoscopic examination of the colon was done in patients who had abnormal PET findings in the abdomen or positive FOB findings (n = 57) (Table 1). The time interval between the gastroscopy and PET was about 1 hour. All examinations were performed by two experienced endoscopists. Radiation doses to two endoscopists were measured in a clinical setting using an electronic pocket dosimeter (EPD) placed on the endoscopists' chest. The examination time per patient was approximately 20 minutes. The average radiation exposure per procedure was 4.5 μSv.

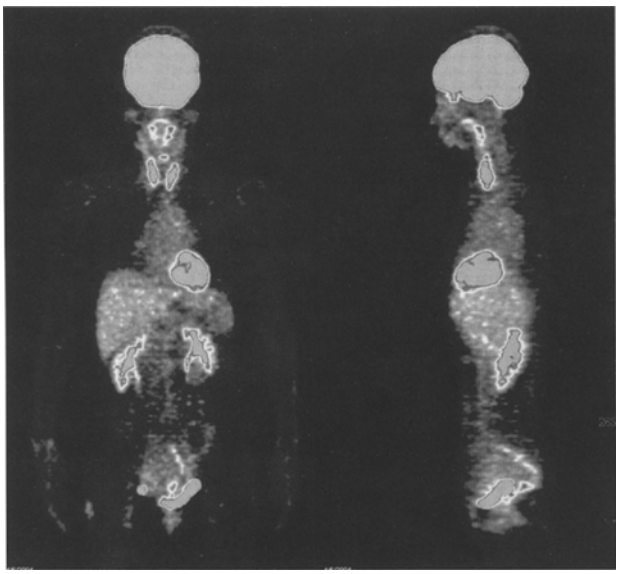

Fig. 1 Typical example of chronic thyroiditis in a 58-year-old woman. Coronal PET scan shows diffuse symmetric FDG uptake localized to the thyroid gland. Chronic thyroiditis was diagnosed after positive tests for anti-thyroid peroxidase antibody and anti-thyroglobulin antibody.

Tumor marker test and Fecal occult blood testing (FOBT)
Blood samples from all subjects were obtained before the FDG injection. For both genders, alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were measured by a chemiluminescent immunoassay (CLIA). Carbohydrate antigen 19-9 (CA19-9) was measured by a counterimmunoelectrophoresis (CLEIA). The reference range of AFP, CEA and CA19-9 was less than 10 ng/m*l*, 5 ng/m*l* and 37 U/m*l*, respectively. The SCC antigen was measured by radioimmunoassay (RIA). The cutoff value for squamous cell carcinoma (SCC) antigen was determined to be 1.5 ng/m*l*. The serum concentration of cytokeratin 19 fragment (CYFRA) was measured utilizing a new electrochemiluminescent immunoassay (ECLIA). The serum CYFRA levels were considered to be elevated when they were >3.5 ng/m*l*. For male participants, prostate specific antigen (PSA) was measured by a counterimmunoelectrophoresis (CLEIA). The reference range of PSA was less than 4 ng/m*l*. For female participants, CA125 was measured utilizing an electrochemiluminescent immunoassay (ECLIA). The reference range of CA125 was less than 35 U/m*l*. A latex-agglutination test for occult blood was performed on two or three different days.

Image analysis
All the studies were evaluated visually and semi-quantitatively using the maximum standardized uptake value (SUVmax) by the two board-certificated nuclear medicine specialists. The criterion for a positive PET finding was focally-increased FDG uptake that appeared different from physiological uptake or uptake of well-recognized benign lesions[1,18] (Fig. 1). Although SUVmax was obtained for reference, its value was not used for diagnosis, because its criteria for abnormal value have not been established. When the PET images were interpreted, the CT/US images provided an anatomical reference.

Table 2 Summary of cancer screening detection results

Site	Number	Rate	PET positive cases	PET negative cases
Colon	15†,‡	0.44%	14	1
Thyroid	11†,§	0.32%	10	1
Lung	10	0.29%	5	5
Stomach	9‡	0.26%	7	2
Liver	4	0.12%	3	1
Bladder	3	0.09%	0	3
Kidney	3	0.09%	1	2
Breast	3‖	0.09%	2	1
Gallbladder	2	0.06%	1	1
Prostate	2	0.06%	0	2
Esophagus	1	0.03%	1	0
Pancreas	1¶	0.03%	1	0
UP*	1	0.03%	1	0
Total	65		46	19

* Unknown primary cancer located in the retroperitoneum
† In a case with colon cancer and thyroid cancer, PET was positive on both lesions.
‡ In a case with colon cancer and gastric cancer, PET was positive only for the colon cancer.
§ Two cases of the thyroid gland cancer were diagnosed as double cancer, located in both thyroid gland lobes; in one case, PET was positive in only one lobe, and in the other case, PET was positive in both lobes.
‖ In a case with double breast cancer, located in the bilateral breast tissue, PET was positive in only the larger tumor. The other lesion was detected by ultrasonography.
¶ In a case with pancreas cancer and colon cancer, PET was positive on only the pancreas cancer. Advanced colon cancer was missed by our screening program.

Diagnosis and staging
When abnormal findings were noted at our screening program, the participant was, as a rule, referred to a local hospital for follow-up or further examination. A final diagnosis for the lesions was obtained by an analysis of the pathological findings or by an analysis of the clinical follow-up data. The stagings of the cancers were based on the 1997 TNM classification of the International Union Against cancer (UICC).[19]

Cancers missed by screening and observation after the screening program
After our screening program, a questionnaire was either sent to the participants or they were interviewed over the telephone. Even when no abnormalities were noted by PET or any other examinations, the patients were asked to undergo our cancer screening program regularly or

Table 3 PET-positive cancer stage

Site	Number	Stage					
		0	I	II	III	IV	NA
Colon	14	5	5(1)	3(1)	1	0	0
Thyroid	10	0	2	3(1)	4	1	0
Lung	5	0	3	1(1)	1(1)	0	0
Stomach	7	0	5	1	0	1	0
Liver	3	0	1(1)	1(1)	1	0	0
Bladder	0	0	0	0	0	0	0
Kidney	1	0	0	0	0	1	0
Breast	2	0	1	1	0	0	0
GB	1	0	0	0	0	1	0
Prostate	0	0	0	0	0	0	0
Esophagus	1	0	0	0	0	1(1)	0
Pancreas	1	0	0	0	0	1	0
UP	1	–	–	–	–	–	1
	46	5	17	10	7	6	1

GB, gallbladder; UP, unknown primary cancer; NA, not applicable. The number in parentheses indicates clinical stage.

Table 4 PET-negative cancer stage

Site	Number	Stage				
		0	I	II	III	IV
Colon	1	0	0	0	1	0
Thyroid	1	0	1	0	0	0
Lung	5	0	5(1)	0	0	0
Stomach	2	0	1	1	0	0
Liver	1	0	0	1(1)	0	0
Bladder	3	2	1	0	0	0
Kidney	2	0	1	0	1	0
Breast	1	0	1	0	0	0
GB	1	0	0	0	0	1
Prostate	2	0	0	2(1)	0	0
Esophagus	0	0	0	0	0	0
Pancreas	0	0	0	0	0	0
UP	0	–	–	–	–	–
	19	2	10	4	2	1

GB, gallbladder; UP, unknown primary cancer. The number in parentheses indicates clinical stage.

consult with an attending physician. When cancer was detected after our cancer screening program, the results were reported to us from each individual or physician. About one third of subjects (15% precision inspection, 17.8% following our cancer screening program) were observed for one year and were used for our analysis.

RESULTS

Malignant tumors were discovered in 65 lesions (60 cases) found in the 3,426 participants (1.90%) (Table 2), and 59 (90.8%) of these 65 lesions were pathologically proven to be malignant.

1. PET-positive cancer

The FDG-PET findings were true-positive in 46 of the 65 cancer cases (70.8%) (Table 2). The detection rate of cancer using FDG-PET alone in asymptomatic individuals was 1.34%. The cancers were found in the following organs: the colon 14 (0.41%); thyroid gland 10 (0.29%); stomach 7 (0.20%); lung 5 (0.15%); liver 3 (0.09%); breast 2 (0.06%); and kidney, gallbladder, esophagus, pancreas and the retroperitoneum in one each (0.03%). The stages of these cancers were as follows: stage 0 5, stage I 17, stage II 10, stage III 7, and stage IV 6 (except for the retroperitoneum) (Table 3). In colon cancers, 5 cases were classified as stage 0, 5 cases as stage I, 3 cases as stage II and 1 case as stage III. In 4 cases with normal immunological FOBT test findings, colon cancers were diagnosed by FDG-PET. In thyroid cancers, 2 cases were stage I, 3 stage II, 4 stage III, and 1 stage IV. There were 9 papillary adenocarcinomas and 1 anaplastic carcinoma. The smallest one measured 7.3 × 7 mm in diameter, and was not palpable. In lung cancers, 3 were stage I, 1 was stage II and 1 was stage III. In gastric cancers, 5 were stage I, 1 stage II and 1 stage IV. Three of 7 PET positive cancers had undergone gastric cancer screening (2 gastroscopy, 1 upper gastrointestinal tract barium examination) within one year at other institutions. In liver cancers, 1 was stage I, 1 stage II and 1 stage III. In breast cancers, 1 was stage I and 1 was stage II. The stage IV cases included cancers of the thyroid gland, stomach, prostate, kidney, gallbladder, esophagus and pancreas.

2. PET-negative cancer

There were 19 false-negative findings on FDG-PET (29.2%) (Table 2); all lesions were screened by other imaging studies or tumor markers. The lesions were located as follows: 5 in the lung; 3 in the bladder; 2 in the stomach; 2 in the kidney; 2 in the prostate; one each in the colon, thyroid gland, liver, breast and gallbladder. The cancer stages were 2 stage 0, 10 stage I, 4 stage II, 2 stage III and 1 stage IV (Table 4). In the lung, all 5 cancers were stage I (3 well-differentiated adenocarcinomas and 2 bronchioloalveolar adenocarcinomas) with less than 18-mm in diameter. All these cancers were detected on CT, but they remained invisible on plain chest radiography. Seven urinary tract malignancies could not be detected on PET. All 3 bladder cancers (2 stage 0 and 1 stage I) were detected by ultrasonography. Two prostate cancers (both stage II) were screened by the measurement of PSA levels. In the kidney, 1 was stage I and 1 stage III. The stage III renal cell carcinoma which measured 40-mm in diameter was negative on PET, but positive on ultrasonography and CT. A case with stage I breast cancer measuring 4.3-mm in diameter was not detected on PET, although it was detected on ultrasonography. One stage I thyroid cancer measuring 4-mm in diameter was not detected on PET, though it was detected on ultrasonography. A stage II liver cancer measuring 33-mm in diameter

Table 5 Cancers missed by PET and other examinations

Case number	Age	Sex	Diagnosis	Histology	Location	Tumor size (mm)	Stage	Methods of detection	FOBT
1	65	F	Gastric ca.	(scirrhous type)	NA	NA	NA	NA	N
2	70	M	Gastric ca.	well diff. adenoca.	midupper body	NA	p-stage II, T2N1M0	Gastroscopy	N
3	71	F	Colon ca.	well diff. adenoca.	sigmoid colon	7 × 10 × 10	p-stage 0, TisN0M0	Colonoscopy	NA
4*	73	M	Colon ca.	well diff. adenoca.	colosigmoid junction	12	p-stage I, T2N0M0	Colonoscopy	N
5	55	M	Larynx ca.	well-mod. diff. SqCC	right glottis	NA	c-stage I, T1aN0M0	Laryngoscopy	N
6	75	M	Pharynx ca.	NA	NA	NA	NA	NA	N

* In a case with colon cancer and pancreas cancer, PET was positive on only pancreas cancer. Advanced colon cancer was missed by our screening program. ca, cancer; SqCC, squamous cell carcinoma; FOBT, fecal occult blood testing; N, negative; NA, not applicable

Table 6 Studies on the cancer screening of PET

Authors	Year	No. of subjects	Total detection rate	PET alone detection rate	PET		Detection rate (PET alone)				
					TP	FN	lung	thyroid	breast	colon	stomach
Kao et al.[15]	2001	299	3.01%	2.34%	77.8%	22.2%	1%	0.33%	0%	0.33%	0%
Shen et al.[13]	2003	1283	1.40%	1.20%	83.3%	16.7%	0.23%	0.16%	0%	0.31%	0.08%
Chen et al.[12]	2004	3631	1.29%	1.05%	84.4%	15.6%	0.25%	0.14%	0.17%	0.25%	0%
Ide[14]	2004	7793	2.61%	1.33%	51.0%	49.0%	0.28%	0.27%	0.15%	0.31%*	0.08%
our study		3426	1.90%	1.34%	70.8%	29.2%	0.15%	0.29%	0.06%	0.41%†	0.20%

TP, true positive; FN, false negative; * including 9 carcinomas arising in adenomas; † including 6 carcinomas arising in adenomas

was negative on PET, but positive on ultrasonography. AFP was elevated in this patient. A case with stage IV gallbladder cancer was undetectable with PET. On ultrasonography, gallstone, polypoid lesion and thickening of the gallbladder wall were seen. Because CA19-9 was elevated (163 IU/m*l*), a laparoscopic cholecystectomy was performed and intraperitoneal neoplastic dissemination was noted.

3. Multiple cancers

In the present study, FDG-PET revealed multiple cancers in 6 (10.0%) out of 60 participants among a total of 3,426 individuals. Two cases of thyroid gland cancer were diagnosed as double cancers, located in the both thyroid gland lobes; in one case, PET was positive in only one lobe (they were determined to be papillary carcinomas), while in the other case, PET was positive in both lobes (they were determined to be papillary carcinoma and anaplastic carcinoma). In a case with double breast cancer, which was located in the bilateral breast tissue (10.2- and 4.3-mm in diameter), PET was positive only for the larger tumor. The other lesion was detected by ultrasonography. Three cases were diagnosed as multiple cancers. In a case with colon cancer and thyroid cancer, PET was positive on both lesions. In a case with colon cancer and gastric cancer, PET was positive only for the colon cancer. In a case with pancreas cancer and colon cancer, PET was positive only for the pancreas cancer. Advanced colon cancer (12-mm in diameter) was missed by our cancer screening program. The lesion was located in the colosigmoid junction, and it was detected by preoperative colonoscopy performed 10 days after the PET study. Histological type of these PET negative cases was all well-differentiated adenocarcinomas.

4. Cancer missed by PET and other examinations

Six cancers (0.18%) were missed in our screening program but were discovered by other examinations at a different hospital (Table 5). The lesions were found in the following organs: 2 in the stomach, 2 in the colon and one each in the pharynx and larynx. The cancer stages were as follows: 1 case was stage 0, 2 cases were stage I and 1 case was stage II. In the colon cancers, 1 was stage 0 and the other was stage I. In larynx cancer, 1 case was stage I. In gastric cancer, 1 case was stage II. The stage 0 sigmoid colon cancer of 10-mm in diameter could not be detected on PET, but was positive on colonoscopy. A case with stage II gastric cancer was negative on PET, but detected by gastroscopy performed 8 months later, because the patient complained of anorexia. A case with stage I larynx cancer was negative on PET, but detected by laryngoscopy performed 6 months later, because the patient complained of hoarseness.

DISCUSSION

Cancer screening is a major healthcare issue. More and more healthy persons are willing to undergo cancer screening. Whole-body PET can be used to survey the entire body seamlessly; the targets are not confined to a single organ in cancer screening.[11–13] FDG-PET screening therefore, is expected to play an important role as a part of

cancer screening program. The detection rate on PET alone of our study is similar to that reported by Chen et al.[12] (1.05%), Shen et al.[13] (1.20%), and Ide[14] (1.33%) (Table 6). On the other hand, Kao et al.[15] reported the detection rate of PET alone to be 2.34%, which was twice as good as ours and others.[12–14] The reason for this good result may be due to a small number of subjects. A wide variety of cancers are detected by PET at potentially curative stages. In our study, colon, thyroid gland, breast and lung cancers were more frequently detected by FDG-PET, similar to the previous reports.[12–15]

On the other hand, cancers undetected with PET are the most troublesome issue on cancer screening by PET. Yasuda et al.[16] reported that PET-negative cancers were categorized into 4 groups: including (A) urologic cancers, (B) cancers of low cell density (signet ring cell cancer of the stomach and scirrhous-type breast cancer), (C) small cancers and (D) hypometabolic or FDG-negative cancers (lung cancer and hepatoma). Similar to the results of previous reports,[12–15] most urologic cancers and some lung cancers were not detected with PET in our study. 84.2% of PET-negative cancers were early stage cancers. However, most cancers could be detected in early stage with PET screening in conjunction with other examinations. Therefore, we propose that PET screening should be performed in conjunction with other appropriate examinations.

The following is a discussion about each type of cancer.

a. Colon cancer

On colorectal cancer screening using a two-day immunological FOBT (fecal occult blood testing),[20] the detection rate was 0.15% and detection rate of stage 0–II cancer was 77.4%.[21] In our study, the detection rate of colon cancer was higher than that of the previous reports (0.25–0.33%).[12–15] Uno et al.[22] reported that the rate of stage 0–II cancer was 80.0%. The detection rate on PET alone thus appears to be superior to that on FOBT, and PET thus may have the potential to detect tumors at an early stage.

b. Thyroid cancer

Quite a number of individuals were found to have thyroid cancer, which has not yet been addressed in cancer screening programs in Japan. Thyroid cancer as identified by ultrasound screening in women occurred with a frequency of 2.6%.[23] Although the prognosis of papillary thyroid cancer is excellent, many stage I tumors surprisingly behave aggressively during the follow-up.[24] Uno et al.[22] reported that the stages of PET positive thyroid cancer were as follows: 33.3% were stage I, 11.1% stage II, 55.6% stage III.

c. Lung cancer

On lung cancer screening using chest radiography, the detection rate of lung cancer was reported to be 0.06%, including 52.42% of stage occult-IIB cancer. On initial screening with low-dose helical CT, the detection rate was 0.87%, including 78% of stage IA–IIA cancer.[25] According to the PET cancer screening reports by Yasuda et al.,[16] 80% of cases were stage I. But, in our study, the rate of stage I cancer was relatively low. This is probably because our participants had not previously received PET screening. Repeat screening may lead to early detection of lung cancer. Low tumor cellularity or a small tumor size may result in a poor FDG accumulation.[26] The detection of early stage lung cancer is difficult on PET.

d. Gastric cancer

On screening using an upper gastrointestinal tract barium examination, the detection rate of gastric cancer was reported to be 0.13%,[20] including 85.4% of stage IA–II cancer.[21] Although the sensitivity of FDG PET in gastric cancer has been reported to be relatively low,[27] the detection rate of our study (0.20%) was superior to that of previous reports (0–0.08%).[12–15]

e. Urologic cancers

The most serious diagnostic limitation of FDG-PET in primary tumor was diagnosis of cancers of kidney and urinary tract. This is due to the excretion of FDG via the efferent urinary tracts.[28] The use of US/CT may complement the PET scan in cancer screening for urologic neoplasms. PET is also insensitive for the detection of early stage prostate cancer. Therefore, tumor markers including PSA can provide an additional help in aged men in cancer screening of prostate.[13]

f. Other cancers

With regard to small-numbered cancers (gallbladder, pancreas, esophagus), the evaluation of each site was difficult. Further observation may be required.

Multiple cancers

Multiple primary cancers in the elderly are not rare. Multiple primary cancers may represent a significant clinical challenge leading to further diagnostic procedures and differentiated therapeutic approaches.[29] When the second primary cancer shows symptoms, it is often beyond the reach of curative therapy.[30] The detection rate of second primary cancer at autopsy was 6.1%.[29] The detection rate of multiple cancers of our study (10.0%) was similar to that of previous reports.[29–31] We believe that FDG-PET is useful not only for detecting metastasis but also for second or third primary cancers.

Cancers missed by PET and other examinations

Some common tumors may be negative on FDG-PET, so FDG-PET alone may be insufficient for cancer screening. Di Martino et al.[32] reported that a panendoscopy may be the best way to detect superficial mucosal tumor lesions. Therefore, PET screening needs to be performed in conjunction with other gastrointestinal examinations, for

example by means of a panendoscopy.

Problems associated with PET screening

There are a couple of potential limitations in our study. First, PET examination involves substantial cost compared to other examinations. No strong evidence has been obtained favoring the use of PET for oncology patients as a cost-effective modality except for lung cancer.[33] On cancer screening, cost-effective analysis may not support the use of PET. Because there is no justification for the use of public funds, each screenee needs to cover the cost by himself at present. In the future, if PET screening is deemed useful for properly-selected, high-risk groups, debates around cost-benefit issues may arise. Second, PET screening involves some radiation exposure. However, the radiation absorbed dose can be effectively reduced by voiding. Regarding CT, we have attempted to reduce radiation exposure to use a pitch of 7.0 (high-speed mode). Radiation dose is linearly related to tube current, scanning time, and scan volume and inversely related to pitch. When the pitch is doubled, radiation dose is reduced by half.[34] In addition, screening is usually applied to individuals after their reproductive years.[35] Regarding the occupational exposure after the FDG-PET study, the following are important to reduce excess radiation exposure: (i) minimize the close contact time with patients, (ii) increase the distance from the source and (iii) provide suitable protective shielding. Third, there may have been some patients with cancer, but these cancers were not discovered within the 1 year period after screening. In this respect, both the follow-up periods and the examinations conducted are not sufficient to confirm the accurate incidence of cancers. For these reasons, although PET has a high detection rate and the potential to detect cancers of many types at early stages, the routine use of FDG-PET in the general population remains controversial, and a reduced mortality has not yet been confirmed. As a result, its diagnostic value needs to be clarified in future studies.

In conclusion, PET imaging has the potential to detect a wide variety of cancers at potentially curative stages. Most PET-negative cancers are early cancers, and could be detected using other conventional examinations such as endoscopy. Combination of PET with these examinations may be an effective approach for cancer screening.

REFERENCES

1. Rigo P, Paulus P, Kaschten BJ, Hustinx R, Bury T, Jerusalem G, et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med* 1996; 23: 1641–1674.
2. Adler LP, Blair HF, Makley JT, Williams RP, Joyce MJ, Leisure G, et al. Noninvasive grading of musculoskeletal tumors using PET. *J Nucl Med* 1991; 32: 1508–1512.
3. Price P, Jones T. Can positron emission tomography (PET) be used to detect subclinical response to cancer therapy? *Eur J Cancer* 1995; 31A: 1924–1927.
4. Okada J, Oonishi H, Yoshikawa K, Itami J, Uno K, Imaseki K, et al. FDG-PET for predicting the prognosis of malignant lymphoma. *Ann Nucl Med* 1994; 8: 187–191.
5. Nakata B, Chung YS, Nishimura S, Nishihara T, Sakurai Y, Sawada T, et al. ^{18}F-fluorodeoxyglucose positron emission tomography and the prognosis of patients with pancreatic adenocarcinoma. *Cancer* 1997; 79: 695–699.
6. Oshida M, Uno K, Suzuki M, Nagashima T, Hashimoto H, Yagata H, et al. Predicting the prognoses of breast carcinoma patients with positron emission tomography using 2-deoxy-2-fluoro^{18}F-D-glucose. *Cancer* 1998; 82: 2227–2234.
7. Guerrero TM, Hoffman EJ, Dahlbom M, Cutler PD, Hawkins RA, Phelps ME. Characterization of a whole body imaging technique for PET. *IEEE Trans Nucl Sci* 1990; 37 (2): 676–680.
8. Conti PS, Lilien DJ, Hawley K, Keppler J, Grafton ST, Bading JR. PET and 18-[F] FDG in oncology: a clinical update. *Nucl Med Biol* 1996; 23: 717–735.
9. Delbeke D. Oncological applications of FDG PET imaging: brain tumors, colorectal cancer lymphoma and melanoma. *J Nucl Med* 1999; 40: 591–603.
10. Lassen U, Daugaard G, Eigtved A, Damgaard K, Friberg L. ^{18}F-FDG whole body positron emission tomography (PET) in patients with unknown primary tumours (UPT). *Eur J Cancer* 1999; 35: 1076–1082.
11. Yasuda S, Shohtsu A. Cancer screening with whole-body ^{18}F-fluorodeoxyglucose positron-emission tomography. *The Lancet* 1997; 350: 1819.
12. Chen YK, Ding HJY, Su CT, Shen YY, Chen LK, Liao AC, et al. Application of PET and PET/CT imaging for Cancer Screening. *Anticancer Res* 2004; 24: 4103–4108.
13. Shen YY, Su CT, Chen GJS, Chen YK, Liao ACF, Tsai FS. The value of ^{18}F-fluorodeoxyglucose positron emission tomography with the additional help of tumor markers in cancer screening. *Neoplasma* 2003; 50 (3): 217–221.
14. Ide M. Cancer screening with FDG-PET. *Jpn J Clin Radiol* 2004; 49: 835–840.
15. Kao CH, Kwan AS, Kwan JK, Chow MJ. The role of ^{18}F-fluorodeoxyglucose positron emission tomography in cancer screening—A preliminary report. *Oncology Reports* 2001; 8: 1145–1148.
16. Yasuda S, Ide M, Fujii H, Nakahara T, Mochizuki Y, Takahashi W, et al. Application of positron emission tomography imaging to cancer screening. *Br J Cancer* 2000; 83 (12): 1607–1611.
17. Jinnouchi S. Could FDG-PET change the conventional scheme of cancer screening? *Jpn J Clin Radiol* 2004; 49: 855–863.
18. Engel H, Steinert H, Buck A, Berthold T, Huch Boni RA, von Schulthess GK. Whole-body PET: physiological and artifactual fluorodeoxyglucose accumulations. *J Nucl Med* 1996; 37: 441–446.
19. Sobin LH, Wittekind CH, eds. *TNM Classification of Malignant Tumors*, 5th ed. New York; John Wiley & Sons, Inc., 1997.
20. Japan Cancer Society. *The Statistics of Cancer Screening 2003*. Tokyo; Japan Cancer Society, 2003.
21. Japanese Society of Gastroenterological Mass Survey. *Annual report of gastroenterological mass survey in Japan 2002*. Tokyo; Japanese Society of Gastroenterological Mass

Survey, 2002.
22. Uno K, Woo J, Suzuki T, Suzuki H, Kosaka N, Matsuo Y, et al. What are the problems of cancer screening using FDG-PET? *Jpn J Clin Radiol* 2004; 49: 841–846.
23. Chung WY, Chang HS, Kim EK, Park CS. Ultrasonographic mass screening for thyroid carcinoma: a study in women scheduled to undergo a breast examination. *Surgery Today* 2001; 31: 763–767.
24. Siironen P, Louhimo J, Nordling S, Ristimäki A, Mäenpää H, Haapiainen R, et al. Prognostic Factors in Papillary Thyroid Cancer: An Evaluation of 601 Consecutive Patients. *Tumor Biology* 2005; 26: 57–64.
25. Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. *J Clin Oncol* 2002; 20 (4): 911–920.
26. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. *Lung Cancer* 2004; 45 (1): 19–27.
27. Stahl A, Ott K, Weber WA, Becker K, Link T, Siewert JR, et al. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. *Eur J Nucl Med* 2003; 30 (2): 288–295.
28. Hofer C, Kubler H, Hartung R, Breul J, Avril N. Diagnosis and monitoring of urological tumors using positron emission tomography. *Eur Urol* 2001; 40 (5): 481–487.
29. Merminod T, Zulian GB. Multiple malignant tumours in the elderly. *Crit Rev Oncol Hematol* 2002; 43 (3): 227–230.
30. Nishiyama Y, Yamamoto Y, Yokoe K, Miyabe K, Ogawa T, Toyama Y, et al. FDG PET as a procedure for detecting simultaneous tumours in head and neck cancer patients. *Nucl Med Commun* 2005; 26: 239–244.
31. Ishimori T, Patel PV, Wahl RL. Detection of Unexpected Additional Primary Malignancies with PET/CT. *J Nucl Med* 2005; 46: 752–757.
32. Di Martino E, Nowak B, Hassan HA, Hausmann R, Adam G, Buell U, et al. Diagnosis and staging of head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2000; 126: 1457–1461.
33. Robert G, Milne R. A Delphi study to establish national cost-effectiveness research priorities for positron emission tomography. *Eur J Radiol* 1999; 30: 54–60.
34. Vade A, Demos TC, Olson MC, Subbaiah P, Turbin RC, Vickery K, et al. Evaluation of image quality using 1:1 pitch and 1.5:1 pitch helical CT in children: a comparative study. *Pediatr Radiol* 1996; 26: 891–893.
35. Yasuda S, Ide M. PET and cancer screening. *Ann Nucl Med* 2005; 19 (3): 167–177.