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Application of PET and PET/CT Imaging for Cancer Screening

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Abstract. *The aim of this study was to evaluate the potential application of 18-fluorodeoxyglucose positron emission tomography (FDG PET) and PET/CT for cancer screening in asymptomatic individuals. The subjects consisted of 3631 physical check-up examinees (1947 men, 1684 women; mean age ± SD, 52.1 ± 8.2 y) with non-specific medical histories. Whole-body FDG PET (or PET/CT), ultrasound and tumor markers were performed on all patients. Focal hypermetabolic areas with intensities equal to or exceeding the level of FDG uptake in the brain were considered abnormal and interpreted as neoplasia. Follow-up periods were longer than one year. Among the 3631 FDG PET (including 1687 PET/CT), ultrasound and tumor markers examinations, malignant tumors were discovered in 47 examinees (1.29%). PET findings were true-positive in 38 of the 47 cancers (80.9%). In addition, 32 of the 47 cancers were screened with the PET/CT scan. PET detected cancer lesions in 28 of the 32 examinees. However, the CT detected cancer lesions in only 15 out of 32 examinees. The sensitivity of FDG PET in the detection of a wide variety of cancers is high. Most cancer can be detected with FDG PET at a resectable stage. CT of the PET/CT for localization and characteristics of the lesion showed an increased specificity of the PET scan. The use of ultrasound and tumor markers may complement the PET scan in cancer screening for hepatic and urologic neoplasms.*

The goal of cancer screening is to detect cancer at an early stage when it is treatable and curable. Screening modalities are constantly changing due to improvements in detection methods. Low-dose computed tomography (CT) has a greater detection rate in lung cancer at an earlier and potentially more curable stage than does chest radiography (1). Recently, CT for screening purposes has been used for the whole body (2,3). Whole-body MR imaging is also used for healthy individuals (4).

18-Fluorodeoxyglucose positron emission tomography (FDG PET) has been shown to detect a wide variety of tumor foci including lymphoma, melanoma, lung cancer, esophageal cancer, breast cancer, head and neck cancer and colorectal cancers (5). The FDG PET scan offers an alternative way of examining the whole body metabolism of glucose. PET with FDG is a diagnostic modality that can non-invasively survey the whole body and sensitively detect cancers. Several studies have suggested an important role for whole-body FDG PET in the detection of malignant lesions (6,7). Morphological changes depicted in CT have been equated to disease manifestation. CT has proved to be an accurate imaging modality for various cancers (8). In this study, we examined the potential application of PET/CT for malignancy cancer screening in asymptomatic individuals.

Materials and Methods

Patients. The analysis was based on data generated from FDG PET examinations, ultrasound examinations and tumor markers of 3631 examinees (1944 used PET and 1687 used PET/CT) from February 2001 through April 2003, within our health-screening program. All study subjects gave informed consent according to the guidelines of the local ethics committee and the Helsinki Declaration.

PET/CT imaging protocol. Our PET center was opened in February 2001 with a Siemens (ECAT EXACT HR+, model 962, Knoxville, TN, USA) whole body scanner and a GE minitrace cyclotron. The second scanner, a PET/CT system (Discovery LS, GE Medical Systems, Waukesha, WI, USA), was added to the center in March. 2002. Patients were required to fast for at least 8 hours before the PET scan; furthermore, patients had to be well hydrated and avoid strenuous work or exercise for 24 hours before the scan. They were scanned in as many sequential images as necessary to include the entire head, thorax, abdomen and pelvis. Transmission images were obtained for 2 minutes per bed position to correct for photon attenuation using a germanium 68 line source. In the PET/CT scanner, the PET attenuation correction factors were calculated

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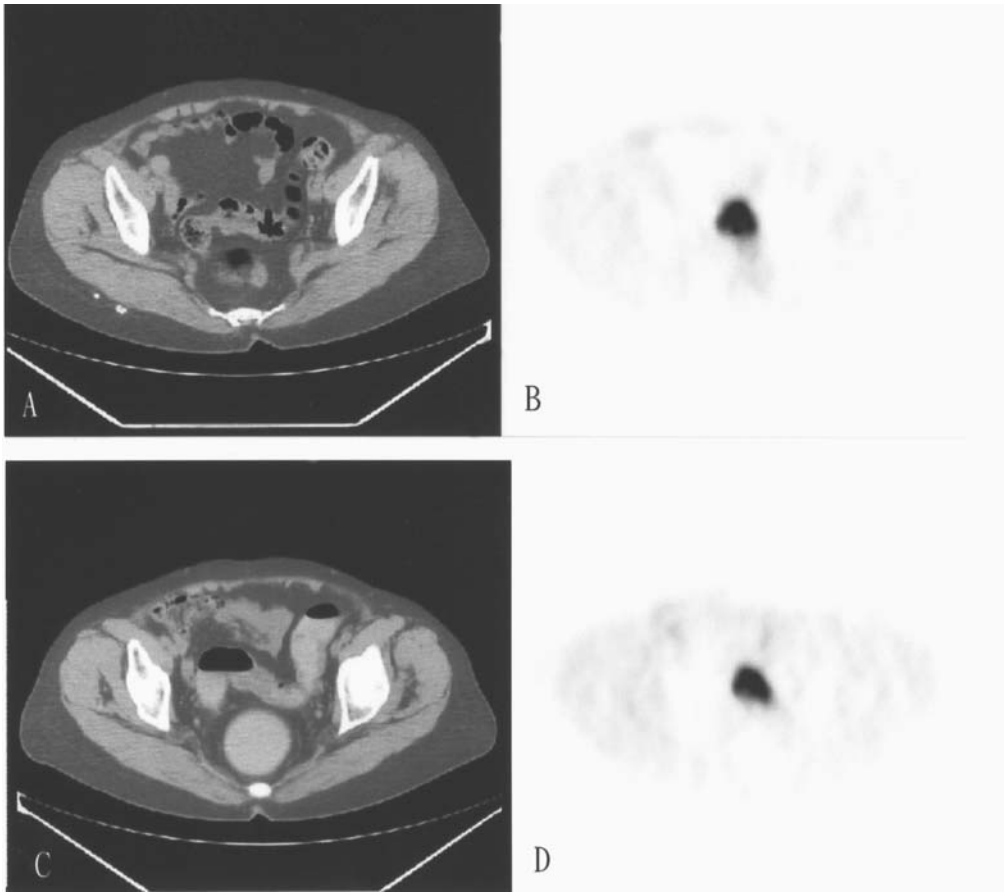

Figure 1. *Transaxial PET images of the illustrative case with FDG PET-positive and CT-negative: A 72-year-old asymptomatic woman underwent PET/CT study which was performed using a GE discovery LS PET/CT hybrid imaging scanner. The arrow points to an intense FDG uptake in the sigmoid of the transaxial (B and D) image. On the second scan (C and D), laxative and dilute contrast medium was give from the anus, and the scan was performed 1 h 38 min after scan 1; tumor was persistently present. Subsequently, colonscopy examination revealed adenocarcinoma at 20 cm from the anus. A low anterior resection for sigmoid colon was then performed and revealed a fungating tumor mass measuring 2.8 x 2.5 cm. Histopathological study showed the adenocarcinoma, moderately-differentiated, in modified Duke's B1 stage. The findings in this case suggest that colonic adenocarcinoma detected by PET is useful in asymptomatic population and can potentially facilitate the detection of early stage malignancy.*

from the CT images. CT was performed using a multidetector helical CT scanner. Acquisitions occurred at 5-7 bed positions and had the following parameters: 140 kV, 40 mA, 0.8 sec per CT rotation, a pitch of 6, a table speed of 22.5 mm/sec, coverage of 722.5-1,011.5 mm, and an acquisition time of 31.9-37 sec. CT was performed before the emission acquisition. CT data were resized from a 512 x 512 matrix to a 128 x 128 matrix to match the PET data so that the images could be fused and CT transmission maps generated. The transaxial resolution (full width at half maximum) of PET and PET/CT were 4.58 mm and 4.8 mm, respectively. After *i.v.* administration of 370 MBq (10 mCi) of FDG, emission images were acquired for 5 minutes per bed position. The uptake period between the FDG injection and the beginning of the emission scan was 60 plus/minus 10 minutes (range 50 to 70). With the use of camera-based PET/CT, acquisition of FDG and low-dose CT were both performed during normal breathing. Image data sets were obtained using iterative reconstruction (ordered-subset expectation maximization method).

Tumor marker test. Blood samples from all patients were obtained before the FDG injection, and the serum was stored at -20˚C. The determination of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), prostate specific antigen (PSA) and CA 199 was based on a solid phase two-site immunoradiometric assay for a direct quantitative measurement in serum. The reference range of AFP, CEA, PSA and CA 199 was less than 10 ng/ml, 5 ng/ml, 2.5 ng/ml and 37 U/ml, respectively. The electrochemoluminescence immunoassay of the determination of CA 125 and CA 153 is intended for use on the Roche Elecsys 1010/2010 based on the sandwich principle. The reference range of CA 125 is less than 35 U/ml, whereas the reference range of CA 153 is less than 30 U/ml.

Data analysis. We retrospectively reviewed the PET/CT images of 32 cases of cancer, divided into PET images and CT images, which were read by two board-certified physicians of radiology and nuclear medicine, respectively. In addition, 32 cases of normal control were added to the cancer cases to be read. Image analysis was performed

Table I. *PET-positive in patients with cancers.*

Patient no.	Age	Sex	Diagnosis	Tumor size (cm)	Metastasis	Tumor marker	Treatment
1	63	M	Lung ca.	3.5	Mediastinal LNs	-	R/T, C/T
2	51	M	Lung ca.	3.5	LNs, rib	-	C/T, R/T
3	59	M	Lung ca.	2.02	-	AFP:129.68, CEA:6.76	Surgery
4	53	F	Lung ca.	3.5	Mediastinal LNs	CA-153:95.89	C/T, R/T
5	60	F	Lung ca.	4	LNs	CEA:31, CA-125:90	C/T, R/T
6	53	M	Lung ca.	2.5	LNs	CEA:6.22	Surgery
7	39	F	Lung ca.	3.7	-	-	C/T, R/T
8	60	M	Lung ca.	3	T7	CEA:15.76	C/T, R/T
9	55	M	Lung ca.	2.5	Mediastinal LNs	-	C/T, R/T
10	70	M	Colon ca.	4.0	-	-	Surgery
11	68	M	Colon ca.	4.5	1/13(+)LN	CEA :13.5	Surgery
12	59	M	Colon ca.	2	-	-	Surgery
13	69	F	Colon ca.	3	-	-	Surgery
14	68	M	Colon ca.	3.1	-	-	Surgery
15	56	F	Colon ca.	3.2	-	-	Surgery
16	72	F	Colon ca.	2.8	-	-	Surgery
17	58	M	Colon ca.	2	-	-	Surgery
18	56	M	Colon ca.	3	-	-	Surgery
19	53	F	Breast ca.	1.5	-	-	Surgery
20	43	F	Breast ca.	1.5	Region LN	-	Surgery,C/T
21	58	F	Breast ca.	1.2	Axillary LN	-	Surgery
22	50	F	Breast ca.	1.1	Region LN	-	Surgery
23	49	F	Breast ca.	1.1	-	-	Surgery
24	51	F	Breast ca.	3.2	Axillary LN, T5	-	Surgery
25	38	M	Thyroid ca.	3	-	-	Surgery
26	71	M	Thyroid ca.	3.5	LN	-	Surgery
27	55	F	Thyroid ca.	2.5	-	-	Surgery
28	27	M	Thyroid ca.	2	-	-	Surgery
29	73	F	Thyroid ca.	1.7	-	-	Surgery
30	56	M	Lymphoma Stage I		NE	PSA:8.87	C/T
31	59	M	Lymphoma Stage III		NE	-	C/T
32	54	M	Lymphoma Stage III		NE	-	C/T
33	81	M	Hepatoma	4.1 (another 4.2)	PV thrombosis	CA-125:85.48, AFP:15.8	RFA
34	56	M	Hepatoma	2.4	-	AFP:16.43	Ethanol inj.
35	70	M	TCC of UB	1.4	-	-	Surgery
36	43	M	TCC of UB	4.5	-	-	Surgery
37	54	M	NPC	3.4	Region LN	-	R/T
38	51	F	Uterus ca.	4	-	CEA:5.69	Surgery

Ca.: cancer; C/T: chemotherapy; LN: lymph node; NE: not evaluated; NPC: nasopharyngeal carcinoma; PV: portal vein; RFA: radiofrequency ablation; R/T: radiotherapy; TCC: transition cell carcinoma; UB: urinary bladder.

Table II. *PET-negative in patients with cancers detected by conventional examinations.*

Patient no.	Age	Sex	Diagnosis	Tumor size (cm)	Tumor marker	Methods of detection
1	55	M	Hepatoma	2.3	AFP:18.18	US
2	37	M	Hepatoma	2.4	-	US
3	46	M	Hepatoma	2	AFP:129.68	US
4	70	M	Hepatoma	3	AFP:701	CT, US
5	78	M	Prostate ca.	Stage I	PSA:8.87	PSA
6	60	M	Prostate ca.	Stage I	PSA:30.34	PSA
7	49	M	Gastric ca.	2.7	CEA:81.48	US

CT: computed tomography; US: ultrasonography.

Table III. *Patients with cancer missed by screening.*

Patient no.	Age	Sex	Diagnosis	Tumor size (cm)	Period after screening
1	41	F	Upper lip, adenoid cystic carcinoma	1.5	3 months
2	48	F	Left breast, infiltrating duct carcinoma	1.8	11 months

in sequential steps. Initially, PET images were analyzed alone. Then, the CT image data were evaluated by the radiology physicians in the same fashion as were the PET images alone.

On FDG PET images, any FDG uptake that clearly exceeded the physiological liver uptake was defined as "lesion". Focal hypermetabolic areas with intensities equal to or exceeding the level of the FDG uptake in the brain that differed from the physiological uptake were considered abnormal and were interpreted as neoplasia. Furthermore, additional pathological information seen in CT only was also classified and localized in a manner that was identical to that for lesions taking up FDG.

Results

A total of 3631 examinees, including 1947 men and 1684 women, were involved in the cancer screening of asymptomatic individuals. The mean age was 52.1 ± 8.2 years old. No complication or mortality was found from FDG PET examination.

Among the 3631 asymptomatic participants, malignant tumors were identified in 47 (1.29%) within one year after screening. PET findings were true-positive in 38 of these cancers (Table I). Most of the patients underwent successful surgical treatment, except for lung cancer patients. Seven out of 9 lung cancers were characterized as equal to or more than stage IIB (AJCC 6th ed.). Of 9 examinees diagnosed with colon cancer, 2 had a Duke's stage A lesion, 6 had a Duke's stage B lesion (Figure 1), and one had a Duke's stage C lesion. Except for one patient with local lymph node (1/13) metastasis, other colon cancer patients had no lymph node or distant metastasis. Of 6 examinees diagnosed with breast cancer, 5 had tumors equal to or less than 1.5 cm. The local lymph node or axillary lymph node metastasis was 4/6. Of 5 examinees diagnosed with thyroid cancer, histopathological results showed papillary adenocarcinomas, and microscopic lymph node metastasis was observed in 1 patient. Of 2 examinees diagnosed with urinary bladder cancer, histopathological results showed transition cell carcinoma; one had a hot spot uptake of FDG, while the other had a mild uptake of FDG with a filling defect in the urinary bladder.

Nine cancers were PET-negative. Seven of these were detected by the conventional examinations performed during the screening (Table II), one was discovered three months later and another was discovered eleven months later through examinations obtained mainly because of clinical symptoms (Table III). Four of these cancers were hepatic cell carcinoma (Figure 2). Two of these cancers were prostate cancer. One of these cancers was gastric cancer detected by ultrasonography. The PET scan showed a mild uptake of FDG and a non-specific finding was found in the CT scan.

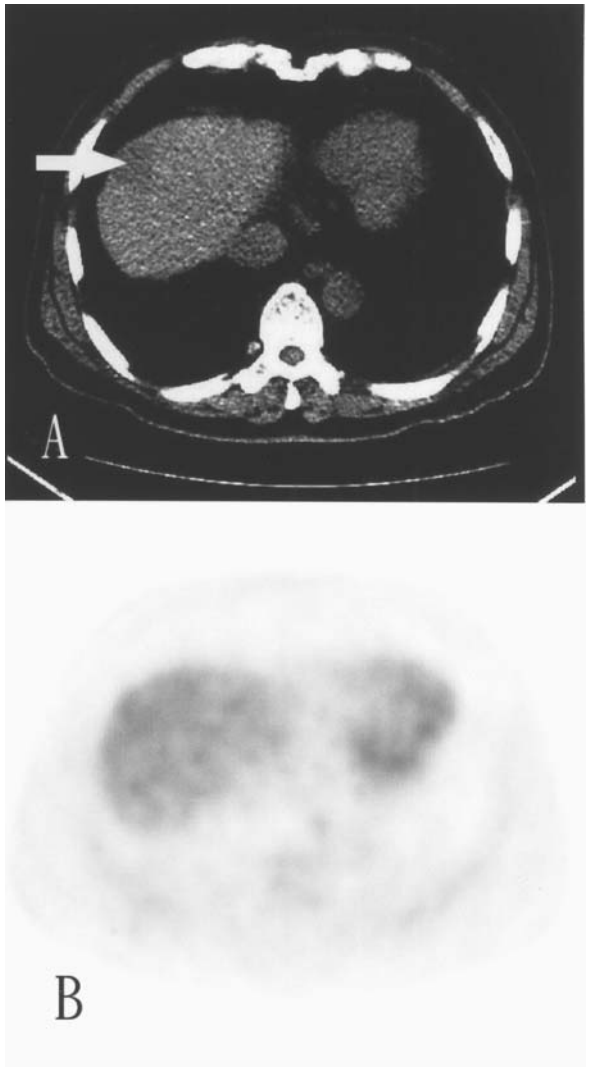

Figure 2. *Transaxial PET images of the illustrative case with FDG PET-negative and CT-positive: A 70-y-old asymptomatic man presented with a 3.0 x 2.2 cm mass in the liver. PET/CT study was performed using a GE discovery LS PET/CT hybrid imaging scanner. The arrow points to a hypodense mass in the right lobe of the liver in the transaxial (A) image. However, in the FDG PET image, no definite evidence of abnormal uptake in the liver (B) was detected. The patient received needle biopsy and histopathological interpretataion showed hepatoma.*

Thirty-two of the 47 cancers were screened with the PET/CT scan. PET/CT images, divided into PET images, and

CT images, were read by two board-certified physicians of radiology and nuclear medicine, respectively. PET detected cancer lesions in 28 of the 32 examinees. However, the CT discovered cancer lesions in only 15 out of the 32 examinees. The CT detected all the lung cancers in this study, colon cancers 2 in 4, breast cancers 1 in 6, thyroid cancers 1 in 3, hepatomas 1 in 4 (Figure 2) and nasopharyngeal carcinoma 1 in 1. One lymphoma, one urinary bladder cancer and one uterine cancer could not be detected by low-dose whole-body CT. Combined PET and CT detected cancer lesions in 29 of the 32 examinees. The hepatomas of 3 examinees were not detected by the PET/CT scan.

Discussion

Positron emission tomography (PET) with 2-[18F] fluoro-2-deoxy-D-glucose (FDG) is a whole-body imaging technique that exploits the increased rate of glycolysis in tumor cells to detect disease. FDG is a glucose analog that is taken up by cellular glucose transport mechanisms and is phosphorylated by hexokinase. In most malignant cells, FDG-6-phosphate then becomes metabolically "trapped" intracellularly because of the relative lack of glucose-6-phosphatase activity in tumor cells. Many studies indicate the greater accuracy of FDG PET in the staging of metastatic or recurrent cancers in comparison to CT and other standard diagnostic modalities, but the routine use of FDG PET in this general population remains controversial (5-7).

Colonoscopy is the gold standard for the diagnosis of colonic neoplasmas. Colonoscopy can be complicated by perforation, hemorrhage and respiratory depression due to sedation, arrhythmia, transient abdominal pain, ileus and nosocomial infection (9). The FDG PET scan offers an alternative way of examining the entire colonic metabolism of glucose. FDG PET depicted primary colorectal carcinomas with sensitivity from 94% to 100% (10-12). In this study, nine examinees were diagnosed with colon cancer, two had a Duke's stage A lesion, six had a Duke's stage B lesion, and one had a Duke's stage C lesion. Except for one patient with one local lymph nodes metastasis, other colon cancer patients had no lymph node or distant metastasis. So, PET with FDG is a diagnostic modality that can non-invasively survey the entire colon and sensitively detect cancers (13,14).

Mammography is widely accepted for breast cancer screening. Subsequent screening trials in other countries have shown, and continue to show, a mortality decrease in their study groups of women undergoing serial screening mammography (15-17). Although mammography has helped to detect breast cancer in many women, a number of cancers are missed in women who have dense breasts, implants, or have been treated previously for breast cancer. For diagnosis of breast cancer, FDG PET has high sensitivity and specificity rates (18,19). In this study, most of the breast tumors were less than 1.5 cm. Regional or axillary lymph node metastasis could be detected by FDG PET scan.

According to the cancer screening report of Yasuda *et al.*, eight of the ten PET-positive lung cancers were stage I (6). In this study, two of the nine lung cancers detected with PET received surgery. Low-dose CT can greatly improve the likelihood of detection of small non-calcified nodules, and thus of lung cancer at an earlier and potentially more curable stage (1,20,21). However, low-dose CT had no marked effect in the 1687 examinees where PET/CT was used for lung cancer screening in this study. Therefore, more cases may need to be studied.

In this study of asymptomatic individuals, PET-negative cancers were due to hypometabolic or no accumulation (phosphorylation similar to dephosphorylation kinetic constant) of FDG cancers (hepatoma), urologic cancers (prostate cancer), low cell density gastric cancers and small cancers. In Taiwan, hepatitis B carriers are common and are more likely to get hepatoma. So, for cancer screening, ultrasonography must be added to studies for liver and urology tumor. While the reason for a low FDG uptake in prostate cancer is not fully understood, the relatively slow growth of most prostate cancers may relate to low glucose metabolism. Therefore, CT is considered the other modality of choice for the evaluation of patients with malignancy, based on the detection of an abnormal mass or enlargement of organs, usually lymph nodes, caused by cancer growth. The role of PET using FDG in the evaluation of cancer is based on the increased glucose use by malignant cells compared with that of normal tissue. Both structural changes on CT and increased cell metabolism expressed by an abnormal FDG uptake should be considered in oncologic imaging. Hybrid imaging, a combined physiologic and anatomic modality, appears to provide new diagnostic opportunities in characterizing the function and morphology in malignancies. By correctly localizing and defining areas of increased FDG uptake as unrelated to cancer, hybrid imaging also leads to a decrease in the rate of false-positive results and improves the specificity of FDG PET.

The higher a person's risk of disease, the greater the potential benefit from screening for that person and the lower the cost of screening per cancer detected. Then, the ultimate goal of cancer screening is to detect curable cancers that would be fatal if left untreated. The FDG PET (PET/CT): (i) has high sensitivity and specificity in detecting cancers, (ii) has no complications, and (iii) is acceptable to patients, except for the relatively high cost. However, the cost of PET scans has been decreasing. Our study showed that most cancer could be detected with FDG PET (or PET/CT) in a resectable stage. Screening cancer with FDG PET (PET/CT) may improve the quality as well as length of life by reducing the extent or urgency of surgery, by decreasing the need for chemotherapy, and finally ameliorate suffering in those who die of the disease.

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