The value of 18F-fluorodeoxyglucose positron emission tomography with the additional help of tumor markers in cancer screening

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Cancer screening is a major healthcare issue. Screening modalities are constantly changing due to improvements in technology. Whole body positron emission tomography (PET) with 18F-fluoro-2 deoxy-D-glucose (FDG) and the additional help of the serum levels of tumor markers have been considered as non-invasive methods for cancer screening in asymptomatic subjects. A total of 1283 subjects underwent whole-body FDG PET studies with the additional help of the serum levels of tumor markers in our center for cancer screening. The final diagnoses were confirmed by other imaging modalities or pathological findings in subjects with positive FDG-PET findings, and follow-up for at least 6 months were held in subjects with negative FDG-PET findings. Among a total of 18 (1.4%) subjects with cancers, FDG-PET detected cancers in 15 (1.2%) subjects but with false negative studies in 3 subjects with hepatoma (AFP = 129.6 ng/ml), prostate cancer (PSA = 25.1 ng/ml), and breast cancer (CEA and CA-153 were normal). False-positive FDG-PET studies were found in 24 (1.9%) subjects. However, none had abnormal serum levels of tumor markers. Whole body FDG-PET with the additional help of tumor markers could reduce the false negative and false positive results of FDG-PET only.

Key words: Positron emission tomography, 18F-fluoro-2 deoxy-D-glucose, cancer screening, tumor markers.

The ultimate goal of cancer screening is to detect curable cancers that would be fatal if left untreated. In this respect, the effectiveness of cancer screening has been confirmed with mammography for breast cancer in women in their fifth decade. A recent study showed CT to be better than chest radiography for detecting lung cancer. However, when they were used for screening, the sensitivity and specificity of mammography is 72% to 97% [13] and CT scan is 68% to 96% [16].

Positron emission tomography (PET) with 18F-flouro-2-deoxyglucose (FDG) has been used to detect various cancers. High sensitivity and high specificity of FDG-PET have been reported to detect most malignancies, such as lung cancer, around 90 to 95% and 85 to 98%, respectively [10, 12, 17, 18]. Therefore, FDG-PET has been used for cancer screening with a very high sensitivity. However, more false-positive results were found in malignancy detected by FDG-PET [8, 15]. Because it is very low cost and easily available, assessment of tumor marker levels is widely used to screen early cancer. However, less sensitivity with more false-negative results was found in detection of malignancy by determination of serum tumor markers.

Therefore, we suppose that, combination of FDG-PET in association with serum tumor markers will significantly increase accuracy in cancer screening by reducing false negative and positive FDG-PET findings in asymptomatic subjects.

Subjects and method

Subjects. A total of 1283 subjects (547 women, 736 men, age ranges 51.2 ± 10.8 years (mean $\pm$SD) underwent whole-body FDG-PET studies with the additional help of the serum levels of tumor markers in our center for cancer screening from February 22, 2001 to June 30, 2002. The final diagnoses were confirmed by other imaging modalities or pathological findings in subjects with positive FDG-PET findings, and follow-up for at least 6 months were held in subjects with negative FDG-PET findings.

Table 1. Characteristics of the cancer patients

Subject No.	Age	Sex	FDG-PET Results	SUV	Final diagnosis	Tumor size (cm)	Metastases	Tumor marker
1	70	M	TP	2.04	Colon Ca	3.1	No	
2	68	M	TP	4.16	Colon Ca	5.2	Liver	
3	63	M	TP	3.56	Lung Ca	4.6	Lymph nodes, liver	
4	59	M	TP	2.72	Colon Ca	2.6	No	
5	70	M	TP	4.90	Urin.bladder Ca	2.1	No	
6	38	M	TP	7.70	Thyroid Ca	4.2	No	
7	56	M	TP	3.18	Gastric Ca	3.6	No	
8	56	M	TP	8.31	Lymphoma	4.9	No	
9	71	M	TP	2.55	Thyroid Ca	2.6	Lymph nodes	
10	56	M	TP	2.85	Hepatoma	2.3	No	
11	51	M	TP	3.27	Lung metastasis	2.7	Bones	
12	59	M	TP	3.15	Lymphoma	4.4	No	
13	59	M	TP	3.10	Lung Ca	3.0	No	
14	50	M	TP	2.60	Lung Ca	1.4	No	
15	69	F	TP	6.30	Colon Ca	3.3	No	
16	45	M	FN		Hepatoma	2.0	No	AFP=129.6
17	60	M	FN		Prostate Ca	MF	No	PSA=25.1
18	31	F	FN		Breast Ca	MF	No	

SUV – standard uptake value, MF – microscopic foci.

FDG-PET. They were required to fast overnight prior to the study. Fasting blood sugar level of each examined subject was obtained and those with fasting blood sugar level under 150 mg/100 ml underwent FDG-PET study. The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from all subjects.

Under sterile conditions, 2-deoxyglucose was labeled with 18F to produce FDG using MINItrace baby cyclotron (General Electric, Milwaukee, Wisconsin). After 10 mCi (370 MBq) of FDG were intravenously administrated to each subject, each subject was allowed lying comfortably in a dim room for 50 minutes, which served as uptake time. After complete void, each subject was positioned on a movable examination table for scanning. Each subject was scanned from the upper 1/3 of thigh to top of head with Siemens EXACT HR+ (CTI, Knoxville, Tenn.) in accordance with whole-body scanning protocol. Seven to eight beds (according to the subject's height), at three-minute transmission intervals and with emission at seven minutes per bed, were performed. Dedicated brain scan was conducted for 20 minutes in subjects with suspected abnormality of the brain. Transmission scans were reconstructed using filtered back-projection and smoothed with a Hann window of 2.5 mm width. Emission data were corrected for scatter, random events and dead-time. Image pixel size was 4.2 mm in a 128 x 128 array. Each whole body image was viewed by the whole-body-viewer using EXACT software (version 7.1). Profile images, with and without attenuation correction, were inspected and analyzed by the agreement of at least two of three experienced physicians.

The determination of AFP, CEA, PSA, and CA 199. Blood samples from all patients were obtained before 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 were 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 were 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 sandwich principle. The reference range of CA 125 is less than 35 U/m, whereas the reference range of CA 153 is less than 25 U/ml.

Results

Among a total of 18 (1.4%) subjects with cancers (Tab. 1), FDG-PET accurately detected cancers in 15 (1.2%) subjects including 4 colon cancers (Fig. 1), 3 lung cancers (Fig. 2), 1 urinary bladder cancer, 2 thyroid cancers, 1 gastric cancer, 2 lymphoma, 1 hepatoma, and 1 lung metastasis. Among the 18 subjects with cancers, false negative FDG-PET studies were found in 3 subjects with hepatoma (AFP=129.6 ng/ml, normal value <10 ng/ml), prostate cancer (PSA=25.05 ng/ml, normal value <5 ng/ml), and breast cancer (CEA and CA-153 serum levels were within the normal limits). False-positive FDG-PET studies were found in 24 (1.9%) subjects including 8 pulmonary tuberculosis

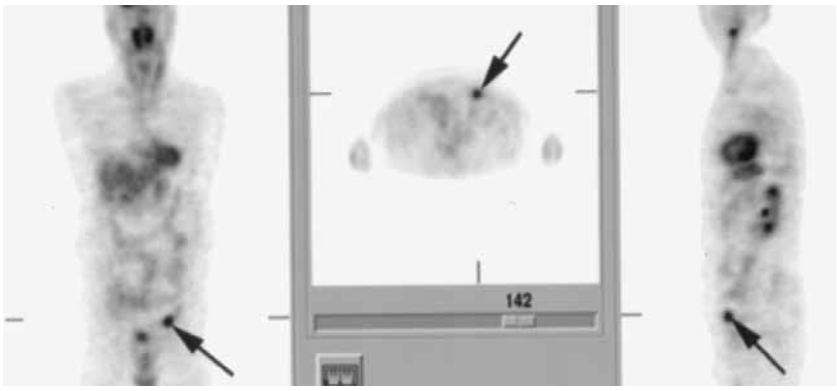

Figure 1. True positive FDG-PET findings demonstrated a hypermetabolism lesion in the left lower quadrant of the abdomen (arrows) with a final diagnosis of colon cancer.

(Fig. 3), 4 colon adenoma (Fig. 4), 2 pneumonia, 1 sarcoidosis, 2 pituitary adenoma, 3 thyroiditis, 1 otitis media, and 3 lymphoid hyperplasia (Tab. 2). Among the 24 subjects with false-positive FDG-PET, none had abnormal serum levels of tumor markers including AFP, CEA, PSA, CA-199, CA-125, and CA-153.

Discussion

FDG-PET has been developed to assess local glucose metabolism. Because malignant tumors exhibit increased glucose me-

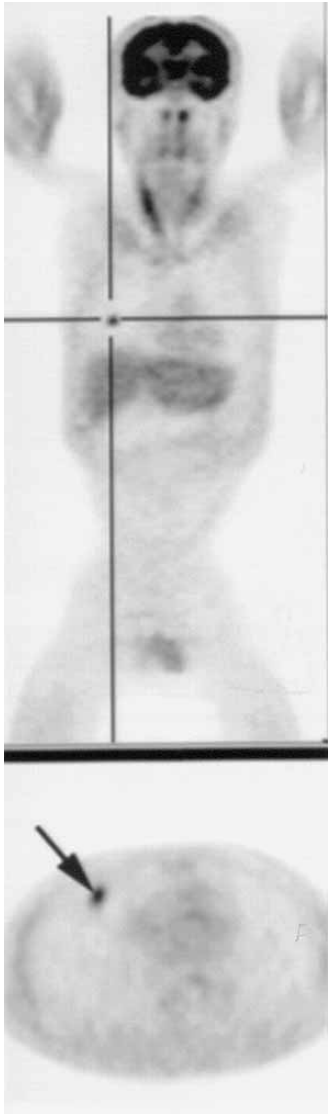

Figure 2. True positive FDG-PET findings demonstrated a hypermetabolism lesion in the right lower lung (arrows) with a final diagnosis of lung cancer.

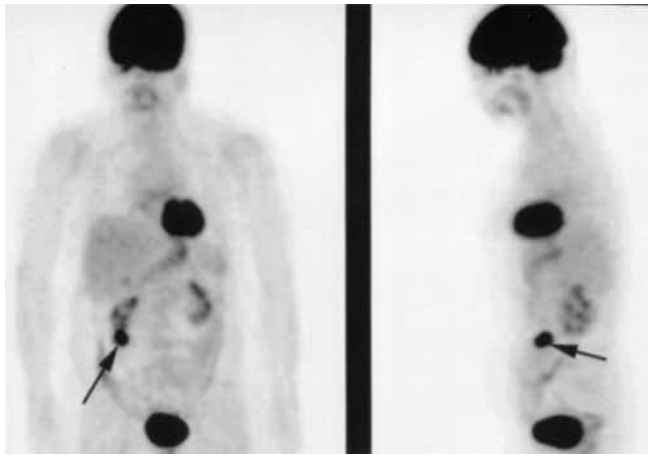

Figure 3. False positive FDG-PET findings demonstrated a hypermetabolism lesion in the right flank region (arrows) with a final diagnosis of colon adenoma.

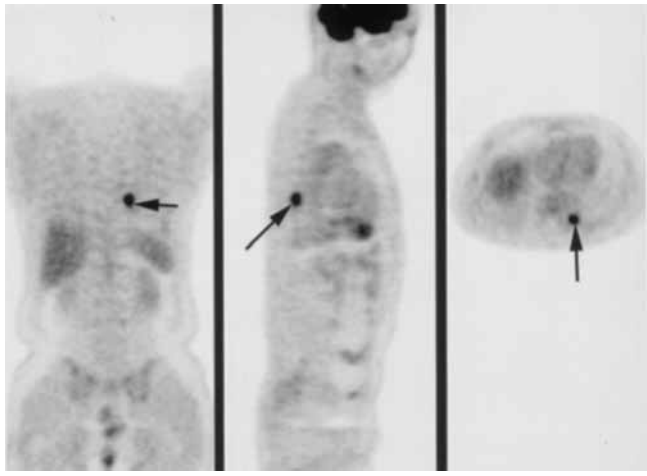

Figure 4. False positive FDG-PET findings demonstrated a hypermetabolism lesion in the left lower middle lung (arrows) with a final diagnosis of pulmonary TB.

Table 2. Characteristics of the patients with false positive FDG-PET studies

Subject No.	Age	Sex	FDG-PET Results	SUV	Final diagnosis	Tumor size (cm)
1	55	M	FP	2.2	Colon adenoma	2.3
2	78	M	FP	4.3	Colon adenoma	3.1
3	69	F	FP	3.3	Colon adenoma	2.3
4	47	F	FP	3.8	Colon adenoma	2.8
5	26	F	FP	2.3	Pulmonary TB	2.8
6	40	F	FP	11.6	Pulmonary TB	2.2
7	48	F	FP	2.9	Pulmonary TB	3.6
8	49	F	FP	1.4	Pulmonary TB	2.8
9	78	M	FP	3.2	Pulmonary TB	1.3
10	68	F	FP	1.3	Pulmonary TB	1.3
11	49	F	FP	9.6	Pulmonary TB	2.3
12	47	M	FP	2.2	Pulmonary TB	1.8
13	62	M	FP	5.0	Pulmonary TB	4.1
14	37	F	FP	5.0	Pneumonia	10.0
15	70	M	FP	3.6	Pneumonia	3.6
16	50	F	FP	5.7	Sarcoidosis	5.9
17	61	M	FP	7.3	Thyroiditis	2.8
18	38	F	FP	2.6	Thyroiditis	1.8
19	40	M	FP	7.2	Thyroiditis	7.0
20	47	F	FP	3.5	Otitis media	2.8
21	34	M	FP	7.9	NLH	1.8
22	55	M	FP	3.5	NLH	2.8
23	54	M	FP	2.9	NLH	2.0

NLH – nasopharyngeal lymphoid hyperplasia.

tabolism, FDG uptake by PET helps to differentiate between benign and malignant tumors [1], to determine the degree of malignancy [14], to evaluate the effectiveness of chemotherapy or radiotherapy [11] and to predict prognosis [6]. Since the invention of the whole-body tomography imaging technique [5], FDG-PET imaging has been shown to be sensitive enough to detect various cancers.

In this study, a total of 1283 subjects who underwent whole-body FDG-PET with the additional help of tumor marker check up participated in cancer screening program. Among of the 1283 subjects, 1241 (96.7%) subjects had true negative FDG-PET studies, 15 (1.2%) subjects had true positive studies, 3 (0.2%) subjects had false negative studies, and 24 (1.9%) subjects had false positive studies. Among the three false negative cases (Tab. 1), two had hepatoma and prostate cancer. The general sensitivity of FDG-PET for detecting hepatoma and prostate cancer is rather low [2, 7]. Therefore, the tumor markers including AFP and PSA can provide an additional help in high-risk patients of hepatitis carrier and aged men in cancer screening to prevent misdiagnosis. In the other subject with a false negative FDG-PET study, microscopic breast cancer was found. The sensitivity of FDG-PET for detecting primary breast cancer ranges from 85 to 97% [3, 4]. However, the resolution of PET limited the detection of microscopic breast cancer. In this condition, tumor markers including CEA and CA 153 could not help to detect the microscopic lesion. In this study, the most common causes of false positive FDG-PET studies were pulmonary TB and pneumonia (Tab. 2). After reviewing the literature, the high FDG uptake in pneumonia [9] and tuberculoma is a pitfall in using FDG-PET scanning for the detection of certain malignancies. However, among the 24 subjects with false positive FDG-PET, none had abnormal serum levels of tumor markers including AFP, CEA, PSA, CA-199, CA-125, and CA-153. When compared with HIMEDIC Imaging Center at Lake Yamanaka, Japan [8] and in PET Center, Chung Shan Medical and Dental College Hospital, Taichung, Taiwan [15], our results combining FDG-PET and tumor marker survey to cancer screening in asymptomatic subjects are encouraging to reduce the false negative and false positive results of FDG-PET only.

One of the major issues of cancer screening is the balance between cost and benefit. FDG-PET examination does involve substantial cost compared to other examinations. In terms of cost-benefit, no strong evidence has been obtained favoring the use of FDG-PET for routine cancer-screening test for the general population. It should be more valuable as a supplemented tool for check up in the subjects with high-risk of developing cancer.

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