Detection of Lung Cancer by FDG-PET Cancer Screening Program: A Nationwide Japanese Survey

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Abstract. *Aim: The aim of this study was to analyze the lung cancer detection rate in asymptomatic individuals by the Fluorine-18 fluorodeoxyglucose-positron emission tomography FDG-PET cancer screening program in Japan. Materials and Methods: A total of 153,775 asymptomatic individuals underwent the FDG-PET cancer screening program; the 854 cases with findings that indicated suspected lung cancer by any detection method were analyzed. Results: Among the 854 cases, 319 were verified as lung cancer. The relative sensitivity and positive predictive value (PPV) of FDG-PET were 86.5% and 38.9% for lung cancer, respectively. The sensitivity of PET/computed tomography (CT) scanner was higher than that of dedicated PET (100.0% vs. 63.2%), indicating that CT imaging was effective for lung cancer screening. The majority of lung carcinomas detected by FDG-PET screening were UICC stage IA or IB, but detection of smaller or less invasive carcinomas was limited. Conclusion: The FDG-PET screening program in Japan detected lung cancer at an early stage.*

The survival of patients with non-small cell lung cancer is directly related to cancer stage at diagnosis (1). The National Comprehensive Cancer Network (NCCN) guidelines for lung cancer prevention and screening indicate that public health policies to prevent initiation of smoking are required to reduce cancer mortality, because approximately 85-90% of cases are caused by voluntary or involuntary cigarette smoking (2). Chest radiography and sputum cytology have shown benefit for groups at high risk of lung cancer (3-6), but randomized trials of screening using them have not shown any reduction in lung cancer mortality (7, 8). Multidetector helical CT can scan the whole chest in a single maximal breath hold, and provides cross-sectional data acquisition and display; these capabilities overcome the limitations of chest radiography, in which there is interference between the lung nodule and existing structures. Recently, lung cancer screening by low-dose CT was proven to reduce lung cancer mortality by 20% in high-risk individuals (age >55 years and smoking ≥30 pack-years) (8).

Fluorine-18 fluorodeoxyglucose (FDG)-positron emission tomography (PET) and PET/CT are used to stage lung cancer, to detect and stage its recurrence, and to evaluate the efficacy of treatment (10).

In Japan, FDG-PET has been used extensively for cancer screening. The performance profile of FDG-PET cancer screening between 2006 and 2009 was reported previously, in which a total of 155,456 healthy individuals underwent FDG-PET scanning (including both PET/CT scanner and dedicated PET), with or without other tests for cancer screening, and cancer was detected in 1,912 cases (1.2%), 319 of which were lung cancer (11).

In the present study, the details of 854 individuals suspected of having lung cancer were further analyzed to clarify the characteristics of lung cancer detection with FDG-PET cancer screening.

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Materials and Methods

Participants. This study was based on the nation-wide survey of the FDG-PET cancer screening program performed between 2006 and 2009 for asymptomatic individuals. Cases with a past history of lung cancer or screening for recurrence requested by the attending physician or patient were excluded from the present report.

All study protocols in this retrospective observational study were approved by our Institutional Review Board (#A090924009). The Japanese Society of Nuclear Medicine published ''The Guidelines of FDG-PET Cancer Screening'' in 2004, revising it in 2007, with the aim of improving the quality of the FDG-PET cancer screening program (12, 13). All facilities performing the FDG-PET cancer screening program followed these guidelines, which included the assessment procedure for the interpretation of FDG-PET and PET/CT in the lung region. The overview of the survey involving the 155,456 individuals who underwent FDG-PET cancer screening has been reported previously (11). The study presented herein focuses on detailed analysis of the above database for suspected lung cancer cases. The entire population of the FDG-PET cancer screening database consisted of 153,775 individuals [92,255 men (60.0%), 61,520 women (40.0%)]. Lung cancer was suspected in 854 cases (208 cases in 2006, 212 cases in 2007, 204 cases in 2008, and 230 cases in 2009), and the detailed results of these 854 cases are discussed in the present report.

Contents of the investigation. Detailed information was collected on all suspected lung cancer cases. The survey included: sex; age group; whether or not repeated annual FDG-PET cancer screening; findings of FDG-PET (including CT findings of PET/CT scanner); results of combined cancer screening tests; and final results obtained by thorough examinations. The final result was categorized into one of three possibilities: proven cancer, cancer excluded, and strict follow-up because cancer was not completely ruled-out despite thorough examination. If the case was proven cancer, the survey collected the following information: definitive diagnostic procedure that proved lung cancer; the anatomical location of lung cancer; The Union for International Cancer Control (UICC) clinical stage (sixth version); the maximum tumor diameter (mm); and clinical and pathological cancer stages of the lung cancer.

Definition of terms. In this article, the term 'FDG-PET' is defined as an examination performed by a dedicated PET or a PET/CT scanner. 'FDG-PET cancer screening program' is defined as a cancer screening program that contains FDG-PET aimed at detection of cancer at an early stage, with or without any combined screening tests. If a cancer screening test was performed using a PET/CT scanner, regardless of the method used or manner of interpretation, the information obtained from the CT integrated in the PET/CT scanner was not regarded as part of the PET/CT imaging, not as a combined independent screening test. This definition was adopted because the CT findings could not be ignored when interpreting the PET/CT imaging. Hence 'PET-positive' in the case of PET/CT scanner represents positive findings on either PET imaging or CT of PET/CT imaging. However, to evaluate a lesion with FDG uptake obtained by PET/CT scanner, the data of the 'PET part of PET/CT scanner' of cases that showed abnormal FDG uptake in a lung lesion are also presented. Staging of lung cancer combines the results of both the clinical staging and pathological staging.

Statistical analysis. The Chi-square test for independence was performed to compare sensitivities among dedicated PET, PET-CT scanner, FDG-PET, carcinoembryonic antigen (CEA) test, squamous cell carcinoma-related antigen (SCC) test, and chest CT. Because participants with negative findings in the FDG-PET screening program did not undergo further screening, only the relative sensitivity of each test, which is defined as the rate of proven lung cancer cases detected by the specific test out of those detected by any test, and positive predictive value (PPV) analysis was performed to measure screening performance. A p-value less than 0.05 was considered significant. Exact methods were used to calculate 95% confidence intervals for all proportions. Data were analyzed with the SPSS software, version 11.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 854 (524 men, 330 women) out of the 153,775 participants had suspected lung cancer in the screening program. Among the 854, 319 cases (197 men, 122 women) of lung cancer and 325 cases of benign disease were finally detected, and the remaining 210 required strict follow-up. The final diagnosis of lung cancer was confirmed by surgical procedures in 217 cases, biopsy or cytology in 63 cases, clinical course in 20 cases, and other clinical information from the hospital conducting thorough examinations in 19 cases. Lung cancer was most frequently detected in the 60-69 year age group, and the detection rate and PPV were found to increase with age (Table I).

FDG-PET (dedicated PET and PET/CT scanner) for lung cancer. The sensitivity with a dedicated PET scanner was lower than that with a PET/CT scanner ($p<0.001$) (Table II). The PPV of PET/CT scanner was practically equivalent to that with dedicated PET ($p=0.21$). Using a PET/CT scanner, lung cancer was visualized as 138 PET-positive cases, with sensitivity of 68.3% and PPV of 46.6%, and visualized as CT-positive in 201 cases, with sensitivity of 99.5% and PPV of 38.7%. Only one lung cancer case was PET-positive, CT-negative.

Combined screening examination. The combination of chest CT with FDG-PET did not increase sensitivity but did increase the PPV. In screening for lung cancer, FDG-PET was much more sensitive than CEA ($p<0.001$) and SCC ($p<0.001$). As far as screening examination combinations, FDG-PET combined with CEA or SCC showed an increased PPV for lung cancer, but no increase in sensitivity (Table II). PET-positive cases had higher rates of lung cancer than negative cases, but included almost an equivalent rate of benign lesions. Not a small number of lung cancers which were found to be PET-negative, were covered by combined screening examinations. Moreover, PET-negative lung lesions tended to require strict follow-up. Twenty-one CT-negative cases included six cases of lung cancer, 11 cases of benign lesions, and four cases of strict follow-up. Out of these six

Table I. *Number of participants who were found to have positive lung lesions by screening FDG-PET and/or one or more of the combined screening tests if any, and the number and positive predictive value for detected cancers.*

Age group years	Number of participants	Total				Male				Female			
		Positive cases	Cancer found	Cancers rate (%)	PPV (%)	Positive cases	Cancer found	Cancers rate (%)	PPV (%)	Positive case	Cancer found	Cancers rate (%)	PPV (%)
30-39	8,923	20	2	0.02	10.0	10	0	0.00	0.0	10	2	0.05	20.0
40-49	26,206	68	17	0.06	25.0	41	7	0.04	17.1	27	10	0.10	37.0
50-59	51,546	242	87	0.17	36.0	128	44	0.14	34.4	114	43	0.21	37.7
60-69	47,712	338	132	0.28	39.1	218	88	0.30	40.4	120	44	0.24	36.7
70-79	16,854	155	66	0.39	42.6	106	46	0.46	43.4	49	20	0.29	40.8
≥ 80	2,534	31	15	0.59	48.4	21	12	0.81	57.1	10	3	0.29	30.0
Total	153,775	854	319	0.21	37.4	524	197	0.21	37.8	330	122	0.20	37.0

PPV: Positive predictive value.

Table II. *Detection of lung cancer by screening FDG-PET and/or by each of the combined screening tests.*

Screening examination	Number of case				Result[a]		FDG-PET[b]		Combination with FDG-PET[c]	
	Total	Positive[a]	Cancer found	Cancer not found	Sensitivity	PPV	Sensitivity	PPV	Sensitivity	PPV
FDG-PET[d]	854	709	276	43	86.5	38.9	-	-	-	-
PET scanner	303	172	74	43	63.2	43.0	-	-	-	-
PET/CT scanner	551	537	202	0	100.0	37.6	-	-	-	-
PET part of PET/CT	551	296	138	64		68.3	46.6			
Chest CT	571	550	228	6	97.4	41.5	81.6	43.9	99.6	58.8
CEA	601	71	47	184	20.3	66.2	87.9	40.1	88.7	60.0
SCC	351	24	12	135	8.2	50.0	88.4	43.8	88.4	56.7

[a]Positive cases by each screening examination; [b]result of FDG-PET in cases performed by each screening examination; [c]result if positive was defined as possibility of cancer by FDG-PET and/or screening examination; [d]result obtained by PET and PET/CT scanner; CT: Computed tomography; CEA: carcinoembryonic antigen, SCC: squamous cell carcinoma-related antigen.

lung cancer cases with negative findings on CT, five cases were suspected to have lung cancer because they were FDG-PET-positive, and two cases were suspected as cancer-positive with combined tumor marker examination (Figure 1).

Locations and diameters of detected lung cancer lesions. The location of lung carcinoma was 192 cases in the right lung (upper lobe: 111, middle lobe: 22, lower lobe: 59), 114 cases in the left lung (upper lobe: 68, lower lobe: 46) 8 cases in the mediastinum. The sensitivity of FDG-PET for lung cancer in the lung and mediastinum were 86.3% (264/306) and 100.0% (8/8), respectively. The sensitivity of FDG-PET for lung cancer was found to increase with tumor size. CEA had a low sensitivity overall (Table III).

Pathology of detected carcinomas. The pathology of the detected lung carcinomas was adenocarcinoma in 216 cases, squamous cell carcinoma in 28 cases, small cell carcinoma in 10 cases, large cell carcinoma in seven cases, and unidentified in 58 cases. The sensitivity of FDG-PET was not dependent on the pathology (adenocarcinoma 86.1%, squamous cell carcinoma 92.9%, small cell carcinoma 90%, large cell carcinoma 100.0%).

FDG-PET (PET scanner and PET/CT scanner) for benign lung lesions. Typical benign lung diseases detected by the screening program were chronic or old inflammatory changes of the lung in 105 cases and active inflammatory changes of the lung in 91 cases. In addition, tuberculosis (10 cases), sarcoidosis (7 cases), silicosis (5 cases), interstitial pneumonitis (4 cases), and abscess (1 case) were found in this screening program. No abnormality was confirmed in 36 cases; these were regarded as physiological FDG uptake.

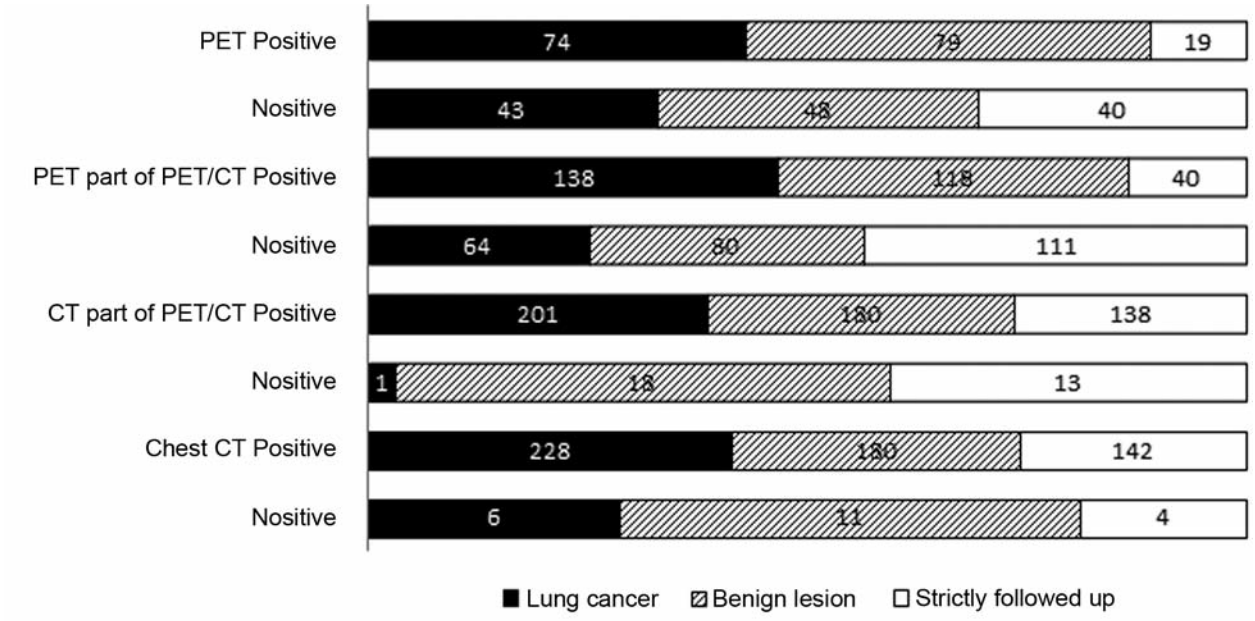

Figure 1. *The results for positive and negative cases by PET, PET/CT and chest CT.*

Cases categorized as requiring strict follow-up. Out of the cases categorized as requiring strict follow-up, 75% (151/201) had no positive FDG uptake, but were identified by the CT part of FDG-PET/CT scanning and/or other combined screening tests. Most cases categorized as requiring strict follow-up were due to the interpretation of pure ground glass opacity (GGO) (113 cases), of which the average maximum diameter was 11 mm (range 4-20 mm). Another major reason was due to the difficulty in interpretation of small nodules (35 cases) that required follow-up, of which the average maximum diameter was 11 mm (range 4-30 mm).

Cancer staging. The results for cancer staging were based on 78 cases with clinical staging and 168 cases with pathological staging. The sensitivity of FDG-PET, CEA, and the combination of the two for lung cancer according to UICC stage is shown in Table IV. Most lung cancers were detected in stage IA or IB (71.7%, 175/244) and lower than or equal to stage IIIA in 86.9%, but 13.1% of the detected lung carcinomas were in advanced stages for whom surgery was not indicated. FDG uptake had limitations for detecting stage I lung cancer.

Repeated screening was performed for 158 individuals. The final result was 55 cases of cancer, 71 cases of benign disease, and 32 cases that required strict follow-up. In only 44 of 55 cases could the staging result be obtained for individuals with repeated screenings. In these 44 cases, most cases (37/44) were detected in UICC stage IA or IB, and the others were IIIA (n=5) and IV (n=2).

Discussion

The potential of a FDG-PET cancer screening program for the detection of lung cancer was evaluated. PET/CT scanner showed a higher sensitivity than dedicated PET, and was more effective at screening lung lesions owing to the contribution by the CT part of the PET/CT scanning.

The rate of detecting lung cancer increased with age, and the rate markedly increased in the 50-59 year age group. Age over 50 years was a high-risk status for lung cancer (2), so this screening program covered these groups to find lung cancer at an early stage. However, the PET cancer screening program was performed at the participants' discretion; thus, the present sample may have been biased toward younger individuals. Identifying which ages would benefit most from such imaging is as yet an unsolved problem.

A limitation of this survey was that the smoking habits of screened individuals were unknown. Cigarette smoking is a major pathway to cancer induction, and not only harms individual smokers, but also affects those exposed to second-hand smoke or who are infrequent cigarette smokers (14). In an investigation of the relationships between several risk factors and the cancer detection rate in an FDG-PET screening program, smoking had significant correlations with detection of lung cancer in males (15). Even though cancer-related risk information for the screened individuals is unknown and differs by race, several studies have reported a high cancer detection rate of low-dose CT (approximately 1.64%; 438/267722; at the first screening and 1-year interval

Table III. *Sensitivity [% (n/N)] for lung cancer detected by FDG-PET and/or by each of the combined screening examinations according to maximum diameter of the cancer.*

Maximum diameter (mm)	Number of carcinomas	Screening modality					
		FDG-PET	PET	PET/CT	PET part of PET/CT	Chest CT	CEA
0-10	63	77.8 (49/63)	48.1 (13/27)	100.0 (36/36)	44.4 (16/36)	100.0 (50/50)	8.9 (4/45)
11-20	93	84.9 (79/93)	61.1 (22/36)	100.0 (57/57)	63.2 (36/57)	100.0 (65/65)	21.5 (14/65)
21-30	48	97.9 (47/48)	91.7 (11/12)	100.0 (36/36)	80.6 (29/36)	100.0 (32/32)	25.0 (9/36)
31-70	25	100.0 (25/25)	100.0 (7/7)	100.0 (18/18)	100.0 (18/18)	100.0 (12/12)	23.8 (5/21)

CEA: Carcinoembryonic antigen; CT: computed tomography.

Table IV. *Sensitivity [% (n/N)] for lung cancer detected by FDG-PET and/or by each of the combined screening examinations according to UICC cancer stage.*

Stage	Number of cancer	Screening modality					
		FDG-PET	PET	PET/CT	PET part of PET/CT	Chest CT	CEA
IA	154	79.9 (123/154)	46.6 (27/58)	100.0 (96/96)	55.2 (53/96)	97.6 (123/126)	13.6 (16/118)
IB	21	95.2 (20/21)	85.7 (6/7)	100.0 (14/14)	85.7 (12/14)	100.0 (15/15)	20.0 (3/15)
IIA	6	83.3 (5/6)	50.0 (1/2)	100.0 (4/4)	100.0 (4/4)	80.0 (4/5)	20.0 (1/5)
IIB	3	100.0 (3/3)	100.0 (1/1)	100.0 (2/2)	100.0 (2/2)	100.0 (1/1)	66.7 (2/3)
IIIA	28	100.0 (28/28)	100.0 (9/9)	100.0 (19/19)	89.5 (17/19)	100.0 (17/17)	33.3 (7/21)
IIIB	10	100.0 (10/10)	100.0 (4/4)	100.0 (6/6)	100.0 (6/6)	100.0 (10/10)	12.5 (1/8)
VI	22	100.0 (22/22)	100.0 (8/8)	100.0 (14/14)	100.0 (14/14)	100.0 (13/14)	44.4(8/18)

CEA: Carcinoembryonic antigen; CT: computed tomography.

screening) (2), which is superior to that of FDG-PET. Furthermore, the results of the PET cancer screening program presented by Terauchi *et al*. showed that approximately 85% (23/27) of detected lung carcinomas were PET-negative, out of which the majority were part-solid nodules (16). These results suggest the possibility of missing some lung carcinomas and a limitation of such a cancer screening program.

In a previous report regarding diagnostic performance, FDG-PET was found to be able to differentiate malignant lesions from others for lesions small as 8-10 mm, with an overall sensitivity, specificity, and accuracy of 96%, 88%, and 94%, respectively (17). In the NCCN guidelines for lung cancer screening, the use of PET/CT scanner should be considered for evaluating the possibility of malignancy in solid or partially solid nodules over 8 mm in diameter detected by low-dose CT (2).

Regarding the sensitivity of the screening modality by cancer stage, dedicated PET and the PET part of PET/CT scanning-alone showed limited detectability for carcinomas with a diameter of 20 mm or less, categorized as stage IA and IB cancer. The difference in the results between the present study and previous reports may be explained by the inclusion of fewer solid type lesions such as GGO type lung cancer and small lesions. FDG-PET has a lower sensitivity for small (less than 10 mm) or slow-growing lesions such as carcinoid tumors, GGOs, and adenocarcinomas with bronchioloalveolar features (18). The sensitivity (10%) and specificity (20%) for GGOs were significantly lower than for solid nodules (90% and 71%, respectively) (19). The cases in which GGO was found on the first screening required short-term follow-up to confirm increase in size and the appearance of the solid tumor part (2). In the PET cancer screening program, the cases that required strict follow-up because cancer was not ruled out, mostly consisted of FDG-negative pure GGO type lesions. Some types of lung cancer can be identified by a systematic process for appropriate follow-up, and the cancer screening program should pick-up cases with a predisposition to lung cancer.

The rate of positive screening tests was 27.3-27.9% with low-dose CT at the first screening and 1-year interval screening, and the true-positive rate was 3.11% (438/14092) (2). The present survey received inadequate answers from those who were judged to have a possible malignancy by the FDG-PET cancer screening program, even though proven malignancies appeared to be identified more frequently. However the frequency of a positive screening test with this program was 0.56% (854/153,775), which was lower than

that with low-dose CT lung cancer screening. This program might exclude cases with no need for therapy, and may prevent unnecessary further testing.

Greater FDG uptake correlates with poorer survival. On the other hand, low uptake is associated with an indolent nature and lack of intratumoral lymphatic invasion and regional metastasis. Cases with positive PET uptake had a higher possibility of lung cancer than PET-negative cases, but PET positivity could not detect all lung carcinomas and over half of the PET-positive cases proved to be benign or required follow-up because cancer was not clearly ruled-out. Therefore, FDG uptake is not a sufficient indicator for lung cancer screening, especially for small, low stage carcinomas. In contrast, chest CT was able to identify many more carcinomas, but these cases also included many benign lesions and those that required follow-up. Low-dose CT detected mostly stage IA cancer, with extremely few false-negative cases. The false-positive rate of low-dose CT increased in stage IIIB or IV cases (2). In contrast, FDG-PET covered high clinical stage cases. This indicates that FDG-PET has a high potential for screening mediastinal lesions or distant metastases that would be beyond the region covered by chest CT. Respiratory motion induces a misregistration between the FDG uptake and CT images in PET/CT scanning. This misregistration causes significant image distortion, misinterpretation of small lesions, and reduction of measured standardized uptake values (20).

A major problem of FDG-PET cancer screening is radiation exposure. The International Commission on Radiation Protection (ICRP) estimated lifetime attributable risk induced by radiation exposure as 0.005% per mSv (21). The average effective dose of radiation exposure is estimated to be 4.4 mSv with a dedicated PET study and 14.2 mSv with a PET/CT study. Risk-benefit analysis has shown that FDG-PET cancer screening is beneficial for examinees above a break-even age, based on a Japanese nationwide survey. However, the general risks and benefits of radiation exposure must be explained to examinees because of the larger radiation dose used in cancer FDG-PET imaging than in other radiological tests (22).

The high cost of FDG-PET cancer screening, which is estimated at over $1,000 per participant, is another major problem, even though FDG-PET cancer screening might detect many kinds of malignancies that cannot be revealed even by the combination of several other screening tests. Assessing the value of FDG-PET cancer screening is left to the judgment of the individual, provided that the advantages, disadvantages, and limitations of FDG-PET for cancer screening are fully disclosed to that individual.

A limitation of this survey is inadequate investigation of these who were judged to be cancer-negative in the FDG-PET cancer screening program. Furthermore, the present survey received inadequate response from these who were judged to have a possible malignancy in the FDG-PET cancer screening program, even though proven malignancies appeared to be identified more frequently.

Conflicts of Interest

None

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