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Detection of Thyroid Cancer by an FDG-PET Cancer Screening Program: A Japanese Nation-wide Survey

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Abstract. *Background/Aim: The [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) cancer screening program is defined as a cancer screening for asymptomatic subjects using FDG-PET (including PET/ computed tomography [CT]) with or without combination of other screening tests. The aim of the present study was to analyze the thyroid cancer detection rate in asymptomatic individuals through a FDG-PET cancer screening program in Japan. Materials and Methods: A total of 153,775 asymptomatic individuals underwent FDG-PET cancer screening. We analyzed 1,308 cases for possible thyroid cancer in all screening tests. Results: Among the 1,308 possible cases, 353 were verified as thyroid cancer. The relative sensitivity and positive predictive value (PPV) of FDG-PET were 90.7% and 29.5% for thyroid cancer, respectively. The relative sensitivity was equivalent to thyroid ultrasonography (US) (90.9%) and higher than neck computed tomography (CT) (75.7%, $p<0.001$), thyroglobulin (36.1%, $p<0.001$), and carcinoembryonic antigen (5.6%, $p<0.001$). The sensitivity with a PET/CT scanner was higher than that with a dedicated PET scanner (94.1% vs. 85.0%, $p<0.001$). Combining thyroid US with FDG-PET increased the relative sensitivity and PPV. The majority of thyroid carcinomas detected by FDG-PET screening were Union for International Cancer Control (UICC) stage I, but a significant number of cases were also detected as stage III or IV. Conclusion: The FDG-PET cancer screening program in Japan detected thyroid cancer at an early stage. FDG-PET showed high sensitivity in detecting thyroid cancer, and it may be more effective if combined with thyroid US.*

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In 2012, the estimated age-adjusted incidence rate of thyroid cancer in Asia was 3.2 *per* 100,000 subjects (male: 1.5, female: 5.0), and the associated mortality rate was 0.5 *per* 100,000 subjects (males: females; 0.3:0.7) (1). The incidence of thyroid cancer has been increasing all over the world, with an average increase of 48.0% in males and 66.7% in females during the past several decades (2, 3).

The increasing incidence of thyroid cancer is caused by increasing detection of small cancers enabled by widespread use of thyroid-specific tests such as ultrasonography (US) and fine-needle aspiration biopsy. Thyroid nodules without abnormalities on palpation have been incidentally found in 16-67% of subjects who underwent neck US (4). Indeed, the increasing use of imaging techniques may be responsible for the high occurrence of incidental thyroid nodules (5), although the risk of malignancy in these thyroid nodules is low (1.5-10.0%) (6). Moreover, the majority of thyroid cancers were papillary carcinomas, which may have a fair prognosis even with metastasis to regional lymph nodes (7-9).

Recently, thyroid nodules have been incidentally found by computed tomography (CT) and [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET), and 5.3-15.9% of the asymptomatic thyroid nodules are malignant (10-15). Moreover, a thyroid mass was incidentally found in 2.3% of patients having other cancers who underwent FDG-PET for evaluation of metastasis, and 47% of these incidentalomas were proven to be malignant (12). Therefore, thyroid incidentalomas with positive findings on FDG-PET may have a high potential of being cancerous (15, 16).

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In Japan, FDG-PET has been extensively used for cancer screening. The performance profile of FDG-PET cancer screening between 2006 and 2009 has been previously reported, in which a total of 155,456 healthy individuals underwent FDG-PET scanning (including both PET/CT and dedicated PET scanners), with or without other tests for cancer screening, and cancer was detected in 1,912 cases (1.2%), 353 of which were of thyroid origin (17).

In the present study, the details of 1,308 individuals suspected of having thyroid cancer were further analyzed to clarify the characteristics of thyroid cancer detection with FDG-PET cancer screening.

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 thyroid cancer or screening for recurrence of any cancer requested by the attending physician or the patients themselves were excluded from the present report.

All protocols in this retrospective study were approved by the Institutional Review Board of Yokohama City University Hospital (#A090924009). The Japanese Society of Nuclear Medicine and the Japanese Council of PET Imaging prepared ‘‘The Guidelines of FDG-PET Cancer Screening’’ in 2004 and revised 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 thyroid region.

The overview of the survey, involving 155,456 individuals who underwent FDG-PET cancer screening, has been reported previously (17). The study presented here focuses on a detailed analysis of the above database for suspected thyroid 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%)). Thyroid cancer was suspected in 1,308 cases, and the detailed results of these cases are examined in the present report.

Data collected in the investigation. Detailed information was collected on all suspected thyroid cancer cases. The survey included: sex, age group, whether the patient underwent repeated annual FDG-PET cancer screening, findings from FDG-PET (including CT findings in case of PET/CT scans), results of combined cancer screening tests other than PET; and final results obtained by thorough examinations. The patients were thus categorized into one of three cases: 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 thyroid cancer, the anatomical location of thyroid cancer, the Union for International Cancer Control (UICC) clinical stage (sixth version), the maximum tumor diameter (mm); and clinical and pathological stages of the thyroid cancer.

Definition of terms. In this article, the term ‘FDG-PET’ is defined as an examination performed by a dedicated PET or 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 image integrated in the PET/CT scanner was not regarded as a combined screening test, but as part of the PET/CT imaging. We adopted this definition because the CT findings cannot be separated from the PET/CT findings. Hence “PET positive” in a PET/CT test is defined as positive findings on PET part or CT part of the PET/CT. Accordingly, cases with FDG/negative but CT/positive on the screening test performed by a PET/CT were defined as “PET/positive”. Staging of thyroid cancer was based on the combined results of clinical staging and pathological staging that were available.

Statistical analysis. The Chi-square test for independence was performed to compare sensitivities among dedicated PET, PET/CT, FDG-PET, neck CT, thyroid ultrasound (US), thyroglobulin (TG) and carcinoembryonic antigen (CEA) tests. Because participants with negative findings in the FDG-PET screening program did not undergo further examination, our analysis provided only relative sensitivity of each test, which is defined as the rate of proven thyroid cancer cases detected by the specific test out of those detected by any test. Positive predictive value (PPV) was also computed to evaluate the screening performance. A p-value of less than 0.05 was considered statistically significant. Data were analyzed with the SPSS software, version 11.0 (SPSS Inc, Chicago, IL, USA).

Results

According to the screening program, a total of 1,308 (470 men, 838 women) of the 153,775 participants (0.85%) had suspected thyroid cancer. Among the 1,308 participants, 353 cases (147 men, 206 women) of thyroid cancer and 794 cases of benign disease were finally detected, and the remaining 161 required strict follow-up. The final diagnosis of thyroid cancer was confirmed by surgical procedures in 206 cases, biopsy or cytology in 134 cases, and other clinical information by conducting thorough examinations in 13 cases. The number of detected thyroid cancers was highest in the 50-59 year age group, and the detection rate and PPV were highest in the 40-49 year age group. More cancers were found in females than in males with the detection rate being more than twice as high (Table I).

FDG-PET (dedicated PET and PET/CT scanners) for thyroid cancer. The relative sensitivity was lower with a dedicated PET scanner than with a PET/CT scanner ($p<0.005$) (Table II). The PPV of the dedicated PET scanner was practically equivalent to that with a PET/CT scanner ($p=0.97$). Using a PET/CT scanner, thyroid cancer was visualized as FDG-positive as focal FDG uptake at thyroid in 191 out of the 207 PET-positive proven cancer cases, FDG having relative sensitivity of 86.8% and PPV of 32.4%, and was visualized as CT-positive in 154 out of the 207 cases, with CT part of PET/CT having relative

Table I. *Number of subjects with suspected thyroid cancer by FDG-PET screening and/or one or more of the combined screening tests, if any, number of proven cancers, detection rate, and positive predictive value.*

Age group	Number of subjects	Total				Male				Female			
		Positive case	Proven cancer	Detection rate (%)	PPV (%)	Positive case	Proven cancer	Detection rate (%)	PPV (%)	Positive case	Proven cancer	Detection rate (%)	PPV (%)
30-39	8,923	40	15	0.17	37.5	16	6	0.12	37.5	24	9	0.27	37.5
40-49	26,206	174	71	0.27	40.8	57	25	0.16	43.9	117	46	0.44	39.3
50-59	51,546	498	130	0.25	26.1	183	57	0.19	31.1	315	73	0.35	23.2
60-69	47,712	445	104	0.22	23.4	162	44	0.15	27.2	283	60	0.33	21.2
70-79	16,854	132	30	0.18	22.7	48	14	0.14	29.2	84	16	0.23	19.0
80-	2,534	19	3	0.12	15.8	4	1	0.07	25.0	15	2	0.19	13.3
Total	153,775	1,308	353	0.23	27.0	470	147	0.16	31.3	838	206	0.34	24.6

PPV: Positive predictive value.

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

	Number of case				Result*		Combination with FDG-PET**	
Screening examination	Total	Positive*	Proven cancer	Unfound cancer	Relative sensitivity	PPV	Relative sensitivity	PPV
FDG-PET***	1,308	1,084	320	33	90.7	29.5	-	-
PET scanner	531	382	113	20	85.0	29.6	-	-
PET/CT scanner	777	702	207	13	94.1	29.5	-	-
Neck CT	589	429	112	36	75.7	26.1	95.9	25.7
Thyroid US	587	529	150	15	90.9	28.4	98.8	27.9
Thyroglobulin	109	48	13	23	36.1	27.1	97.2	35.0
CEA	951	33	14	238	5.6	42.4	89.7	28.8

*Positive cases by each screening examination, **result if positivity is defined based on FDG-PET and/or each of the combined screening examinations, ***result obtained by PET and PET/CT, CEA: carcinoembryonic antigen, SCC: squamous cell carcinoma-related antigen.

sensitivity of 80.6% and PPV of 29.9%. Only 16 thyroid cancer cases were PET-negative and CT-positive.

Combined screening examinations. Combination of FDG-PET with other tests increased sensitivity and PPV. In screening for thyroid cancer, FDG-PET was much more sensitive than neck CT (p<0.001), TG (p<0.001), and CEA (p<0.001), while combination of FDG-PET with any of neck CT (p=0.01), thyroid US (p<0.001), or TG (p<0.001) contributed to a significant increase in sensitivity. Combination of FDG-PET with TG showed a significant contribution to increasing the PPV (Table II). Otolaryngological inspection (n= 20, sensitivity 16.7%, PPV 20.0%) and neck magnetic resonance imaging (MRI) (n= 36, sensitivity 53.3%, PPV 50.0%) were performed in few cases in this study and therefore, they were not evaluated.

Locations and diameters of detected thyroid cancer lesions. The location of thyroid carcinoma was in the right lobe in 181 cases, in the left lobe in 158 cases, and in the isthmus in 21 cases. About half (48.3%, 112/232) of the thyroid cancers were 10 mm or less in maximum diameter. The sensitivity of FDG-PET and thyroid US did not differ by location or size (Table III).

Pathology of detected carcinomas. The pathology of the detected thyroid cancers was papillary carcinoma in 315 cases, follicular carcinoma in 10 cases, medullary carcinoma in 2 cases, and anaplastic carcinoma in 1 case. FDG-PET and thyroid US were positive in 90.2% (284/315) and 90.8% (139/153) of the papillary carcinoma cases, respectively, and were positive in 90.0% (9/10) and 83.3% (5/6) of the follicular carcinoma cases, respectively.

Table III. *Relative sensitivity of FDG-PET or each of the combined screening examinations for detecting thyroid cancer according to size (maximum diameter).*

Maximum diameter (mm)	Number of cancer	Screening modalities						
		FDG-PET*	Dedicated PET	PET/CT	Neck CT	Thyroid US	Thyroglobulin	CEA
1-10	112	90.2 (101/112)	82.4 (28/34)	93.6 (73/78)	53.7 (22/41)	87.5 (49/56)	25.0 (1/4)	2.6 (2/77)
11-20	99	91.9 (91/99)	90.0 (36/40)	92.7 (51/55)	83.7 (36/43)	96.4 (53/55)	15.4 (2/13)	5.6 (4/72)
21-	21	90.5 (19/21)	77.8 (7/9)	100.0 (12/12)	100.0 (11/11)	90.0 (9/10)	66.7 (2/3)	10.0 (1/10)

*Result obtained by PET and PET/CT, US: ultrasound, CEA: carcinoembryonic antigen.

Table IV. *Relative sensitivity of FDG-PET or each of the combined screening examinations for detecting thyroid cancer according to UICC cancer stage.*

Stage	Number of cancer	Screening modalities						
		FDG-PET*	Dedicated PET	PET/CT	Neck CT	Thyroid US	Thyroglobulin	CEA
I	102	93.1 (95/102)	84.8 (28/33)	97.1 (67/69)	69.8 (30/43)	90.2 (46/51)	25.0 (2/8)	2.7 (2/75)
II	12	100.0 (12/12)	100.0 (6/6)	100.0 (6/6)	66.7 (4/6)	100.0 (9/9)	0.0 (0/3)	10.0 (1/10)
III	37	94.6 (35/37)	93.3 (14/15)	95.5 (21/22)	68.4 (13/19)	100.0 (18/18)	33.3 (1/3)	3.4 (1/29)
IV	34	88.2 (30/34)	78.9 (15/19)	100.0 (15/15)	71.4 (15/21)	100.0 (12/12)	50.0 (1/2)	0.0 (0/20)
IV A	31	87.1 (27/31)	77.8 (14/18)	100.0 (13/13)	70.0 (14/20)	100.0 (12/12)	0.0 (0/1)	0.0 (0/17)
IV C	3	100.0 (3/3)	100.0 (1/1)	100.0 (2/2)	100.0 (1/1)	-	100.0 (1/1)	0.0 (0/3)

*Result obtained by PET and PET/CT, US: ultrasound, CEA: carcinoembryonic antigen, UICC: Union for International Cancer Control.

Benign thyroid lesions detected by the program. Typical benign thyroid diseases detected by the screening program were adenomatoid goiter in 355 cases, chronic thyroiditis in 93 cases, benign nodular goiter in 92 cases, follicular adenoma in 52 cases, and thyroid cyst in 28 cases. PET was positive in 76.9% (273/355) of adenomatoid goiters, in 94.6% (88/93) of chronic thyroiditis, in 58.7% (54/92) of benign nodular goiters, in 88.5% (46/52) of follicular adenomas, and in 75.0% (21/28) of thyroid cysts. No pathological lesion was found in the thorough examination of 40 PET-positive cases; these were regarded as physiological FDG uptake.

Cancer staging. The sensitivity of FDG-PET as a screening modality for thyroid cancer according to UICC stage is shown in Table IV. Although most thyroid cancers were detected in stage I (55.1%, 102/185), 38.4% (71/185) of the cases were in advanced stages. Among the 34 cases with stage IV, 31 cases were stage IV A based on the existence of lateral node metastases (N1b), and 3 cases were stage IV C with proven distant metastases.

A total of 162 out of the 1,308 suspected cases were those who had undergone an FDG-PET cancer screening program a year before. The final results of the 162 cases were 37 cases of cancer, 104 cases of benign disease, and 21 cases that required strict follow-up. In only 14 of the 37 cases, the staging result was obtained. The majority of cases (8/14) were detected in UICC stage I, and the others were II (n=1), III (n=2), and IV (n=3).

Discussion

The present report evaluated the potential of an FDG-PET cancer screening program for the detection of thyroid cancer. The combined PET/CT scanner showed a higher sensitivity than a dedicated PET scanner and was more effective in screening thyroid lesions. Furthermore, the majority of the thyroid cancers found by the FDG-PET screening program was in stage I, although a number of cases were found in stages III and IV.

The rate of detecting thyroid cancer increased from the age range of 40-49 years with the female rate being approximately twice as high as the male rate. Because the PET cancer screening program was performed at the participants' discretion, the present data may have been biased toward younger individuals. Identifying, however, which ages would benefit most from this type of screening, is as yet an unresolved issue.

Thyroid US has been used for evaluation of thyroid nodules based on their size, shape, components, and vascularity. Moreover, many thyroid nodules are incidentally detected by US of the neck (6). The present results showed that US had higher sensitivity than neck CT, TG, and CEA. PET/CT showed higher, though not statistically significant, sensitivity and PPV than thyroid US, and the sensitivity for thyroid cancer was increased if FDG-PET was combined with thyroid US. TG has been effective for the prediction of post-surgical recurrence for thyroid cancer. However, it has not been recommended for use in preoperative diagnosis because of low specificity, the level of which is affected by the volume and activity of the thyroid (18). TG itself had low sensitivity and PPV in the present investigation, but it could increase the sensitivity and PPV of FDG-PET if used as a combined test. The CEA is included as a screening test for many kinds of malignancies in this program. Although CEA levels may be increased in cases with medullary carcinoma (19), it is not specific to thyroid cancer, and its elevation may detect several kinds of cancer other than thyroid cancer. The calcitonin level has shown high sensitivity for patients with medullary carcinoma (20), which is a minor type of thyroid cancer, it has not been recommended as a screening test (18), and it has not been widely used in this screening program. Neck CT, which was performed as part of the chest examination of the whole-body CT scan in this screening program, showed relatively high sensitivity. However, CT has a lower sensitivity and its detection rate is less associated with nodule size at pathology than thyroid US (21, 22).

Shie *et al*. found that the prevalence of malignant incidental thyroid nodules on FDG-PET in 18 articles was 1.0% (571 of 55,160 patients). In the present report, there was a significant difference in FDG uptake between benign nodules and malignant nodules, but this may not be useful because of substantial overlap between them (23).

The main point to be discussed for screening thyroid cancer is not only the issue of high specificity but also to sort-out thyroid cancers that have a high mortality. In fact, as in a previous report (24), the majority of thyroid cancers detected in this program were papillary in origin, which are well-differentiated, having a good prognosis with a 30-year survival rate of 95% (25). In contrast, only one case of life-threatening anaplastic thyroid carcinoma was found in the screening program. Therefore, there could be overdiagnosis due to the screening of many thyroid cancers.

UICC TNM classification is one of the most reliable criteria for risk stratification (26, 27). Common major indices for these risk classifications include age, tumor diameter, local invasion, and existence of metastases, but the TNM classification covers all these indices, showing significant differences in the survival rate between stages (28-32). Most thyroid cancers (55.0%, 102/185) were found in stage I, however, the rate of finding advanced cases with stages III and IV was higher than that for other malignancies found in this screening program (17). Most stage IV thyroid cancers (n=34) were stage IV A (n=31) based on the presence of lateral node metastases. PET/CT and neck US covered stage IV cases well, but there has been a debate about whether the presence of lymph node metastases would be a prognostic factor in patients with thyroid carcinoma (33-35).

A major problem of the FDG-PET cancer screening is radiation exposure. The average effective dose of radiation exposure is estimated to be 13.5 mSv according to a PET/CT study. Risk-benefit analysis has shown that FDG-PET cancer screening is beneficial for examinees above the age range of 50-60 years, based on a Japanese nation-wide survey (36). 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 (36).

The high cost of FDG-PET cancer screening is another major problem, even though this procedure might detect many kinds of malignancies that cannot be detected even by the combination of several other screening tests. Assessing the value of FDG-PET cancer screening should be left to the judgment of the individual, provided that its advantages, disadvantages, and limitations are fully-disclosed to that individual.

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

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Conflicts of Interest

None.

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