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FULL PAPER

Ability of 18-fludeoxyglucose positron emission tomography/CT to detect incidental cancer

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Objective: To determine the prevalence and clinical features of pathologically proven incidental cancer (IC) detected by whole-body fluorine-18 fludeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/CT, as well as the incidence of false-positive and false-negative results.

Methods: We retrospectively reviewed reports derived from ¹⁸F-FDG PET/CT images of 3079 consecutive patients with known or suspected malignancies for 3 years. Discrete focal uptake indicating IC was identified from reports as well as pathological or clinical diagnoses, and the clinical courses were investigated. The false-positive result was defined as uptake indicating IC but not pathologically confirmed as malignant during follow-up. The false-negative result was defined as pathologically proven IC detected

by another modality at initial clinical work-up or diagnosed during the follow-up period.

Results: We found ¹⁸F-FDG uptake indicating IC in 6.7% of all patients, and IC was pathologically proven in 2.2% of all patients. The most common sites were the colon, lung and stomach. The median survival duration of patients with IC was 42 months. The results were false positive in 4.5% of all patients, and the results were false negative in 2.3% of all patients.

Conclusion: ¹⁸F-FDG PET/CT is a valuable tool for detecting IC. The rates of false-positive and false-negative results are within acceptable range.

Advances in knowledge: This is the first report to describe the survival of patients with IC, and the detailed features of false-negative results at actual clinical settings.

Integrated whole-body positron emission tomography (PET)/CT using the glucose analogue fluorine-18 fludeoxyglucose (¹⁸F-FDG) is an established modality for oncologic imaging. Combined metabolic and morphological images yielded by ¹⁸F-FDG PET/CT can provide accurate information on the staging, restaging and therapeutic monitoring of many common cancers.¹ Furthermore, ¹⁸F-FDG PET and PET/CT have the potential for cancer screening. Owing to the non-specific nature of ¹⁸F-FDG uptake, a wide range of malignant tumours can be visualized as incidental foci of hypermetabolism. For instance, new malignant tumours have been detected in asymptomatic individuals,² patients with head and neck cancer,³ oesophageal cancer⁴ and malignant lymphoma.⁵ Incidental focal ¹⁸F-FDG uptake within the gastrointestinal tract frequently represents malignant and pre-malignant tumours.^{6,7} The detection of incidental cancer (IC) significantly impacts clinical oncological practice. Namely, the detection of a primary cancer can lead a patient to a new treatment, and the

detection of a second primary cancer can lead a patient to a more suitable treatment.

IC has been detected by ¹⁸F-FDG PET or PET/CT in the past decade.^{8–15} Table 1 summarizes the findings of these reports. The rate of detected incidental foci ranges from 3.0% to 12.3%.^{8–13} The detection rate of IC ranges from 0.9% to 4.4%,^{8–15} and a few reports have described a wider range (0.1–4.4%) of false-negative findings.^{13–15} However, the survival of patients with IC has not been detailed. Differences in detection rates and other findings arise owing to many factors, including country, age, symptomatic or asymptomatic individuals, ¹⁸F-FDG PET or PET/CT, judgment criteria, method and period of follow-up.

The purpose of our study was to prove the diagnostic efficacy and feasibility of ¹⁸F-FDG PET/CT to detect IC. We defined IC as a pathologically proven primary or second primary cancer, the existence of which was not suspected at

Table 1. Previous studies evaluating detection rate of incidental cancer (IC)

Author	Study design	Patients (n)/ mean age (years)	Modality	Rate of uptake indicating IC (%)	Rate of IC detected by PET or PET/CT (%)	Three most common sites of IC	Rate of PET or PET/CT negative IC (%)	Survival data
Agress Jr and Cooper ⁸	P patients	1750/NA	PET	3.0	1.7 ^a	Colon, breast and larynx	NA	NA
Ishimori et al ⁹	R patients	1912/58.9	PET/CT	4.1	1.2	Lung, thyroid and colon	NA	NA
Choi et al ¹⁰	P patients	547/60.5	PET/CT	8.2	4.4	Head and neck, lung and stomach	NA	NA
Wang et al ¹¹	R patients	1727/63.0	PET/CT	11.5	0.9 ^b	Lung, colon and breast	NA	NA
Beatty et al ¹²	R patients	2219/61.0	PET/CT	12.3	1.8	Lung, breast and colon	NA	Nine dead (median follow-up of 22 months)
Xu et al ¹³	R patients	677/NA	PET/CT	5.2	3.0	Colon, lung and thyroid	0.1	NA
Terauchi et al ¹⁴	P healthy participants	2911/59.8	PET	Not described	1.0	Colon, breast and thyroid	4.4	NA
Nishizawa et al ¹⁵	P healthy participants	1197/46.7	PET/CT	Not described	1.3 ^c	Thyroid, lung and breast	0.6	NA

NA, not available; P, prospective; PET, positron emission tomography; R, retrospective.

^aIncludes patients with pre-malignant tumour.

^bNon-thyroidal cancer.

^cDetected during initial cancer screening.

the time of examination. We determined the clinical details of patients with IC, as well as with false-positive and false-negative results by retrospective investigation of pathological or clinical diagnoses, clinical courses and survival data of all patients who underwent ¹⁸F-FDG PET/CT for 3 years.

METHODS AND MATERIALS

Patient population

Between June 2008 and June 2011, 3079 consecutive patients with known or suspected malignancies underwent 3881 whole-body ¹⁸F-FDG PET/CT scans at our institution, which is a regional principal hospital for cancer management. Cancer was suspected in 766 patients, and 2313 had either confirmed cancer or a history of cancer at the time of the initial ¹⁸F-FDG PET/CT scan. The reports were retrospectively reviewed. When patients had been assessed more than once by ¹⁸F-FDG PET/CT, we assessed the presence of IC only in the first image. Table 2 shows the characteristics of the patients, all of whom provided written, informed consent to undergo ¹⁸F-FDG PET/CT assessment. The ethics committee in Ogaki Municipal Hospital, Ogaki, Japan, approved the study.

Fluorine-18 fludeoxyglucose positron emission tomography/CT scans

Whole-body ¹⁸F-FDG PET/CT images were acquired using a dedicated PET/CT scanner (Biograph™ 16; Siemens Medical Solutions, Erlangen, Germany) from patients who had fasted for at least 6 h before the procedure. The average patient blood glucose level was 103 ± 26 mg dl⁻¹. The patients underwent intravenous injection with 200–250 MBq of ¹⁸F-FDG (Nihon Medi-Physics Co., Ltd, Tokyo, Japan) at 60 min before the scan and then rested in a quiet room.

¹⁸F-FDG PET/CT images from the brain to the upper thighs were acquired with the arms up (body lesions) or down (head or neck lesions) using a spiral 16-slice CT scanner under the following conditions: 120 kV, automatic milliampere-second adjustment, slice thickness of 5 mm and a matrix of 512 × 512 pixels. After CT data acquisition, PET images were obtained in three-dimensional (3D) mode in the same position. The PET emission time was 2 min per bed position, and a complete patient study typically involved eight to nine overlapping bed positions. CT-based attenuation correction of the emission

Table 2. Patients' characteristics at baseline

Characteristics	Patients, <i>n</i>
Males/females	1793/1286
Mean age $\pm$ SD (years)	66.0 $\pm$ 13.0
Malignancy status (suspected/known)	766/2313
Site of known primary malignancy ^a	
Lung	569
Colorectal	288
Lymphoma	269
Head and neck	221
Gynaecological	210
Stomach	203
Hepatobiliary or pancreas	101
Oesophagus	89
Breast	86
Genitourinary	74
Blood	54
Skin	52
Thyroid	50
Others	47
Mean months of follow-up $\pm$ SD	21.9 $\pm$ 13.0

SD, standard deviation.

^aLatest cancer or higher stage cancer was listed when double or triple primary cancers were identified.

images was applied, and the PET images were reconstructed by iterative ordered subset expectation maximization (two iterations and eight subsets) using a 3D gaussian filter at a full width at half maximum of 5.5 mm.

When uptake was unusual or equivocal (1365 of 3079 patients), a diagnostic radiologist ordered a dual-time-point PET/CT scan at the same site.

Fluorine-18 fludeoxyglucose positron emission tomography/CT interpretation

All ¹⁸F-FDG PET, CT and PET/CT fusion images were evaluated using a dedicated PET/CT workstation (Syngo® MultiModality Workplace; Siemens Medical Solutions). The clinical reports were originally generated as follows. The ¹⁸F-FDG PET and CT images were interpreted by one diagnostic radiologist who had access to the relevant clinical information. All clinical reports were issued after review by a single board-certified nuclear medicine physician and diagnostic radiologist.

Discrete focal and abnormal uptake that was discovered on ¹⁸F-FDG PET/CT was defined as indicating primary cancer. Such uptake differed from physiological or non-specific uptake, or the uptake of recognized benign lesions.^{16,17} We focused on morphological alterations on CT images of lesions with abnormal uptake. If cancer with weak uptake (such as renal clear

cell carcinoma or gastric signet ring cell carcinoma) was suspected, tumour manifestation was necessary on the CT images. The uptake of ¹⁸F-FDG indicating a metastasis from established primary cancer was excluded. Practically, the lesion could be considered as IC if it was in a location atypical of a metastasis from the known primary, or if it was of a size atypical of a metastasis from the known primary.

Data analysis and patient follow-up

Imaging findings indicating IC were analysed based only on issued clinical reports. Uptake of ¹⁸F-FDG indicating IC was judged as true positive if the lesion was pathologically proven to be malignant. Such uptake was judged as false positive if it was pathologically proven to be benign or considered benign after clinical follow-up, or the lesion was not confirmed by further examination. Such uptake was also judged as false positive when no further examination was undertaken. A false-negative result meant a pathologically proven IC that was not identified as uptake indicating IC at the time of the initial ¹⁸F-FDG PET/CT scan. Such findings consisted unrecognizable lesions at interpretation and recognizable lesions that were considered

Table 3. Clinical characteristics of patients with incidental cancer detected by fluorine-18 fludeoxyglucose positron emission tomography/CT

Characteristics	Patients, <i>n</i>
Patients/overall sites	67/67
Males/females	46/21
Mean age $\pm$ standard deviation (years)	70.9 $\pm$ 10.3
Primary/synchronous/metachronous	28/25/14
Site	
Colorectal	20
Lung	14
Stomach	11
Prostate	6
Hepatobiliary or pancreas	5
Breast	4
Uterus	3
Kidney	2
Thyroid	1
Ureter	1
Overall TNM stages 0/I/II/III/IV	5/23/17/12/10
Treatment	
Surgery	44
Supportive therapy	8
Endocrine therapy	6
Chemoradiation or chemotherapy	5
Endoscopic resection	4

TNM, tumour, node metastasis.

Figure 1. Incidental colonic cancer in a 58-year-old male. Patient underwent fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT imaging to stage oesophageal squamous cell carcinoma (a, b, large arrows). Small focal uptake in sigmoid colon (small arrows) is evident in maximum-intensity-projection ^{18}F -FDG PET (a) and PET/CT (c) images. Colonoscopic biopsy revealed adenocarcinoma. Simultaneous operation of both cancers was performed.

benign or simply physiological uptake. False-negative IC in patients was detected by other modalities at initial clinical work-up, or diagnosed during the follow-up period. The date of diagnosis was defined as the date of pathological confirmation.

Follow-up records were collected between June 2008 and June 2012. Patient follow-up period was defined as the interval between the date of the initial ^{18}F -FDG PET/CT scan to the date of death or the last visit. We investigated whether all patients were alive or dead. Patients remaining alive had at least a potential 12-month follow-up. The mean follow-up period was 21.9 ± 13.0 months (Table 2). The final diagnosis was confirmed from pathological findings and medical records including the clinical course.

The clinical and pathological stages of IC and false-negative IC were determined according to the tumour, node, metastasis (TNM) classification of the 8th Union for International Cancer Control. In cases where IC or false-negative IC was a second primary, we defined that its pathological findings were different from those of a primary. Second primary IC or false-negative IC found within 1 year after the detection of a primary cancer was regarded as synchronous cancer according to the criteria frequently used in Japan.¹⁸

Statistical analysis

Continuous variables are expressed as means $\pm$ standard deviation. Positive rate and detection rate of ^{18}F -FDG PET/CT for detecting IC were calculated. Survival curves determined according to the Kaplan–Meier method were compared for

statistical significance using the log-rank test. Statistical significance was defined as $p < 0.05$.

RESULTS

Among 3079 patients with known or suspected malignancies, we found uptake of ^{18}F -FDG indicating IC in 211 sites in images from 207 patients. Pathologically proven IC was detected in 67 sites in 67 patients and the findings of 144 sites were false positive in 140 patients. On the other hand, 71 sites were false negative in 71 (2.3%) of 3079 patients. The positive rate and detection rate were 6.7% (207/3079) and 2.2% (67/3079), respectively.

Table 3 shows the clinical characteristics of patients with IC detected by ^{18}F -FDG PET/CT. The common sites of IC were the colon, lung, stomach and prostate. The stages of IC were widely distributed, and 45 (67.2%) of the 67 lesions were found to be early stage disease (0, I and II). 48 (71.6%) of the 67 lesions were resected with surgery and endoscopy. Eight patients were given the best supportive therapy owing to being elderly or having advanced malignancies. Figure 1 shows a representative patient. During the follow-up period, 24 (35.8%) of the 67 patients died of IC ($n = 15$), known primary malignancies ($n = 6$) and other diseases ($n = 3$). The 1-, 2- and 3-year survival rates were 86.4%, 73.7% and 59.3%, respectively, and the median survival time was 42 months.

The most common false-positive sites were the colon ($n = 38$), thyroid ($n = 21$), lung ($n = 20$), stomach ($n = 18$) and prostate ($n = 18$). Of 144 sites, 47 (32.6%) were pathologically proven as being benign, including pre-cancerous lesions of 13 colonic

Table 4. Clinical characteristics of patients with false-negative incidental cancer

Characteristics	Patients, <i>n</i>
Patients/overall sites	71/71
Males/females	53/18
Mean age $\pm$ standard deviation (years)	70.2 $\pm$ 8.8
Primary/synchronous/metachronous	21/20/30
Site	
Colorectal	13
Stomach	13
Lung	9
Hepatobiliary or pancreas	7
Lymphoma or leukaemia	6
Breast	4
Oesophagus	4
Prostate	4
Urinary bladder	4
Others	7
Overall TNM stages 0/I/II/III/IV/unclassified	11/22/16/8/11/3 ^a
Treatment	
Surgery	40
Chemoradiation or chemotherapy	15
Endoscopic resection	6
Supportive therapy	4
Endocrine therapy	3
Others	3

TNM, tumour, node, metastasis.

^aLeukaemia.

adenomas and 1 thyroid adenoma, 39 (27.1%) were not confirmed by further examination, clinical course showed benign for 31, and no further examination performed for 27.

Table 4 summarizes the false-negative results. The common sites were the colon, stomach and lung. The stages of false-negative IC were widely distributed, and 49 (69.0%) of the 71 lesions were confirmed as early stage disease (0, I and II). The average interval from initial ¹⁸F-FDG PET/CT assessment to a diagnosis of false-negative IC was 14.7 months. The major clues for detection were the regular follow-up examinations for 32 lesions (45.1%), and the appearance of symptoms for 30 (42.3%). The major modality for detection was endoscopy for 24 lesions (33.8%), CT for 11 (15.5%) and 8 (11.3%) for subsequent PET/CT. 46 (64.8%) of the 71 lesions were resected with surgery or endoscopy. Figure 2 shows representative patients. During the follow-up period, 15 (21.1%) of the 71 patients died of false-negative IC (*n* = 14) and other diseases (*n* = 1). The 1-, 2- and 3-year survival rates were 85.3%, 74.4% and 62.0%, respectively, and the median survival was 42.2 months. Figure 3 shows the Kaplan–Meier curves of overall survival from diagnosis. There

was no significant difference between patients with IC and patients with false-negative IC.

DISCUSSION

This study yielded three principal findings. The first principal finding of the present study is that ¹⁸F-FDG PET/CT detected IC in 2.2% of all patients. Our positive rate and detection rate were within the so far reported range of IC.^{8–15} Two-thirds of IC were detected at the early stage, and most patients with IC underwent aggressive treatment. The median survival of IC patients was fairly long. The estimated age-standardized incidences of cancer in Japan are the highest for the breast, colorectum, stomach, lung and prostate.¹⁹ The most frequently detected cancers in our study were essentially consistent with these findings. Cancers that were far advanced or located at rare sites did not comprise the majority of IC. The fact that we usually detected treatable cancer in common sites in our country might have contributed to general clinical practice.

The second principal finding of the present study is that the results were false positive in 4.5% of all patients. Except for the thyroid, the common sites of false-positive findings (the colon, lung, stomach and prostate) were similar to the above-mentioned common sites of cancer in Japan.¹⁹ The prevalence of false-positive findings at a specific organ depends on the difference in the ¹⁸F-FDG avidity among cancer, benign lesion and physiological uptake. Some false-positive results may be inevitable because abnormal uptake at a common site of cancer was actively identified.

The third principal finding is the clarification of false-negative results. False-negative IC developed in 2.3% of all patients after an average follow-up of 1 year from the initial assessment. Malignancies were found at various sites compared with IC detected at the initial ¹⁸F-FDG PET/CT scan. On the other hand, overall survival from diagnosis showed little difference between the patients with false-negative IC and the patients with IC. Two-thirds of false-negative IC were detected at the early stage. These malignancies included superficial cancer of the gastrointestinal tract, urinary tract and skin, where they frequently had low ¹⁸F-FDG avidity owing to hypometabolism or a small tumour volume. We presumed that most patients with known malignancies had already visited a hospital and had undergone regular follow-up examinations. By contrast, one-third of false-negative IC was detected at an advanced stage. These malignancies included pancreatic cancer, small-cell lung cancer, malignant lymphoma and acute leukaemia. We believe that these lesions could not be identified at initial ¹⁸F-FDG PET/CT because they were too hypometabolic or too small for high uptake to be recognized, or the lesion had not yet reached the macroscopic level.

This study is limited by the retrospective nature of patient data collection. Detectability of IC was not always evaluated under the same conditions, and the timing of the initial ¹⁸F-FDG PET/CT assessments and follow-up intervals were not uniform. Another limitation inherent in this study design is that of the judgment criteria. False-positive results might have included patients with IC without pathological confirmation, as they were not further examined. Moreover, false-negative results might have included a few *de novo* malignancies that developed after the initial ¹⁸F-FDG PET/CT scan as described above.

Figure 2. False-negative incidental lung cancer in a 78-year-old male. Patient underwent initial fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT imaging to stage laryngeal squamous cell carcinoma (a, arrow). Tumour shadow in right lower lung undetectable by CT (b). Chemoradiation resulted in complete tumour regression, but cough and hoarseness developed 18 months later. Maximum-intensity-projection ^{18}F -FDG PET (c) and PET/CT (d) images show intense focal uptake in right lower lung (large arrows). Multiple lymph node and bone metastases were detected (small arrows). Transbronchial biopsy revealed small-cell carcinoma. Despite chemoradiation, patient died of lung cancer 25 months after the initial ^{18}F -FDG PET/CT scan.

Figure 3. Kaplan-Meier survival curves of patients with incidental cancer (IC) and patients with false-negative IC.

The significance of IC detection has not been described in previous reviews of the clinical applications of ^{18}F -FDG PET in oncology.^{20,21} However, affirmative results of IC detection have accumulated for nearly a decade. IC detection leads patients and referring physicians to appropriate oncologic therapy. Recently, a worldwide web-based survey of referring physicians' experience with ^{18}F -FDG PET/CT was conducted. In this survey, referring physicians expressed considerable uncertainty about the appropriate use of oncologic ^{18}F -FDG PET/CT, and the experience and skill level of the interpreting physician was considered very important.²² High accuracy of IC detection might increase referring physicians' reliance and raise the position of oncologic ^{18}F -FDG PET/CT.

In conclusion, the results of our study demonstrated the usefulness of whole-body ^{18}F -FDG PET/CT for the detection of IC. Most of the patients with IC were treatable, and the patients' survival was fairly long. Detection of IC by ^{18}F -FDG PET/CT can be a standard clinical procedure for patients with known or suspected malignancies.

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