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PET and cancer screening

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Various carcinomas are discovered incidentally during FDG PET study. This points to the potential use of PET as a cancer screening modality. Our experience using three PET scanners showed that PET can be performed in many individuals, and a wide variety of carcinomas can be detected at potentially curable stages. PET screening targets various organs that conventional organ-specific screening tests cannot cover. PET used simultaneously with conventional tests can prevent the overlooking of cancer, reduce false-positive results, and assist in the interpretation of CT and MR images. Thus, PET can play a supportive role when used with conventional screening tests. To reduce false-positive and false-negative results in PET screening, however, experienced PET oncologists who can differentiate between distinct physiological FDG uptake and faint abnormal FDG uptake are needed. In Japan, more than half of the PET facilities offer PET examinations for cancer screening of asymptomatic persons. Not a few individuals pay for sophisticated cancer screenings. Guidelines concerning the use of PET for cancer screening were issued by the Japanese Society of Nuclear Medicine in 2004. The guidelines provide for maintenance of study quality and warn of overselling PET screening. It is unclear how much PET contributes to sophisticated cancer screening. Data are lacking as to whether mortality is reduced by PET screening. Scientific evidence should be presented demonstrating the value of PET in cancer screening.

Key words: PET, cancer screening, FDG PET

INTRODUCTION

IT IS NOT UNUSUAL for carcinoma to be discovered incidentally during ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) study. With careful image interpretation, carcinomas might be found at certain rates. This points to a potential use of PET as a cancer screening modality.

In Japan, many people are interested in cancer screening. Not a few Japanese medical congresses deal with cancer screening as a main theme. Many nuclear medicine physicians and radiologists who engage in oncology PET have an interest in cancer screening, and PET is used for cancer screening of healthy persons in many PET facilities. Not a few individuals pay for sophisticated cancer screening. However, there have been disputes over the efficacy of cancer screening, and it is unclear how much PET contributes to cancer screening.

CURRENT STATUS OF PET SCREENING IN JAPAN

PET was applied to cancer screening for the first time in Japan in 1994.[1,2] In an institution equipped with one cyclotron and three whole-body PET scanners, FDG PET studies were performed in conjunction with other modalities for cancer screening of many asymptomatic individuals. Through study of many asymptomatic persons, PET was shown to be performed on many individuals. It was also shown that some cancers can be screened by PET but others cannot, and that various patterns of physiological FDG uptake should be kept in mind in image interpretation.

Since 2002, the Japanese Ministry of Health, Welfare and Labour approved public medical insurance coverage of FDG PET in the evaluation of 10 malignant diseases

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(Table 1). The examination fee is 75,000 yen (approximately US$ 735, euro 560). This approval triggered an increase in the number of PET facilities. Newly constructed PET facilities intended to use PET for patients with insurance coverage and for healthy persons without insurance coverage. By November 2004, as many as 47 of 77 PET facilities (61%) in Japan offered PET examinations for cancer screening or health check-ups (data obtained from URL:http://pet.jrias.or.jp/index.cfm/28,367,95,html [in Japanese, accessed January 17, 2005]). This examination fee is not covered by public health insurance, and screenees pay the total costs. The examination fee varies, depending on the PET facility. It is, in most cases, approximately 80,000 yen (US$ 780, euro 600). PET examinations are performed with or without other imaging studies. The news media have exaggerated the advantages of PET, leading the public to believe that PET can detect small carcinomas of only a few millimeters or that it can be used to examine whole organs. Thus, people's expectations have been raised unrealistically. We checked the websites of most of PET facilities to see whether the advantages of PET screening were overblown. Most websites properly explained the limitations of PET, for example, that it cannot detect early gastric carcinoma, hepatocellular carcinoma, or carcinoma of the urinary tract.

Guidelines concerning the use of PET for cancer screening were issued by the Japanese Society of Nuclear Medicine (*KAKU IGAKU (Jpn J Nucl Med)* 2004; 41: 1–21). The guidelines are aimed at maintaining the quality of PET study, promoting the proper use of PET, and evaluating the efficacy of PET screening. The guidelines warn of overselling of PET screening. In 2004, the National Cancer Center in Japan begun prospective studies to investigate the efficacy of various cancer screening modalities including FDG PET study. Several PET facilities in Japan are also evaluating the contribution of PET to sophisticated cancer screening programs.

DISPUTE OVER CANCER SCREENING

It is undisputed that patients with early-stage cancer have a better prognosis than patients with more advanced cancer and early detection is essential. Cancer screening is aimed at early cancer detection; the ultimate goal is to detect curable cancers that would be fatal if left untreated. In other words, no practical benefit can be obtained from finding incurable cancers (e.g., advanced pancreatic cancer) or nonfatal cancers (e.g., indolent thyroid cancer). However, the natural courses of cancers are not fully understood, and the practical goal is reduced mortality. Reduced mortality has been confirmed with the fecal occult blood test (FOBT) for colorectal cancer, mammography for breast cancer, and cytologic examination of cervical smears for cervical cancer. These three screenings are widely implemented as a matter of public policy.

Table 1 Ten malignant diseases covered by public medical insurance in Japan

Lung cancer
Breast cancer
Colorectal cancer
Pancreatic cancer
Metastatic liver tumor
Head and neck cancer
Malignant lymphoma
Malignant melanoma
Brain tumor
Origin unknown malignant tumor

The question is whether screenings with an unproven mortality benefit should be recommend for the general population. For example, there are arguments for[3] and against[4] prostate cancer screening by assay of prostate-specific antigen (PSA) although such assay can detect prostate cancers in the early clinical stages. Objections to prostate cancer screening include the morbidity associated with prostate biopsy, low positive predictive value of screening, and overtreatment of indolent disease. To the contrary, those who support widespread prostate cancer screening quote the positive predictive value of widely accepted screening programs for other common malignancies, and they draw attention to the fact that prostate cancer screening has led to positive stage migration and paralleled a decrease in the prostate cancer mortality rate.[5]

Similarly, lung cancer screening by computed tomography (CT) can detect lung cancer in early stages. In a study of simultaneous CT, chest x-ray, and sputum cytology screenings, the cancer detection rate was as high as 0.28–0.87%, and the mean tumor diameter was as small as 14.6–19.8 mm.[6] However, several potential harmful events were noted. False-positive results led to unnecessary biopsies, and there may have been overdiagnosis and overtreatment of adenocarcinomas of the lung. In colorectal cancer screening with verified mortality benefits, screening tests vary from the conventional FOBT to newer modalities such as endoscopic and radiologic screenings.[7] As time passes, new screening tests based on new technologies will emerge. A large-scale clinical trial (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) was begun by the U.S. National Cancer Institute to determine whether certain cancer screening tests reduce death from cancer (available from URL:http://www3.cancer.gov/prevention/plco [accessed January 17, 2005]).

There is no justification for implementation of screening tests with uncertain benefits as a matter of public policy. Individuals can decide on their own whether or not to undergo such screening tests. Because screening has advantages and disadvantages (Table 2), screening providers should help individuals weigh the complex advantages and disadvantages. Informed decision-

Table 2 Advantages and disadvantages in cancer screening

Advantages	Disadvantages
Early detection	Overlooked lesion
	Overdiagnosis
	Excessive or unnecessary examination
Chance of less invasive treatments	Overtreatment for unimportant diseases
Improved QOL	
Mortality reduction	
	Radiation exposure
Cost-benefit	Cost or financial burden
Relief	Anxiety

Table 3 Detection of primary colorectal carcinoma

Authors	No. of tumor	Sensitivity	Specificity	Reference
Falk et al.	15/15	100%	—	13
Abdel-Nabi et al.	37/37	100%	43%	14
Mukai et al.	22/23	96%	—	15
Oku et al.	40/40	100%	—	16
Kantorova et al.	35/37	95%	—	17
Total	149/154	98%		

making regarding cancer screening tests is likely to become more important as more tests become available and individual choices become more complex.[8]

SENSITIVITY AND SPECIFICITY OF CANCER SCREENING TESTS

Test sensitivity and specificity are important in cancer screening. Low sensitivity leads to missed diagnosis (false-negative results), and low specificity leads to overdiagnosis (false-positive results).

Sensitivity of the FOBT is 60–90% in patients with advanced colorectal cancer. Its sensitivity as a screening test is 40–70%, and its positive predictive value is 3.7–8.4%.[9] Although the FOBT is valuable for mass screening, its sensitivity is limited, and false-positive results due to hemorrhoidal diseases are often encountered.

Estimation of the sensitivity of mammography depends on the method of calculation used.[10] The reported sensitivity of mammography as a screening test ranges from 32% to 75%. When performed simultaneously with clinical breast examination, the reported sensitivity is 73%. The specificity of mammography is as high as 94%.[10] The reported positive predictive value is 1.5–15%, but this is in conjunction with physical examinations in some series.[11]

Cytologic examination of cervical smears yields some false-negative results due to "reader error" and "taker error"; sensitivity of the smear is approximately 75%.[12] Although the test is invasive, cervical cancer screening can detect not only invasive cancer but also carcinoma *in situ*.

SENSITIVITY AND SPECIFICITY OF PET

For tumors to be imaged by PET, they must be FDG avid and be of a certain volume. From the stand point of PET screening, we reviewed the sensitivity and specificity of PET for various cancers.

Colorectal cancer

Several PET studies have focused on patients with primary colorectal cancers (Table 3).[13–17] One hundred forty-nine of 154 (98%) primary lesions were PET-positive. The smallest PET-positive tumor was a 1.4-cm rectal carcinoma.[14] One false-negative result occurred in a patient in whom high skeletal FDG-uptake resulting from intravenous injection of glucose just prior to the PET examination obscured FDG uptake of the tumor.[15] A second PET-negative case was of an invasive carcinoma in a 1.5-cm villous adenoma, and a third was of a rectal carcinoma obscured by high physiological FDG uptake of the rectum.[17]

Prognosis after surgery for colorectal cancer is favorable if metastasis is not found. Patients with Dukes A or B advanced colorectal cancer (tumor confined to the bowel wall and no regional lymph node metastasis or distant metastasis) have 5-year survival rates of more than 80%.[18] According to previous reports, most Dukes A or B advanced colorectal cancers seem to be detectable by PET. Histopathologically, however, high FDG uptake is not observed in mucinous carcinoma or signet ring cell carcinoma. Mucinous carcinoma and signet ring cell carcinoma comprise 3.3% and 0.3% of colorectal carcinomas, respectively.[18] Consequently, at least 3.6% of

advanced colorectal carcinomas could be missed by PET study. In addition, physiological FDG uptake in the intestine may hinder the detection of lesions, leading to false-negative results or incomplete studies. Furthermore, precise interpretation of PET images requires experienced nuclear medicine physicians or radiologists.

Polyps of the colon and rectum are often discovered by PET. The dominant histopathologic types of colonic polyp are adenoma and hyperplastic polyp (or metaplastic polyp). Adenoma has a potential for cancer development and is considered a precancerous lesion. Because FDG accumulation is observed in adenomas and not in hyperplastic polyps, PET is beneficial in terms of colorectal cancer screening. Detection of an adenoma as small as 1 cm has been reported, and 90% of adenomas equal to or larger than 1.3 cm are reported to be detectable by PET.[19]

Controversy exists regarding the minimum size of an adenoma indicated for removal. Many physicians agree that an adenoma of 5 mm or greater is an indication for removal. However, growth retardation is observed in some medium-sized adenomas (5–9 mm). Hence, it is suggested that follow-up of an unresected colorectal polyp up to 9 mm is safe.[20] Many adenomas or carcinomas of the polypoid type no less than 1.3 cm in size are detectable by PET.[19] Adenomas or carcinomas of the superficial type, however, are below the detection level of PET; the tumor volume is insufficient even though the diameter is large. This is also true for the FOBT. For the detection of superficial types of adenoma and carcinoma, colonoscopy is unrivaled. However, even experienced colonoscopists who can reach the cecum within 3 minutes overlook colonic carcinomas at a rate of 12.5%, and careful survey is advised, especially in portions of the colon easily overlooked [*SHOUKAKIGEKA* 2000; 23: 1715–1722 (in Japanese)].

Breast cancer

Because most breast carcinomas are spherical and FDG-avid, they are fundamentally suited for PET visualization. However, small breast carcinomas tend to yield false-negative results. Avril et al.[21] showed the sensitivity of PET to be 48–68% for pT1 tumors (≤2 cm), 81–91% for pT2 tumors (2 < ≤ 5 cm), and 79–100% for pT3 tumors (>5 cm). Although sensitivity is as low as 8.3–16.7% for tumors less than 1 cm, sensitivity of 62.5 (definite uptake)–84.4% (definite or probable uptake) was reported for 32 lesions 1–2 cm in size.[21] It is unknown whether PET is inferior to mammography in the detection of breast carcinoma 1–2 cm in diameter. Patients with tumors 1–2 cm have a relapse-free survival rate of 80% for 5 years and 75% for 10 years.[22] This suggests that PET has the potential to detect breast carcinomas in curable stages. We discovered a small breast carcinoma by PET in an asymptomatic individual.[23] The surgical specimen was 6 mm, and the pathological specimen was 3 mm. Although the patient had undergone PET study 9 months earlier, abnormal FDG uptake was not observed, even retrospectively.

Histopathologically, high FDG uptake is observed in ductal carcinomas. Lobular carcinomas comprise 7–10% of invasive breast carcinomas, and tubular carcinomas comprise 1–2%, and both can yield false-negative findings. The sensitivity of FDG PET for detecting breast carcinoma seems to depend not only on tumor size but also on the histopathologic subtype.[24,25]

High FDG uptake is reported in some fibroadenomas,[24] whereas high FDG uptake is not observed in fibrocystic disease. Recent studies of FDG PET for differentiation between benign and malignant tumors of the breast showed 80–93% sensitivity and 75–76% specificity.[21,24] Positive PET scans provide a high positive-predictive value (96.6%) for breast carcinoma.[25] Although PET is clearly limited in screening breast carcinomas as a single study, it has potential for detecting breast carcinomas in curable stages.

Lung cancer

The sensitivity and specificity of PET as a screening test for lung cancer are unknown. In a study of 89 patients with an indeterminate solitary pulmonary nodule, PET showed an overall sensitivity and specificity of 92% and 90%, respectively, when nodules less than 7 mm were excluded.[26] Small carcinomas can yield false-negative results. A decrease in sensitivity from 92% to 80% was seen when the nodules were ≤1.5 cm. Conversely, most lung carcinomas larger than 1.5 cm can be detected by PET. PET has the potential to detect T1 (≤3 cm) lung carcinoma. The 5-years survival rate is 67% for patients with T1N0 non-small cell lung carcinoma, and 55% for patients with T1N1 non-small cell lung carcinoma.[27] Histopathologically, primary lung carcinomas include adenocarcinoma (including bronchioloalveolar carcinoma), squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and others. Small cell carcinoma is highly malignant and FDG-avid.[28] Bronchioloalveolar carcinoma is not so FDG-avid[29]; neither is it so aggressive.[30] Thus, the sensitivity of PET is high in detecting biologically aggressive lung carcinomas.

In most cases, CT is more sensitive than PET in detecting small nodules. However, CT has limited value in patients with abnormal lung shadows due to thoracic surgery, atelectasis, emphysema, or fibrosis. Some central lesions are easily overlooked in CT studies. Some lung carcinomas have an atypical CT appearance. For these cases, PET is superior to CT. We encountered three patients in whom PET was more helpful than CT. The first was a patient with emphysema and a 1.0-cm lung carcinoma. CT was not useful for differentiating the carcinoma from fibrosis. The second was a patient with a lung carcinoma at the pulmonary hilum. The tumor was not detect by CT. The third was a patient with atypical CT findings. High FDG uptake was observed in the abnormal shadow, which led to a final diagnosis of lung carcinoma.

In the diagnosis of lung carcinomas with PET, false-positives are well known. When high FDG accumulation is noted in the lung, CT images should be referred to. CT and selective PET in conjunction have been effectively used in the early detection of lung carcinoma.[31] It is likely that PET-CT will be used for lung cancer screening in the near future.

Pancreatic cancer

Higashi et al.[32] noted in their excellent review that sensitivity and specificity of PET for detection of pancreatic cancers are reported to range from 65% to 100% and 64% to 100%. A small cancer less than 20 mm in diameter without lymph node metastasis is defined as T1 in the UICC classification system. Higashi et al. reported that FDG PET detected 13 of 16 cases (81%) of T1 pancreatic cancer, among which the smallest cancer detected by FDG PET was 7 mm. In general, however, there is a high rate of false-negative results for stage I (≤2 cm) cancers,[33,34] whereas three 1.5-cm pancreatic cancers were correctly diagnosed,[35] and CT-negative 1.2-cm pancreatic cancer was detected with PET.[36]

Histopathologic changes affect FDG uptake. Ductal adenocarcinoma and its variants make up over 90% of pancreatic exocrine tumors.[37] Usually, high FDG uptake is observed in ductal adenocarcinomas. However, as Higashi et al. noted, abundant connective tissue is often observed in pancreatic carcinomas (marked desmoplasia, scirrhous type). In such cases, PET study yields false-negative results due to poor cellularity, even if the tumor is large. Mucinous adenocarcinoma, a low cellularity tumor, comprises 2% of pancreatic cancers and is likely to yield a false-negative result,[35] and cystic type cancers are also poor in cellularity. We must be aware of the possibility of false-negative results due to poor cellularity even when the tumor is fairly large. An active inflammatory process at the histologic level can lead to FDG accumulation; chronic pancreatitis can yield a false-positive result.[33,34,38,39] In PET diagnosis of pancreatic cancer, two issues should be kept in mind: false-negative results due to poor cellularity and false-positive results due to microscopic inflammation.

Esophageal cancer

Histopathologically, most esophageal carcinomas consist of squamous cell carcinoma or adenocarcinoma. Both types are FDG-avid, and a certain tumor volume is required for PET visualization. Kato et al.[40] reported that the primary tumor was visualized by FDG PET in 119 of 149 patients (80%). FDG accumulation was observed in 3 of 17 patients (18%) with a pT1a tumor (remaining within the muscularis mucosae) and in 14 of 23 patients (61%) with a pT1b tumor (involving the submucosa). FDG uptake rates in patients with pT2, pT3, and pT4 tumors were 83%, 97%, and 100%, respectively. Superficial carcinomas are undetectable by PET. Even if the tumor is FDG-avid, superficial carcinoma of the esophagus, stomach, or colon and rectum is usually below the sensitivity of PET because of insufficient tumor volume. In detecting these superficial carcinomas of the gastrointestinal tract, endoscopy is unrivaled.

Other malignant tumors

Thyroid tumors can be incidentally identified during FDG PET study. There are no reports regarding the sensitivity and specificity of PET for primary thyroid carcinoma. It seems that most primary thyroid carcinomas have increased FDG uptake. Because increased FDG accumulation is observed in benign adenomas, FDG PET is unlikely to successfully differentiate benign and malignant thyroid nodules. In FDG PET studies of patients and healthy subjects, thyroid abnormalities were noted at a frequency of 2.3%[41] and 2.2%[42] including carcinomas and adenomas. We agree with the comment that the ability of FDG PET for early detection of thyroid cancer should not be overlooked.[43]

In the detection of malignant lymphomas, PET is superior to CT.[44] In the initial stage, the sensitivity and specificity were 79–100% and 76–100% with PET and 26–100% and 17–100% with CT. In the evaluation of ovarian tumors and other adnexal masses, the overall sensitivity and specificity of FDG PET were 58% and 75%, but the number of malignant tumors was low.[45] Sufficient data are not available concerning the sensitivity and specificity of PET for primary uterine or cervical cancer.

PET SCREENING

Results of PET screening

We reported the initial results of cancer screening by PET imaging.[1,2,46] A total of 3,165 asymptomatic individuals (2,017 men and 1,148 women; mean ± SD age, 52.2 ± 10.4 years) participated in 5,575 screening sessions. PET was performed in conjunction with conventional physical examination, laboratory study, ultrasonography, and chest CT. The study lasted 4 years and 6 months, and follow-up periods were no less than 10 months. Within 1 year after screening, malignant tumors were discovered in 67 of the 3,165 participants (2.1%). PET findings were true-positive in 36 of the 67 cancers (54%). Most of the 36 patients underwent potentially curative surgery; thus, cancers of a wide variety were detected by PET at potentially curable stages.

Eight of 10 lung cancers were characterized as stage I tumors. Figure 1 shows a case of lung cancer in which multiple abnormal lung shadows secondary to emphysema were observed on chest x-ray films and chest CT scans obtained at the same time. High FDG uptake was observed in one of the shadows. Surgery revealed a 1-cm papillary adenocarcinoma, and no regional lymph node metastasis was found. The lung cancer would have been

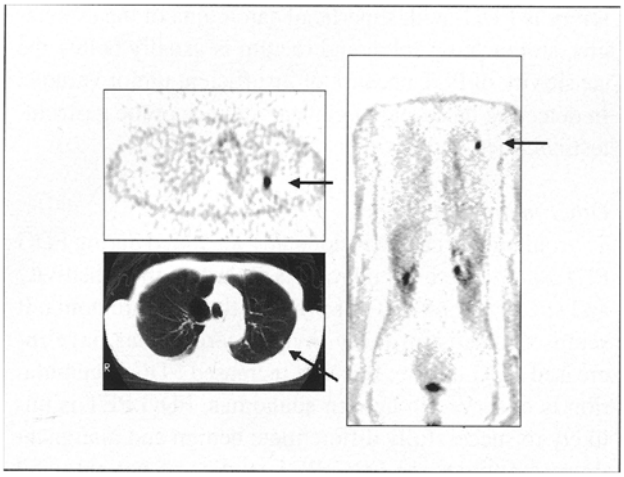

Fig. 1 A 66-year-old man with emphysematous lung. Multiple fibrotic changes were observed on CT images. In accordance with one of the lung shadows, a focal FDG uptake was noted with PET. Surgery revealed a papillary adenocarcinoma (1 cm, p-stage I).

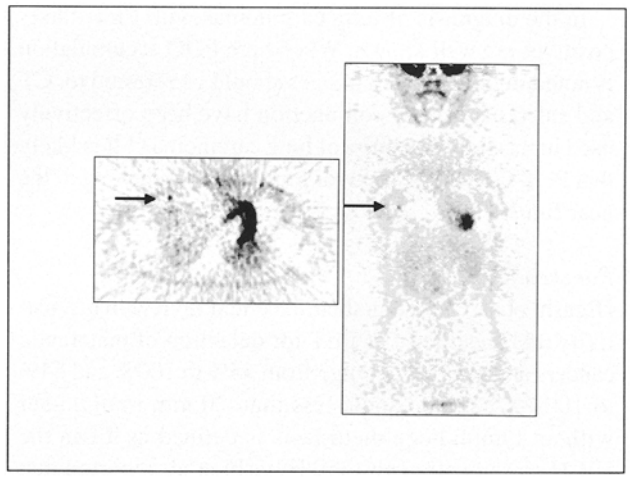

Fig. 3 A small breast carcinoma (intraductal carcinoma) was discovered in a 45-year-old woman. According to the cut surface of the resected specimen, the tumor was 6 mm in diameter. Although this subject had undergone a PET study 9 months earlier, abnormal FDG accumulation was not noted even in retrospective analysis.

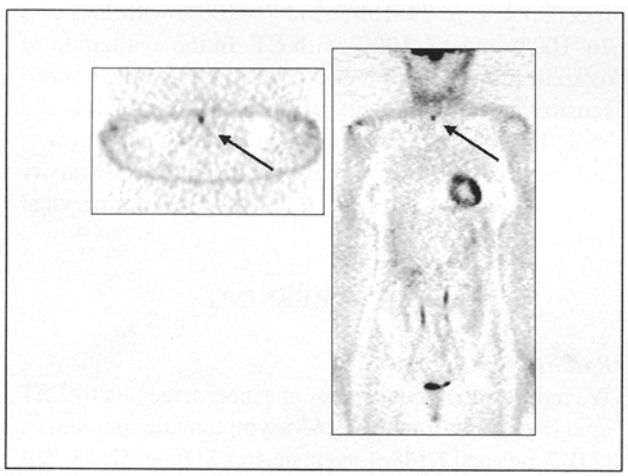

Fig. 2 A 6 mm thyroid carcinoma was discovered in a 39-year-old asymptomatic woman.

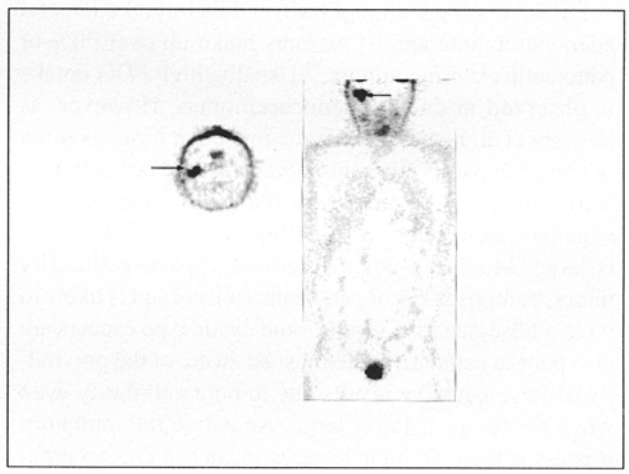

Fig. 4 High FDG uptake was noted in a 64-year-old asymptomatic man. Surgery revealed a 4.4-cm parapharyngeal carcinoma, which could have been missed without PET.

overlooked without PET. Three PET-negative lung cancers consisted of an 8-mm tubular adenocarcinoma and a 1.1-cm and 1.5-cm bronchioloalveolar carcinoma. These were small or biologically non-aggressive tumors.

Eight participants were found to have thyroid cancer and underwent surgery. The smallest was a nonpalpable 6-mm tumor (Fig. 2). Five participants with breast cancer including the nonpalpable 6-mm cancer (Fig. 3) underwent potentially curative surgery. The 6-mm breast cancer was not visible on a mammogram obtained later at the patient's local hospital. However, there was a PET-negative 1.5-cm breast cancer.

Four participants were found to have colorectal cancer and underwent potentially curative surgery. In addition, PET was helpful in detecting malignant lymphoma, ovarian cancer, parapharyngeal cancer (adenoid cystic carcinoma) (Fig. 4), and chronic myelogenous leukemia. In a case of chronic myelogenous leukemia, high FDG uptake was clearly seen in bone marrow. Carcinomas that could have been overlooked without PET were a 1-cm lung carcinoma, 6-mm breast carcinoma, malignant lymphoma, ovarian carcinoma, and parapharyngeal carcinoma. However, PET findings were false-negative in 31 of the 67 patients (46%). Fourteen of the 31 tumors (45%) were of urologic origin. Because of the possibility of PET-negative carcinoma, PET, as a single study, cannot target all carcinomas.

PET imaging has the potential to detect a wide variety

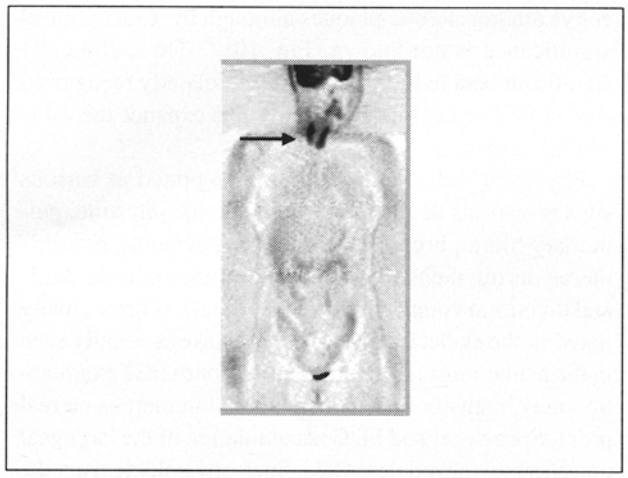

Fig. 5 Diffuse thyroidal FDG uptake was seen in women in our study group at a rate of 8.9%.

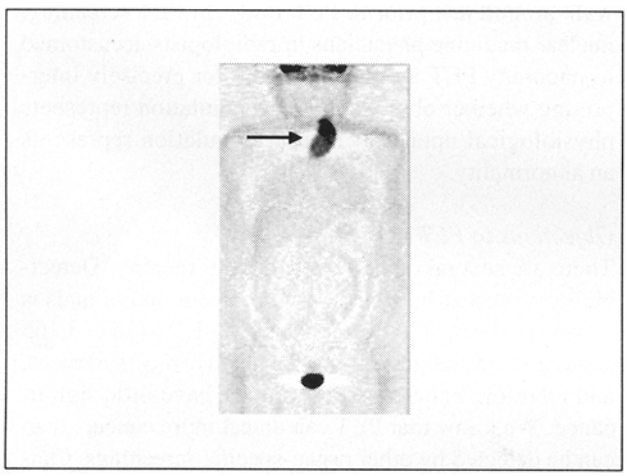

Fig. 6 High FDG uptake was noted in a 60-year-old asymptomatic man. The tumor was palpable. Needle aspiration cytology after PET study revealed a 6-cm malignant lymphoma of the thyroid.

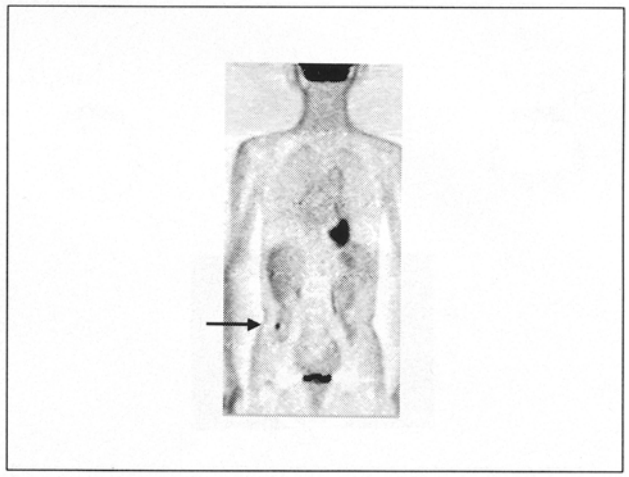

Fig. 7 High FDG uptake was observed in a 74-year-old asymptomatic man. Colonoscopic polypectomy revealed an 11-mm adenoma of the ascending colon. Focal FDG accumulation in this subject was recognizable retrospectively on PET images taken 15 months before.

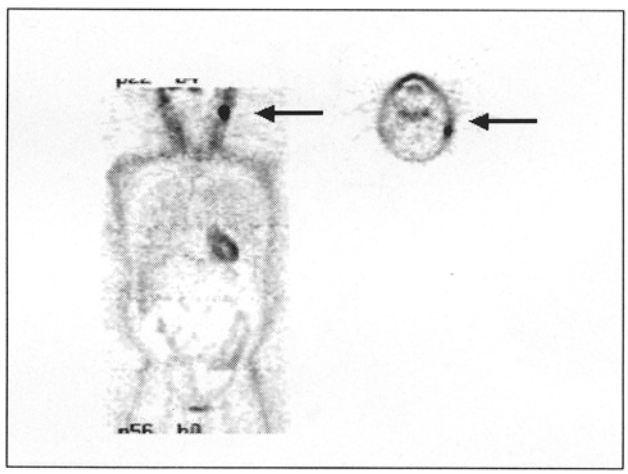

Fig. 8 Warthin's tumor in a 60-year-old asymptomatic man. Surgery revealed the diagnosis. In our earlier study, the prevalence of Warthin's tumor was 4 of 1,214 males (0.3%) with a mean age of 52 years.

of cancers at potentially curable stages. Carcinomas can be found that are difficult to detect by conventional study. Furthermore, we believe that combined use of PET with other modalities can decrease the number of false-positive results.

Non-malignant FDG uptake

In PET screening, the possibility of non-malignant lesions with high FDG uptake should be understood for evaluating PET images properly. Diffuse thyroidal FDG uptake is common (8.9%) among elderly Japanese women and usually indicates subclinical chronic thyroiditis (Hashimoto's thyroiditis) (Fig. 5).[47] Diffuse thyroidal FDG uptake is noted in other countries besides Japan.[41,42] Identification of such diffuse uptake should prompt further assessment of thyroid function to rule out hypothyroidism. Because diffuse thyroidal FDG uptake is not unusual, we feared that malignant lymphoma of the thyroid gland might be overlooked. Nevertheless, we encountered a patient with diffuse FDG uptake in the left thyroid lobe (Fig. 6). A tumor was also found upon palpation. Biopsy performed later at another hospital confirmed the diagnosis of malignant lymphoma of the thyroid gland.

An adenomatous polyp of the colon is clinically important as a precancerous lesion and can be detected by PET at a certain rate. In our study, an adenoma as small as 1 cm was detected, and the PET-positive rate was 90% for adenomas that were ≥13 mm (Fig. 7).[19] Distinct focal

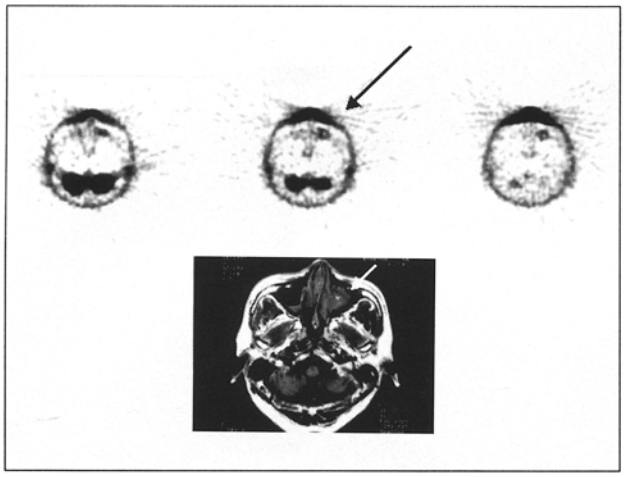

Fig. 9 Maxillary sinusitis in a 60-year-old man. Unilateral maxillary FDG accumulation is not rare. FDG tends to accumulate along the sinus wall. Disappearance of FDG uptake was confirmed in one subject after erythromycin treatment lasting 3 months.

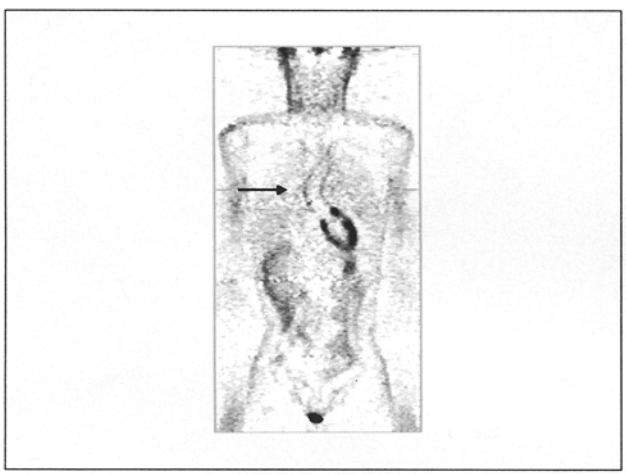

Fig. 10 FDG accumulation in aortic wall was not infrequently observed in elderly subjects. The findings may be an indicator of active atherosclerotic plaques.

FDG uptake along the large intestine calls for prompt barium enema study or colonoscopy. We stress one advantage of PET, namely that it does not require bowel preparation. Bowel preparation is time-consuming, inconvenient, and somewhat uncomfortable.

Warthin's tumor of the parotid gland was noted at a frequency of 0.3% among men in our study (Fig. 8).[48] The tumor tends to occur in patients in their sixties and seventies, most often in smokers. FDG accumulation caused by maxillary sinusitis is usually recognized unilaterally (Fig. 9). Sarcoidosis may be seen by PET before chest x-ray or CT reveals the lesion. Marked FDG uptake is recognized in affected joints in patients with rheumatoid arthritis. Vascular wall FDG uptake is related to active atherosclerotic plaques although the exact clinical significance is not known (Fig. 10).[49] Thus, clinically significant benign lesions are not infrequently recognized during PET screening. We believe this expands the value of PET screening.

Physiological FDG uptake is recognized at various sites in various degrees. Sites include the intestine, pulmonary hilum, brown adipose tissue, lactating breast,[50] uterus during menstruation,[51] wall of the right atrium,[52] and thymus in young adults.[53] FDG uptake is occasionally noted in the skeletal muscle. High uptake is usually seen in the ocular muscles. Reading just prior to PET examination may intensify this accumulation, but there is no real proof. Speech-related FDG accumulation of the laryngeal muscles is also well described. Such physiological uptake hampers the search for lesions at these sites. Tension-related shoulder stiffness increases FDG uptake in the shoulder muscles. Therefore, we instruct PET examinees to be relaxed, to close their eyes, not to speak, and not to walk around just prior to PET study. In PET screening, nuclear medicine physicians or radiologists accustomed to oncology PET are indispensable for precisely interpreting whether obvious FDG accumulation represents physiological uptake or faint accumulation represents an abnormality.

Objections to PET screening

There are several objections to PET screening. Detectability of cancer by PET in asymptomatic individuals is reported to be 0.6 (36 of 5,575 studies)–1.1% (36 of 3,165 subjects), and malignancy was not found in most screenees, and therefore expensive PET studies have little significance. We know that PET can detect more cancers than can be detected by other organ-specific screenings. Cancer detection rates are 0.15–0.2% with the FOBT,[54] 0.14–0.27% with mammography,[10] and 0.4% (including dysplasia) with cervical cancer screening.[55] PET screening targets many organs rather than a single organ.

Another concern is that combinations of modalities not including PET are adequate for screening. We believe that one of the advantages of PET is that it can screen various areas at once such as the head and neck, mediastinum and retroperitoneum, bone and skeletal muscle, and gastrointestinal tract. Low-prevalence cancers can be targeted in PET screening. In addition, we believe that use of PET together with conventional screening tests can help prevent overlooking of cancers and reduce false-positive results. In other words, PET is useful as a backup or support for conventional screening tests.

The third objection is that it is very costly to discover one cancer by PET. Indeed, the main shortcoming of PET screening is its high cost. Cost-benefit analysis will not favor the use of PET. Because there is no justification for the use of public funds, each screenee will have to cover the cost. In Japan, bone scintigraphy costs 46,000 yen (US$ 450, euro 340), gallium scintigraphy costs 56,000

yen (US$ 550, euro 420), and PET costs 75,000 yen (US$ 735, euro 560). PET is probably less expensive in Japan than in other countries.

The fourth concern is that there are many false-negative and false-positive findings when PET is applied to the general population. In colorectal screening with the FOBT or PET, however, it is uncertain which yields more false-negative or false-positive results. We suppose PET is superior to the FOBT in the detection of advanced colorectal carcinoma. Whereas breast carcinoma *in situ* and dysplasia and carcinoma *in situ* of the cervix are below the sensitivity level of PET, PET has the potential to detect mammography-negative breast carcinoma. We have experienced one such case. Cytologic examination of cervical smears is invasive and seems to be inferior to PET in the detection of endometrial cancer and ovarian cancer. To decrease the number of false-negative and false-positive results, however, PET images have to be evaluated by experienced PET oncologists.

There may be other objections. PET screening involves some radiation exposure. However, the radiation absorbed dose can be effectively reduced by voiding. In addition, screening is usually applied to individuals after their reproductive years. There is no evidence that PET screening reduces mortality. Potential screenees should be informed accordingly. It is the same as with other screening tests with unproven benefits. The biggest problem is that it is difficult to verify the effectiveness of PET screening. We must continue to seek scientific data on the benefits of PET screening.

According to our experience, PET is sensitive for revealing the presence of abnormalities. PET images must be interpreted in light of possible PET-negative carcinomas and non-malignant FDG accumulations. This will reduce the frequency of false-nagative results and false-positive results. If abnormal FDG accumulation is absent, interpretation of PET images is easy and less time-consuming than interpretation of CT and MR images. Furthermore, simultaneous use of PET is helpful in reading CT and MR images. We believe several screenees' lives were saved by PET screening. This is only a personal experience; we must establish scientific proof.

CONCLUSION

To reduce false-positive or false-negative results of PET screening, there is a need for experienced PET oncologists who can differentiate between distinct physiological FDG uptake and faint abnormal FDG uptake. PET can noninvasively survey the entire body, but it cannot screen all organs. Potential screening candidates must be informed of not only the advantages but also the limitations of PET screening. Exaggerated claims by the mass media and haphazard screenings offered by a few health-care providers hamper the progress of PET screening. Scientific evidence is needed to show the value of PET or the contribution of PET to sophisticated or hi-tech cancer screening. To accomplish this, we must carefully follow-up participants after screening and collect precise data. Such studies are in progress at several institutions in Japan. With further development of PET scanners, PET will be strengthened as a screening modality. At this point in time, however, we can say only that PET study is feasible for cancer screening.

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