^{11}C-Acetate can be Used in Place of ^{18}F-Fluorodeoxyglucose for Positron Emission Tomography Imaging of Non-small Cell Lung Cancer with Higher Sensitivity for Well-Differentiated Adenocarcinoma

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Objectives: Although positron emission tomography (PET) using ^{18}F-fluorodeoxy-glucose (FDG) frequently gives false-negative results for slow-growing tumors, ^{11}C-acetate (AC)-PET has been reported to be able to detect them. To determine the usefulness of AC-PET for imaging non-small cell lung cancers (NSCLCs), the sensitivity and specificity were compared between the AC-PET and FDG-PET with a multicenter study.

Materials and Methods: A total of 284 pulmonary lesions (227 NSCLCs and 57 benign lesions) were examined using both AC-PET and FDG-PET before surgery at seven Japanese institutes. The AC- or FDG-uptake in each lesion were quantitatively measured using the contrast ratio of the standard uptake value between the lesions and the contralateral lung.

Results: The sensitivity of AC-PET for diagnosing NSCLC was 0.71, which was significantly higher than the value of 0.57 obtained by FDG-PET ($p < 0.001$). No significant difference in the specificity was seen between AC- and FDG-PET. For the 146 well-differentiated adenocarcinomas, the sensitivity of AC-PET was 0.62, which was significantly higher than the value of 0.37 obtained by FDG-PET ($p < 0.001$). Of the 51 moderately- or poorly-differentiated adenocarcinomas and 30 nonadenocarcinomas, there was no significant difference of sensitivity between AC- and FDG-PET.

Conclusions: AC-PET could be used in place of FDG-PET for imaging NSCLC, with higher sensitivity for well-differentiated adenocarcinoma compared with FDG-PET.

Key Words: Positron emission tomography, Acetate, Fluorodeoxyglucose, Non-small cell lung cancer, Lung adenocarcinoma.

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Recent advances in positron emission tomography (PET) using ^{18}F-fluorodeoxy-glucose (FDG) have contributed significantly to the ability to differentiate between non-small cell lung cancer (NSCLC) and benign pulmonary nodules. Nevertheless, FDG-PET sometimes gives false-negative results, particularly for well-differentiated (W/D) adenocarcinoma because of their low glucose metabolism.[1–4] We previously reported that 60% of W/D adenocarcinomas less than 3 cm in size failed to be identified by FDG-PET.[2] Therefore, other PET tracers should be used for the imaging of W/D adenocarcinoma of the lung.

Radio-labeled acetate (AC) has long been used to examine lipid and cholesterol synthesis in biochemistry.[5,6] Clinically, ^{11}C-AC has been widely used as a PET tracer to evaluate myocardial oxidative metabolism.[7,8] Recently, ^{11}C-AC has also been reported to be a useful PET tracer for imaging of slow-growing tumors that cannot be visualized by FDG-PET, such as W/D hepatocellular carcinoma, prostate cancers, and thymoma.[9–11] We previously reported that AC-PET was able to image 8 of 22 (36%) W/D adenocarcinomas that could not be visualized by FDG-PET.[12] In the present study, to examine the diagnostic usefulness of AC-PET for NSCLC, the sensitivity and specificity for the discrimination between NSCLC and benign nodules were compared between the AC-PET and FDG-PET in patients with NSCLC recruited with a multicenter study.

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MATERIALS AND METHODS

Eligibility

The study protocol was to perform AC-PET and FDG-PET in patients with lung adenocarcinomas or lesions suspected of lung adenocarcinomas before surgery. The study was approved by the ethical committee of each of the seven institutes involved in the study (see Appendix). Informed consent was obtained from all patients after a discussion of the risks and benefits of the study with their surgeons.

Patients

Between April 2005 and December 2007, a total of 248 patients with 284 pulmonary lesions larger than 1 cm in size, who were suspected of or diagnosed as having lung adenocarcinomas, prospectively underwent both AC-PET and FDG-PET before surgery. The final diagnosis of the 284 lesions were NSCLC in 227 and benign nodules in 57 (Table 1). The histologic types of the 227 NSCLCs were W/D adenocarcinoma in 146 lesions, moderately-differentiated (M/D) or poorly-differentiated (P/D) adenocarcinomas in 51, and nonadenocarcinomas in 30. The histologic types of the 30 nonadenocarcinomas were squamous cell carcinoma in 27, adenosquamous carcinoma in 2, and large cell carcinoma in 1. Of the 57 benign nodules, 20 were acute inflammations, 32 were old inflammations, and the remaining 4 were benign tumors. The 32 old inflammatory lesions were incidentally found away from lung cancers and were diagnosed clinically as old inflammations without histologic examination based on the following reasons: (1) a review of retrospective chest radiograph or computed tomography (CT) examinations performed before surgery (mean observation period, 41 ± 23 months; range, 24–97 months) revealed that the sizes of the lesions had remained unchanged, and (2) postoperative follow-up CT examinations showed that the sizes of the lesions had remained unchanged for more than 12 months (mean follow-up period, 16 ± 2 months; range, 12–20 months). Therefore, the sizes of the 32 old inflammatory nodules had remained unchanged for more than 36 months throughout the preoperative and postoperative periods. The other 18 acute inflammatory lesions, 4 benign tumors, and 227 NSCLCs were histologically diagnosed using the resected specimens.

TABLE 1. Characteristics of Pulmonary Nodules

Non-small cell lung cancer (n = 227)	
Mean size (range) (cm)	2.0 ± 1.0 (1.0–6.0)
Histologic subtype	
W/D adenocarcinoma	146
M/D or P/D adenocarcinoma	51
Nonadenocarcinoma	30
Benign nodules (n = 57)	
Mean size (range) (cm)	1.7 ± 1.2 (1.0–6.9)
Histologic type	
Active inflammation	20
Old inflammation	32
Benign tumor	5

W/D, well-differentiated; M/D, moderately-differentiated; P/D, poorly-differentiated.

Preparing of ^{11}C-Acetate

^{11}C-AC was prepared according to the method reported by Ishiwata et al.,[13] which was based on the guidelines for synthesis and quality control of PET tracer by the Japanese Isotope Association. Production of AC was carried out by using a ^{11}C multipurpose synthesizer at the two PET centers, i.e., C-11-BII (Sumitomo Heavy Industries Ltd., Tokyo) at Nishidai Clinic in Tokyo and AMMC-05 (JFE Engineering Corporation, Tokyo) at Japanese Red Cross Kumamoto Health Care Center in Kumamoto, Japan.

PET Scanning

PET scanning was performed at Nishidai Clinic and Japanese Red Cross Kumamoto Health Care Center by using a POSICAM.HZL mPOWER scanner (Positron Co., Houston, TX) and an Advance Nx (GE Medical Systems, United Kingdom), respectively. The PET parameters in the former were as follows: transmission scan, 1 minute/bed; emission scan, 2 minutes/bed; bed positions, eight beds; and field of view, 16.2 cm in z axis with 12 cm in overlap. Those parameters in the latter were as follows: emission scan, 3 minutes/bed; bed position, eight beds; and field of view, 15.7 cm in z axis with 12 cm in overlap. The AC- and FDG-PET examinations were performed on the same day within 1 month before surgery, according to a previously reported protocol.[12] Briefly,^{11}C-AC at a dose of 125 μCi/kg (4.6 MBq/kg) was administered first. PET imaging was performed approximately 10 minutes after the administration of ^{11}C-AC. Approximately 60 minutes after AC-PET imaging,^{18}F-FDG at a dose of 125 μCi/kg (4.6 MBq/kg) was administered, ensuring a gap of at least 120 minutes between the administration of ^{11}C-AC and that of ^{18}F-FDG, i.e., more than six decay half-lives of ^{11}C (20 minutes). FDG-PET imaging was performed approximately 60 minutes after the administration of FDG. It took approximately 3 hours in total to examine both AC- and FDG-PET.

PET Data Analysis

PET images were reviewed by each one radiologist at the two PET centers (Uno and Nakashima with respective 34 and 20 years of experience for diagnosing radioisotope scintigraphy and PET). After image reconstruction, a two-dimensional circular region of interest (ROI) (1.0–6.9 cm in diameter) was drawn surrounding the lesions with positive findings. For the lesions with negative and faintly positive PET findings, the ROI was drawn on the fusion image with the corresponding CT to measure their standard uptake value (SUV). The AC- and FDG-uptake were calculated by the contrast ratio of SUV (SUV-CR) between the lesion and the contralateral lung, as described previously.[2,3] Briefly, the values of maximum SUV (SUV-max) in the tumor ROI (T) and in the corresponding point of contralateral normal lung ROI (N) were then measured. The SUV-CR was calculated according to the formula of T/N for each lesion as an index of AC or FDG uptake.