Detection and Staging of Preinvasive Lesions and Occult Lung Cancer in the Central Airways with ^{18}F-Fluorodeoxyglucose Positron Emission Tomography: A Pilot Study

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Abstract

Purpose: To evaluate the role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in radiologically occult preinvasive lesions and lung cancer in the central airways.

Experimental Design: Twenty-two patients with 24 preinvasive lesions and early squamous cell cancer (SCC) being occult on high-resolution computed tomography were studied. All lesions were diagnosed based on histology sampled using autofluorescence bronchoscopy. FDG-PET findings were correlated with WHO histologic classification. FDG-PET was considered true-positive when the final diagnosis was SCC and true-negative when the lesions were classified as severe dysplasia or less.

Results: FDG-PET was true-positive in 8 of 11 and true-negative in 11 of 13 cases corresponding with a sensitivity of 73% [95% confidence interval (CI), 0.43-0.91] and specificity of 85% (95% CI, 0.57-0.97). Positive and negative predictive values were 80% (95% CI, 0.48-0.96) and 79% (95% CI, 0.52-0.93), respectively.

Conclusions: Our very preliminary data suggest that FDG-PET might be useful for the evaluation of early central airway lesions, being positive in most SCC and negative in cases of severe dysplasia. Validation in a larger multicenter study is needed.

Low-dose spiral computed tomography (CT) is a promising tool for the detection of early lung cancer in the lung parenchyma but is unfortunately insensitive for early detection of cancer in the central airways (1). Sputum cytology examinations combined with autofluorescence bronchoscopy are increasingly being used for detecting early invasive squamous cell cancer (SCC) as well as carcinoma *in situ* and its precursor lesions (2, 3). Being from a referral center for early intervention (4) and minimal invasive techniques, we have developed strict diagnostic and therapeutic algorithms to select patients who may benefit from intraluminal bronchoscopic treatment (3, 5–7). In some cases, additional information using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful for additional staging prior to choosing the most appropriate treatment strategy (3, 7). In a pilot study, we showed that FDG-PET was able to detect cancer lesions with a diameter of ≥3 mm (8).

In the present study, the potential of FDG-PET, in addition to autofluorescence bronchoscopy and high-resolution CT, for a more accurate interpretation of high-resolution CT occult lung cancer has been analyzed.

Patients and Methods

Patients referred with intraluminal superficial lesions in the central airways down to the segmental bronchial level, high-resolution CT occult, and after pathology review, were confirmed to have preinvasive or microinvasive SCCs, were included in this study. FDG-PET was done prior to bronchoscopic biopsy resampling at our institution. Therefore, the first bronchoscopic biopsy was mostly taken at the referring institutions, where the diagnosis of early lung cancer is made. This was, on average, 3 weeks prior to subsequent work-up, including FDG-PET, in our institution. All subjects gave their consent for repeat interventional procedures according to the various existing protocols approved by the medical ethical committee of our hospital.

Baseline autofluorescence bronchoscopy (ONCO-LIFE; Richmond, British Columbia, Canada) in addition to conventional fiberoptic bronchoscopy was done to visualize the proximal and distal borders, and accurately measure the dimension of the lesion (3). The size of the flexible biopsy forceps is used as a variable (jaws closed, 1.6 mm; jaws open, 6 mm). Autofluorescence bronchoscopy was also used for accurate tissue sampling for histologic classification (3, 6). Two routine staff pathologists reviewed all bronchial specimens according to the WHO histologic criteria (9). In case of non–consensus reading, the expert pathologist (E.K. Risse) who has been involved in the carcinogenesis study (4, 10), had the final say about the definite WHO classification.

FDG-PET (ECAT EXACT HR+; Siemens/CTI, Knoxville, TN) was done using two-dimensional emission acquisitions scans (5 min/bed position) with 3-minute transmission scanning 60 minutes after i.v.

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Note: Both Dr. A. Pasic and Dr. H.A. Brokx contributed equally to this work.

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injection of 370 MBq FDG (8, 11). All scans were read initially by one trainee and by an experienced nuclear medicine specialist, and were reviewed independently by another nuclear medicine specialist (staff member). They were blinded for any information except the code of the study (high-resolution CT occult lesions). In case of disagreement, a consensus reading by the two nuclear medicine specialists was reached. The scans were analyzed visually and scored positive if the uptake of the tracer was focal and higher than the surrounding tissue. The location of possible FDG uptake and all other information obtained during the interpretation of images, including the possible findings not concerning the target lesions, were noted and analyzed. No (semi-)quantitative measurements were done, as the primary aim of the study was the detectability of small lesions. In the literature, no valid partial volume correction methods have been proposed for radiographically occult lesions. Without such correction, the SUV values in many of the smaller lesions in our study may be underestimated by a factor of 4 (12).

FDG-PET readings were correlated with the highest category result of the final histologic examination of the specimens, sampled after FDG-PET examination—either by repeat bronchoscopy or surgery. FDG-PET was considered true-positive when the final diagnosis was SCC and true-negative when the diagnosis was severe dysplasia or less.

Statistical analysis. Sensitivity, specificity, and the positive and negative predictive values of FDG-PET were calculated. Their confidence intervals (95% CI) were determined using Confidence Interval Analysis (version 1.0).

Results

Between 1998 and 2003, 22 individuals (18 males) with 24 high-resolution CT occult lesions, median age 66 years (range 52-76), have been prospectively studied. Minimum follow-up was 1 year. The correlation between FDG-PET findings and the histologic classifications of the biopsy taken at our institution is shown in Fig. 1.

Two patients had a relatively long time interval (16 and 32 weeks) between FDG-PET and bronchoscopic resampling because of primary resection of the synchronous tumor in one and due to personal circumstances in the other. These two lesions were compared with the biopsy at the referral center and were found congruent.

Two SCC lesions on first biopsy (both FDG-PET-positive) showed on repeat biopsy dysplasia. This may be caused by complete eradication of tiny lesions by biopsy rather than representing its natural history (4). However, the result of these two particular cases was considered false-positive, as no progression to SCC has thus far been shown. Three lesions were false-negative.

In general, only intraluminal superficial SCC <1 cm^2, being high-resolution CT occult, and having visible borders on autofluorescence bronchoscopy, were included in this study (3, 6). In cases where the distal border is invisible, surgical resection is the treatment of choice in operable candidates. Lesions sizes ranged from 3 mm to 1 cm, being superficial intraluminal type.

FDG-PET was true-positive in 8 of 11 and true-negative in 11 of 13 cases corresponding with a sensitivity of 73% (95% CI, 0.43-0.91) and specificity of 85% (95% CI, 0.57-0.97). Positive and negative predictive values were 80% (95% CI, 0.48-0.96) and 79% (95% CI, 0.52-0.93), respectively (Fig. 2).

FDG-PET for nodal disease was positive in two cases, of which one was false-positive and led to unnecessary mediastinoscopy and anterior mediastinotomy (Fig. 3).

Discussion

High-resolution CT and autofluorescence bronchoscopy improve accurate diagnosis and staging of early SCC and its precursor lesions in the central airways (3, 6). However, autofluorescence bronchoscopy is limited by the possibility to visualize the distal border of a lesion. If there is spread beyond the visual area, this may indicate a more advanced "early stage SCC" and preclude effective intraluminal bronchoscopic treatment (3, 7, 13, 14). Surgical resection is, in that situation, the only therapeutic option.

We extended our pilot study (8) to evaluate FDG-PET in detection and staging of early central lesions. FDG-PET was compared with the histologic classification on repeat biopsies during autofluorescence bronchoscopy or with the microscopic findings after surgical resection (15). Although, in some cases, FDG-PET was shown to detect lesions of 2 to 3 mm in size (8), current data show that the majority of positive FDG-PET lesions are comprised of high-resolution CT occult lesions but with invisible distal margins on autofluorescence bronchoscopy that may suggest a submucosal and surface area ≥ 1 cm^2. Two out of 10 FDG-PET-positive lesions were limited on autofluorescence bronchoscopy and ~2 to 3 mm in size, but we considered

Histology at referral center	PET image	Histology after PET
SCC	**Positive**	SCC
SCC		SCC
SCC	**10 lesions**	SCC
SCC		SCC
≤ SeD	**Sensitivity**	SCC
≤ SeD	**73%**	SCC
≤ SeD		SCC
≤ SeD		SCC
SCC		***≤SeD#***
SCC		***≤SeD#***
SCC	**Negative**	***SCC****
CIS		***SCC****
≤SeD		***SCC****
SCC	**14 lesions**	≤ SeD
CIS		≤ SeD
≤ SeD		≤ SeD
≤ SeD	**Specificity**	≤ SeD
≤ SeD	**85%**	≤ SeD
≤ SeD		≤ SeD
≤ SeD		≤ SeD
≤ SeD		≤ SeD
≤ SeD		≤ SeD
≤ SeD		≤ SeD

Note: #false positive cases; * false negative cases

Fig. 1. WHO histology classification of 24 radiographically occult mucosal lesions. Scoring of the initial biopsy is based on review at the referral center. PET images were correlated with the repeat histology classification, sampled after FDG-PET. Regression of some lesions on repeat biopsy compared with the histology at the referral center, may be caused by the impact of biopsy sampling of minute lesions rather than showing its natural history.

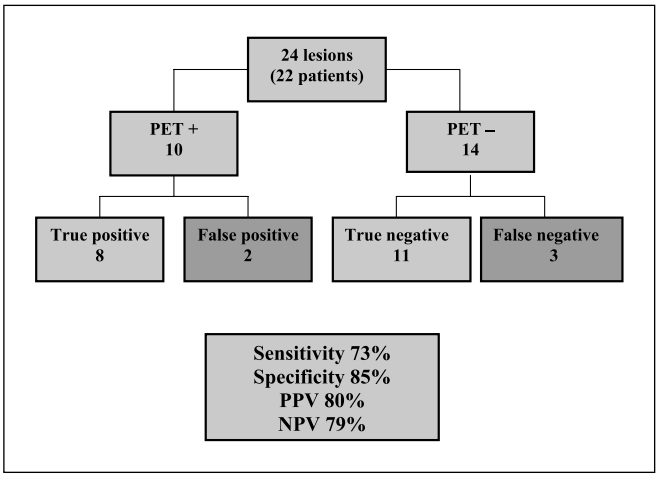

Fig. 2. Sensitivity, specificity, and predictive values based on PET scan images in correlation with the histology results on repeat biopsies or surgical materials.

them "false-positives" as WHO histologic classification thus far showed dysplasia only. However, apart from intra- and interindividual variabilities of histology reporting (10), it is questionable whether morphologic classification could accurately predict the malignant potential of precursor lesions or if other methods might be more promising (16, 17). One cannot predict from current histologic data regarding preneoplastic lesions, whether these two "false-positive" FDG-PET lesions may represent the cohort which might gradually progress (>40% rate) towards SCC (18, 19).

FDG-PET-positive lung cancer lesions with a high uptake ratio (SUV) have been considered to represent a more malignant biology resulting in a significantly worse survival rate (20, 21). However, SUV measurement in the current series was impossible as lesions were invisible on thin section high-resolution CT, and the smallest lesions measured only several millimeters. In the literature, no valid partial volume correction methods have been proposed for measuring high-resolution CT occult lesions. Without a proper algorithm for these particular lesions, SUV values might be greatly underestimated (12).

To our knowledge, this is the first report dealing with the use of FDG-PET to evaluate high-resolution CT occult preinvasive and early cancer lesions in the tracheobronchial mucosa, aside from its use in the lung cancer screening setting for solitary pulmonary nodules (4, 22). Based on current data thus far, a few cases of severe dysplastic lesions tend to be FDG-PET-negative, whereas the majority of SCC was FDG-PET-positive. Neoplastic tissue is characterized by increased expression of glucose transporter proteins as an important feature for FDG uptake (23). Whether preneoplastic bronchial lesions also have elevated glucose transporter protein expression is unknown. It therefore seems acceptable to assume that in squamous cell carcinogenesis, the increasing volume of preneoplastic cells from dysplasia to microinvasive cancer may increase image contrast based on signals from metabolically active cell clones. However, the signals' dispersion of superficial spreading type of mucosal lesion may also influence image contrast per target tissue volume, making it FDG-PET-negative.

It is premature to assume that PET-negative lesions are relatively benign, which may justify a wait-and-see approach for early mucosal changes (24). However, the low risk and superior cost-effectiveness of intraluminal bronchoscopic intervention, combined with the inherent risk for malignant transformation of these lesions may lead to the implementation of practical measures not supported by foolproof scientific data (25). This may fuel controversies regarding overdiagnosis and treatment of pseudodiseases (26, 27). Thus, our very preliminary results suggest that FDG-PET might be useful for the evaluation of early central airway lesions in selected high-risk individuals. As a noninvasive diagnostic tool for early stage lesions, its full potential needs to be further explored in a large multicenter study.

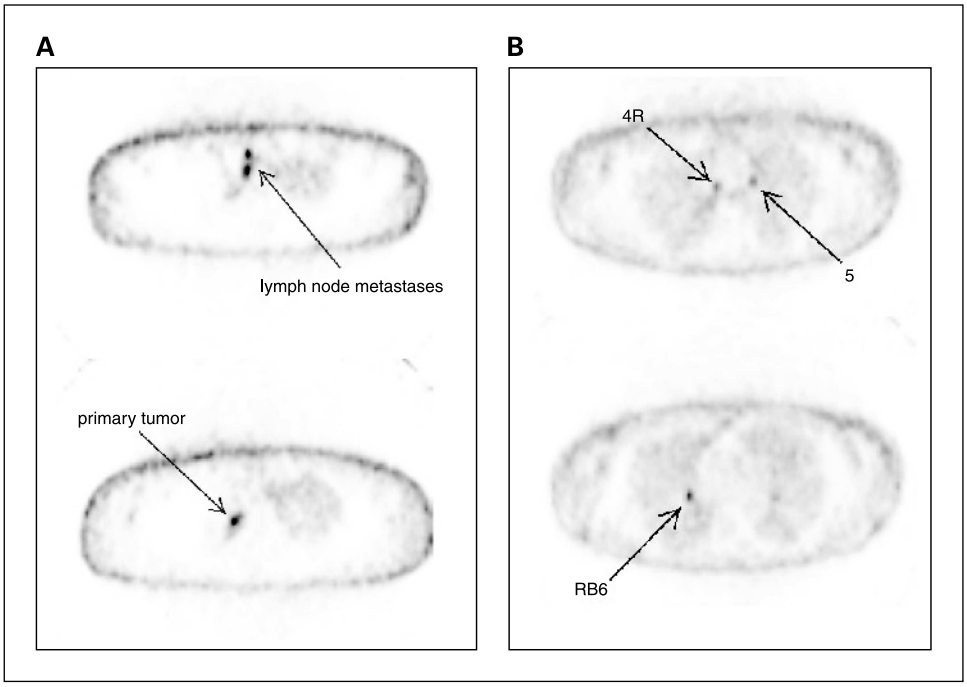

Fig. 3. *A*, FDG-PET of patient with true-positive occult tracheal SCC and mediastinal lymph node (N2). There is a strong shift to the right thorax due to previous right pneumonectomy. *B*, FDG-PET of patient with occult SCC in the RB6. PET was false-positive for both primary lesion and N2/3 involvements.

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