INVITED COMMENTARY

Changing Pattern of Lung Cancer and Its Imaging: ^{201}Tl SPECT Versus [^{18}F]FDG PET

The diagnostic accuracy of lung cancer has been reported to be as high as >90% using [^{18}F]FDG PET. This observation may give the impression that FDG PET is the ultimate imaging modality for lung cancer. In this issue of *The Journal of Nuclear Medicine*, Higashi et al. (*1*) report that ^{201}Tl SPECT has an advantage compared with FDG PET in a certain type of lung cancer, bronchioloalveolar cell carcinoma (BAC). In their study, ^{201}Tl SPECT identified 4 additional lung cancers that FDG PET did not reveal: 3 BACs and a well-differentiated adenocarcinoma.

BAC

The standard World Health Organization diagnostic criteria distinguish small cell carcinoma from non–small cell lung carcinoma (NSCLC). NSCLC is composed of squamous cell carcinoma, adenocarcinoma, and large cell undifferentiated carcinoma. Previously, it had been thought that squamous cell carcinoma, which typically originates from the central bronchial surface, accounted for 60%–70% of all primary lung carcinoma. However, several recent large surveys have shown a change in the incidence of the histologic type of lung cancer, with a dramatic increase in adenocarcinoma and a decrease in squamous cell carcinoma. Four subtypes of adenocarcinoma are recognized: acinar, papillary, mucous secreting, and bronchioloalveolar. An increase in BAC is responsible for most of the increase in adenocarcinoma (*2*). Barsky et al. (*3*) analyzed 1,527 cases of lung carcinoma from 1955 to 1990. They reported a decrease in squamous cell carcinoma from 56.1% to 22.2% and an increase in adenocarcinoma from 14.6% to 46.5%, with most of the increase in adenocarcinoma being attributed to an increase in BAC, from 5% to 24.0% (*3*). The frequency of BAC, as defined retrospectively by Auerbach and Garfinkel (*4*), increased from 9.1% of cases before 1978 to 20.3% of cases from 1986 to 1989. BAC is no longer a rare special type of lung cancer but one of the major subtypes of adenocarcinoma consisting of 20%–24% of total lung cancers.

Patients with BAC tend to be younger, are more likely to be female, and are less likely to be cigarette smokers compared with patients with other NSCLC. BAC is characterized by a peripheral parenchymal location, no distortion of pulmonary interstitial structure, and cancer cells growing along the alveolar septa. Typically, BAC has been considered more indolent than other types of NSCLC. Patients who have solitary lesions of BAC amenable to surgical resection have improved survival compared with patients with other types of NSCLC (*2*). Therefore, the diagnosis and accurate evaluation of the extent of disease are especially important in patients with BAC.

WHY DOES FDG PET MISS BAC?

Probably the most important characteristic of BAC for nuclear medicine is its slower growth rate compared with that of other types of NSCLC. Higashi et al. (*5*) analyzed the proliferation potential of NSCLC and correlated it with FDG uptake. The proliferating cell nuclear antigen (PCNA) labeling index (representing the relative number of cells expressing the PCNA) and FDG uptake were significantly lower in BAC than in non-BAC. No significant differences in the cellular density of BAC and non-BAC were found. FDG uptake correlated significantly with PCNA labeling index and not with cell density, which means that FDG uptake in NSCLC may be an indicator of growth rate. Ahuja et al. (*6*) evaluated various clinical parameters and FDG uptake for the contribution to survival of 155 patients with NSCLC. Multivariate analysis showed that an FDG standardized uptake ratio of >10 provided prognostic information independent of the clinical stage and lesion size. FDG uptake within the primary lesion of NSCLC correlates with survival. Low FDG uptake by BAC is most likely explained by its slow growth rate and may be an indicator of better survival. FDG is not a simple imaging agent of cancer but represents molecular events in glucose metabolism, in which elevation is associated with malignant transformation of cells (*7*). Because of this unique character, FDG uptake of slow-growing tumors may become as low as that of benign tumors, and some BACs are likely to show false-negative studies with FDG PET.

WHY CAN ^{201}Tl SPECT DETECT BAC?

^{201}Tl is a potassium analog, and tumor uptake of ^{201}Tl is dependent on blood flow and on the Na^+,K^+-adenosinetriphosphatase (Na^+,K^+-ATPase) system similar to that in the myocardium. Other contributing factors include tumor viability, ion cotransport system, calcium ion channel exchange, vascular immaturity with leakage, and increased cell membrane permeability (*8*). Tonami et al. (*9*) reported 100% sensitivity (147/147) for pulmonary

Received Apr. 30, 2001; revision accepted Jun. 11, 2001.

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malignant lesions of >20 mm in diameter with ^{201}Tl SPECT. However, 70% of benign lesions (16/23) also had significant ^{201}Tl uptake. They proposed measuring a retention index from the early (15 min) and delayed (3 h) images of SPECT. The retention index was defined as the difference between the delayed ratio and the early ratio divided by the early ratio expressed as a percentage. When benign and malignant lesions were compared, no significant difference in the delayed ratio was found but a significant difference in the retention index was observed (*9*).

Suga et al. (*10*) studied 106 lung lesions suspected of being lung cancer with ^{201}Tl SPECT. All 48 malignant lesions (100%) and 38 of 58 benign lesions (67%) were visualized on the early scan. No significant differences were found in the early or delayed uptake ratios in benign lesions compared with malignant lesions. However, the difference in the retention index was statistically significant (*10*). Takekawa et al. (*11*,*12*) reported that the tumor-to-contralateral normal lung uptake ratio on the delayed scan (delayed uptake ratio) of ^{201}Tl SPECT studies of lung adenocarcinoma was significantly higher for Na^+,K^+-ATPase–positive tumors than that for Na^+,K^+-ATPase–negative tumors. The sensitivity on the delayed scan was 64% (9/14) for well-differentiated, 83% (5/6) for moderately differentiated, and 100% (9/9) for poorly differentiated adenocarcinomas. The delayed ratio was significantly lower for the well-differentiated group than that for the moderately and poorly differentiated groups (*11*). Also, on multivariate analysis, the delayed ^{201}Tl uptake ratio of lung cancer was an independent prognostic factor for survival (*12*). However, Higashi et al. (*1*) did not find a correlation between the degree of differentiation of adenocarcinoma and the early uptake ratio or the delayed uptake ratio of ^{201}Tl. On the basis of these reports, ^{201}Tl SPECT has a good sensitivity for lung cancer, whereas ^{201}Tl uptake is also seen in many benign lesions

^{201}Tl SPECT VERSUS FDG PET FOR LUNG CANCER

^{201}Tl SPECT has shown a good sensitivity for lung cancer and may be better than FDG PET in BAC. However, in the study by Higashi et al. (*1*), FDG PET identified 3 additional lung cancers that ^{201}Tl SPECT did not reveal. Two of these were <2 cm in diameter. ^{201}Tl has a longer half-life (73 h), with limits on the injection dose. The low photon energy (80 keV) is reflected by the poor resolution and significant attenuation by normal tissue. Therefore, it is reasonable to assume that FDG PET would have higher detectability, especially for small-sized lesions, than ^{201}Tl SPECT. ^{201}Tl tumor uptake is usually lower than that of normal myocardium, liver, spleen, kidney, and thyroid. ^{201}Tl-avid tumors cannot be identified in the proximity of high ^{201}Tl uptake in normal organs. Higashi et al. missed a moderately differentiated adenocarcinoma localized near myocardium with ^{201}Tl SPECT. In the detection of mediastinal lymph node metastasis, delayed ^{201}Tl SPECT showed a sensitivity of 50% and a specificity of 80% (*13*), lower than the sensitivity and specificity of FDG PET. ^{201}Tl SPECT is not useful for detecting tumors in the abdomen. For the detection of small-sized lesions in the lung and metastases in the whole body, FDG PET is clearly superior to ^{201}Tl SPECT.

If both FDG and ^{201}Tl are available, FDG may still be the first choice for imaging lung tumors. For tumors that are suspected of being BACs, ^{201}Tl SPECT may be recommended. Recent thin-section CT scanning showed characteristic findings of BAC. Ground-glass opacity is a feature of nonmucinous types of BAC, and air-space consolidation is dominant for mucinous types of BAC (*14*,*15*). Thin-section CT findings might be helpful for the selection of further evaluation methods of nuclear medicine.

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