Use of a Dual-Head Coincidence Camera and ^{18}F-FDG for Detection and Nodal Staging of Non–Small Cell Lung Cancer: Accuracy as Determined by 2 Independent Observers

Henk Stevens, MD, PhD[1]; Patricia F.A. Bakker, MD, PhD[2]; Noël J.J. Schlösser, MD, PhD[3]; Peter P. van Rijk, MD, PhD[1]; and John M.H. de Klerk, MD, PhD[1]

[1]Department of Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Department of Thoracic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands; and [3]Department of Pulmonology, University Medical Center Utrecht, Utrecht, The Netherlands

The accurate detection of lung carcinoma and the determination of its stage remain significant clinical problems. ^{18}F-FDG PET has been shown to improve detection and staging of lung cancer and to prevent unnecessary invasive procedures. Positron imaging with dual-head gamma cameras may not be as sensitive as PET, but recent studies have shown good results with these cameras. **Methods:** In the present study, we investigated 100 patients, 76 of whom were male and 24 female (mean age ± SD, 60.7 ± 9.4 y), with suspected non–small cell lung cancer. ^{18}F-FDG scanning was performed using a dual-head coincidence camera 1 h after the intravenous injection of 185 MBq of ^{18}F-FDG. For 46 patients, attenuation correction was also performed. Two independent observers unaware of clinical status analyzed all imaging studies. TNM classification was assigned after surgical staging. **Results:** In 44 patients with clinically suspected bronchogenic carcinoma, no evidence of malignancy was found. However, in 56 patients a pulmonary neoplasm was demonstrated. At interobserver analysis, a κ value of 0.94 ($P < 0.0001$) was found for detection of the primary tumor and a κ value of 0.63 ($P < 0.0001$) was found for mediastinal staging. A sensitivity of 96%, a specificity of 93%, and an accuracy of 95% were found for detection of pulmonary neoplasm. Assessment of lymph node involvement showed a sensitivity of 50%, a specificity of 92%, and an accuracy of 77%. The sensitivity of CT in assessing lymph node involvement was 36%, the specificity was 86%, and the accuracy was 67%. Attenuation correction provided more anatomic information, but no differences were seen between attenuation-corrected and non–attenuation-corrected images for detecting lesions or lymph node involvement. **Conclusion:** The present study confirms earlier data showing that ^{18}F-FDG scans obtained with dual-head coincidence cameras are useful in the detection of non–small cell lung cancer and less suitable for staging of lymph node involvement, with accuracy comparable to that of CT.

Key Words: non–small cell lung cancer; ^{18}F-FDG; dual-head coincidence camera; interobserver variability; mediastinal staging

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Lung cancer is among the most frequent and most lethal of cancers in both men and women. Lung cancer makes up 22% of all cancers in men and 8% of all cancers in women. Five-year survival for non–small cell lung cancer (NSCLC) depends on the stage. For stages I, II, III, and IV, the 5-y survival is 42%, 22%, 5%, and 3%, respectively (*1*). Many lung malignancies present as single pulmonary nodules (SPNs) and are potentially cured by resection. Unfortunately, up to one third of patients with SPNs who undergo surgery are found to have benign lesions at thoracotomy (*2*). In both detection and staging of lung cancer, conventional techniques lack sensitivity and specificity for adequate clinical work-up (*3*). ^{18}F-FDG PET allows the visualization of metabolic activity in tissue. Several studies have already shown that ^{18}F-FDG PET is the most accurate noninvasive imaging test for the diagnosis of pulmonary nodules. Moreover, recent studies showed that PET better assesses the stage of NSCLC and provides more accurate prognostic stratification than does conventional staging (*4–8*). Although PET has the advantage of high spatial resolution and allows quantification, its limited availability may prevent routine clinical application. In contrast, coincidence imaging with dual-head gamma cameras may allow routine applications, because of more widespread availability. Previous studies performed using ^{18}F-FDG PET and dual-head gamma cameras showed excellent results for staging and detection in head and neck cancer and encouraging results for mediastinal staging in lung cancer (*9–11*). In the present study, we investigated the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of

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For correspondence or reprints contact: Henk Stevens, MD, PhD, Department of Nuclear Medicine, HP E02.222, University Medical Center Utrecht, Heidelberglaan 100, 3508 GA Utrecht, The Netherlands.

E-mail: H.Stevens@azu.nl

^{18}F-FDG PET in detection and nodal staging of NSCLC using a dual-head coincidence camera. The ^{18}F-FDG PET images were analyzed by 2 independent observers.

MATERIALS AND METHODS

Patients

A total of 100 consecutive nondiabetic patients (76 male and 24 female; mean age ± SD, 60.7 ± 9.4 y) suspected of having NSCLC were studied retrospectively. Suspicion of malignancy was based on clinical course and radiologic examination (planar chest radiography, CT, or MRI). A clinical diagnosis of lung cancer was histologically confirmed at surgical staging or CT-guided biopsy. If no histologic diagnosis was available, the pulmonary nodule was considered benign if during a year of follow-up no signs of progression or metastases were seen on radiologic examination.

Imaging Protocol

For all 100 patients, ^{18}F-FDG PET was performed after an overnight fast. Blood glucose levels were measured for all patients using a routine clinical test. A blood glucose level higher than 10 mmol/L was used as an exclusion criterion. ^{18}F-FDG PET was performed, using a SPECT scanner with PET capability (Vertex-MCD; ADAC Laboratories, Milpitas, CA), 1 h after the intravenous administration of 185 MBq of ^{18}F-FDG. The spatial resolution of this scanner is 5 mm. The acquisition (peak to peak and Compton to peak; full-field detector mask) involved a 180° rotation of each detector with 32 stops at 45 s per stop and a 128 × 128 matrix. A transmission scan was obtained with an external ^{137}Cs-point source, to measure photon attenuation and to correct subsequent emission scans. PET images were generated using iterative reconstruction by an ordered-subsets expectation maximization algorithm with 2 iterations and 8 order subsets, followed by Wiener filtering.

All PET images were evaluated qualitatively by 2 independent observers experienced in describing PET scans and unaware of clinical status and radiologic data. In cases of disagreement, a consensus was obtained. Uptake in the lung lesions and mediastinum was scored with reference to liver uptake: 0 = no uptake, 1 = uptake equal to that in the liver, and 2 = uptake more than that in the liver. Uptake of 1 or more was considered to indicate malignancy. Because of the limited resolution with ^{18}F-FDG, the same lymph node categories as described in the study of Pieterman et al. were used to compare the results of CT, ^{18}F-FDG imaging, and histopathologic examination (Fig. 1) (*6*).

Surgical Lymph Node Staging

Cervical mediastinoscopy was performed within 3 wk of imaging studies, with the patient under general anesthesia. The left and right upper paratracheal nodes (nodes 2L and 2R, according to the classification of Naruke, the paratracheal node (node 3), the left and right lower paratracheal nodes (nodes 4L and 4R), and the subcarinal node (node 7) were routinely sampled. At the left parasternal mediastinoscopy, the subaortic node (node 5) and the para-aortic node (node 6) were sampled. In patients whose N2 nodes were not accessible by mediastinoscopy, these nodes were sampled using video-assisted thoracic surgery. Thoracotomy, if indicated, was usually performed within 2 wk of mediastinoscopy. The precise anatomic location of the removed lymph nodes was recorded using the lymph node map and the definitions of the American Thoracic Society (*12,13*).

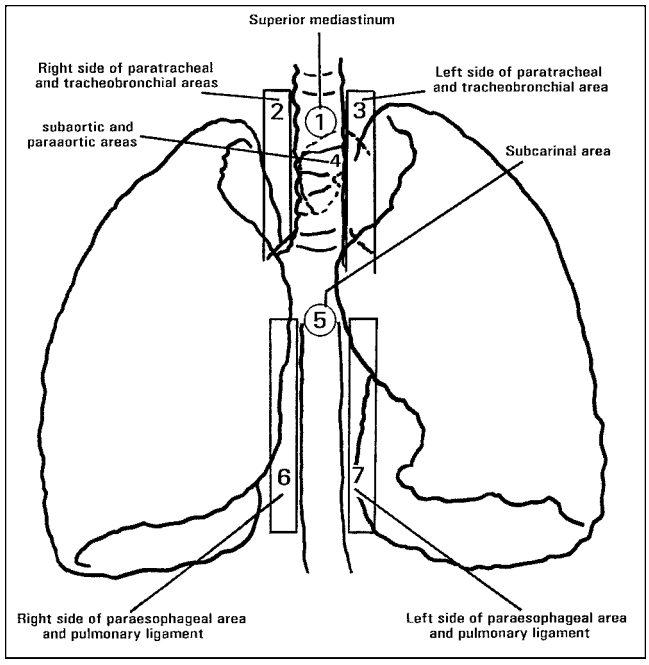

FIGURE 1. Mediastinal lymph node levels used to compare results of ^{18}F-FDG imaging, CT, and histopathologic examination.

CT

Chest CT was performed on a spiral CT scanner (Philips Medical Systems, Best, The Netherlands) using a 5-mm slice thickness and a recovery index of 2 mm. A power injector was used to achieve a 2 mL/s bolus injection of contrast medium during 45 s. The scan delay was 25 s. Each CT scan was evaluated by an experienced radiologist. Mediastinal lymph nodes were considered to be involved if they exceeded 10 mm in short-axis diameter.

Statistical Analysis

Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were calculated for ^{18}F-FDG PET and CT, using the mediastinoscopy or thoracotomy as the gold standard.

Agreement statistics (κ) were analyzed to compare the 2 observers. A value of 1 indicates perfect agreement. A value of 0 indicates chance agreement. The McNemar test was used to calculate any significant difference in the sensitivity and specificity of CT and ^{18}F-FDG for staging the mediastinum.

RESULTS

^{18}F-FDG PET was performed without attenuation correction for the first 54 patients and with attenuation correction for the following 46. The clinical data of all patients are summarized in Table 1. Fifty-six patients had NSCLC (26 patients with squamous cell carcinoma, 18 with adenocarcinoma, 9 with large cell neuroendocrine carcinoma, and 3 with large cell undifferentiated carcinoma), and for all patients the diagnosis was confirmed histologically. The mean tumor size was 3.3 cm (±1.8 cm), with a range of 0.5–9 cm; size was determined at pathologic examination. Two tumors of 0.5–1 cm were seen, 7 tumors of 1–2 cm, 9 of 2–3 cm,

TABLE 1
Clinical Data of the 100 Patients with Suspected Lung Cancer

Characteristic	No. of patients
Male/female	76/24
Cervical and or parasternal mediastinoscopy	52
Video-assisted thorascopic surgery	1
Thoracotomy	42
Attenuation correction	46
Pathologic stage	
T0	44
T1 4N0	28
T1 4N1	8
T1 4N2	20

Mean patient age (±SD) was 60.7 ± 9.4 y.

and 21 larger than 3 cm. In 17 patients, the tumor size could not be established because they could not undergo surgery.

In 35 patients with a benign lesion, the tumor size could be established on radiologic examination; mean size was 2.3 cm (±1.4), with 2 lesions of 0.5–1 cm, 11 of 1–2 cm, 15 of 2–3 cm, and 7 larger than 3 cm. In the remaining 9 patients, no tumor size could be established reliably.

The sensitivity and specificity of ^{18}F-FDG PET for the detection of lung cancer were 96% and 93%, respectively (Table 2). False-negative lesions were seen in 2 patients: one with a 1.1-cm lesion with little uptake and another with a 1.7-cm lesion with diffuse uptake in the lung due to diffuse metastases. False-positive lesions were seen in 3 patients: in one because of infection, in another because of tuberculosis, and in a third because of sarcoidosis.

In the staging of mediastinal lymph node involvement, ^{18}F-FDG PET showed a sensitivity of 50% and a specificity of 92% (Table 2). CT had a sensitivity of 36% and specificity of 86% for the detection of mediastinal lymph node involvement (Table 2). CT and ^{18}F-FDG PET did not significantly differ in sensitivity and specificity for staging the mediastinum ($P = 0.2$ and $P = 0.4$, McNemar test).

The scoring of the 2 observers was nearly the same for detection of the primary tumor ($\kappa = 0.94$ [$P < 0.0001$], indicating almost perfect agreement). In the group of patients with lung cancer, the scoring of the 2 observers agreed well for detection of mediastinal lymph node involvement ($\kappa = 0.63$ [$P < 0.0001$]).

The 46 images of patients for whom attenuation correction was performed were not scored differently from the non–attenuation-corrected images. Attenuation correction provided more information only about anatomic borders, which are less well defined in images without attenuation correction. In judging mediastinal lymph node involvement, both observers preferred the images without attenuation correction (Fig. 2).

DISCUSSION

The results we describe here for the diagnosis and nodal staging of NSCLC confirm earlier data showing that ^{18}F-FDG PET with coincidence imaging is accurate for differentiation between benign and malignant pulmonary nodules (*14–17*). A sensitivity of 97% and a specificity of 93% were found. There were 3 false-positive studies, which were due to inflammatory diseases. Because the study was retrospective, the patient selection may have been biased. Patients with known extrapulmonary tumors were not excluded; probably because of the sample size, we did not see lung metastases in our group. Patients with small cell lung cancer are often diagnosed in an earlier stage of the diagnostic tract and therefore do not undergo further staging and are treated with chemotherapy. In the whole population, we saw 2 patients with small cell lung cancer (not mentioned in our article, both true-positive).

Recent studies have shown that the introduction of ^{18}F-FDG imaging with a dedicated PET camera is cost effective in the management of solitary pulmonary nodules (*18,19*). Therefore, considering the lower costs of a dual-head PET camera and the results of our study, ^{18}F-FDG PET with a dual-head gamma camera may be a useful imaging technique in the analysis of SPNs when dedicated PET is absent. Several studies have shown that a full-ring ^{18}F-FDG PET system is the most accurate noninvasive method for preoperative mediastinal staging of NSCLC, with a sensitivity of 91% and specificity of 86% (*6*). Moreover, different studies have shown that inclusion of ^{18}F-FDG PET in the work-up to surgery is cost effective (*20,21*). Because of the limited availability of full-ring PET scanners, dual-head coincidence SPECT cameras have been used for ^{18}F-FDG imaging in lung cancer and for staging.

TABLE 2
Performance of ^{18}F-FDG Dual-Head PET and CT for Detection and Staging

Modality	Site	% Sensitivity	% Specificity	% Accuracy	% PPV	% NPV
^{18}F-FDG dual-head PET	Lung	96 (91–100)	93 (86–100)	95	95	95
	Mediastinum	50 (28–72)	92 (86–98)	77	77	77
CT	Mediastinum	36 (12–60)	86 (73–99)	67	56	71

Within parentheses are shown 95% confidence intervals.

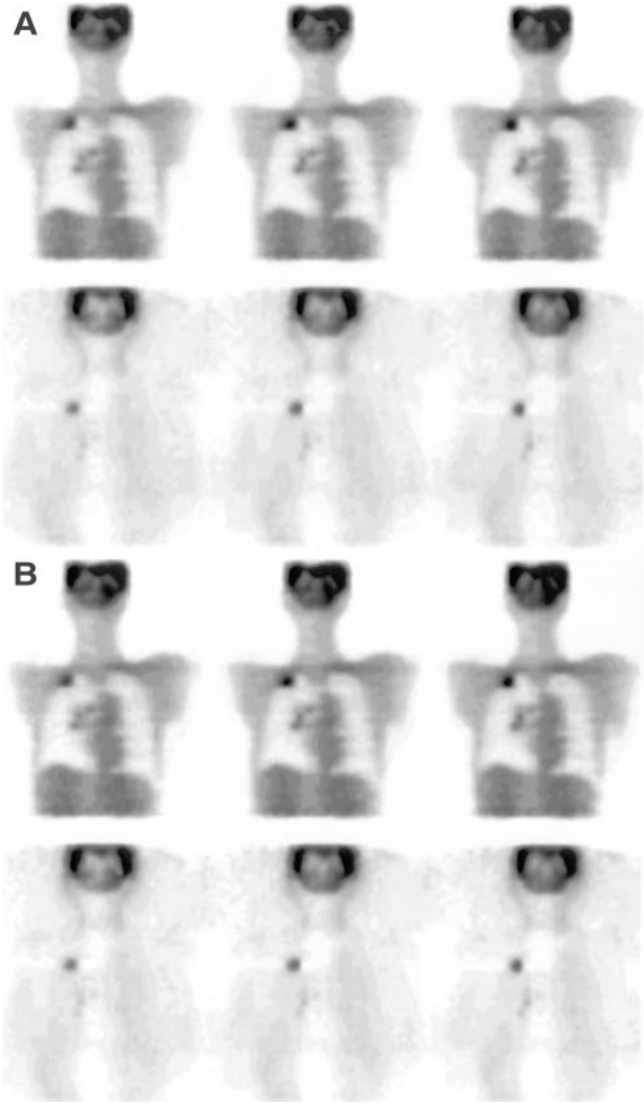

FIGURE 2. ^{18}F-FDG images obtained with attenuation correction (A) and without attenuation correction (B) of patient with T3 N2 M0 non–small cell lung carcinoma.

To be as clinically useful as dedicated PET systems, dual-head gamma cameras with ^{18}F-FDG PET need to provide accurate information about the mediastinal stage. A few studies have described the sensitivity and specificity of the use of a dual-head coincidence gamma camera in staging of the mediastinum. A study by Tatsumi et al. reported a sensitivity of 78% and a specificity of 93% in determining the stage of mediastinal lymph nodes (*15*). In another study, by Shreve et al., a sensitivity of 58% was reported for detection of metastatic disease in mediastinal lymph nodes (*22*). In an earlier study from our department, by Stokkel et al., a sensitivity of 90% and a specificity of 97% were found for the assessment of lymph node involvement in patients with NSCLC (*23*). In the present study, we could not reproduce our earlier results. However, the sample size was small, and the confidence intervals of our earlier data were consequently wide and overlapped those of the present study. Considering the lack of diagnostic accuracy for dual-head gamma cameras with PET capability in the staging of mediastinal lymph nodes, dedicated PET cameras should be preferred.

The spatial resolution of dual-head gamma cameras with PET capability is about 6–8 mm transversely and 6–10 mm axially for a line source in water (*9*). However, these dual-head systems are less sensitive for detection of annihilation radiation, and the counting rate is limited because of the thin sodium iodine detectors (*9*). These limitations may result in poor image quality and low contrast resolution. Moreover, gamma camera–based PET systems use only 2 detectors; therefore, the camera has to rotate for 30–40 min around the patient, increasing the possibility of movement artifacts. All these factors may cause the lack of sensitivity for small lesions in the mediastinum.

Measured attenuation correction using a transmission scan improves image quality and, with the absence of the artifacts present on non–attenuation-corrected images, better delineates anatomic structures. In dedicated PET cameras, attenuation correction did not improve the diagnostic accuracy of ^{18}F-FDG (*24*,*25*). In contrast, 2 recent studies found better image quality and minimization of the limits of dual-head PET for the detection of small lesions when attenuation correction was used for oncologic patients (*26*,*27*). In our study, attenuation correction indeed gave more information about anatomic location, but the analysis of the nonattenuated data and the attenuated images did not differ. However, in our study we did not separately describe the images with and without attenuation; therefore, our results concerning the effect of attenuation correction should be interpreted cautiously.

CONCLUSION

The present study showed excellent sensitivity and specificity for ^{18}F-FDG PET with a dual-head gamma camera in the analysis of SPNs, thus indicating that these systems do have a role in the diagnostic procedure for SPNs. For routine clinical use in the work-up of patients with NSCLC, ^{18}F-FDG PET with a dual-head gamma camera proved less suitable, having an accuracy comparable to that of CT.

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REFERENCES

1. Fry WA, Menck HR, Winchester DP. The national cancer data base report on lung cancer. *Cancer.* 1996;77:1947–1955.
2. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. *Arch Intern Med.* 1997;157:849–855.
3. Webb WR, Gatsonis C, Zerhouni EA, et al. CT and MR imaging in staging non-small cell bronchogenic carcinoma: report of the Radiologic Diagnostic Oncology Group. *Radiology.* 1991;178:705–713.
4. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s—meta-analytic comparison of PET and CT. *Radiology.* 1999;213:530–536.

5. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA.* 2001;285:914–924.
6. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med.* 2000;343:254–261.
7. Hicks RJ, Kalff V, MacManus MP, et al. The utility of ^{18}F-FDG PET for suspected recurrent non-small cell lung cancer after potentially curative therapy: impact on management and prognostic stratification. *J Nucl Med.* 2001;42:1605–1613.
8. Hicks RJ, Kalff V, MacManus MP, et al. ^{18}F-FDG PET provides high-impact and powerful prognostic stratification in staging newly diagnosed non-small cell lung cancer. *J Nucl Med.* 2001;42:1596–1604.
9. Ak I, Blokland JA, Pauwels EK, Stokkel MP. The clinical value of ^{18}F-FDG detection with a dual-head coincidence camera: a review. *Eur J Nucl Med.* 2001;28:763–778.
10. Stokkel MP, Terhaard CH, Hordijk GJ, van Rijk PP. The detection of local recurrent head and neck cancer with fluorine-18 fluorodeoxyglucose dual-head positron emission tomography. *Eur J Nucl Med.* 1999;26:767–773.
11. Stokkel MP, ten Broek FW, van Rijk PP. Preoperative assessment of cervical lymph nodes in head and neck cancer with fluorine-18 fluorodeoxyglucose using a dual-head coincidence camera: a pilot study. *Eur J Nucl Med.* 1999;26:499–503.
12. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest.* 1997;111:1718–1723.
13. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710–1717.
14. Bousson V, Moretti JL, Weinmann P, et al. Assessment of malignancy in pulmonary lesions: FDG dual-head coincidence gamma camera imaging in association with serum tumor marker measurement. *J Nucl Med.* 2000;41:1801–1807.
15. Tatsumi M, Yutani K, Watanabe Y, et al. Feasibility of fluorodeoxyglucose dual-head gamma camera coincidence imaging in the evaluation of lung cancer: comparison with FDG PET. *J Nucl Med.* 1999;40:566–573.
16. Weber W, Young C, Abdel-Dayem HM, et al. Assessment of pulmonary lesions with ^{18}F-fluorodeoxyglucose positron imaging using coincidence mode gamma cameras. *J Nucl Med.* 1999;40:574–578.
17. Weber WA, Neverve J, Sklarek J, et al. Imaging of lung cancer with fluorine-18 fluorodeoxyglucose: comparison of a dual-head gamma camera in coincidence mode with a full-ring positron emission tomography system. *Eur J Nucl Med.* 1999;26:388–395.
18. Dietlein M, Weber K, Gandjou A, et al. Cost-effectiveness of FDG-PET for the management of solitary pulmonary nodules: a decision analysis based on cost reimbursement in Germany. *Eur J Nucl Med.* 2000;27:1441–1456.
19. Gambhir SS, Shepherd JE, Shah BD. Analytical decision model for the cost-effective management of solitary pulmonary nodules. *J Clin Oncol.* 1998;16:2113–2125.
20. Scott WJ, Shepherd J, Gambhir SS. Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis. *Ann Thorac Surg.* 1998;66:1876–1883.
21. Dietlein M, Weber K, Gandjour A, et al. Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results. *Eur J Nucl Med.* 2000;27:1598–1609.
22. Shreve P, Stevenson R, Gross M, Wahl R. Lesion detection in oncologic diagnosis: comparison of dual head coincidence with dedicated PET FDG imaging [abstract]. *J Nucl Med.* 1998;39(suppl):109P.
23. Stokkel MP, Bakker PF, Heine R, Schlosser NJ, Lammers JW, van Rijk PP. Staging of lymph nodes with FDG dual-headed PET in patients with non-small-cell lung cancer. *Nucl Med Commun.* 1999;20:1001–1007.
24. Bengel FM, Ziegler SI, Avril N, Weber W, Laudenbacher C, Schwaiger M. Whole-body positron emission tomography in clinical oncology: comparison between attenuation-corrected and uncorrected images. *Eur J Nucl Med.* 1997;24:1091–1098.
25. Kotzerke J, Guhlman A, Moog F, Frickhofen N, Reske SN. Role of attenuation correction for fluorine-18 fluorodeoxyglucose positron emission tomography in the primary staging of malignant lymphoma. *Eur J Nucl Med.* 1999;26:31–38.
26. Zimny M, Kaiser HJ, Cremerius U, et al. Dual-head gamma camera 2-[fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography in oncological patients: effects of non-uniform attenuation correction on lesion detection. *Eur J Nucl Med.* 1999;26:818–823.
27. Chan W-L, Freund J, Pocock NA, et al. Coincidence detection FDG PET in the management of oncological patients: attenuation correction versus non-attenuation correction. *Nucl Med Commun.* 2001;22:1185–1192.