^{18}F-FDG PET in Evaluation of Adrenal Lesions in Patients with Lung Cancer

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The purpose of this study was to assess the role of PET with ^{18}F-FDG in differentiating benign from metastatic adrenal masses detected on CT or MRI scans of patients with lung cancer. **Methods:** This retrospective study analyzed ^{18}F-FDG PET scans of patients with lung cancer who were found to have an adrenal mass on CT or MRI scans. One hundred thirteen adrenal masses (75 unilateral and 19 bilateral; size range, 0.8–4.7 cm) were evaluated in 94 patients. PET findings were interpreted as positive if the ^{18}F-FDG uptake of the adrenal mass was greater than or equal to that of the liver. PET findings were interpreted as negative if the ^{18}F-FDG uptake of the adrenal mass was less than that of the liver. All studies were reviewed independently by 3 nuclear medicine physicians, and the results were then correlated with clinical follow-up or biopsy results when available. **Results:** PET findings were positive in 71 adrenal masses. Sixty-seven of these were eventually considered to be metastatic adrenal disease. In the remaining 4, no changes in lesion size were noted on follow-up examinations. PET findings were negative in 42 adrenal masses, of which 37 eventually proved to be benign. Among the 5 adrenal masses that were false-negative, one was a large necrotic metastasis; 1 was a 2.4-cm lesion with central hemorrhaging, and the remaining 3 were lesions of less than 11 mm. The sensitivity, specificity, and accuracy for detecting metastatic disease were 93%, 90%, and 92%, respectively. **Conclusion:** ^{18}F-FDG PET is an accurate, noninvasive technique for differentiating benign from metastatic adrenal lesions detected on CT or MRI in patients with lung cancer. In addition, PET has the advantage of assessing the primary cancer sites and detecting other metastases.

Key Words: ^{18}F-FDG PET; lung cancer; adrenal masses; CT; adrenal metastases

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Lung cancer is the most common cause of death in men from cancer and increasingly more common in women. Five-year survival has improved among lung cancer patients who have limited disease and undergo surgery (*1,2*). However, the disease stage of most patients will actually be increased when they undergo surgical exploration, thus preventing them from being candidates for surgical intervention. There is a need for more accurate preoperative staging to better select appropriate candidates for surgery. Autopsy series have shown a high occurrence of adrenal metastases in patients with lung cancer, ranging from 35% to 59% (*3,4*). The incidence of adrenal masses in clinical studies of patients with non–small cell lung carcinoma (NSCLC) may vary from 4.1% to 18% (*5*). However, not all adrenal masses can be assumed to represent metastasis, because 2%–9% of the general population has been shown to harbor benign adenomas (*6*). Therefore, it is important to characterize adrenal masses accurately when they are discovered in patients with lung cancer. Percutaneous biopsy remains the gold standard for confirmation of the nature of the lesion. However, percutaneous biopsy is an invasive technique often associated with complications. The diagnostic accuracy of aspirated material ranges from 80% to 100% (*7*).

Noninvasive imaging techniques, which include CT and MRI, have been used to differentiate metastases from benign adrenal adenoma. CT has shown usefulness because of its ability to measure attenuation, on both unenhanced images and on delayed contrast-enhanced images, to differentiate benign from malignant lesions (*8,9*). But diagnosis based on attenuation measurement is often not feasible in unenhanced or delayed contrast-enhanced CT (*10*). MRI has shown initial promise in T2-weighted and chemical shift imaging, but the signal intensity of benign and malignant lesions overlaps considerably (*11,12*). Recently, ^{18}F-FDG PET has shown encouraging results in differentiating benign from metastatic adrenal masses in patients with known or suspected malignancies (*13–15*). However, only a few studies, with few patients, on the use of ^{18}F-FDG PET for evaluating adrenal masses in lung cancer patients have been reported in the literature (*16,17*). This study investigated the usefulness of ^{18}F-FDG PET in the evaluation of adrenal masses detected on CT or MR imaging of patients with lung cancer.

MATERIALS AND METHODS

Patients

From 1999 to 2003, 94 patients (49 men and 45 women; age range, 35–86 y; mean age ± SD, 65 ± 11 y) who presented with

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TABLE 1
Patient Characteristics

Characteristic	Value
Total number of patients	94
Sex	
Number of male patients	49
Number of female patients	45
Age (y)	
Mean	65 ± 11
Range	35–86
Number of adrenal lesions on CT/MRI	
Total	113
Unilateral	75
Bilateral	19
Histopathology/clinical follow-up findings	
Number of benign lesions	41
Number of malignant lesions	72

a diagnosis of lung cancer and adrenal mass detected on CT or MRI were included in this study. A total of 113 adrenal lesions (75 unilateral and 19 bilateral) based on reports of CT or MRI from referring physicians were evaluated. The size of the adrenal lesions on CT or MRI scans ranged from 0.5 to 5.4 cm, with a mean of 2.6 cm. All patients underwent ^{18}F-FDG PET for primary staging or evaluation of metastatic disease. The final diagnosis of the adrenal lesion was based on clinical follow-up or histopathologic examination of biopsy specimens, when available. An adrenal lesion was considered benign if it had not changed for at least 6 mo, and it was considered malignant if the size had increased or decreased after treatment or if a new adrenal lesion had developed.

^{18}F-FDG PET Imaging

PET was performed on a dedicated whole-body scanner (Allegro; Philips Medical System, or C-PET; ADAC UGM). The patients fasted for at least 4 h to ensure a serum glucose level below 140 mg/dL for all patients. PET was initiated 60 min after intravenous administration of 2.516–5.2 MBq (0.068–0.14 mCi) of ^{18}F-FDG per kilogram of body weight. Sequential overlapping scans were acquired to cover the neck, chest, abdomen, and pelvis. Transmission scans using a ^{137}Cs point source were interleaved between the multiple emission scans to correct for nonuniform attenuation. The images were reconstructed using an iterative reconstruction algorithm, and both attenuation-corrected and non–attenuation-corrected images were interpreted.

^{18}F-FDG PET Image Interpretation

Three nuclear medicine physicians who were unaware of other clinical or imaging information independently interpreted the ^{18}F-FDG PET images. The interpretation included a review of both uncorrected and attenuation-corrected scans. Special attention was given to ^{18}F-FDG uptake in the region of the adrenal glands. PET findings were interpreted as positive if the ^{18}F-FDG uptake of the adrenal mass was greater than or equal to that of the liver. PET findings were interpreted as negative if the ^{18}F-FDG uptake of the adrenal mass was less than that of the liver. In cases of disagreement, a final decision was made by consensus. On the basis of past experience, we have noted that visual assessment of suspected lesions may be just as effective in differentiating active from inactive disease as is semiquantitative analysis using the standardized uptake value (*13*). Therefore, the standardized uptake value was not used to differentiate a benign adrenal lesion from a malignant adrenal lesion. Furthermore, it was often difficult to generate a region of interest over lesions that were not visualized on PET images.

RESULTS

Table 1 shows the characteristics of all patients. Of the 113 lesions, 71 were positive for ^{18}F-FDG uptake. Sixty-seven of these were eventually considered—after surgery (n = 4), percutaneous biopsy (n = 8), autopsy (n = 2), or clinical follow-up (n = 53)—to represent metastatic adrenal disease. The remaining 4 showed no change in size on follow-up CT, MRI, or PET. Forty-two lesions were negative for ^{18}F-FDG uptake. Thirty-seven of these were eventually proven—either by surgery (n = 3), percutaneous biopsy (n = 5), or clinical follow-up for at least 6 mo (n = 29)—to be benign. Among the 5 adrenal masses that gave false-negative findings, 1 was a large necrotic metastasis, 1 was a 2.4-cm lesion with central hemorrhaging, and the remaining 3 were lesions of 8, 9, and 11 mm.

Among all the metastatic adrenal lesions, 90% (65/72) had significantly higher ^{18}F-FDG uptake and 2 had ^{18}F-FDG uptake equal to or slightly higher than that of the liver (Figs. 1 and 2). Of the remaining 5 metastases, in which ^{18}F-FDG uptake was less than that of the liver, 1 had necrosis, 1 had central hemorrhaging, and 3 were small lesions on CT. Ten of the 65 metastatic lesions that had significantly higher ^{18}F-FDG uptake than that of the liver also had a central photopenic area surrounded by intense ^{18}F-FDG uptake suggestive of central necrosis (Fig. 3). Of the 41 benign lesions, one had ^{18}F-FDG uptake significantly higher than that of the liver, 3 lesions had uptake equal to or slightly greater than that of the liver, and 37 had uptake equal to that of the background (Fig. 4). The lesion that had ^{18}F-FDG uptake significantly higher than that of the liver was found to be pheochromocytoma by positive findings on ^{99m}Tc-pentetreotide scanning. Three lesions that had uptake equal to or slightly higher than that of the liver did not show any change in uptake or size on follow-up PET and CT scans and were therefore considered to be benign adenomas.

Table 2 illustrates the ^{18}F-FDG PET results and final outcome. The sensitivity, specificity, and accuracy for de-

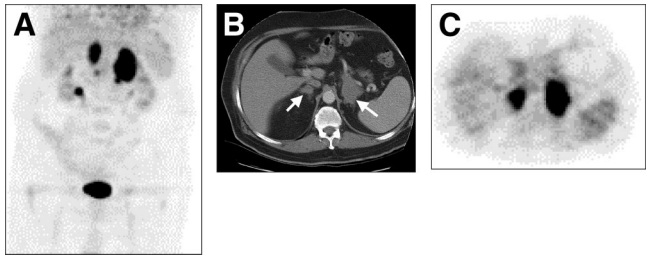

FIGURE 1. (A) ^{18}F-FDG PET scan shows intense, bilateral uptake in adrenal masses. (B) CT scan shows bilateral adrenal masses (arrows); left adrenal lesion is larger, with irregular borders. (C) ^{18}F-FDG PET axial view at same level as for CT shows intense, bilateral uptake in adrenal masses.

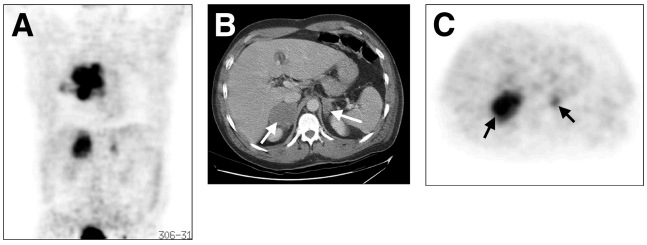

FIGURE 2. (A) ^{18}F-FDG PET scan shows intense uptake in right adrenal mass and uptake slightly higher than that of liver in left adrenal mass. (B) CT scan shows bilateral adrenal masses; right adrenal lesion is larger than left (arrows). (C) ^{18}F-FDG PET axial view at same level as for CT shows intense uptake in right adrenal mass and uptake slightly higher than that of liver in left adrenal mass (arrows).

tecting metastatic disease were 93%, 90%, and 92%, respectively. The positive predictive value was 94%, and the negative predictive value was 88%.

DISCUSSION

Adrenal metastases originating from NSCLC and small cell lung carcinoma are not uncommon. It is estimated that up to 4% of patients with otherwise operable NSCLC will have a unilateral adrenal mass; up to 40% of these may be malignant and present as a solitary site of metastasis (*18*). Detection of adrenal metastases in these patients has major clinical implications because an isolated ipsilateral adrenal metastasis in a patient with resectable primary NSCLC is considered to be localized disease (*19*). Resection of isolated adrenal metastases has been shown to improve the long-term disease-free survival of these patients. Luketich and Burt showed improved survival in patients with NSCLC and solitary adrenal metastasis when treated by surgical resection after chemotherapy, compared with treatment by chemotherapy alone (31 vs. 8.5 mo) (*20*). Therefore, accurate differentiation of benign from metastatic adrenal masses is essential for optimal management of patients with lung cancer.

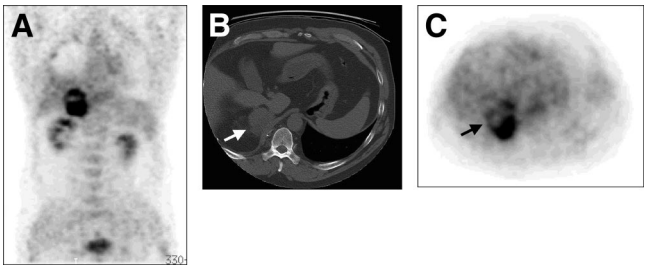

FIGURE 3. (A) ^{18}F-FDG PET scan shows intense uptake in right adrenal mass, with central photopenic area. (B) CT scan shows large right adrenal mass with central lower-attenuation area indicating central necrosis (arrow). (C) ^{18}F-FDG PET axial view at same level as for CT shows intense uptake in right adrenal mass, with central photopenic area indicating central necrosis (arrow).

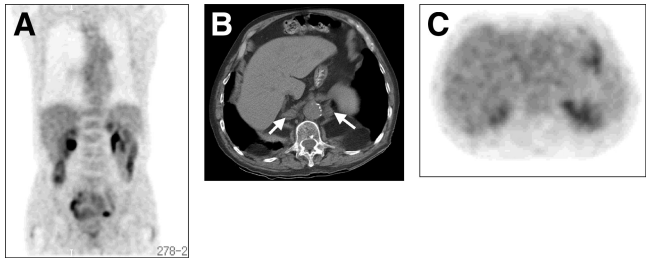

FIGURE 4. (A) ^{18}F-FDG PET scan shows no uptake in the region of either adrenal. (B) CT scan shows soft-tissue masses in both adrenal glands (arrows). (C) ^{18}F-FDG PET axial view at same level as for CT shows no abnormal uptake in the region of either adrenal.

CT is considered most important in evaluating adrenal masses. The CT attenuation value has been helpful in differentiating benign adenomas from malignant lesions (*21*). Unenhanced CT can reliably characterize adrenal masses using density measurements of the adrenal gland. However, controversy exists as to the optimal density threshold required to differentiate benign from malignant lesions. Sensitivity for characterizing a lesion as benign has ranged from 47% at a threshold of 2 HU to 88% at a threshold of 20 HU in a metaanalysis of 10 CT studies (*8*). Delayed enhanced CT could help by analyzing the washout patterns seen in adrenal lesions (*9*). Adenomas demonstrate rapid washout after administration of intravenous contrast medium. Diagnosis of adrenal adenomas based on attenuation measurement at unenhanced or delayed contrast-enhanced CT is often not feasible in clinical practice. Unenhanced CT scans are not obtained routinely, and patients frequently leave the department before the contrast-enhanced CT scans are reviewed. The usefulness of mean CT attenuation of adrenal masses at contrast-enhanced CT is limited because there is too much overlap between the 2 groups to accurately differentiate between adrenal adenomas and nonadenomas (*21,22*). Signal intensity on T2-weighted MR images and chemical-shift MR sequences are most commonly used to differentiate benign adenomas from malignancy. Any lipid-containing tissue would show a signal loss caused by cancellation of the signal from fat and water. However, signal intensity overlaps considerably between benign and malignant lesions (*11,12*). Burt et al. reported false-positive results for 67% of 25 adrenal lesions in their prospective study (*18*).

Unlike CT and MRI, ^{18}F-FDG PET is based on increased glucose metabolism in malignant lesions. However, in the

TABLE 2
PET Findings and Final Diagnosis for 113 Adrenal Lesions

Biopsy/clinical follow-up finding	PET finding	
	Positive	Negative
Positive	67	5
Negative	4	37

TABLE 3
Results of Published ^{15}F-FDG PET Studies on Patients with Lung Cancer and Adrenal Lesions

Study	Year	Total no. of patients	No. of lung cancer patients	Sensitivity (%)	Specificity (%)	Accuracy (%)
Boland et al. (*14*)	1995	20	10	100	100	100
Erasmus et al. (*16*)	1997	27	27	100	80	94
Maurea et al. (*15*)	1999	27	—	100	93	96
Yun et al. (*13*)	2001	41	28	100	94	96
Gupta et al. (*17*)	2001	30	30	94	92	93
Present study	2004	94	94	93	90	92

literature only limited data are available on the role of ^{18}F-FDG PET in patients with lung cancer and adrenal masses (Table 3). But the results of these studies are encouraging and justify the use of ^{18}F-FDG PET in the management of lung cancer patients. Boland et al. reported a sensitivity and specificity of 100% with ^{18}F-FDG PET in 20 patients with cancer (*14*). Of these 20 patients, 10 had lung cancer. Erasmus et al. (*16*) evaluated 33 adrenal masses in 27 patients with bronchogenic carcinoma. PET findings were interpreted as positive when ^{18}F-FDG uptake was higher in the adrenal mass than in the background. The sensitivity for detecting metastasis was 100%, and the specificity was 80%. Gupta et al. (*17*) studied 30 patients with lung cancer and considered adrenal ^{18}F-FDG uptake to be abnormal when it was higher than background liver uptake. ^{18}F-FDG PET showed abnormally increased ^{18}F-FDG uptake in 17 of 18 malignant lesions. In benign lesions, PET was true negative in 11 of 12 lesions. Yun et al. (*13*) interpreted the ^{18}F-FDG uptake of the adrenal as positive if it was equal to or greater than that of the liver. The authors reported a sensitivity of 100%, a specificity of 94%, and an accuracy of 96% in 41 patients, 30 of whom had lung cancer.

In the present study, ^{18}F-FDG PET showed a high sensitivity of 93%, a specificity of 90%, a positive predictive value of 94%, a negative predictive value of 88%, and an accuracy of 92% to differentiate between benign and malignant adrenal masses in patients with lung cancer. The results of our study were similar to the results of previously published studies using ^{18}F-FDG PET to assess adrenal masses in cancer patients. All previously published studies and the present study had a sensitivity and accuracy of more than 92% for PET. The common causes of false-positive ^{18}F-FDG PET results are pheochromocytomas and benign adenomas (*13,23*). Among our false-positive PET results, 3 were in patients with adenomas and one in a patient with pheochromocytoma. Pheochromocytoma, whether benign or malignant, has been shown to accumulate ^{18}F-FDG, although uptake is found in a greater percentage of malignant pheochromocytomas (*23*). The common causes of false-negative PET results are small lesion size, necrotic metastases, and metastases from neuroendocrine tumors (*13,24*). In the present series, we had 5 false-negative lesions: 1 necrotic metastasis, 1 metastasis with central hemorrhaging, and 3 small metastatic lesions. Small metastatic lesions can be missed because of the limited resolution of PET or the absence of sufficient tumor cells with increased glycolysis.

Our results are similar to those of Yun et al. and indicate that if a lesion shows ^{18}F-FDG uptake less than or significantly higher than that of the liver, the study can be interpreted with high confidence (*13*). Adrenal lesions with an ^{18}F-FDG uptake equal to or slightly higher than that of the liver should be read as indeterminate since these properties can be seen in either benign or malignant lesions. In such patients, additional imaging with MRI should be performed to further characterize the lesions.

CONCLUSION

^{18}F-FDG PET is an accurate, noninvasive technique for differentiating benign from metastatic adrenal lesions detected on CT or MRI in patients with lung cancer. In addition, PET has the advantage of assessing the primary cancer site and detecting other metastases. These results suggest the importance of ^{18}F-FDG PET in the management of these patients, especially since a solitary adrenal metastasis is considered to be treatable.

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