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Imaging of Adrenal Tumors Using FDG PET: Comparison of Benign and Malignant Lesions

OBJECTIVE. The aim of this study was to differentiate benign from malignant adrenal tumors using positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (FDG) in patients with unilateral adrenal masses originally detected by CT or MR imaging.

CONCLUSION. PET imaging with FDG can metabolically characterize adrenal masses. Abnormally increased FDG uptake in adrenal malignancies allows one to differentiate these abnormalities from benign lesions. Whole-body PET can also reveal extraadrenal tumor sites in patients with malignant tumors, using a single imaging technique for accurate disease staging.

The high resolution of imaging techniques such as CT and MR imaging in patients with suspected abdominal diseases frequently results in detection of unexpected adrenal masses [1]. In such patients, the main clinical question is to differentiate between benign and malignant adrenal lesions to select the appropriate treatment [1].

As an initial diagnostic approach, clinical and laboratory assessment of cortical and medullary adrenal function allows identification of secreting adrenal lesions and, hence, characterization of such tumors [2]. However, an adrenal mass may not cause adrenal hyperfunction [1]. In this setting, although CT and MR imaging can accurately provide anatomic details of adrenal tumors, no definite criteria histologically characterize the nature of these lesions [3, 4]. On the other hand, radionuclide imaging using labeled radiopharmaceuticals offers functional information to characterize adrenal masses [3, 5–9]. In particular, ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been proposed in nuclear oncology to evaluate tumor metabolism [10]. In this study, whole-body FDG PET was performed

in patients with unilateral adrenal masses detected on CT or MR imaging to differentiate benign from malignant lesions.

Subjects and Methods

Patient Population

In this prospective study, from April 1995 to February 1998, 27 consecutive patients (seven males and 20 females; age range, 16–74 years; mean age, 50 ± 17 years) with unilateral adrenal masses detected on CT (*n* = 13) or on MR imaging (*n* = 14) underwent whole-body PET with FDG. The selection criterion for patient enrollment was the presence of adrenal tumors in subjects undergoing CT or MR imaging for the diagnostic evaluation of other disorders. Adrenal tumors consisted of seven adenomas, one pseudocyst, one myelolipoma, one neurinoma, one ganglioneuroma, one benign pheochromocytoma, two pseudotumors (renal cyst and fat tissue), seven carcinomas, five metastases, and one malignant pheochromocytoma. Adrenal biopsy was obtained in 15 patients. The remaining 12 patients had adrenal surgery after imaging studies. The patient population was divided into two groups. Group 1 (*n* = 14) consisted of patients with benign lesions, and group 2 (*n* = 13) consisted of those with malignant tumors. Diabetic patients (*n* = 3) were not included in the study because high glucose serum levels competitively inhibit the transport of FDG into malignant cells, potentially

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decreasing the ability to detect and characterize adrenal lesions. Two patients were excluded because of body motion during the imaging. Patients underwent CT or MR imaging for the diagnostic evaluation of abdominal pain ($n = 9$), abdominal trauma ($n = 2$), hypertension ($n = 4$), biliary tract calculosis ($n = 2$), renal cysts ($n = 1$), anemia ($n = 1$), anuria ($n = 1$), and diffuse bone pain ($n = 1$), or during follow-up after surgery for benign abdominal disease ($n = 1$) or malignant tumors ($n = 5$). In all patients, cortical and medullary hormone measurements were performed for laboratory evaluation of adrenal function. Informed consent was obtained in all patients as part of the protocol approved by the institutional clinical research subpanel on human studies of our institution.

FDG PET Imaging

Fluorine-18 (^{18}F) was produced by an MC-1704 cyclotron (Scanditronix, Uppsala, Sweden) and was transferred to an automatic system for synthesis of ^{18}F -FDG. The quality of ^{18}F -FDG production was tested for sterility, pyrogenicity, and radiochemical purity. PET imaging was performed using a whole-body PET EXACT 47 scanner (Siemens, Erlangen, Germany). This tomograph has a 16.2-cm axial field of view and yields 47 image planes for each bed position used for abdominal and whole-body acquisition. Patients were studied in fasting conditions for at least 4–6 hr before FDG injection. Patients were positioned on the PET gantry using a rectilinear scan computerized program localized on the superior abdomen. Before injection of ^{18}F -FDG, abdominal transmission scanning using a rod source of germanium-67 for the attenuation correction of the corresponding emission scans was performed for 20 min. Thereafter, patients were injected IV with 370 MBq of ^{18}F -FDG. Abdominal emission imaging was acquired between 30 and 45 min after FDG administration. Finally, whole-body imaging using seven bed positions with an acquisition time of 5 min each were performed within 1 hr after tracer injection. No brain FDG activity was included in whole-body PET scans. Images were reconstructed using filtered back projection smoothed with a Hann filter (Siemens) with a cutoff frequency of 0.4 cycles per pixels using a SUN workstation system (Siemens) generating three-dimensional PET scans as axial, coronal, and sagittal views.

CT Imaging

CT studies were performed in 13 patients using a Somatom DR2 scanner (Siemens). Contiguous sections, 5-mm thick, of the abdomen were obtained before and after contrast enhancement. Oral and IV contrast agents were used.

MR Imaging

MR imaging studies were performed in 14 patients with a 1.5-T superconducting magnet scanner (Magnetom; Siemens). A spin-echo technique was used to obtain 5-mm contiguous three-dimensional sections of the abdomen. T1-weighted im-

ages (TR/TE, 600/15 msec) and T2-weighted images (TR/TE range, 2000/15–90) were obtained. T1-weighted images were also acquired after the IV administration of 0.2 ml/kg of body weight of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany). In seven patients, MR imaging studies were also integrated using a chemical-shift sequence acquiring in-phase and out-of-phase images (100/4–6).

Data Analysis

Adrenal function, both cortical and medullary, was considered normal when the corresponding hormone values were in the normal range. Conversely, cortical or medullary adrenal hypersecretion was defined in cases of increased levels of the corresponding hormones.

FDG PET images, three-dimensional abdominal views, and whole-body scans were qualitatively evaluated on a high-resolution display by two independent and experienced nuclear medicine physicians. In cases of disagreement, final interpretation was determined by consensus. PET studies were assessed independently without knowledge of clinical and pathologic findings. On abdominal views, the presence of abnormally increased FDG uptake was analyzed in the adrenal regions. Adrenal FDG uptake was considered abnormal when tracer uptake was greater than the uptake of the blood pool and that of background activities with no similar uptake on the contralateral side. In particular, a significant FDG accumulation in adrenal lesions was defined as a focus of increased tracer uptake above the intensity of the surrounding activity, excluding the renal pelvis if present. In lesions with increased FDG uptake, the heterogeneity of tracer distribution was assessed. The results of abdominal PET images were directly compared between group 1 and group 2. On whole-body PET images, the presence of abnormal FDG uptake in extraadrenal locations was assessed using the same criteria previously mentioned for the evaluation of abdominal PET images.

To evaluate differences in adrenal tumor size between groups 1 and 2, lesion maximum diameter in centimeters was measured on CT and MR images, and the results were directly compared using the Student's t test for unpaired data. Data were expressed as mean \pm 1 SD. Probability values of less than .05 were considered significant. On CT and MR imaging, a qualitative evaluation of imaging parameters in each adrenal mass was performed. The characteristics of lesion margins (regular or irregular) were assessed. CT density (hypo- or hyperdense) and CT enhancement (yes or no) after IV administration of contrast material were analyzed. On MR images (T1- and T2-weighted), the signal intensity of adrenal tumors compared with that of liver was evaluated. Lesion enhancement after gadolinium administration and loss of signal intensity on chemical-shift images were also assessed. Finally, the presence of lesion necrosis on CT and MR imaging was evaluated and compared with FDG PET images. In cases of abnormal extraadrenal foci of FDG uptake, CT or MR imaging was

performed to confirm or rule out the presence of space-occupying tumor lesions. Because in patients with extraadrenal disease spread not all lesions could be evaluated by surgical or histologic proof, the results of CT or MR imaging were considered the standard of reference.

Results

Adrenal Function

Laboratory evaluation showed normal adrenal function in most patients (22/27; 81%). Conversely, adrenal hypersecretion was documented in the remaining five patients and included one adenoma (increased aldosterone), two carcinomas (increased cortisol), and two pheochromocytomas (increased catecholamines or metabolites).

CT and MR Imaging

The results of abdominal CT and MR imaging studies showed 13 and 14 well-capsulated tumor lesions of the left and right adrenal glands, respectively. In all cases, the margins of the adrenal masses were regular. The size of the adrenal lesions ranged from 1.5 to 13 cm, with a mean size of 5.6 ± 3.1 cm. In group 1, adrenal lesions ranged from 1.5 to 13 cm. In group 2, the adrenal tumors ranged from 3 to 12 cm. No significant difference in lesion size between group 1 and group 2 (4.7 ± 3.5 cm versus 6.5 ± 2.5 cm) was observed.

In group 1, eight patients had CT and the other six underwent MR imaging. CT density (hypodense) and no contrast enhancement were similar for adenoma ($n = 4$) and for other benign lesions (two pseudotumors, one pseudocyst, and one neurinoma). On MR imaging, no change in signal intensity between T1- and T2-weighted images was observed in adenomas ($n = 3$), and in these lesions no gadolinium enhancement occurred; conversely, a clear signal intensity loss in adenomas was found on chemical-shift images. High signal intensity on both T1- and T2-weighted images with no gadolinium enhancement was observed in a case of myelolipoma. High signal intensity on T2-weighted images with significant gadolinium enhancement was found in the remaining two cases (one ganglioneuroma and one pheochromocytoma).

In group 2, five patients had CT and the other eight underwent MR imaging. CT density (hypodense) and significant contrast enhancement were similar for metastases ($n = 4$) and pheochromocytoma ($n = 1$). On MR imaging, high signal intensity on T2-weighted images was ob-

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served in all cases (seven carcinomas and one metastasis); significant gadolinium enhancement was found in three carcinomas and one metastasis, whereas no gadolinium enhancement occurred in the remaining four carcinomas. No signal intensity loss on chemical-shift images was found in three carcinomas. In group 2, five lesions (four carcinomas and one metastasis; 38%) showed on CT or MR imaging the presence of large tumor necrosis.

FDG PET Imaging

In group 1, no abnormally increased FDG uptake was observed in most adrenal masses (93%). Clearly increased FDG uptake was found only in the benign pheochromocytoma. In this group, whole-body PET images had normal findings, showing extraadrenal physiologic FDG distribution (Figs. 1 and 2).

Conversely, in group 2 all adrenal lesions showed abnormally increased FDG uptake,

suggesting a high glucose tumor metabolism (Fig. 3). In the five lesions of this group with a large area of necrosis on CT or MR imaging, FDG uptake was heterogeneous, showing increased activity only in the solid component of the tumor mass (Fig. 4). In this group, whole-body PET images had abnormal findings in nine patients, of whom five had metastatic adrenal carcinomas, three had adrenal metastases by other primary tumors, and one had malignant pheochromocytoma. A total of 30 foci of increased FDG uptake were detected in extraadrenal anatomic sites represented by chest ($n = 5$) and abdominal ($n = 8$) lymph nodes as well as lung ($n = 8$), liver ($n = 5$), pancreatic ($n = 1$), and skeletal ($n = 3$) lesions, as documented by CT or MR imaging studies. In six of these patients, the extraadrenal lesions were unknown before those imaging studies were performed (Fig. 5).

Discussion

The results of this study show that FDG PET is a noninvasive imaging technique able to metabolically characterize adrenal masses. In particular, abnormally increased FDG uptake in malignant adrenal lesions allows one to differentiate these abnormalities from benign tumors. Furthermore, whole-body FDG PET images allow the detection of extraadrenal tumor sites in patients with malignant lesions for accurate disease staging using a single imaging technique.

The *in vivo* tissue characterization of adrenal masses is useful in diagnostic imaging. Although in CT and MR imaging the differential diagnosis between benign and malignant adrenal lesions may depend on criteria such as large tumor size, high contrast material or gadolinium enhancement, and increased signal intensity on T2-weighted MR images or no signal change on chemical-shift MR sequences, these patterns are suggestive but not diagnostic of malignancy [3, 4]. In this setting, radionuclide scanning using labeled norcholesterol, metaiodobenzylguanidine, somatostatin analogues, gallium-67, and positron emission compounds provides significant information reflecting different and specific cellular functions [3, 5–9].

Previous experiences clearly showed the potential of FDG PET in the diagnostic evaluation (staging, follow-up, and characterization) of brain tumors, head and neck masses, lung cancer, lymphomas, and other tumor types [10]. However, limited data are available regarding the role of FDG PET in pa-

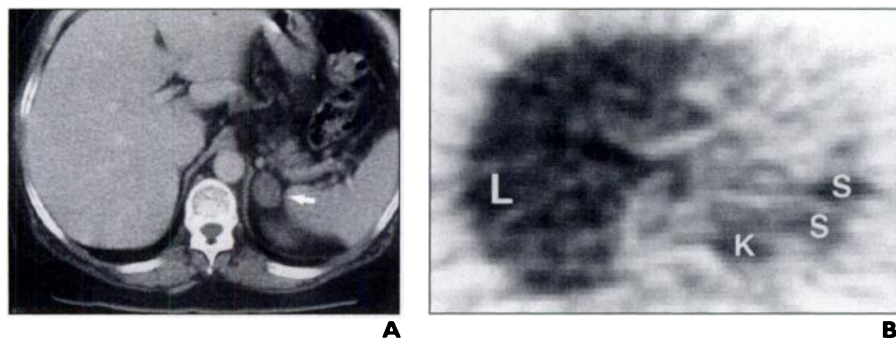


Fig. 1.—66-year-old woman with left adrenal adenoma (group 1).
A, Contrast-enhanced abdominal CT scan shows round left adrenal mass (arrow).
B, Abdominal axial FDG PET image shows no lesion uptake. Note diffuse liver (L) FDG activity and focal tracer uptake corresponding to spleen (S) and to upper pole of left kidney (K).

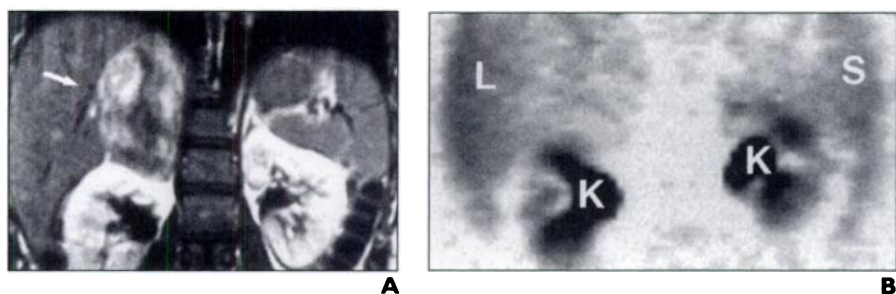


Fig. 2.—19-year-old woman with large right adrenal ganglioneuroma (group 1).
A, Abdominal T1-weighted coronal MR image (TR/TE, 600/15) shows large right adrenal mass (arrow).
B, Abdominal coronal FDG PET image shows no lesion uptake. Note normal activity in both renal pelves (K) and diffuse FDG uptake in liver (L) and spleen (S).

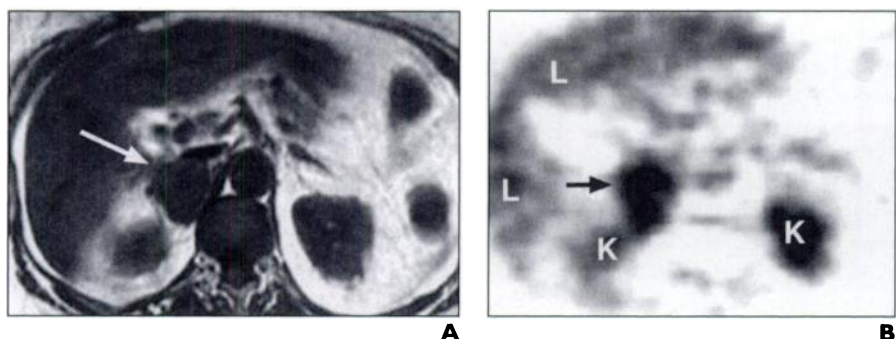


Fig. 3.—68-year-old woman with right adrenal metastasis from melanoma (group 2).
A, Abdominal T1-weighted axial MR image (TR/TE, 600/15) shows right adrenal mass (arrow).
B, Abdominal axial FDG PET image shows significantly increased tracer uptake by adrenal lesion (arrow). Note activity is normal in liver (L) and both kidneys (K).

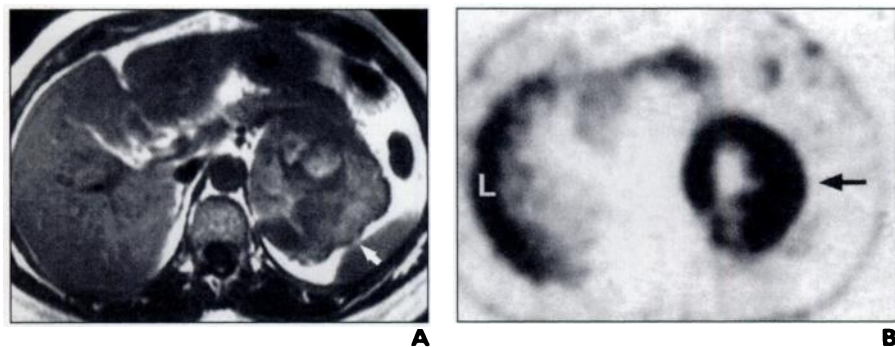


Fig. 4.—37-year-old woman with left adrenal carcinoma (group 2).

A, Abdominal T1-weighted axial MR image (TR/TE, 600/15) shows large left adrenal tumor with central necrosis (arrow).

B, Abdominal axial FDG PET image shows heterogeneous tracer uptake by adrenal lesion with a central defect of activity (arrow). Note normal activity in liver (L).

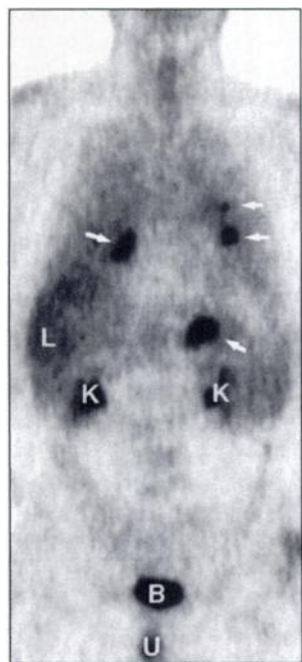


Fig. 5.—51-year-old man with left adrenal carcinoma associated with multiple lung metastases (group 2). Whole-body FDG PET image shows abnormally increased tracer uptake in all tumor sites (arrows). Note normal activity in liver (L), both renal pelves (K), urinary bladder (B), and urethra (U).

tients with adrenal masses. In previous studies [7, 8], the role of FDG PET in adrenal imaging was investigated in patients with malignant tumors, most of whom had lung cancer during the follow-up after treatment. These reports showed that PET imaging with FDG could differentiate benign from metastatic adrenal masses in such patients. Recently, preliminary data also showed that ^{11}C -metomidate may be used to characterize adrenal cortical tumors [9].

In our study, we evaluated the use of FDG PET in a different population of patients with adrenal tumors than in the studies of Boland et al. [7] and Erasmus et al. [8]. In fact, most patients (82%) included in our study had unilateral adrenal masses incidentally detected on CT or MR imaging studies performed for the diagnostic evaluation of disorders not related to cancer. Only the remaining 18% of patients were assessed during the follow-up

after surgery for tumor disease. Furthermore, in our series most adrenal lesions ($n = 22$) were nonsecreting; therefore, laboratory assessment was not able to characterize these tumors. Adrenal hypersecretion was shown only in the remaining five patients.

In most benign adrenal lesions, no increased FDG uptake was observed on abdominal PET images. Conversely, intense FDG accumulation was found only in the individual case of a benign pheochromocytoma. These findings are concordant with previous experiences [7, 8]. Similarly, intense FDG concentration in a patient with benign pheochromocytoma was also reported by Shulkin et al. [11]. The mechanism of increased FDG activity in benign pheochromocytoma is unclear.

In our experience, the analysis of abdominal PET images in patients with proven malignant adrenal masses showed clearly increased FDG uptake in all tumors. This finding reflects an

increase in glucose metabolism of adrenal malignancies and, thus, the possibility of PET to characterize malignant adrenal masses and to differentiate these lesions from benign tumors. In this regard, the presence of increased FDG uptake in malignant lesions could depend on the size of these abnormalities compared with the size of benign tumors. However, no difference in lesion size between the two groups was found. Therefore, because increased FDG uptake in cancer cells has been shown to be related to proliferative tissue activity and amount of viable cells [12], our results suggest that FDG uptake is an accurate indicator of tissue viability of adrenal lesions; hence, this radionuclide technique adds functional information to the results of anatomic imaging studies such as CT or MR imaging.

A particularly interesting finding of our study is represented by the results of whole-body FDG PET images in patients with malignant adrenal tumors (group 2). In fact, in most of these patients (70%), many extraadrenal tumor sites showing increased FDG activity were detected by PET imaging. The presence of extraadrenal lesions with abnormal FDG uptake was subsequently confirmed by anatomic cross-sectional imaging techniques (CT or MR imaging or both). Therefore, whole-body FDG PET allowed the accurate staging of such patients using a single imaging technique.

The differential diagnosis between benign and malignant adrenal masses as well as the staging of patients with malignant tumors using FDG PET have relevant clinical implications. This diagnostic information allows one to plan appropriate treatment, avoiding surgical interventions in cases of benign tumors or metastatic malignant lesions. Conversely, the accurate characterization of an adrenal mass as a malignant tumor (with localized increased FDG activity) suggests the need for surgical resection. In this regard, in a patient of our study with a small and well-capsulated adrenal carcinoma

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significantly concentrating FDG, the results of PET imaging were fundamental for clinical decision making. In fact, the patient, in whom standard adrenal imaging had misleadingly suggested a lesion diagnosis of adenoma, underwent timely surgical treatment after FDG PET imaging. Similarly, the accurate staging of adrenal malignancies using a single imaging technique, such as whole-body FDG PET, as an alternative to several conventional diagnostic techniques, could be also helpful. In this regard, in six patients with adrenal malignancies, whole-body PET discovered the presence of unknown extraadrenal tumor lesions. This finding has been clinically relevant for treatment planning; in fact, adrenal surgery was not performed, and chemotherapy was used instead.

Some potential limitations of this study deserve comment. First, the population is not wide but is, however, representative considering the low incidence of patients with adrenal masses. Additional studies in larger series are welcome to confirm our results. Second, the identification of adrenal FDG uptake on abdominal PET images might be obscured by renal pelvicaliceal tracer accumulation. This potential problem did not occur in our series. However, to minimize kidney activity in abdominal PET imaging, water-load or diuretic administration may be used.

In conclusion, whole-body FDG PET is a noninvasive imaging technique able to metabolically characterize adrenal masses. Abnormally increased FDG uptake in malignant adrenal lesions allows one to differentiate these abnormalities from benign tumors. Whole-body PET imaging can detect extraadrenal tumor sites in patients with malignant lesions for accurate disease staging using a single imaging technique.

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References

1. Gross MD, Shapiro B. Clinical review 50: clinically silent adrenal masses. *J Clin Endocrinol Metab* 1993;77:885-888
2. Ross MS, Aron DC. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. *N Engl J Med* 1990;323:1402-1405
3. Francis IR, Gross MD, Shapiro B, et al. Integrated imaging of adrenal disease. *Radiology* 1992;184:1-13
4. Lee MJ, Mayo-Smith WW, Hahn PF, et al. State-of-the-art MR imaging: imaging of the adrenal gland. *RadioGraphics* 1994;14:1015-1029
5. Maurea S, Lastoria S, Caracò C, et al. The role of radiolabeled somatostatin analogs in adrenal imaging. *Nucl Med Biol* 1996;23:677-680
6. Truong B, Jolles PR, Mullaney JM. Primary adrenal lymphoma: gallium scintigraphy and correlative imaging. *J Nucl Med* 1997;38:1770-1771
7. Boland GW, Goldberg MA, Lee MJ, et al. Indeterminate adrenal mass in patients with cancer: evaluation at PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1995;194:131-134
8. Erasmus JJ, Patz EF Jr, McAdams HP, et al. Evaluation of adrenal masses in patients with bronchogenic carcinoma using F-18 fluorodeoxyglucose positron emission tomography. *AJR* 1997;168:1357-1360
9. Sundin A, Juhlin C, Bonasera T, Lu L, Langstrom B, Bergstrom M. C-11 metomidate PET imaging and characterization of adrenal tumors (abstr). *Radiology* 1997;205(P):400
10. Rigo P, Paulus P, Kaschten BJ, et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med* 1996;23:1641-1674
11. Shulkin BL, Koeppe RA, Francis IR, Deeb GM, Lloyd RV, Thompson NW. Pheochromocytomas that do not accumulate metaiodobenzylguanidine: localization with PET and administration of FDG. *Radiology* 1993;186:711-715
12. Minn H, Joensuu H, Ahonen A, Klemi P. Fluorodeoxyglucose imaging: a method to assess the proliferative activity of human cancer in vivo—comparison with DNA flow cytometry in head and neck tumors. *Cancer* 1988;61:1776-1778