Adrenal Lesions: Characterization with Fused PET/CT Image in Patients with Proved or Suspected Malignancy—Initial Experience

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Purpose:
To retrospectively evaluate the accuracy of the fused positron emission tomographic (PET)/computed tomographic (CT) image for characterization of adrenal lesions in patients who have proved malignancy or are suspected of having malignancy.

Materials and Methods:
Institutional review board approval was received for this retrospective HIPAA-compliant study, and informed consent was waived. Forty-one adrenal lesions in 38 patients (21 men, 17 women; mean age, 66 years; range, 37–86 years) were evaluated with PET/CT. Of the 41 lesions, nine were assumed to be malignant with documentation of enlargement (n = 8) or reduction in size in response to treatment (n = 1), and 32 were assumed to be benign with documentation of stability for 6 months (n = 31) or with confirmation with biopsy results (n = 1). The PET examination findings were positive when adrenal lesion maximum standardized uptake values (SUVs) exceeded hepatic maximum SUVs. CT contrast medium washout analysis was used to further characterize two lesions with PET findings positive for malignancy. The t test was used to assess significant (P < .05) differences between fluorine 18 fluorodeoxyglucose (FDG) uptake of benign lesions and that of malignant adrenal lesions.

Results:
At PET/CT, findings for all malignant lesions were positive (mean adrenal lesion–liver activity ratio, 4.04; range, 1.53–17.08). Of the 32 benign lesions, most (30 of 32) had activity less than that of the liver (mean ratio, 0.66; range, 0.22–0.94). PET/CT demonstrated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, 93.8%, 81.8%, 100%, and 95.1%, respectively. Incorporating contrast material–enhanced CT with delayed imaging increased specificity to 100% because two lesions with PET findings positive for malignancy were characterized as benign. There was a significant difference between maximum SUV (P < .05) and the ratio of adrenal lesion–liver FDG activity (P < .001) in benign versus malignant adrenal lesions.

Conclusion:
PET/CT provides a powerful combination of functional and attenuation information for adrenal lesion characterization. All malignant lesions were detected at PET/CT, with no false-negative results.

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The adrenal glands are a common site of metastatic disease. Even in a patient with a known malignancy other than an adrenal malignancy, however, an adrenal lesion is still more likely to be benign than to be malignant (1). This is mainly attributable to the frequency of adrenal adenomas in the general population, and that frequency ranges from 2% to 9% in published autopsy series (1–3). Thus, the ability to characterize these lesions on images is essential both to accurately classify them according to stage of malignancy and to avoid unnecessary percutaneous biopsies of adrenal lesions. Currently, computed tomography (CT) forms the mainstay of adrenal imaging, but magnetic resonance (MR) imaging also is useful for characterization of indeterminate lesions (4–7). Preliminary data have suggested that fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) has excellent sensitivity for detection of malignant adrenal masses (8–13). PET/CT offers a unique hybrid imaging technique that combines the attenuation and morphologic detail of CT with the metabolic information from PET. These images can be fused to allow accurate coregistration of anatomic and functional data, and the combination of the two types of images leads to more assured anatomic localization of areas of increased metabolic activity. Currently, relatively high costs generally limit the availability of PET/CT to tertiary referral centers, but its widespread application for imaging of tumors is anticipated in the future. The purpose of our study, therefore, was to retrospectively evaluate the accuracy of the fused PET/CT image for characterization of adrenal lesions in patients who have proved malignancy or are suspected of having malignancy.

Materials and Methods

We received approval from our institutional review board to undertake this retrospective Health Insurance Portability and Accountability Act–compliant study, and informed consent was waived. An electronic search of our picture archiving and communication system (Agfa Gevaert, Mortsel, Belgium) database of all PET/CT examinations performed during 8 months from January to August 2004 was performed by two investigators (J.M.A.S., M.A.B.). We identified 38 patients (21 men, 17 women; mean age, 66 years; range, 37–86 years) who had a confirmed adrenal mass and had undergone PET/CT because they had proved malignancy or were suspected of having malignancy. All relevant prior and subsequent CT scans, including nonenhanced, contrast material–enhanced, and delayed contrast-enhanced scans, were reviewed to determine lesion stability or change by one author (G.W.B., with 12 years of experience in adrenal CT). Thirty-six patients had proved malignancy as follows: lymphoma, 14 patients; lung carcinoma, eight patients; colorectal carcinoma, four patients; cervical carcinoma, two patients; cholangiocarcinoma, two patients; and adenocortical, skin, thyroid, laryngeal, gallbladder, and endometrial carcinoma, one patient each. Two patients had indeterminate lung nodules.

Medical records of each patient were reviewed to exclude the possibility of diabetes, because high serum glucose levels decrease the capability of FDG PET for depiction and characterization of adrenal lesions. Forty-one adrenal lesions were detected in 38 patients. Of the 41 adrenal lesions, 32 lesions in 31 patients were classified as benign because they exhibited stability on serial images during a minimum of 6 months (mean, 12 months; range, 6–30 months) (31 lesions), and one lesion in one patient was classified as benign at percutaneous biopsy (one lesion). Nine lesions in six patients were classified as malignant because an interval growth \( n = 8 \) or a reduction in size in response to treatment \( n = 1 \) was documented on serial images. Mean follow-up for the malignant lesions was 8 months (range, 6–9 months). In two patients, delayed contrast-enhanced CT scans were obtained for contrast material washout analysis performed at 2 and 3 months after the initial PET/CT image was obtained.

Scanning Technique

FDG was produced by using a 230-MeV isochronous cyclotron (Northeast Proton Therapy Center, Massachusetts General Hospital, Boston, Mass). All patients fasted for 6 hours prior to image acquisition. Two 10-oz cups of water were administered as negative contrast material 1 hour prior to scanning. A dose of 15 mCi (555 MBq) of FDG was administered intravenously at 45 minutes to 1 hour prior to scanning. All imaging was performed with a 16-section hybrid PET/CT gantry (Biograph Sensation 16; Siemens, Erlangen, Germany) that comprises a 16-section high-performance multi–detector row CT scanner with a lutetium oxyortho-silicate–based PET scanner. Initially, low-dose CT was performed primarily for attenuation correction with patients holding their breath in the midexpiration phase (suspended breath hold) and included an area from the external auditory meatus to below the symphysis pubis. The parameters were as follows: section thickness, 5 mm; table feed per rotation, 18 mm; time per table rotation, 0.5 second; tube voltage, 120 kVp; tube current, 150 mA; and field of view, 70 cm. PET images were acquired in a three-dimensional mode. The intrinsic spatial resolution of the system is 5 mm (full width half maximum in the center of the field of view). Seven acquisition beds were performed per patient. Scanned acquisition time ranged from 3 to 4 minutes for patients who weighed less than 170 lb (76 kg) to a maximum of 7 minutes for patients who weighed more.
than 230 lb (104 kg). Images were reconstructed at 2.4-mm section thickness.

Diagnostic contrast-enhanced CT was performed subsequent to PET/CT by using 100 mL of 300 mg iodine per milliliter along with 20 mL saline injected by using a dual-head injector (Stellant; Medrad, Indiana, Pa) at 2 mL/sec with a 60-second postinjection delay and a suspended breath hold and included an area from the external auditory meatus to the midthigh. The parameters were as follows: section thickness, 5 mm; table feed, 15 mm/sec; pitch, 1.5; tube voltage, 140 kVp; and effective tube current–pitch, 1.5; tube voltage, 140 kVp; and effective tube current–time product (mAseff) is defined as follows: mAseff = (GR/PF) × (TC/H18528) × (H11005/PF), where TC is the tube current (in milliamperes), GR is the gantry rotation time (in seconds), and PF is the CT pitch factor. Images were reconstructed with 2-mm section thickness at 2-mm intervals.

Image Analysis: CT Component of PET/CT
Two gastrointestinal-genitourinary subspecialty radiologists (M.A.B., J.M.A.S., with 5 years and 1 year of subspecialty experience, respectively) reviewed the CT images from the PET/CT examination. Images were reviewed with a digital picture archiving and communication system diagnostic workstation (Reveal-MVS; Mirada Solutions, Oxford, England) by two authors (J.M.A.S., M.A.B., each with 1 year of PET/CT experience). PET/CT image analysis was performed separately from the CT component image analysis and was performed subsequent to it, and the two analyses were performed with a 1-week interval between them. Where initial automatic coregistration of CT and PET images was unsatisfactory (three patients), the manual coregistration function in both the transverse and coronal planes was used to ensure that renal and collecting system activity coincided with the corresponding renal structures on CT scans to avoid misregistration of renal activity over the adrenal bed. Quantitative analysis of FDG uptake in the adrenal lesions was performed by creating a free-hand region of interest over a minimum of two-thirds of the adrenal lesion on the fused PET/CT image. Care was taken to avoid the periphery of the lesion to ensure that lesion activity was not altered because of partial volume averaging from surrounding tissue. Maximum standardized uptake values (SUVs) were automatically generated according to the following equation: SUVmax(bw) = Cbw/Dbw, where SUVmax(bw) is maximum SUV normalized for body weight; Cbw, tissue concentration expressed as megabecquerels.

Adrenal Lesion Characterization with PET/CT Blake et al

Note.—All numbers are percentages.

* The threshold value of 2.68 was used for detection of malignancy.
† Quantitative and qualitative (visual) analysis was used, and a ratio of more than one was considered positive for malignancy.

Figure 1: Box plot of SUVs for benign and malignant lesions (excluding the highest value for a malignant lesion of 26.13) demonstrates considerable difference between absolute SUV values of benign lesions and those of malignant lesions.
per milliliter; \(D_{\text{inj}}\), injected dose expressed as megabecquerels; and bw, body weight expressed as kilograms.

Average maximum SUV measurements (mean of two measurements) were obtained. Maximum SUV measurements from the right lobe of the liver in the same coronal plane as the adrenal lesion were obtained in a similar fashion by using a region of interest with a fixed area of 15 cm\(^2\). The region of interest in the liver was free of visible metastatic disease and was of uniform signal intensity. Qualitative comparison of the adrenal FDG activity with the hepatic FDG activity was undertaken, whereby the PET/CT image was considered positive if FDG activity in the adrenal gland appeared visually greater than or the same as that of the liver and negative if it appeared visually less than that of the liver. Qualitative analysis was performed in consensus.

### Statistical Analysis

The recorded data were entered into a worksheet (Excel; Microsoft, Redmond, Wash). Ratios of adrenal lesion activity to liver activity were calculated by dividing the adrenal lesion SUV by the liver SUV measured in the same coronal plane. Both absolute adrenal lesion SUV and adrenal lesion–liver SUV ratios were correlated with the final diagnosis of the lesion as malignant or benign. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated. The Student \(t\) test was used to determine whether there was a statistically significant difference between the SUV and the adrenal lesion–liver FDG ratios for benign and malignant lesions (a difference with \(P < .05\) was considered statistically significant). To assess data clustering and/or dependency, data from patients with bilateral adrenal lesions (\(n = 3\)) were omitted, and the \(t\) test was repeated.

### Results

#### Analysis of Nonenhanced CT Findings from PET/CT Examination

The 41 masses ranged from 0.5 to 9.5 cm in diameter, with a mean diameter of 2.0 cm; 15 were present on the left side, and 26 were located on the right side. The mean diameter of the malignant lesions was 2.7 cm (range, 0.5–9.5 cm). The mean diameter of the benign lesions was 1.9 cm (range, 0.6–7.2 cm). The mean CT attenuation for malignant lesions was 32.3 HU (range, 12.3–46.8 HU). All malignant lesions were thereby indeterminate according to nonenhanced CT criteria. Most benign lesions (\(n = 19\)) had attenuation values on nonenhanced CT scans of less than 10 HU (range, –25.4 to 7.9 HU; mean, 4.2 HU), but 13 benign lesions were indeterminate according to nonenhanced CT criteria (attenuation range, 12.1–44.6 HU). Two of the benign lesions contained macroscopic fat and were consistent with myelolipomas (16). Although none of the adrenal glands af-
fected by metastatic disease appeared morphologically normal on CT scans in our series, one metastatic lesion manifested as minimal adrenal limb thickening.

Analysis of PET Findings from PET/CT Examination

Quantitative PET analysis: absolute adrenal lesion SUV.—The SUVs of malignant lesions ranged from 2.31 to 26.13, and the SUVs for benign lesions ranged from 0.54 to 3.34 (Fig 1). Despite that we demonstrated a statistically significant difference between the absolute SUV values of benign lesions and those of malignant lesions ($P < .05$, Student $t$ test), seven of 32 benign lesions (SUV range, 2.35–3.34) had SUVs in the malignant range: Two of these lesions were adenomas according to CT criteria (attenuation, $<10$ HU), one was an adenoma proved at biopsy, one was a myelolipoma with macroscopic fat at CT, and the remaining three lesions were indeterminate at CT, with attenuation values ranging from 24.3 to 44.6 HU. When one applies a threshold SUV of 2.68 for the detection of malignancy, SUV analysis yields a sensitivity value of 100%, a specificity value of 78.1%, a positive predictive value of 56.3%, a negative predictive value of 100%, and an accuracy value of 82.9% (Table).

Analysis of adrenal lesion–liver FDG activity ratios from PET/CT examination.—All malignant lesions demonstrated FDG activity, with respect to the SUV, greater than that of the liver, with a sensitivity value of 100% (mean adrenal lesion–liver activity ratio, 4.04; range, 1.53–17.08). Most (six of nine) malignant lesions demonstrated greater than twice the FDG activity of the liver, while three of nine malignant lesions demonstrated less than twice the FDG activity of the liver (ratios of 1.53, 1.65, and 1.73). In none of the examinations were findings false-negative. Of the 32 benign lesions, 30 had activity ratios that were less than the activity ratio of the liver (mean adrenal lesion–liver activity ratio, 0.66; range, 0.22–0.94). Two benign lesions had adrenal lesion–liver FDG activity ratios of 1.45 and 1.47, which were greater than the ratio of the liver and, thus, were regarded as false-positive results, yielding a specificity value of 93.8% (Table). There was no overlap between FDG activity ratios of benign lesions and those of malignant lesions (Fig 2). Results of Student $t$ test analysis confirmed that adrenal lesion–liver FDG activity in the malignant adrenal lesions was significantly higher than it was in the benign lesions ($P < .001$). Results of the $t$ test analysis showed a similar significant difference after the analysis was repeated with the omission of the data in the three patients with bilateral adrenal lesions.

Qualitative PET analysis from PET/CT examination.—Findings of qualitative analysis of adrenal lesion FDG activity were concordant with the findings of the quantitative analysis. Both readers were in agreement for all lesions. FDG uptake was very high in most (six of nine) malignant adrenal lesions (Fig 3). Three malignant lesions demonstrated only moderate uptake intensity relative to uptake of the liver at visual analysis of the PET images. Thirty of 32 benign lesions demonstrated a paucity of uptake intensity relative to uptake of the liver (Fig 4). Two of 32 benign lesions demonstrated moderate uptake intensity relative to uptake of the liver and were thus deemed false-positive results (Fig 5).

PET/CT analysis with incorporation of CT contrast medium washout analysis.—Both of the false-positive lesions on PET scans were indeterminate according to nonenhanced CT attenuation criteria (14.7 and 44.6 HU). Both were classified as benign on subsequent delayed contrast-enhanced CT scans, however, because they both demonstrated a relative percentage of contrast medium washout of 59% at 5 minutes and an absolute percentage of contrast
medium washout of 87% at 10 minutes (15). One was a benign adenoma and was confirmed at percutaneous biopsy, and the other was a benign lesion because of demonstrated stability on serial images over 6 months. Incorporation of the analysis of delayed contrast-enhanced CT scans caused an increase in overall PET/CT specificity to 100% (Table).

Discussion

Researchers in several published series have evaluated the utility of measurement of the attenuation levels in Hounsfield units on nonenhanced, contrast-enhanced, and delayed contrast-enhanced CT scans for the characterization of adrenal lesions. Because of an abundant concentration of intracytoplasmic fat, lesions with attenuation of 10 HU or less on nonenhanced CT scans are typically benign (17–19) and lesions with attenuation of greater than 10 HU are considered indeterminate. More recently, contrast medium washout studies have enabled differentiation of adrenal metastases from lipid-poor adenomas, with good accuracy (15,20–22). Magnetic resonance (MR) imaging can also aid the characterization of indeterminate adrenal masses (4–7).

In contrast to CT or MR imaging, FDG PET imaging yields metabolic information that is based on increased glucose metabolism in malignant lesions. Boland and co-workers (8) were the first to report the use of PET for adrenal lesion analysis. In their study of 24 adrenal masses, findings indicated that PET had a 100% sensitivity and specificity for distinguishing benign lesions from metastases. Investigators in subsequent studies have reported sensitivity values that range from 94.4% to 100% (9–12) and specificity values that range from 80% to 100% (9,11,13). Despite its recent introduction to clinical use, PET/CT may become the imaging modality of choice for patients with tumors (23). Through a combination of morphologic and metabolic information, PET/CT, compared with PET alone, can significantly increase diagnostic accuracy in regard to lesion classification (24). We applied PET/CT fusion imaging to the analysis of adrenal lesions in patients who had a known malignancy or in those who were suspected of having a malignancy. In our study of 41 adrenal lesions, we chose to both quantitatively and qualitatively analyze adrenal lesion uptake of FDG by comparing it with liver uptake. This method has been shown to be highly sensitive for the detection of adrenal malignancy by using FDG PET (13).

The results of our study are consistent with previously published data for the individual performance of both PET and CT. All malignant lesions (nine of nine) in this series were positive for malignancy at the PET component of PET/CT, and no false-negative lesions were encountered. Results of qualitative (visual) analysis of adrenal lesion FDG activity relative to results of liver FDG activity analysis were in accordance with the quantitative ratios. Although SUV analysis alone has had higher specificity than visual analysis for the differentiation of malignant tumors from benign tumors in the lung and the breast (25,26), this was not the case in our series in which visual analysis was more specific than was SUV analysis (93.8% vs 78.1%) for a given sensitivity of 100% (SUV threshold of 2.68). Therefore, application of a specific SUV threshold may cause a tumor to be missed or may lead to classification of a benign lesion as malignant. At our institution, interpretation of PET/CT images generally relies on visual inspection.

By comparing adrenal lesion FDG activity with FDG activity of the liver, adrenal metastatic lesions were de-
tected with 100% sensitivity in this study. On the basis of our findings, we would suggest that adrenal lesions that demonstrate marked FDG uptake (more than 2.0 times that of the liver) in the setting of a known malignancy are almost certainly metastatic. Poorly FDG-avid necrotic metastases (13) and frankly non-FDG-avid adrenal metastases, however, have been reported previously (12,27). In our study, three metastases and two benign lesions demonstrated only moderately intense FDG activity on PET images. Thus, an attempt to differentiate between benign and malignant lesions in the setting of mild or moderate FDG activity may cause problems, and further imaging or biopsy may be required for ultimate lesion characterization. In such cases, an interpretation that is based on the combined information from prior CT imaging, the attenuation value on nonenhanced CT scans, findings from further imaging with contrast medium washout analysis, and results of MR imaging may be useful.

Results of contrast medium washout analysis on delayed CT scans were used to correctly characterize the two benign lesions that were positive for malignancy at PET and classified as adenomas in our series of patients. This method has been shown to be sensitive and specific (threshold washout value of 40%, with a corresponding sensitivity of 83% and specificity of 93%) for differentiation of benign from malignant adrenal lesions (15). In both instances in which lesions were correctly characterized as adenomas, determination of the nature of the adrenal disease was critical to further patient treatment. One patient was considered for partial hepaectomy for an isolated metastasis from colon cancer, and the other patient was considered for pneumonectomy for a non-small cell lung carcinoma. Although these scans were obtained in a separate examination subsequent to the performance of PET/CT, at our institution full-dose contrast-enhanced CT is a routine component of the PET/CT protocol, and prospective incorporation of delayed imaging could assist in the clarification of indeterminate PET findings in the adrenal glands when clarification is critical to patient treatment. Naturally, this would entail prospective analysis of the adrenal glands with a priori knowledge of prior imaging findings and clinical relevance of adrenal metastases.

Both false-positive PET interpretations from the PET/CT examination were attributable to increased activity in adrenal adenomas, and both of these lesions had an attenuation value measured at nonenhanced CT of more than 10 HU. Published reports (13,27) have not documented adrenal adenomas with an attenuation value of less than 10 HU on nonenhanced scans, a value that demonstrates increased FDG activity, with the exception of a case explained by the rare entity of adrenal collision tumors (28). Therefore, it is as yet unclear whether an attenuation value of less than 10 HU on nonenhanced CT scans takes precedence over increased FDG uptake for the diagnosis of adrenal adenomas.

Our study had limitations. First, this was a retrospective analysis of a relatively small patient population. To the best of our knowledge, however, this is the largest study of the use of FDG PET analysis of the adrenal glands and the first report of experience with adrenal PET/CT. Second, only one patient had a histologically proved diagnosis at percutaneous biopsy. In the remaining patients, the lesions were assumed to be benign or malignant on the basis of follow-up imaging findings. Although not ideal, this is a recognized method for assessment of adrenal lesions and has been employed in several of the previous studies in which the researchers addressed PET in adrenal imaging (13).

Furthermore, this is a reflection of a change in practice in regard to adrenal lesion analysis, whereby the number of adrenal lesion biopsies is diminishing (29). Finally, contrast medium washout analyses were performed in only two cases, and these analyses were not contemporaneous with the PET/CT analyses. Further studies are required to investigate whether contrast medium washout analysis can be practically and successfully incorporated into a PET/CT protocol.

In conclusion, results of our study indicate that PET/CT is a highly sensitive method for detection of adrenal metastases, and all malignant adrenal lesions demonstrated increased FDG activity relative to that of the liver. More important, on the basis of our data and findings in previous studies about individual PET and CT, a negative PET/CT image can be used to exclude metastases with a high degree of certainty. False-positive results, however, occur with subtle increases in FDG activity that may need clarification with alternative imaging methods or adrenal lesion biopsy. In the case of a positive PET scan, incorporation of delayed contrast-enhanced CT for washout analysis is a useful diagnostic adjunct when determination of the nature of the adrenal disease is essential for patient treatment.

References


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