Evaluation of the Sensitivity and Specificity of ^{11}C-Metomidate Positron Emission Tomography (PET)-CT for Lateralizing Aldosterone Secretion by Conn's Adenomas

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Context: Identification of unilateral aldosterone-producing (Conn's) adenomas has traditionally required lateralization by the invasive and technically difficult procedure of adrenal vein sampling (AVS). ^{11}C-metomidate, a potent inhibitor of adrenal steroidogenic enzymes, is a positron emission tomography (PET) radiotracer that is selectively accumulated by Conn's adenomas.

Objective: The objective of the study was to compare the sensitivity and specificity of ^{11}C-metomidate PET-computed tomography (CT) against the current gold standard of AVS.

Design: The design of the study was within-patient comparison of diagnostic techniques.

Setting: The study was conducted at a single center-university teaching hospital.

Patients: Thirty-nine patients with primary hyperaldosteronism (PHA) and five with nonfunctioning adenomas (incidentalomas) participated in the study.

Intervention(s): The first six PHA patients were studied on three occasions to determine whether steroid pretreatment reduced ^{11}C-metomidate uptake by normal adrenal. Subsequent patients received dexamethasone for 3 d prior to injection of ^{11}C-metomidate 150–500 MBq.

Main Outcome Measure(s): Maximum standardized uptake values (SUV_{max}) over regions of interest determined from 35–45 min after injection were measured.

Results: Dexamethasone increased tumor to normal adrenal SUV_{max} ratio by 25.6 ± 5.0% ($P < 0.01$). PET-CT visualized subcentimeter adenomas and distinguished hot from cold adenomas within a gland. In 25 patients with PHA and AVS lateralization to the side of an adenoma, SUV_{max} over tumor (mean ± SEM) of 21.7 ± 1.6 was greater than over normal adrenal, 13.8 ± 0.6 ($P = 0.00003$); this difference was absent in 10 patients without lateralization on AVS ($P = 0.28$) and in four of five incidentalomas. On receiver-operator characteristics analysis, an SUV_{max} ratio of 1.25:1 provided a specificity of 87% [95% confidence interval (69, 104)] and sensitivity of 76% (59, 93); in tumors with SUV_{max} greater than 17, the specificity rose to 100%.

Conclusions: ^{11}C-metomidate PET-CT is a sensitive and specific noninvasive alternative to AVS in the management of PHA. ***(J Clin Endocrinol Metab* 97: 100–109, 2012)**

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Abbreviations: AVS, Adrenal vein sampling; CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PHA, primary hyperaldosteronism; ROC, receiver-operator characteristic; SUV, standardized uptake values; SUV_{max}, maximum standardized uptake values.

Primary hyperaldosteronism (PHA) has a mixed underlying pathology, which includes the most common curable cause of hypertension, an adrenal (Conn's) aldosteronoma (1–5). Currently only a minority of eligible patients progress to surgery, in part because proof that the adenoma is the sole cause of PHA is often problematic (6). The assessment of eligibility for surgery requires distinguishing unilateral Conn's adenomas from cases of bilateral adrenal hyperplasia and nonfunctioning adrenal nodules (incidentalomas) (7). However, the procedure of adrenal vein sampling (AVS) is commonly nondiagnostic because of technical difficulties in cannulating the right adrenal vein or intermittent aldosterone secretion (8, 9).

Scintigraphy with ^{131}I-β-iodomethyl-norcholesterol (NP-59) or ^{75}Se-selenomethyl-19-norcholesterol has been used historically for imaging of Conn's adenomas (10). However, these tracers, which are no longer widely available, require pretreatment with dexamethasone for up to 3 wk to suppress uptake of tracer by normal (*i.e.* nontumorous) adrenal, and lack the resolution to image lesions less than 2 cm. ^{11}C-metomidate, a potent inhibitor of 11β-hydroxylase and aldosterone synthase, has been advanced as a positron emission tomography (PET) radiotracer (11–15). In a series from Uppsala, ^{11}C-metomidate PET findings were correlated with histopathological diagnosis in 73 patients with suspected adrenal tumors (16). Only six patients with histologically confirmed aldosterone secreting adrenal adenomas were included in this series, but these aldosteronomas showed the highest standardized uptake values (SUV), averaging 30.7 compared with 18.4 in nonfunctional adenomas. These data suggested that ^{11}C-metomidate PET could be developed into a noninvasive alternative to AVS. Our objective was to compare ^{11}C-metomidate PET-computed tomography (CT) against the current gold standard of AVS for identifying and lateralizing Conn's adenomas in patients with PHA and an adrenal adenoma on CT or magnetic resonance. As a preliminary, we assessed whether pretreatment with dexamethasone or dexamethasone/fludrocortisone would improve the sensitivity of ^{11}C-metomidate PET-CT.

Patients and Methods

Patient selection

We aimed to recruit patients with a unilateral aldosteronoma to estimate sensitivity of PET-CT and two groups of controls to estimate specificity: patients with PHA and bilateral disease; and patients with an adrenal adenoma but no PHA. The inclusion criteria for the cases of unilateral aldosteronoma were age 18 yr or older; a biochemical diagnosis of PHA based on a suppressed plasma renin and/or an elevated plasma aldosterone to renin ratio (after correction of hypokalemia); an adrenal adenoma on CT or magnetic resonance imaging (MRI); and either lateralization on AVS, measured as a 4-fold or greater higher aldosterone to cortisol ratio in the adrenal vein draining the adenoma than in the contralateral adrenal vein or prior decision by the referring clinician to proceed to adrenalectomy together with subsequent evidence of surgical cure (7). The inclusion criteria for the negative controls were: 1) bilateral PHA, demonstrated by less than 4-fold excess in the aldosterone to cortisol ratio in the adrenal vein draining the adenoma or less than 4-fold difference between sides if neither or both adrenals had an adenoma; or 2) normotensive patients with nonfunctional adrenal adenomas (so-called incidentalomas) found serendipitously during a prior CT or MRI. Further diagnostic details for cases and controls are provided in Supplemental Methods, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. To enable broad extrapolation from our results, we recruited most subjects from serially diagnosed PHA or incidentaloma patients in our own and referring clinics.

Preliminary study: pretreatment

To assess the number of studies required and whether the tumor-normal adrenal signal might be improved by suppressing ^{11}C-metomidate binding to the 11β-hydroxylase in normal adrenal, we undertook a preliminary study in six patients. These were aged older than 50 yr and had AVS confirmation of unilateral PHA. Three ^{11}C-metomidate PET-CT studies were undertaken in each patient. One was performed without prior drug therapy, the second after oral administration of 0.5 mg dexamethasone every 6 h for 3 d, and the third after the oral administration of both 0.5 mg dexamethasone every 6 h and 400 μg fludrocortisone once daily for 3 d. The studies were performed at least 1 wk apart and the dose order randomized. Blood samples were collected each time for electrolytes, cortisol, renin, and aldosterone. The pretreatment protocol giving the largest average difference in Maximum standardized uptake values (SUV_{max}) between tumor and normal adrenal was selected for future studies.

Synthesis of ^{11}C-metomidate

^{11}C-metomidate was manufactured in compliance with good manufacturing practice using a GE Medical Systems PETtrace cyclotron (Milwaukee, WI). In a modification of the previously published synthesis, ^{11}C-methyl iodide was passed through a solution of (R)-methyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylic acid in anhydrous dimethylformamide, containing tetrabutylammonium hydroxide as a catalyst and loaded directly into the injector loop of a GE TracerLab FX-C system (17). This captive solvent methylation method produced ^{11}C-metomidate with a radiochemical purity of greater than 99% and specific activity between 19.8 and 404.8 GBq/μmol (average 132.7 GBq/μmol, about 10-fold that previously described) (17).

^{11}C-metomidate PET-CT imaging

PET-CT was performed on a GE Discovery 690 PET-CT scanner (GE Medical Systems). Noncontrast CT images were acquired over the adrenals (140 kV, 64 mA, slice width 3.75 mm). After an iv injection of ^{11}C-metomidate (150–500 MBq), dynamic PET images were acquired for 45 min. Attenuation and decay-corrected images were converted to SUV maps through division by (injected activity per patient weight). The maximum SUV values over regions of interest were determined for 10-min static images starting 35 min after the injection.

Analysis of ^{11}C-metomidate PET-CT studies and AVS

^{11}C-metomidate PET-CT studies were independently analyzed by two attending radiologists blinded to clinical diagnosis, AVS result, and treatment. A consensus report was generated commenting on the presence or absence of an adenoma and providing a tumor and normal adrenal SUV_{max}. The latter was estimated in both adrenals but not used in subsequent analyses on the side(s) in which a tumor was present. Dynamic measurements of SUV were made in 14 patients with unilateral functioning adenomas.

Outcomes and analysis

We defined cure by surgery as normalization of plasma renin together with a blood pressure at least 2 months postoperatively, which was either less than 140/90 mm Hg or lower by greater than 20/10 mm Hg on no drugs or fewer drugs than at diagnosis. We also sought histopathological confirmation of an adrenocortical adenoma, with additional biochemical evidence that the adenoma was functional. Using fresh pieces of the adrenal collected into culture medium or RNAlater (Ambion Inc., Austin, TX) at the time of surgery, we looked for an excess of aldosterone secretion from primary cultures of collagenase-dispersed cells from tumor compared with adjacent normal adrenal and the enzyme CYP11B2 expression measured by quantitative PCR (18–20).

We calculated the sensitivity of ^{11}C-metomidate PET-CT by determining the proportion of patients in whom a given ratio of SUV_{max} over the adenoma, compared with that over the normal adrenal, would correctly predict lateralization by AVS or cure of hypertension. We calculated specificity by determining the proportion of patients with bilateral hypersecreting adrenals, or nonfunctional incidentalomas, in whom the SUV_{max} ratio was lower than that used to predict lateralization in the unilateral PHA patients. A receiver-operator characteristics (ROC) curve was constructed from the pairs of sensitivity and specificity measured at each SUV_{max} ratio. The primary ROC analysis was conducted using all the PHA patients in whom lateralization was shown to be present or absent and the controls with a nonfunctional incidentaloma. A secondary ROC analysis excluded the PHA patients in whom confirmation of lateralization depended on postoperative outcome.

Sample size

The Administration of Radioactive Substances Advisory Committee granted approval for the preliminary study of six patients on three occasions. After this, we powered the full study at 25 positive (unilateral) and 15 negative (bilateral or incidental) cases to detect ($\alpha = 0.05$, $\beta = 0.9$) a sensitivity of 80% and specificity of 85% and demonstrate significant difference from the null hypothesis (50% sensitivity and specificity) on ROC analysis. Values for SUV_{max} and biochemical data are mean ± SEM.

All patients gave informed written consent to the study, which was approved by Cambridgeshire Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee.

Results

Patient characteristics

Fifty-six ^{11}C-metomidate PET-CT studies were performed in 44 patients, whose characteristics are shown in Table 1. Thirty-nine patients had PHA and five patients had an incidentaloma. Of the PHA group, 25 met the inclusion criteria for a unilateral aldosteronoma: either a 4-fold, or greater, excess of the aldosterone to cortisol ratio in the vein draining an adrenal adenoma (19 patients) or cure of PHA biochemistry and hypertension by removal of an aldosteronoma (six patients). Ten patients with PHA met the criteria for bilateral disease. There was no significant difference in biochemistry at the time of PET-CT between those patients with a unilateral aldosteronoma and those with bilateral disease (Table 1). Four patients were excluded from final analysis because of inconclusive AVS and no clear indication for surgery.

TABLE 1. Patient characteristics

	Incidentaloma	PHA with adenoma and AVS lateralization to side of adenoma and/or surgical outcome	PHA without AVS lateralization to side of adenoma	Significance (*P* value)
Number of subjects	5	25	10	
Age (yr)	49.6 ± 6.0	50.4 ± 2.1	52.9 ± 3.0	0.63
Plasma Na^+ (mM)	140.6 ± 1.0	141.8 ± 0.6	143.3 ± 0.7	0.10
Plasma K^+ (mM)	4.50 ± 0.20	3.54 ± 0.10	3.51 ± 0.12	0.62
Plasma HCO_3^- (mM)		30.0 ± 0.49	28.2 ± 0.9	0.31
Aldosterone (100–500; pM)	242 ± 34	803 ± 117	623 ± 137	0.37
Renin (4–78; mU/liter)	21.7 ± 5.7	5.0 ± 1.0	9.5 ± 4.1	0.14
Tumor location	Left = 4 Right = 1	Left = 13 Right = 9 Bilateral = 3	Left = 5 Right = 1 Bilateral = 1 None = 3	
AVS lateralization ratio		8.81 ± 1.28	3.60 ± 1.46	<0.01

Mean ± SEM values are shown. *P* values refer to comparisons between PHA patients with and without AVS lateralization. Normal ranges are shown in parentheses.

TABLE 2. Tumor and normal adrenal SUV_{max} values in subjects with unilateral PHA, bilateral PHA, and adrenal incidentaloma

Subject		AVS ratio[a]	Tumor SUV_{max}[b]	Contralateral SUV_{max}	SUV ratio (T/N)	ROC analysis	At diagnosis: Renin (mU/liter)	At diagnosis: Aldosterone (pmol/liter)	After adrenalectomy: Renin	After adrenalectomy: Aldosterone
Unilateral PHA										
1		4	38.9	12.6	3.09	TP	10	1557	25	72
2		26.7	34.9	15.5	2.25	TP	<2	1439	10	87
3		6.6	29.5	11.3	2.61	TP	14	477	350	231
4	[c]		29.5	11.2	2.63	TP	<2	995	14	209
5	[a]	5.1	29.3	18.8	1.63	TP	4	429	93	78
6	[d]	14.6	28.8	12.4	2.32	TP	5	1720	109	99
7	[a]	15.8	27.6	16.1	1.71	TP	<2	179	226	95
8		10.8	27.2	15.7	1.73	TP	6	411	181	280
9	[c]		26.6	18.5	1.44	TP	8	1298	57	171
10	[a]	4	26.5	19.7	1.35	TP	23	458	120	253
11	[c]		23.2	18.5	1.25	TP	3	690	39	577
12	[a,c]	2.15	22.2	17.2	1.29	TP	<2	884	91	131
13	[c]	1.85	21.7	12.9	1.68	TP	<2	559	40	111
14		10	21.6	12.3	1.76	TP	<2	2321	14	94
15		5.2	18.9	14.1	1.34	TP	2	794	11	367
16	[c]		17.8	13.4	1.33	TP	<2	787	10	94
17		5.6	16.6	10.6	1.57	TP	<2	1926	43	126
18	[a]	4	16.3	17.5	0.93	FN	3	177	Not operated	
19		6.8	14.1	11.2	1.26	TP	3	301	31	136
20	[d]	7.8	13.4	11.8	1.11	FN	<2	337	12	275
21	[d]	9	13.1	8.9	1.47	TP	<2	243	96	185
22	[a]	6.3	11.7	12.5	0.94	FN	4	406	12	67
23		12.5	11.2	10.3	1.09	FN	9	551	Not operated	
24	[d]	4.5	11.1	11.8	0.93	FN	11	270	Not operated	
25		21.7	10.3	9.2	1.12	FN	<2	787	4	115
Bilateral PHA										
26	[d]	1.4	24.2	23.3	1.05	TN	12	320	Not operated	
27		3.1	18.2	17.3	1.05	TN	4	640	Not operated	
28		2.4	16.9	14.6	1.16	TN	<2	459	Not operated	
29		1.4	14.5	14.2	1.02	TN	7	662	Not operated	
30		1.1	10.5	7.2	1.46	FP	11	286	Not operated	
31	[b]	2.6	20.3	18.4	1.1	TN	8	338	Not operated	
32	[b]	1.5	15.3	12.5	1.23	TN	44	1782	Not operated	
33	[b]	1.5	14.8	12.1	1.22	TN	4	568	Not operated	
34		0.15	20.3	16.9	1.2	TN	<2	686	Not operated	
35		0.065	17.7	16.3	1.04	TN	2	493	Not operated	
Adrenal incidentaloma										
36		Not performed	16.6	7.5	2.21	FP	46	350	Not operated	
37			14.9	14.6	1.02	TN	13	116	Not operated	
38			14.1	13.9	1.01	TN	35	32	Not operated	
39			11.9	10.4	1.14	TN	16	251	Not operated	
40			0	11.6		TN	7	195	5	65

Patients (35 with PHA and five with incidentalomas) are grouped according to clinical diagnosis, subgrouped according to AVS and/or surgical outcome, and listed in descending order of tumor SUV_{max} (if present). After ROC analysis, a cut point SUV_{max} ratio of 1.25 was used to code patients as true positives (TP), true negatives (TN), false positives (FP), or false negatives (FN), depending on agreement between prescan diagnosis and the SUV ratio. Postoperative biochemistry was measured between 3 and 7 months after adrenalectomy. T, Tumor; N, normal.

[a] In most patients, adrenal vein cannulation was confirmed by greater than 10-fold higher values of aldosterone or cortisol than in inferior vena cava. In five of the unilateral PHA patients, the right adrenal vein step-up was between 1.5- and 2.5-fold.

[b] SUV_{max} was measured over tumor (if present) and normal adrenal on each side; for clarity, only the former is shown. PET CT showed no discrete tumor in patients 31–33; in these cases, the higher SUV_{max} is shown in the tumor column.

[c] Lateralization is inferred from surgical cure (see text) when diagnostic AVS data were not available.

[d] Bilateral adenomas.

All but three of the unilateral PHA patients underwent adrenalectomy, which corrected hypokalemia and caused 10- to 440-fold reversal of aldosterone to renin ratio (average 115-fold, Table 2). Histology confirmed an adrenal adenoma; and fresh tissue taken at adrenalectomy from 18 patients operated in Cambridge demonstrated higher expression of CYP11B2 and greater secretion of aldosterone from the adenoma compared with adjacent normal adrenal.

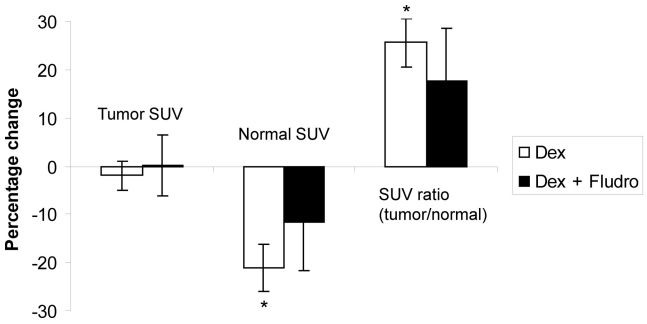

FIG. 1. Effect of pretreatment on SUV. Mean ± SEM values are shown in six subjects. Percentage changes are shown for tumor SUV_{max}, normal adrenal SUV_{max}, and SUV ratio compared with the study with no pretreatment. *, $P < 0.01$. Dex, Dexamethasone; Fludro, fludrocortisone.

Effects of pretreatment

In the six patients who underwent three ^{11}C-metomidate PET-CT studies, pretreatment with dexamethasone reduced the SUV in normal adrenal tissue by 21.2 ± 4.9% ($P < 0.01$), with no significant change in tumor SUV. This resulted in a 25.6 ± 5.0% ($P < 0.01$) increase in the ratio of tumor to normal SUV. The combination of dexamethasone and fludrocortisone did not change significantly the tumor SUV or the tumor to normal SUV ratio (Fig. 1). On the basis of this result, all subsequent scans were performed after 3 d of dexamethasone suppression.

Tumor and normal SUV

Table 2 shows ^{11}C-metomidate uptake calculated as the SUV_{max} during the last 10 min of data acquisition. In patients with PHA and a unilateral adenoma, mean tumor SUV_{max} at 21.7 ± 1.6 (range 10.3–38.9) was significantly greater than normal adrenal SUV_{max} at 13.8 ± 0.6 ($P = 0.00003$). In comparison, patients with an incidentaloma had a mean tumor SUV_{max} of 11.5 ± 3.3 (range 0–16.6). Patients with PHA and bilateral adrenal hyperplasia/bilateral adenomas had an intermediate SUV_{max} of 17.3 ± 1.2.

Representative ^{11}C-metomidate PET-CT studies

Figure 2A shows the CT, PET, and overlay images of three patients with PHA and greater than 4-fold AVS lateralization to the side of an adenoma. Subject 1 had the highest tumor SUV_{max}. Subject 6 had a single hot nodule on a background of multiple bilateral adenomas; after adrenalectomy, those on the right were separately analyzed, with the hot nodule secreting greater than 40,000 higher level of aldosterone in cell culture and showing similar overexpression of CYP11B2 (aldosterone synthase) on quantitative PCR. Subject 15 illustrates the spatial resolution of ^{11}C-metomidate PET-CT in one of the smallest adenomas, at 0.5 cm diameter. These patients are all true positives in the ROC analysis. Figure 2B shows images of three patients, subjects 28, 29, and 31, who did not lateralize on either AVS or PET-CT. Figure 2C shows images of three patients with incidentalomas and no clinical or biochemical abnormality. Subject 40 was exceptional in that her large adrenal lesion was completely cold on PET. Subject 38 is more typical of the true negative incidentalomas in the ROC analysis. Subject 36 was our single false positive among the incidentalomas.

Dynamic SUV measurements

Figure 3 shows a subgroup of 14 patients with PHA in whom we undertook dynamic measurements of tumor and normal adrenal SUV over the 45-min PET-CT data acquisition period. For this, we used the mean SUV, instead of SUV_{max}, because the latter can be erroneous at early time points when considerable ^{11}C-metomidate is still in the blood pool. Greater uptake into tumor, than normal adrenal, is evident within 5 min and maintained throughout the study (ANOVA, $P < 0.0001$).

ROC analysis

The ROC analysis shown in Fig. 4 is based on the SUV_{max} ratios shown in Table 2. An SUV ratio greater than 1.25 gives the optimal mix of sensitivity and specificity. Using this cut point, 19 of 25 patients were true positives, giving a sensitivity of 76% [95% confidence interval (CI) 59 to 93], whereas 13 of 15 patients were true negatives, giving a specificity of 87% (95% CI 69–104). Specificity rises to 100% in patients with an SUV_{max} ratio greater than 1.25 and tumor SUV_{max} greater than 17. The secondary ROC analysis, restricted to patients with lateralization on AVS, reached a similar result (Fig. 4).

Discussion

There are two main stages to the diagnosis of a unilateral Conn's adenoma: biochemical proof of autonomous hypersecretion and determination with radiological help of the tumor's location (6, 21). The present study was directed at the second stage, with the objective of improving the ease and, perhaps, accuracy of determining whether a diagnosis of biochemical PHA could be attributed to a unilateral hot nodule. We believe this has been achieved, with the SUV_{max} ratio of 1.25:1 providing an optimal balance of 87% specificity and 76% sensitivity in a condition that is virtually always benign (22).

^{11}C-metomidate, a methylated imidazole, was first proposed as an adrenocortical radiotracer in the 1990s, after the recognition that the anesthetic drug, etomidate, a closely related ethyl-imidazole analog of metomidate, is a potent inhibitor of adrenal steroidogenesis (23, 24). Metomidate itself was widely used as a veterinary anesthetic

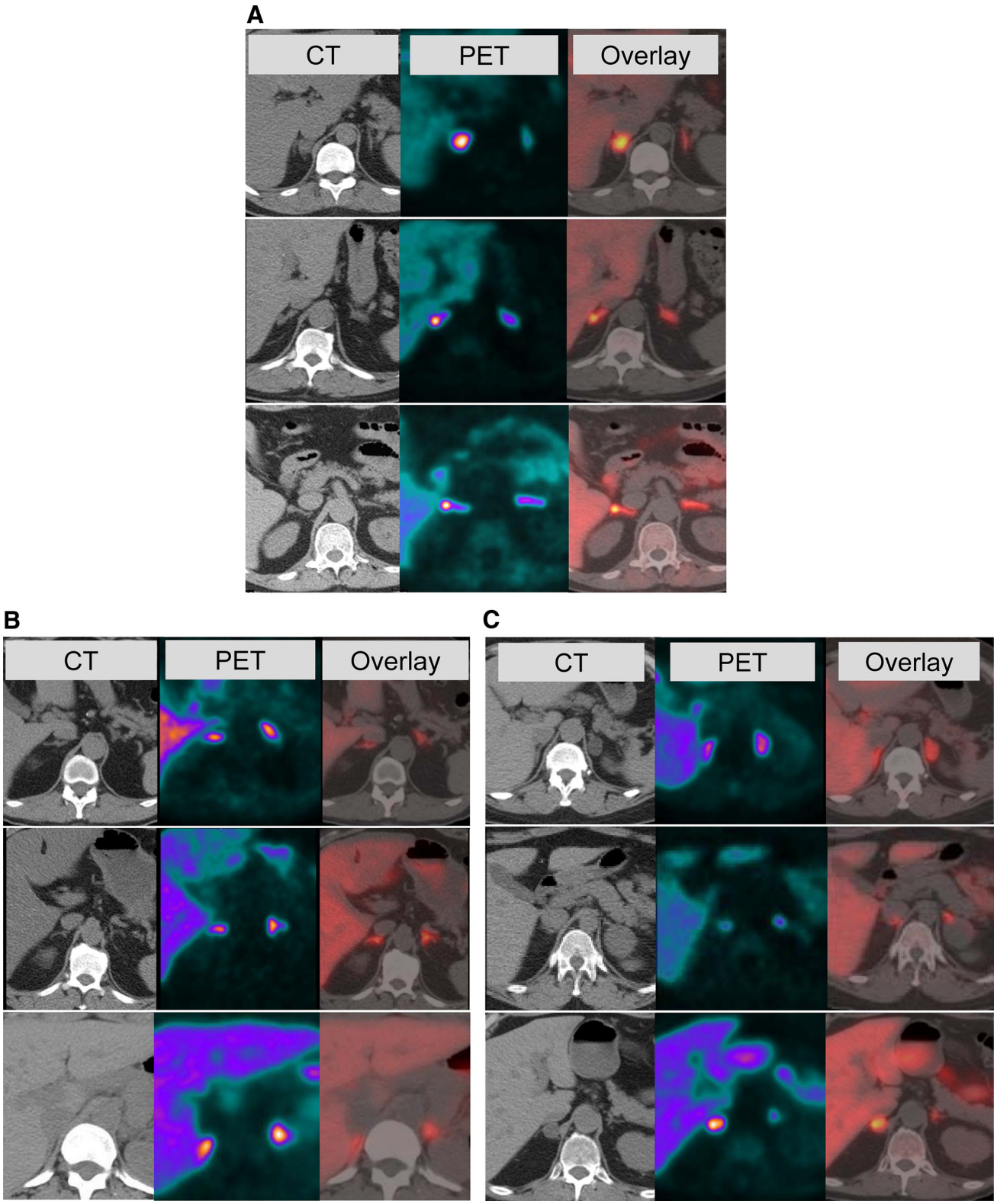

FIG. 2. PET-CT images from illustrative patients in each diagnostic group. A, Unilateral PHA and positive lateralization on PET-CT. CT, PET, and overlay images are shown for subjects 1 (*upper panels*), 6 (*middle panels*), and 15 (*lower panels*). All three patients lateralized to the right on AVS. B, Bilateral PHA and no lateralization on PET-CT. CT, PET, and overlay images are shown for subjects 28 (*upper panels*), 31 (*middle panels*), and 29 (*lower panels*). These subjects did not lateralize significantly on AVS and are true negatives in the ROC analysis. C, Nonfunctional adrenal incidentalomas. CT, PET, and overlay images are shown for subjects 38 (*upper panels*), 40 (*middle panels*), and 36 (*lower panels*), illustrating the heterogeneity of tumor uptake in this patient cohort.

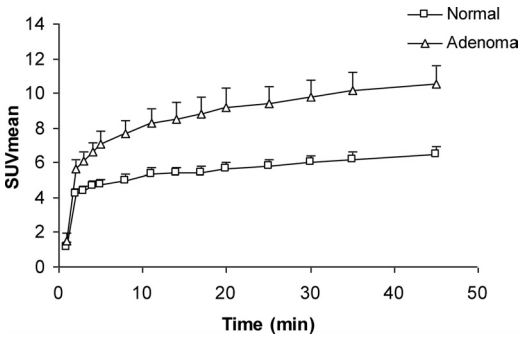

FIG. 3. Dynamic measurements of the mean SUV. Mean ± SEM values are shown in 14 subjects with PHA. Adenoma and contralateral normal adrenal were defined as regions of interest and ^{11}C-metomidate uptake determined over the 45-min data acquisition period.

in the 1960–1970s, conveniently providing toxicological support for its clinical application as a PET ligand (15). A number of reports of adrenal visualization followed, and the six Conn's adenomas in a series of 73 adrenal studies showed the highest average uptake of ^{11}C-metomidate (16). The radiotracer has not, however, entered clinical usage, and we considered this unlikely to happen without a prospective study to evaluate both sensitivity and specificity of the investigation. The question was what to compare as the gold standard. Demonstration that increased ^{11}C-metomidate uptake correlated with the existence of a surgically and biochemically proven aldosterone-secreting adenoma is necessary but insufficient; equally or more important is the demonstration that the adrenal with normal ^{11}C-metomidate uptake is not contributing to autonomous aldosterone secretion. Such adrenals would only rarely (*e.g.* a large incidentaloma) be deliberately removed and available for analysis. Despite its imperfections, therefore, we used lateralization on AVS as the standard. However, the most problematic patients are those in whom there is an absence of lateralization on AVS, usually due to failure to cannulate the right adrenal vein. We therefore permitted the inclusion of a few such patients who were committed to surgery, *e.g.* because of unequivocal PHA and adrenal adenoma, in a young patient.

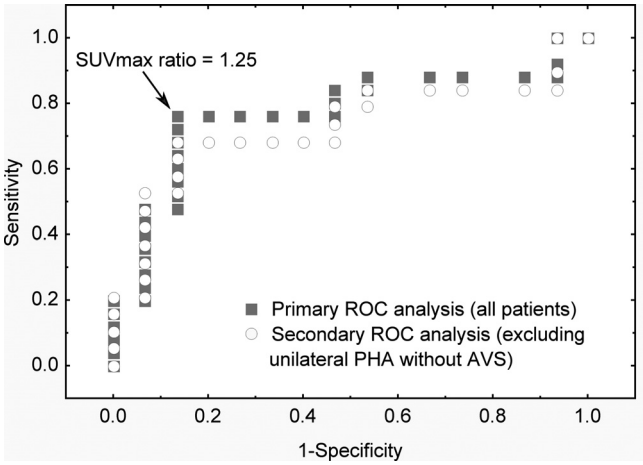

FIG. 4. ROC analysis. Pairs of sensitivity and specificity were calculated using each recorded SUV_{max} ratio. For the unilateral PHA group, this was the SUV_{max} of adenoma divided by SUV_{max} of contralateral normal adrenal. In the controls, the numerator was SUV_{max} on the side of higher aldosterone to cortisol ratio, on AVS, or over adenoma in the case of the five nonfunctional incidentalomas. An SUV ratio of 1.25 gives a specificity of 87% and a sensitivity of 76% [area = 0.77 (95% CI [0.62,0.97], $P = 0.004$)]. When replotted excluding six unilateral PHA patients without lateralization by AVS, the SUV ratio of 1.25 gives a specificity of 87% and sensitivity of 68% [area = 0.73 (95% CI [0.56,0.91]), $P = 0.02$].

We introduced some innovations that appear each to have improved sensitivity and precision. In particular, PET-CT improved spatial resolution over PET alone. This enabled us to quantify the SUV accurately and separately over tumor and normal adrenal and to determine qualitatively whether subcentimeter adenomas were hot or cold and in patients with bilateral nodules to distinguish between unilateral and bilateral hot nodules. As with previous scintigrams of the adrenal cortex, we wanted to determine the potential benefit of suppressing uptake into the normal adrenal upon overall signal to noise. The modest, 26% increase in the ratio of tumor to normal SUV_{max} after pretreatment of patients with dexamethasone for 3 d is consistent with one report in 11 patients studied before and after 3 d of dexamethasone (25). Although we found the expected, large suppression by dexamethasone of 11β-hydroxylase activity, as assessed by plasma cortisol, the SUV reflects binding of ^{11}C-metomidate to 11β-hydroxylase protein. One study of its turnover, in bovine adrenal cells, had reported a modest reduction in a half-life from 24 to 16 h in the absence of ACTH (26). We chose 3 d as consistent with a new steady state after 3–4 half-lives of enzyme decay. A small bonus from the dexamethasone pretreatment is the detection of occasional patients whose adenomas cosecrete cortisol with aldosterone and who are thus at risk of postoperative adrenal suppression (27).

We explored the added benefit of pretreating patients with fludrocortisone after our discovery of a mineralocorticoid response pathway in normal zona glomerulosa cells (18). The lack of any benefit suggests that mineralocorticoid receptor activation over this time period does not produce detectable changes in 11β-hydroxylase or aldosterone synthase expression. Our study has not addressed whether pretreatment affects ^{11}C-metomidate uptake into incidentalomas, but a previous pilot study suggested that uptake was not suppressed by dexamethasone (25).

The heterogeneity in aldosteronoma SUV illustrated in Table 2 may reflect variable expression levels of 11β-hydroxylase and aldosterone synthase. In support of this, we have noted a significant positive correlation between tumor SUV_{max} and plasma aldosterone concentration measured at the time of the ^{11}C-metomidate study (data not

shown). In a *post hoc* regression analysis, we did not find any effect of spironolactone treatment on the correlation. Because one of the practical problems with AVS has been the question of confounding by medication and consequent advice to withdraw some or all drugs from a patient group often having resistant hypertension, we were keen that our study assessed patients on current treatment. This enabled us to see long-distance referrals on just two occasions: once for screening, consent, and dispensing of the dexamethasone and once for the PET-CT study itself.

Despite the variation in SUV_{max} between patients, the ratio of adenoma to normal within patients was much tighter (as illustrated in Fig. 3). This explains the high significance, $P < 0.0005$, of the SUV difference between paired adenoma and normal and why a ratio of just 1.25:1 is diagnostic for ^{11}C-metomidate PET-CT, whereas a lateralization ratio of 4:1 is usually required on AVS (28). Metomidate binds to both the CYP11B1- and CYP11B2-encoded enzymes, and the up-regulation of the latter (aldosterone synthase) in adenomas is offset by a reduction in the former (11β-hydroxylase) (19, 29). The heterogeneity within the incidentaloma group is more surprising and may partially reflect the variable pathology of these lesions. Most incidentalomas showed some ^{11}C-metomidate uptake, indicative of low-level expression of 11β-hydroxylase, whose sum throughout an adrenal mass might account for the incomplete suppression of cortisol by dexamethasone reported in some patients and contribute to an increased risk of cardiovascular disease (30, 31). Indeed, our false-positive patient within this group (subject 34) may not be completely false because his postdexamethasone level fell to only 47 nmol/liter, and his scan suggests a hot nodule forming within the adenoma (Fig. 2C); its influence on the SUV ratio may have been additionally exaggerated by the use of a fluticasone inhaler, which may have partially suppressed 11β-hydroxylase expression in the normal adrenal.

The true sensitivity of ^{11}C-metomidate PET-CT is probably higher than appears from the comparison with AVS. Our study design dictated that PET-CT could perform only the same as, or worse than, AVS. However, there is little agreement on the analysis of AVS (32, 33). We followed recommendations to use at least 4-fold difference between adrenal veins in aldosterone to cortisol ratio to diagnose lateralization (34). Three of our false-negative cases (18, 22, and 24 in Table 2) narrowly met criteria for unilateral PHA, with either the step-up of aldosterone and cortisol from inferior vena cava to the right adrenal vein or the difference in aldosterone to cortisol ratio between sides in the borderline range (29, 34). Conversely, Table 2 shows five patients with unilateral PHA who were not diagnosed by AVS, including patient 12, illustrated in Supplemental Fig. 1, and patient 13, in whom PET CT and surgical outcome showed AVS to be the false negative despite clear-cut cannulation. Occasionally, as in subjects 34 and 35, AVS points to the opposite adrenal from an adenoma on CT/MRI, and we would not usually recommend surgery in such patients. Although our prestudy definition of a positive diagnosis resulted in the six false negatives of Table 2, all are toward the lower end of the unilateral PHA group, having low SUV_{max} over the adenoma. In reaching recommendations on the optimal application of PET-CT, we suggest that neither PET-CT nor AVS alone is 100% reliable when any of the following are obtained: bilateral adenomas; greater signal (PET-CT or AVS) from the adrenal contralateral to a single adenoma on CT/MRI; or suppression of SUV_{max} on either side to less than 10. Our study design also does not provide evidence for or against use of PET-CT in patients with suspected unilateral hyperplasia.

Cure of hypertension, and hypokalemia, is the goal of surgery. But in older patients with resistant hypertension on multiple drugs, a good outcome can be some reduction in blood pressure, fewer side effects, and fewer drugs. This group is likely to have a variable degree of sustained hypertension due to either long-standing secondary changes or coexistent essential hypertension. So although improved blood pressure is the goal, the degree of improvement is an unreliable indicator of accuracy in measuring lateralization of aldosterone secretion. As is apparent from Table 2, a good measure is the cure of the biochemical abnormalities leading to diagnosis of PHA, namely low renin and/or elevated aldosterone to renin ratio. These were normalized in all patients who proceeded to surgery, with an average increase in the ratio of 115-fold. In addition, we can comment that all these patients have been either cured of hypertension (off all treatment) or have a blood pressure less than 140/90 mm Hg on fewer drugs than required preoperatively.

The ^{11}C-metomidate PET-CT can now be established, with limited training, wherever there is a cyclotron. Although some patients may travel farther than for AVS, this is offset by the immediacy of the result. Even for patients needing to travel overseas, at $4500 per study PET-CT is a cost-effective alternative to AVS at most North American or European centers. ^{18}F and ^{123}I derivatives of metomidate dispense with the need for a cyclotron (35, 36). However, these alternatives lack the safe toxicological profile of native metomidate resulting from its long use as a veterinary anesthetic, and their accuracy has yet to be evaluated.

In conclusion, we recommend that ^{11}C-metomidate PET-CT be considered an accurate, noninvasive alternative to AVS in the management of patients with PHA and adrenal adenoma. PHA is a heterogeneous condition, in-

cluding the group with single adenomas (37). Further experience of ^{11}C-metomidate PET-CT will be of value in determining whether there are clinical characteristics that should influence the choice between PET-CT and AVS.

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