^{18}F-Fluorodeoxyglucose Positron Emission Tomography for the Diagnosis of Adrenocortical Tumors: A Prospective Study in 77 Operated Patients

Lionel Groussin, Gérald Bonardel, Stéphane Silvéra, Frédérique Tissier, Joël Coste, Gwenaelle Abiven, Rossella Libé, Marie Bienvenu, Jean-Louis Alberini, Sylvie Salenave, Philippe Bouchard, Jérôme Bertherat, Bertrand Dousset, Paul Legmann, Bruno Richard, Hervé Foehrenbach, Xavier Bertagna, and Florence Tenenbaum

Institut National de la Santé et de la Recherche Médicale Unité 567, Centre National de la Recherche Scientifique Unité Mixte de Recherche 8104, Institut Cochin, Department of Endocrinology, Metabolism and Cancer (L.G., F.Ti., R.L., J.B., X.B.), 75014 Paris, France; Université Paris Descartes (L.G., S.Si., F.Ti., J.C., M.B., J.B., B.D., P.L., B.R., X.B.), 75006 Paris, France; Assistance Publique des Hôpitaux de Paris, Hôpital Cochin, Department of Endocrinology, Center for Rare Adrenal Diseases (L.G., G.A., R.L., J.B., X.B.), Departments of Pathology (F.Ti.), Radiology (S.Si., M.B., P.L.), Digestive and Endocrine Surgery (B.D.), Nuclear Medicine (B.R., F.Te.), Biostatistics Unit (J.C.), and INCa Comete Network (R.L., X.B.), 75014 Paris, France; Hôpital d'Instruction des Armées du Val de Grâce, Department of Nuclear Medicine (G.B., H.F.), 75005 Paris, France; Assistance Publique des Hôpitaux de Paris, Hôpital Saint Antoine, Endocrinology Unit (P.B.), 75012 Paris, France; Assistance Publique des Hôpitaux de Paris, Hôpital de Bicêtre, Department of Endocrinology and Reproduction (S.Sa.), 94275 Le Kremlin-Bicêtre, France; and Department of Nuclear Medicine, Centre René Huguenin, Université Versailles-St-Quentin (J.-L.A.), 92210 Saint Cloud, France

Context: Most adrenal incidentalomas are nonfunctioning adrenocortical adenomas (ACAs). Adrenocortical carcinomas (ACCs) are rare but should be recognized at an early stage.

Objective: The objective of the study was to evaluate the usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) to predict malignancy in patients without a previous history of cancer.

Design: This was a prospective, multicenter study from 2001 to 2006.

Setting: The study was conducted at a network of seven university hospitals in Paris.

Patients: Seventy-seven patients were included. All underwent surgery because of hypersecretory and/or growing benign lesions (n = 18), obvious ACCs (n = 21), or radiologically indeterminate lesions (n = 38).

Main Outcome Measure: The degree of ^{18}F-FDG PET uptake [maximum standardized uptake value (maxSUV)] was related to the pathological findings serving as a reference, and its diagnostic value was compared with that of computerized tomography (CT) scan.

Results: Pathology eventually diagnosed 43 ACAs, 22 ACCs, and 12 nonadrenocortical lesions. Using a cutoff value above 1.45 for adrenal to liver maxSUV ratio, the sensitivity and specificity to distinguish ACAs from ACCs were, respectively, 1.00 (95% confidence interval 0.85–1.00) and 0.88 (95% confidence interval 0.75–0.96). Among the 38 indeterminate lesions at CT scan, we could analyze a subgroup of 16 adrenocortical tumors with high unenhanced density (>10 HU) and an inappropriate washout: ^{18}F-FDG PET correctly predicted the benignity in 13 of 15 ACAs.

Conclusions: In a multidisciplinary team approach, ^{18}F-FDG PET helps to manage suspicious CT scan lesions. An adrenal to liver maxSUV ratio less than 1.45 is highly predictive of a benign lesion. **(*J Clin Endocrinol Metab* 94: 1713–1722, 2009)**

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Abbreviations: ACA, Adrenocortical adenoma; ACC, adrenocortical carcinoma; ACT, adrenocortical tumor; AEW, absolute enhancement washout; CI, confidence interval; CT, computerized tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; HU, Hounsfield unit; maxSUV, maximal standardized uptake value; MEN1, multiple endocrine neoplasia type 1; PET, positron emission tomography; REW, relative enhancement washout; ROC, receiver-operating characteristic; ROI, region of interest; SUV, standardized uptake value; UFC, urinary free cortisol.

Incidental adrenal masses (incidentalomas) are frequent in the general population, with a prevalence of 4–10% on abdominal computerized tomography (CT) scans (1). A diagnostic evaluation is systematically performed to determine whether the lesion is hormonally active or nonfunctioning and whether it is malignant or benign (2).

Most incidentalomas are nonfunctioning adrenocortical adenomas (ACAs), even in patients with a known extraadrenal primary malignancy. By contrast, adrenocortical carcinoma (ACC) is rare, with an estimated prevalence between 4 and 12 per million in adults (2). Early diagnosis and complete surgical removal of a localized tumor is the only opportunity to cure patients with ACC, a tumor with an extremely poor prognosis, the overall survival rate being approximately 20–37% at 5 yr (3, 4).

The tools to diagnose ACC from other adrenal lesions are careful investigations of clinical, biological, and morphologic features. The size, homogeneity, and lipid content determined by unenhanced CT attenuation value expressed in Hounsfield units (HU) may help distinguish between benign and malignant lesions. A homogeneous mass with a smooth border and an attenuation value of less than 10 HU on an unenhanced CT strongly suggests the diagnosis of an ACA. The specificity of this criterion is close to 100% with a weaker sensitivity because some ACAs are lipid poor (5).

For adrenal masses with unenhanced CT attenuation value of more than 10 HU, other criteria in addition to size are needed to identify patients at high risk for developing ACC. Delayed enhanced CT might help characterizing these tumors (6, 7).

Among various diagnostic tests, positron emission tomography (PET) with ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) deserves prospective investigation. ^{18}F-FDG PET/CT has proved to be highly efficient for diagnosing malignancy in different types of tumors (8).

A limited number of studies have been applied to metastatic lesions and very few have been performed on primary adrenocortical tumors (ACTs). We now report the results of a prospective study focusing on 77 lesions of the adrenal region that were all operated. This design allowed us to correlate ^{18}F-FDG uptake with the final histopathological diagnosis. To minimize the possibility of adrenal metastases, patients with a past history of malignancy were excluded. The diagnostic value of ^{18}F-FDG was also compared with that of the currently most used CT scan imaging.

Patients and Methods

Patients

Inclusion criteria were as follows (Fig.1): patient with a solid lesion in the adrenal region with an indication for surgery. Patients were operated on for hypersecretory and/or growing benign lesion, obvious ACC, or radiologically indeterminate lesion. Characteristics on imaging were size, shape, texture, and attenuation density on unenhanced CT. Rapidity of washout of contrast medium was evaluated by relative enhancement washout (REW = 100 × enhanced attenuation value-delayed attenuation value/enhanced attenuation value). A lesion was diagnosed as indeterminate if the unenhanced density was above 10 HU and the REW under 50% (7). Exclusion criteria were a diagnosis of pheochromocytoma or a past history of cancer. Seventy-seven patients were included from 2001 to 2006 at seven University Hospitals in Paris.

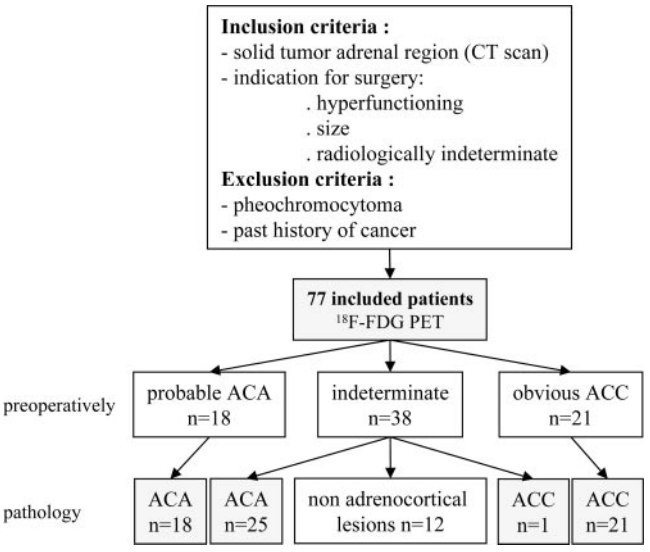

FIG. 1. Study design and patients. It includes study design and description of the 77 operated patients. Three groups of patients were defined preoperatively: probable ACA, radiologically indeterminate lesion and obvious carcinoma (ACC).

Hormonal investigations were performed: 24-h urinary metanephrines and normetanephrines, 24-h urinary cortisol, 1 mg overnight dexamethasone suppression test, plasma aldosterone to renin concentration ratio for patients with high blood pressure, testosterone, dehydroepiandrosterone sulfate, estradiol, compound S, desoxycorticosterone, and baseline and postcorticotrophin 17-hydroxyprogesterone. Assays were performed as previously reported (9–13).

Tumor was defined as nonfunctioning if there was no hormonal hyperactivity. The definition of subclinical Cushing relies on an abnormal overnight dexamethasone suppression test (cortisol level greater than 50 nmol/l) and normal 24-h urinary cortisol. Functional tumors were characterized by the steroid oversecretion: glucocorticoid, mineralocorticoid, androgen.

Histopathological diagnostics were reviewed by a single pathologist (F.Ti.). For ACTs, the Weiss pathological criteria were recorded. For ACCs, staging was performed using MacFarlane's criteria, as modified by Sullivan *et al.* (14) based on surgical and/or imaging results (9).

The study was approved by and performed according to the recommendations of the Institutional Review Board of Cochin Hospital. Written informed consent was obtained from all patients.

PET cameras

Between 2001 and 2002, PET was performed in nine cases with a C-PET camera (ADAC, Milpitas. CA). Between 2002 and 2004, PET was performed in 28 cases with an Allegro GSO system (Philips Medical Systems Inc., Cleveland, MA). For both PET cameras, the three-dimensional acquisitions of emission and transmission data were performed sequentially, with 7 min per bed position for C-PET and 3 min for Allegro. The images were reconstructed with and without attenuation correction using a cesium-137 transmission source with the manufacturer's software three-dimensional row-action maximum-likelihood algorithm. The last 40 patients, from 2004 to 2006, were scanned on a Gemini PET/CT system (Philips Medical Systems) that combines a helical dual-slice CT and a PET machine, with an emission scan of 3-min duration per bed position.

Patients fasted 12 h. Diabetic patients were prepared with oral antidiabetic medications or insulin the days before ^{18}F-FDG PET to obtain a glycemia less than 150 mg/dl (Tables 1 and 2). They were premedicated orally with diazepam and then rested for 1 h. Imaging was performed 60 min after iv administration of ^{18}F-FDG (2.5 MBq/kg for C-PET and 5 MBq/kg for Allegro and Gemini).

TABLE 1. Features at presentation and imaging data in 43 patients with ACA (Weiss score ≤2)

Patients	sex	Age (yr)	Clinical presentation	Functional status	Tumor size (mm)	Attenuation value on unenhanced CT (HU)	Adrenal maxSUV	Adrenal to liver maxSUV	Adrenal maxSUV to liver mean SUV	Plasma glucose (mg/dl)	Weiss score
ACA1	F	59	Incidentaloma	SC	40	−27	4.5	0.93	1.66	81.8	0
ACA2	F	41	Incidentaloma	SC	33	−11	2.8	1.16	1.33	ND	0
ACA3	M	57	Incidentaloma	SC	50	−10	2.1	0.91	1.4	120	0
ACA4	M	58	Incidentaloma	SC	38	−6	1.9	0.86	1.11	86.3	0
ACA5	F	51	Incidentaloma	SC	40	−5.4	4.9	1.04	1.63	80	0
ACA6	F	60	Incidentaloma	SC	58	−4	4.3	1.72	2.04	81.8	1
ACA7	M	56	Incidentaloma	NF	40	0	2.2	0.88	1.22	ND	0
ACA8	F	66	Incidentaloma	SC	48	0	2.8	0.82	1.07	90.9	0
ACA9	F	64	Incidentaloma	SC	49	1.8	3.8	1.08	1.35	120	0
ACA10	F	38	Incidentaloma	SC	45	5	2.8	0.87	1.21	80	0
ACA11	F	67	Incidentaloma	SC	48	5	2.4	1.04	0.75	85.5	2
ACA12	F	75	Incidentaloma	SC	60	5	2.9	1	1.31	76.4	0
ACA13	M	52	Incidentaloma	SC	45	10	2.5	0.92	1.19	101.8	0
ACA14	M	59	Incidentaloma	GC	52	11	2.3	0.95	1.27	101.8	0
ACA15	F	53	Incidentaloma	SC	35	12	3	0.75	0.96	ND	0
ACA16	F	50	Incidentaloma	GC	30	20	7.7	1.83	2.65	78.9	1
ACA17	F	51	Endocrine symptoms	GC	20	37	2.8	1.33	1.55	90	2
ACA18	F	41	Endocrine symptoms	GC	30	39	4.2	0.91	1.27	ND	1
ACA19	F	56	Endocrine symptoms	GC	30	11	3.2	1.03	1.23	72.7	0
ACA20	F	55	Incidentaloma	NF	35	11.6	3.2	1	1.33	83.6	0
ACA21	F	58	Incidentaloma	SC	29	13	2	0.9	1.17	84.5	0
ACA22	F	28	Endocrine symptoms	GC	37	15	2.9	1.07	1.31	66.4	1
ACA23	F	56	Incidentaloma	SC	25	18	2.6	0.86	1.04	86.4	2
ACA24	M	69	Incidentaloma	SC	65	19	1.8	0.64	0.78	88.2	0
ACA25	M	60	Incidentaloma	NF	40	22	1.7	0.75	1	92	0
ACA26	F	60	Tumor syndrome	SC	45	23	2.5	0.96	1.25	135.5	0
ACA27	F	64	Incidentaloma	NF	47	24	2.3	0.76	1	107.3	0
ACA28	F	77	Incidentaloma	SC	60	24	2.6	0.92	1.23	80	0
ACA29	F	36	Endocrine symptoms	GC	40	25	3.3	1.1	1.2	90.9	1
ACA30	F	62	Incidentaloma	SC	43	29	2.7	0.81	1.22	111.8	0
ACA31	F	32	Endocrine symptoms	GC	33	30	2.3	0.82	1.09	116.4	2
ACA32	F	72	Incidentaloma	SC	41	30	5.4	1.92	2.45	77.3	0
ACA33	F	39	Incidentaloma	SC	30	32	5.1	1.1	1.54	89.1	1
ACA34	F	43	Endocrine symptoms	GC	30	32	4	1.02	1.42	90	1
ACA35	M	45	Incidentaloma	SC	40	34	4.7	1.67	2.04	77.3	2
ACA36	F	30	Endocrine symptoms	GC	25	37	2.7	0.9	0.78	80	1
ACA37	F	35	Endocrine symptoms	GC	35	37	3.5	1.29	1.75	81.8	1
ACA38	F	36	Endocrine symptoms	GC	35	38.4	2.3	0.92	1.21	ND	0
ACA39	F	54	Incidentaloma	NF	35	39	2.4	0.77	0.96	90	0
ACA40	F	41	Endocrine symptoms	SC	30	40	3	0.75	1	118.2	2
ACA41	M	64	Incidentaloma	NF	40	40	2.6	0.89	1.23	73.6	1
ACA42	F	34	Endocrine symptoms	GC	35	ND	6.9	1.11	1.53	78	1
ACA43	F	56	Tumor syndrome	GC	60	ND	7.8	2.36	3	64.9	2

NF, Nonfunctional; SC, subclinical Cushing; GC, glucocorticoid; F, female; M, male; ND, not determined; tumor syndrome, abdominal pain or flank discomfort.

Image analysis

Studies were retrospectively analyzed by a consensus of two experienced nuclear medicine physicians who were unaware of the patient data, except for the side of the lesion.

When interpreting the dedicated PET images, the first step was a visual assessment. PET findings were interpreted as positive if the ^{18}F-FDG uptake was greater than the background and as negative if the uptake was less than the background.

Adrenal lesions were then objectively analyzed by measurement of the calculated standardized uptake value (SUV). The activity in the adrenal mass was obtained by drawing a region of interest (ROI) that encompassed the central two thirds of the mass if relatively homogeneous or the most uniform area if the mass was heterogenous. The area of maximal standardized uptake value activity (maxSUV) was identified within the ROI. In patients with no apparent localized increase of radioactivity, the ROI was positioned in the typical area for the adrenal gland.

To minimize the possible change related to the different cameras used and to improve reproducibility and performance of the quantification, the tumor to normal uptake ratio for each PET image was computed. The ROI for normal uptake ratio was positioned in the middle liver at the boundary between segments VIII and V. Normalizing adrenal maxSUV by liver mean SUV or liver maxSUV was not significantly different. We analyzed the adrenal maxSUV to liver maxSUV ratio.

Statistical analysis

In a first stage, the discriminative properties of the ^{18}F-FDG PET were investigated by receiver-operating characteristic (ROC) analysis (15). This technique summarizes the validity coefficients of a test and

TABLE 2. Features at presentation and imaging data in 22 patients with ACC (Weiss score ≥3)

Patients	Sex	Age (yr)	Clinical presentation	Functional status	Tumor size (mm)	Attenuation value on unenhanced CT (HU)	Adrenal maxSUV	Adrenal to liver maxSUV	Adrenal maxSUV to liver meanSUV	Plasma glucose (mg/dl)	Weiss score	McFarlane staging
ACC1	F	41	Incidentaloma	SC	50	55	7	3.18	4.66	80.9	3	I
ACC2	F	51	Endocrine symptoms	GC+A	50	30	5.3	1.7	2.2	96	3	I
ACC3	F	25	Endocrine symptoms	GC+A	110	0, 7	17.2	5.73		86.4	5	IV
ACC4	F	81	Incidentaloma	SC	165	22	3.5	1.66	2.05	78	4	II
ACC5	F	67	Endocrine symptoms	GC+A	110	27	5.8	2.9	2.52	143.6	8	IV
ACC6	F	40	Endocrine symptoms	GC+A	150	27	11.4	4.56	6.55	80.9	8	II
ACC7	F	35	Endocrine symptoms	GC	150	30	10.5	4.56	5.83	77.3	4	II
ACC8	F	59	Endocrine symptoms	SC+A	110	32	7.3	3.65	4.56	64.5	5	II
ACC9	F	24	Endocrine symptoms	GC+MR+A	78	34	11.2	4.14	5.33	78.2	9	IV
ACC10	F	37	Endocrine symptoms, MEN1	GC+A	90	34	18	7.5	10	63.6	6	II
ACC11	M	30	Tumor syndrome	NF	250	37	10.3	3.96	6.05	80.9	5	II
ACC12	F	61	Tumor syndrome	SC	90	40	3.8	1.72	2.11	ND	7	II
ACC13	F	46	Endocrine symptoms	GC+A	130	40	15.9	6.11	8.3	84.5	9	III
ACC14	F	40	Tumor syndrome	NF	85	41	12.2	4.7	6.1	85.5	6	II
ACC15	F	54	Tumor syndrome	NF	100	42	4.6	1.58	2	ND	6	II
ACC16	F	65	Endocrine symptoms	SC+MR	120	42	13	5.9	10	87.3	8	II
ACC17	F	30	Endocrine symptoms	SC	80	46	16.3	6.1	8.57	ND	9	III
ACC18	F	42	Endocrine symptoms	SC+A	55	ND	10.5	4.4	5.25	ND	4	II
ACC19	F	43	Endocrine symptoms	GC+A	160	ND	9.7	3.03	4.21	ND	6	III
ACC20	F	60	Tumor syndrome	GC+A	160	ND	12	3.8	5.71	84	6	II
ACC21	F	37	Endocrine symptoms and tumor syndrome	GC+A	240	ND	13.5	4.65	5.62	ND	9	IV
ACC22	F	76	Incidentaloma, MEN1	GC+A	170	ND	26.2	15.4	26.2	63.6	5	III

NF, Nonfunctional; SC, subclinical Cushing; GC, glucocorticoid; MR, mineralocorticoid; A, androgen; F, female; M, male; ND, not determined; tumor syndrome, abdominal pain or flank discomfort.

provides an overall index of accuracy (*i.e.* the area under the ROC curve) by plotting sensitivity against the false-positive rate (one minus specificity) for all possible cutoff scores. Two different quantifications of ^{18}F-FDG PET uptake on the same patients can therefore be compared on the ROC scale. In a second stage, sensitivities and specificities, and their confidence intervals, for selected cutoff points were calculated.

Nonparametric Spearman rank correlation tests were used to examine relationships between ^{18}F-FDG uptake and functional status. Spearman partial correlations was used to control for the confounding effect of histopathology (in other words, to account for the dependence of variables on Weiss score).

Results

Preoperative evaluation of the patients

We separated the patients into three different groups, preoperatively (Fig. 1). Eighteen patients had presumed ACA based on an homogeneous tumor with smooth margins and unenhanced CT attenuation of 10 HU or less and/or REW of 50% or greater. Twenty-one patients had presumed ACC based on a tumor with a size of 5 cm or greater, heterogeneous, with irregular margins and unenhanced CT attenuation greater than 10 HU (usually

>20) and REW less than 50% and/or androgen secretion and/or metastases. Thirty-eight patients had indeterminate lesion (unenhanced CT attenuation >10 HU and <50% or lack of precise characteristics on CT scan).

Definitive pathological diagnosis

Definitive pathological diagnosis was obtained for all patients after surgery (Fig. 1). All 18 patients with presumed ACA had their diagnosis confirmed (Weiss score ≤2). All 21 patients with a presumed ACC also had their diagnosis confirmed (Weiss score ≥3). Among the group of 38 patients with indeterminate adrenal tumors, three categories of diagnosis were ultimately obtained: 25 were ACAs, 12 were nonadrenocortical lesions, and one was an ACC.

The ultimate pathological approach allowed the definitive diagnosis of 43 ACAs and 22 ACCs. Nonadrenocortical lesions were not included in the final analysis.

Patient demographics, clinical findings, and ^{18}F-FDG PET results

Data are summarized in Table 1 for the 43 ACAs. Eighteen (ACA1 to ACA18) were correctly diagnosed preoperatively, 25 (ACA19 to ACA43) were among the 38 tumors classified as indeterminate lesions.

Table 2 represents data for the 22 ACCs. As a group, ACCs had a higher tumor size and a higher spontaneous density on CT scan compared with ACAs. Yet there was a fairly large overlap, explaining the number of suspicious lesions.

All ACCs had a tumor size greater than 5 cm in diameter (ranging from 5 to 25). Available unenhanced CT attenuation values were all above 20 HU (ranging from 22 to 46), except for ACC3 who had a value suggestive of a benign lesion (<0.7 HU in different areas of the lesion). This tumor was preoperatively diagnosed as malignant because of the size, the heterogeneity, an androgen oversecretion, and metastases. The tumor was carefully reviewed by the pathologist who described a spongiocyte hyperplasia, and the Weiss score was 5. Hormonal investigations showed steroid excess for most ACCs, with androgen secretion in 13. Patients ACC10 and ACC22 remind us of the possibility of ACC in multiple endocrine neoplasia type 1 (MEN1).

For one radiologically indeterminate lesion (ACC1), the diagnosis was made only after pathology (Weiss score of 3).

^{18}F-FDG distinguishes between ACA and ACC

Each individual maxSUV (absolute and relative to liver) was plotted against the Weiss score (Fig. 2, A and C, respectively).

MaxSUVs in the ACA group were lower than those in the ACC group (Fig. 2A). Figure 2B displays the ROC plots for maxSUV: discrimination was very good with an area under ROC curve of 0.96 [95% confidence interval (CI) 0.91 to 1.00]. Using 3.4 as a cutoff value for maxSUV, a sensitivity of 1.00 (95% CI

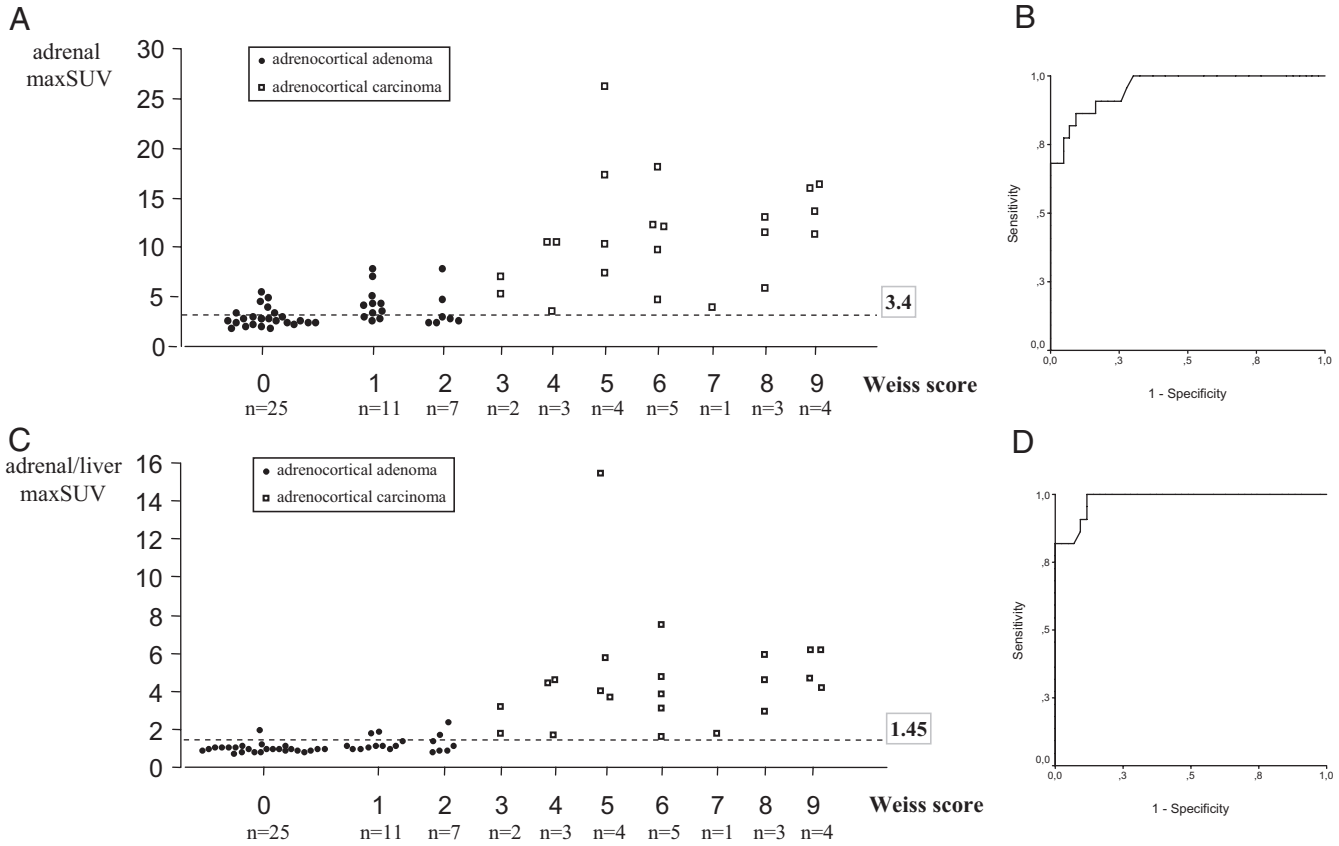

FIG. 2. ^{18}F-FDG PET and Weiss score. ACAs (*black circles*) and ACCs (*white squares*) are compared. A, ^{18}F-FDG uptake expressed as adrenal tumor maxSUV. B, ROC curve generated from adrenal maxSUV. C, ^{18}F-FDG uptake expressed as adrenal to liver maxSUV ratio. D, ROC curve generated from adrenal to liver maxSUV ratio.

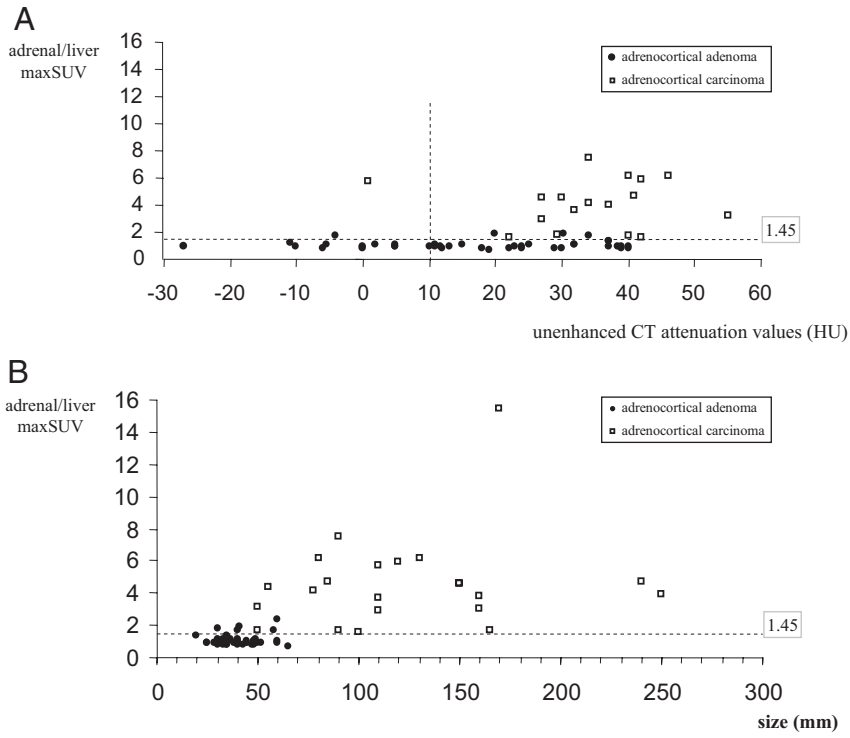

FIG. 3. ^{18}F-FDG and CT scan. A, ^{18}F-FDG uptake compared with unenhanced CT attenuation values. B, ^{18}F-FDG uptake compared with tumor size.

0.85–1) and a specificity of 0.70 (95% CI 0.54–0.83) were achieved to distinguish between ACAs and ACCs.

To determine whether background metabolic activity could be responsible for some false-positives among ACAs, we used a specific interpretative criterion, the adrenal uptake of ^{18}F-FDG relative to the liver uptake (Fig. 2C). Figure 2D displays the ROC plots for maxSUV ratio: discrimination was (slightly not statistically different) better with an area under ROC curve of 0.98 (95% CI 0.96–1.00). Using 1.45 as a cutoff value for adrenal to liver maxSUV ratio, a sensitivity of 1.00 (95% CI 0.85–1.00) and a specificity of 0.88 (95% CI 0.75–0.96) were achieved to distinguish ACC from ACA. In our series, none of the ACCs had an uptake less than that of the liver (*i.e.* a zero false negative rate).

Among tumors with a Weiss score of 2 or less, five of 43 tumors had an adrenal to liver maxSUV ratio above 1.45.

^{18}F-FDG PET compared with CT scan

To determine the usefulness of ^{18}F-FDG preoperatively for diagnosing the malignancy of an adrenal mass, we compared adrenal to liver maxSUV ratio with two key parameters obtained with conventional CT imaging: unenhanced CT attenuation values (Fig. 3A) and tumor size (Fig. 3B).

Because of our inclusion criteria (radiologically indeterminate lesions), most of our patients had an unenhanced CT density above 10 HU. Except ACC3, discussed previously, all our tumors with an unenhanced CT attenuation under 10 HU were ACAs. It is worth noting that ACC3 was correctly diagnosed as malignant by ^{18}F-FDG (Fig. 3A). As expected all the remaining ACCs had an unenhanced attenuation value above the threshold of 10 HU; actually all were above 20 HU. Twenty-eight ACAs had an unenhanced attenuation value above the threshold of 10 HU. Interestingly, 18 of these 28 ACAs had a spontaneous density equivalent to that of ACCs. For this subgroup of ACAs, a ^{18}F-FDG uptake under the cutoff value of 1.45 for adrenal to liver maxSUV correctly predicted the benignity of the tumor.

The second CT scan parameter used to predict malignancy is the tumor size (2). The prevalence of ACCs increases when the size is superior to 4 cm. For intermediate lesions between 4 and 6 cm, the likelihood of malignancy is difficult to predict based on size alone. The choices of our inclusion criteria gave us a significant number of tumors with a size between 4 and 6 cm (Fig. 3B). Again, for this subgroup of patients, a low ^{18}F-FDG uptake is highly predictive of a benign lesion. Three ACCs had a size around 5 cm and were correctly diagnosed as malignant tumors with ^{18}F-FDG. All the tumors larger than 7 cm were ACCs with a high ^{18}F-FDG uptake.

The density washout after contrast media injection during CT scan is also a parameter used for tumor dignity assessment. Among the 38 suspicious tumors, 16 adrenocortical tumors had been evaluated with dynamic CT scan sequences: all had spontaneous densities above 10 HU and a REW less than 50%, necessitating the elimination of the possibility of a malignant tumor (Fig. 4). Only one of these tumors ultimately was diagnosed as an ACC (Weiss score of 3), which had an elevated adrenal to liver maxSUV ratio of 3.18. The 15 other tumors were all ACAs (Weiss score between 0 and 2), and only two had a minor elevation of adrenal to liver maxSUV ratio, at 1.92 and 1.67. Thus, the ^{18}F-FDG allowed a correct diagnosis in 13 of 15 benign tumors. Figure 5 illustrates how adrenal to liver maxSUV ratio may help in diagnosing benignity in a patient with a suspicious CT scan incidentaloma (ACA24).

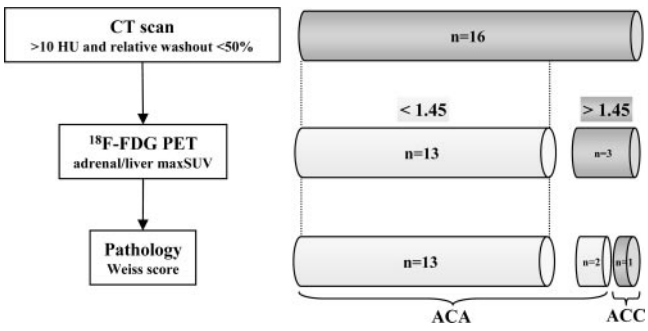

FIG. 4. ^{18}F-FDG PET in 16 suspicious adrenocortical lesions on CT scan. Sixteen patients with suspicious adrenocortical lesions (unenhanced attenuation value >10 HU and relative washout <50%) were studied. Thirteen had an adrenal to liver maxSUV ratio under the cutoff value of 1.45 and were finally diagnosed as ACAs.

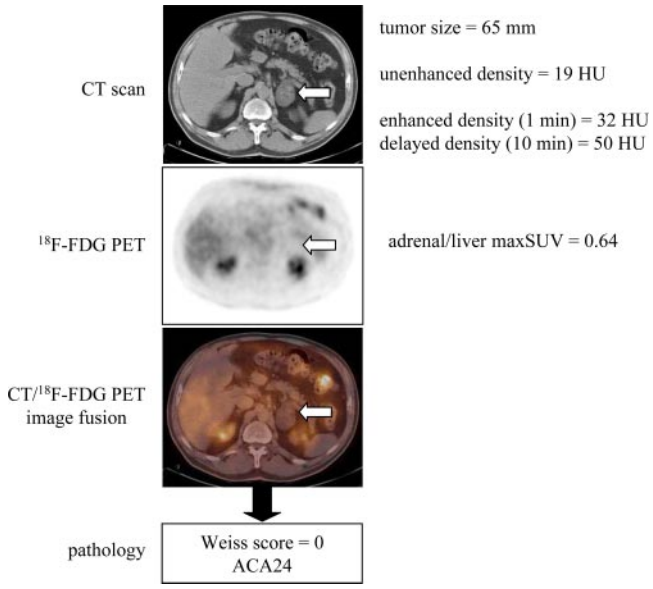

FIG. 5. ^{18}F-FDG predicts benignity of adrenal incindentalomas.

Intensity of ^{18}F-FDG adrenal uptake does not correlate with hormonal status

Figure 6 shows the relationship between ^{18}F-FDG adrenal uptake and adrenocortical activity as determined by 24-h urinary free cortisol (UFC).

In this series, ^{18}F-FDG uptake was not different between cortisol-secreting ACAs (UFC >90 μg/d) and nonfunctional ACAs. Only two of 14 cortisol-secreting ACAs had a ^{18}F-FDG adrenal uptake above the cutoff value of 1.45.

By analyzing all adrenocortical lesions, a weak correlation between UFC and adrenal to liver maxSUV ratio (r = 0.32; P = 0.01) is found, which disappeared when we adjusted for histopathology (Weiss score) (partial r = 0.05; P = 0.69). The apparent correlation was probably due to ACCs having the highest UFC and uptake values.

Our results suggest that a secreting status is probably not a good explanation for false-positive results in ACAs.

Discussion

The prevalence of adrenal masses in autopsy series may be as high as 1.4–12.4% (16). It explains the high frequency of adrenal incidentalomas detected with imaging techniques such as CT scan (17). Conventional imaging has some limitations to predict malignancy, justifying the studies of new imaging technologies. It would be disastrous to miss an ACC at the stage of a localized tumor.

The concept of ^{18}F-FDG PET is based on the increased glucose uptake associated with malignant lesions. ^{18}F-FDG PET has proved to be highly efficient for diagnosing malignancy (8). The usefulness of ^{18}F-FDG PET is recognized for the extension workup of ACCs (18–20).

The aim of our study was to determine whether ^{18}F-FDG PET could predict before surgery the benignity or malignancy of an ACT. The study was designed to include mainly patients with primary adrenocortical lesions. Because ^{18}F-FDG PET may depict uptake in benign adrenal chromaffin tumor, we excluded patients with pheochromocytomas (21). This is the first prospective study that compares the results of ^{18}F-FDG adrenal quantitative uptake with the final pathology obtained in all cases. Our criteria for surgery allowed us to finally analyze the results of two thirds of ACAs (n = 43) and one third of ACCs (n = 22).

Previous studies on ^{18}F-FDG PET and adrenal were mostly dedicated to patients with known primary malignancy. ^{18}F-FDG demonstrated a high sensitivity ranging from 93 to 100% to detect adrenal metastases (22–29). In these oncology cohorts, hormonal evaluation and CT scan density were not constantly reported, and the diagnosis was based merely on minimal follow-up assessing the change in tumor size. Different adrenal maxSUV uptake cutoff values have been proposed: 2.68 (25), 3.1 (27), and 3.4 (26) to distinguish between benign and malignant lesions with a good sensitivity and a relatively weaker specificity.

Few studies have included patients without known malignancy (30–32). In a preliminary study, we reported the visual assessment of 11 ACTs (33). However, visual analysis alone appeared to be less accurate than the measurement of SUVs.

In this study, using adrenal maxSUV measurements alone, the predictive value of the ^{18}F-FDG was good but imperfect. Using as a cutoff value 3.4 to have a sensitivity of 100% to correctly diagnose all malignant lesions, we had a specificity of only 70% to distinguish between ACAs and ACCs.

Many factors may interfere with SUV measurement, including patient weight or blood glucose level, the length of uptake period, a partial-volume effect, the recovery coefficient, and the type of ROI (34–38). Some authors proposed the use of tumor to background ratio as an adjunct to monitor the reliability of SUV (35). Paquet *et al.* (38) showed that SUVs measured in normal liver and mediastinum are stable over time, no matter which correction method of SUV is used.

Previous studies found that calculating adrenal to liver SUV ratio, rather than adrenal maxSUV alone or background activity, improved the ability to correctly classify adrenal tumors (23–25, 28, 32).

In this study, we used the adrenal to liver maxSUV ratio. We could observe a strong correlation between this ratio and the Weiss score. Two thresh-

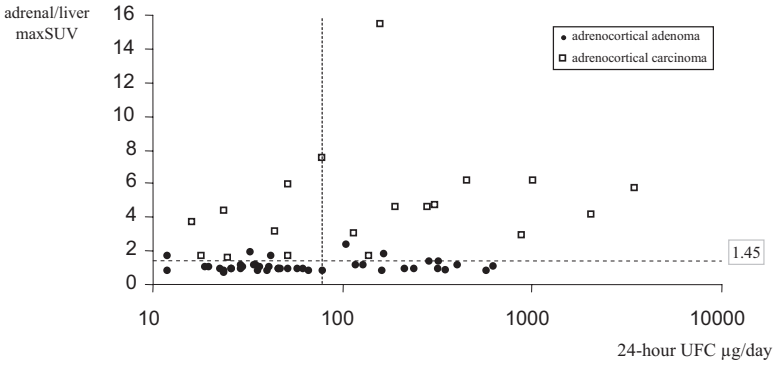

FIG. 6. ^{18}F-FDG and hormonal activity. Twenty-four-hour UFC (micrograms per day) had no correlation with ^{18}F-FDG uptake. The *vertical dotted line* indicates the location of the threshold value for normal UFC (90 μg/d).

olds are worth discussing. The first one is our main outcome measure allowing us to perfectly distinguish benign from malignant ACTs. To obtain a sensitivity of 100% for the detection of ACCs, a ratio above 1.45 for adrenal to liver maxSUV was determined. The related specificity of 88% was higher than the specificity of 70% obtained with adrenal maxSUV alone. From a clinical practice point of view, it is worth noting that among the 12 nonadrenocortical lesions, five were malignant (data not shown). Except one, all had an adrenal to liver maxSUV ratio above 1.45 and would have been correctly diagnosed as suspicious for malignancy before surgery (two leiomyosarcomas and two metastases of unknown renal carcinomas). The remaining tumor (a rare synovialosarcoma with a ratio of 1.23) was preoperatively highly suspicious for malignancy because of a size greater than 10 cm, a heterogeneous aspect, irregular margins, and an unenhanced CT attenuation greater than 10 HU. ^{18}F-FDG PET should be interpreted in the proper context. The second threshold of 2.63 for adrenal to liver maxSUV was determined to have a specificity of 100%. The related sensitivity was 82%. Between the two thresholds, we observed four ACCs with an adrenal to liver maxSUV ratio ranging from 1.58 to 1.72. There was no doubt regarding the malignant nature of these tumors because of the size and/or the steroid oversecretion and finally the Weiss score. Between the two thresholds, five ACAs were present with an adrenal to liver maxSUV ratio ranging from 1.67 to 2.36. In comparison with the other ACAs we could not find any significant difference. The explanation of these false-positive results is not clear. We can only discuss several hypotheses. First, it is worth noting a study by Bagheri *et al.* (39) describing normal adrenal gland uptake with a wide range (maxSUV from 0.95 to 2.46). It has been suggested that the functional state of an adenoma could be a factor determining the intensity of uptake, with ^{18}F-FDG uptake being increased in functioning adrenal masses (40–42). In our study, however, steroid oversecretion does not seem to explain false-positive ACAs because of the lack of correlation between secretion and uptake.

Another hypothesis could be the limitations of our diagnostic tools, *i.e.* the Weiss score, to distinguish ACAs from ACCs. Some of the ACAs with a high ^{18}F-FDG uptake could be tumor with a potential malignant behavior. It is well known that distinction between localized tumors with malignant behavior and benign ACT based on clinical presentation, imaging studies, and even histopathologic analysis can be difficult. The evaluation of combined histologic features and establishment of specific scores, as proposed by Weiss, bears some technical difficulties, even for skilled pathologists. The five Weiss scores of our ACAs with a high ^{18}F-FDG uptake were analyzed twice by our trained pathologist (F.Ti.) with the same score each time. It is remarkable that in these tumors (Weiss score of 1 or 2) traditionally considered as benign, there is still a significant percentage of them (around 12% for Weiss score of 1 and 50% for Weiss score of 2), which bear molecular abnormalities such as 17p13 loss of heterozygosity and/or IGF-II overexpression, that are highly prevalent in ACCs (9). It is therefore possible that we are constantly dealing with a borderline population of tumors. The biology of these tumors and maybe their pathophysiology might differ from the one of clearly benign ACA (Weiss of 0). Weiss classification could also be inaccurate for some tumors to predict behavior. The follow-up of patient with a Weiss score of 2 or less and a high ^{18}F-FDG uptake could be particularly important.

Our second objective was to compare the diagnostic value of ^{18}F-FDG to that of the classical approach with CT scan. Researchers in several published series evaluated the utility of measurement of the attenuation levels in Hounsfield units on unenhanced, contrast-enhanced, and delayed contrast-enhanced CT scans (43). In a metaanalysis, Boland *et al.* (44) concluded that an attenuation value of less than 10 HU on unenhanced CT had a sensitivity of 71% and a specificity of 98% for the diagnosis of ACA. Conversely, all noncalcified, nonhemorrhagic adrenal lesions with precontrast attenuation of greater than 43 HU are considered suspicious for malignancy. Lesions with attenuation of greater than 10 HU and less than 43 HU are considered indeterminate. More recently, contrast medium washout studies have enabled differentiation of adrenal metastases from lipid-poor adenomas, with good accuracy. Adenomas tend to deenhance faster than nonadenomatous lesions. Calculation of REW may lead to a highly specific test for adrenal lesion characterization with an accuracy estimated between 96 and 98% (7, 45, 46). However, many centers do not perform washout studies for organization reasons. Among our patients with indeterminate lesions, we could identify 16 patients who had been evaluated with dynamic CT scan sequences: all had spontaneous densities above 10 HU and a REW less than 50%. Using the cutoff value of 1.45 for adrenal to liver maxSUV ratio, we could accurately diagnose one malignant lesion and 13 benign lesions. Two ACAs had an uptake equivalent to malignant lesions. Again, they may represent true false-positive ACAs or just reflect the limitations of the pathological diagnosis with Weiss score. Absolute enhancement washout (AEW), if the unenhanced attenuation value is available, can be calculated. Recently AEW value has been reported as more reliable than REW (47). An AEW greater than 60% characterizes an ACA. Using this criteria, five indeterminate lesions would have been correctly classified as ACA (data not shown). In our opinion, ^{18}F-FDG is a useful tool to help distinguish potential malignant lesion from benign tumor in radiologically indeterminate adrenal lesions. Patients who have adrenal lesions with inconclusive CT densitometry or washout analyzes should be referred for characterization with ^{18}F-FDG PET.

In conclusion, this is the largest series with ACCs that were all operated on for a final pathological diagnosis. It allowed us to propose a cutoff value for adrenal to liver maxSUV ratio, which should help physicians to distinguish between benign and malignant ACTs. It is particularly useful for patients with a radiologically indeterminate adrenal mass. A negative ^{18}F-FDG PET is highly predictive of a benign lesion and might help avoid surgery (elderly patient) or delay it if necessary. If surgery is indicated, it might help the surgeon decide between minimally invasive approach (^{18}F-FDG negative) and laparotomy (^{18}F-FDG positive).

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Address all correspondence and requests for reprints to: Dr. Lionel Groussin, Service des Maladies Endocriniennes et Métaboliques, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, 75014 Paris; France. E-mail: lionel.groussin@cch.aphp.fr.

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