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18F-FDG PET for the Identification of Adrenocortical Carcinomas among Indeterminate Adrenal Tumors at Computed Tomography Scanning

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Abstract
Background 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) has been proposed for the evaluation of adrenal tumors. However, only scarce data are available to evaluate its usefulness for the identification of primary adrenal carcinomas in patients with no previous history of cancer and equivocal tumors on computed tomography (CT) scan. The objective of the present study was to evaluate the diagnostic performance of 18F-FDG-PET to predict malignancy in such patients.
Methods and Patients This was a retrospective study carried out from 2006 to 2009 in a single university hospital center. Twenty-three consecutive patients without previous history of cancer investigated for adrenal tumors without features of benign adrenocortical adenoma on CT scan but no obvious ACC underwent 18F-FDG PET. All patients underwent adrenalectomy because of CT scan characteristics regardless of the results of 18F-FDG PET. The ratio of maxSUV adrenal tumor on maxSUV liver (adrenal/liver maxSUV ratio) during 18F-FDG PET was compared to Weiss pathological criteria.
Results Seventeen patients had an adrenal adenoma, 2 had small size adrenal carcinomas (<5 cm), 1 had an angiosarcoma, and 3 had noncortical benign lesions. An adrenal/liver maxSUV ratio above 1.6 provided 100% sensitivity, 90% specificity, and 100% negative predictive value for the diagnosis of malignant tumor.
Conclusions Because of its excellent negative predictive value, 18F-FDG-PET may be of help in avoiding unnecessary surgery in patients with non-secreting equivocal tumors at CT scanning and low 18F-FGD uptake.

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Introduction

The diagnosis of cortical carcinoma in patients with adrenal tumors (ACC) is often obvious at presentation in view of large size, local invasion, or distant metastases and eventually combined adrenocortical hypersecretion [1]. Less frequently, preoperative recognition of ACCs may be difficult in the presence of small, noninvasive (MacFarlane, stage 1 and 2) [2], and non-hypersecretory tumors that may eventually present as an incidentaloma [3]. Identification of ACCs in such a context in order to proceed rapidly with surgery is of extreme importance, because ofboth the poor prognosis of this cancer and the lack of efficient alternative medical treatment. 18F-FDG PET has been recently been proposed for this purpose but most studies published to

date are oncologic series including mainly patients with adrenal metastases [4–7]. Only one recent study focused on the identification of ACCs in patients without known malignancy and concluded that 18F-FDG PET may be of help because an adrenal-to-liver maxSUV ratio under 1.45 is highly predictive of a benign lesion [4]. However, this series included only a few patients with really challenging ACCs from a diagnostic perspective, e.g., adrenal tumors with no categorical benign or malignant feature on CT. Additional independent studies are therefore needed to confirm the usefulness of 18F-FDG PET in the evaluation of equivocal adrenal masses. We report herein our experience of the 18F-FDG PET on a series of 23 consecutive patients with atypical features on CT scan.

Patients and methods

Patients with obvious ACC on CT scanning, patients with previous history of cancer or with pheochromocytoma were excluded from this series. All patients recruited between 2006 and 2009 that met these criteria and presented an atypical adrenal tumor on CT scan underwent prospectively 18F-FDG PET (Table 1). A tumor was diagnosed as atypical if the unenhanced density was above 10 UH and if there was eventual washout of contrast media <50% on the CT scan.

Fifteen of the 23 tumors were discovered as incidentalomas and 8 tumors during the evaluation of adrenal hypersecretion syndrome. All patients underwent hormonal investigation including 24 h urinary cortisol, circadian rhythm of plasma cortisol and ACTH, dexamethasone suppression test, serum aldosterone and plasma renin activity, and plasma androgen measurement. For 18F-FDG PET, patients fasted for at least 6 h, and imaging was performed on a single camera 60 min after intravenous administration of 5 MBq/kg of 18 F-FDG in our center. Diabetic patients were prepared with oral antidiabetic medications the day before 18F-FDG PET to obtain a glycemic level below 110 mg/dl. None was treated with insulin. Three-dimensional images were acquired from the skull base to the upper thigh with a General Electric

Table 1 Features at presentation and imaging data in 23 patients

Patients	Age, years	Sex	Hormonal status	Tumor size, mm	Unenhanced density (UH)	Washout (%)	Adrenal maxSUV	Adrenal/liver maxSUV	Pathology
1	72	F	No secretion	33	30	<50%	4.8	2.67	ACA (Weiss 0)
2	69	F	No secretion	44	20	<50%	2.8	0.34	ACA (Weiss 0)
3	52	F	No secretion	30	25	<50%	6.2	1.63	ACA (Weiss 1)
4	54	F	No secretion	39	30	<50%	4.5	1.45	ACA (Weiss 0)
5	60	F	Hypercortisolism	27	34	<50%	5.7	1.42	ACA (Weiss 1)
6	27	F	No secretion	20	26	<50%	4.7	1.51	ACA (Weiss 2)
7	54	F	Hypercortisolism	24	40	ND	6.3	1.31	ACA (Weiss 0)
8	32	F	Hypercortisolism	28	37	ND	3.9	1.56	ACA (Weiss 1)
9	51	F	Hypercortisolism	42	Heterogeneous	ND	1.9	0.55	ACA (Weiss 0)
10	49	F	Hypercortisolism	30	Heterogeneous	<50%	2	0.66	ACA (Weiss 0)
11	56	F	Hypercortisolism	49	Heterogeneous	ND	3.1	0.64	ACA (Weiss 1)
12	64	F	Hypercortisolism	34	Heterogeneous	ND	4.5	0.75	ACA (Weiss 0)
13	26	F	No secretion	34	31	ND	5	2.60	ACA (Weiss 0)
14	74	M	No secretion	23	22	<50%	1.6	0.72	ACA (Weiss 1)
15	62	F	No secretion	23	Heterogeneous	ND	2.2	0.60	ACA (Weiss 0)
16	79	F	Hypercortisolism	45	Heterogeneous	ND	5.4	1.35	ACA (Weiss 0)
17	48	M	No secretion	24	39	ND	3.8	1.00	ACA (Weiss 0)
18	39	M	Hyperaldosteronism	31	35	<50%	13	2.76	ACC (Weiss 5)
19	61	M	No secretion	145	Heterogeneous	ND	5.8	3.05	Angiosarcoma
20	33	F	Hypercortisolism	42	39	ND	6.6	2.10	ACC (Weiss 6)
21	68	F	No secretion	25	24	ND	2	0.71	Benign cystic lesion
22	51	M	No secretion	37	18	ND	1.3	0.30	Benign cystic lesion
23	64	M	No secretion	70	40	<50%	2.9	0.83	Hematoma

ND not determined, *F* female, *M* male, *ACA* adrenocortical adenoma, *ACC* adrenocortical carcinoma

Discovery ST PET/CT hybrid scanner. Measurement of the calculated SUV was obtained by drawing a region of interest (ROI) that encompassed the central two-thirds of the adrenal tumor. The area of maximal activity (maxSUV) was identified within the ROI. The use of an adrenal to liver maxSUV ratio has been previously recommended to improve the reproducibility and performance of the 18F-FDG TEP [4–6, 8]. All PET/CT scan interpretations were performed by two experienced nuclear medicine physicians. All patients underwent adrenalectomy because of atypical characteristics on the CT scan. In no case was surgery decided on the results of 18F-FDG PET. Adrenalectomy and histopathological diagnostics were performed by an experienced surgeon and a pathologist from our center. Patients underwent either laparoscopic or open surgery depending on the tumor volume and on the suspicion of malignancy from the preoperative imaging. All procedures were total adrenalectomy. Conversion to an open procedure would have been considered in case of tumor morcellation, fracture of the tumor capsule, or other procedural complications. Weiss pathological criteria were recorded for adrenocortical tumors. The Weiss criteria are mitoses >5/50 HPF, atypical mitoses, necrosis, venous invasion, sinus invasion, capsular invasion, diffuse growth, nuclear atypia and clear cells <25%. The results of 18F-FDG-PET were compared to pathological findings that served as a reference.

Receiver operating characteristic (ROC) analysis was used for estimation of the threshold SUVmax optimal value.

Results

Findings of the endocrine evaluation, surgery, histopathology, CT imaging, and 18F-FDG PET studies are summarized in Table 1.

Endocrine evaluation

Ten patients had a hypersecreting tumor (9 with mild or obvious cortisol oversecretion, 1 with hyperaldosteronism). Thirteen had no evidence of hormonally active tumors.

Surgery

Of the 23 patients, 21 were operated by laparoscopy and 2 by laparotomy. There was 1 conversion due to a spleen injury during procedure in a hypercortisolic patient. During the laparoscopic procedure, no patient suffered a tumor fracture. One patient developed a postoperative hematoma (4.3%).

The mortality rate for this series was 4.3% ($n = 1$): one patient had acute pancreatitis in the postoperative course and died of sceptic complication with organ failure.

Histopathology

Seventeen patients had ACAs (Weiss score <2), 2 patients had ACCs (Weiss score = 5 and 6). The remaining lesions were 1 malignant angiosarcoma, 1 hematoma, and 2 benign cysts. Among patients with ACCs, postoperative follow-up identified local recurrence in patient 20 after 3 months and peritoneal metastases in patient 18 after 7 months.

CT imaging

The mean size of adrenal tumors was 39.1 ± 26 mm (range: 20–145 mm). Maximal diameter ranged from 20 to 49 mm for ACAs, 31 to 145 mm for malignant tumors, and 25 to 70 mm for other lesions. Interestingly, the size of the 2 ACCs was within the range of that of ACA (31 and 42 mm). All tumors had unenhanced density >10 UH (range: 18–40 UH). Contrast material washout was performed in 10 of these and was <50% in all cases.

18F-FDG PET

The mean adrenal/liver maxSUV ratio for benign tumors was 1.2 ± 0.6 (range: 0.3–2.7) and 2.6 ± 0.5 (range: 2.1–3.0) for malignant tumors ($p < 0.02$) (Fig. 1). The minimal SUV ratio for malignant tumors was 2.1. Two adrenal adenomas (Weiss = 0) had an SUV ratio within the range of ACCs. Thus an adrenal/liver maxSUV ratio of 1.6 provided 100% sensitivity and 90% specificity for the diagnosis of malignant tumor (Fig. 1). Using this threshold, the negative predictive value of 18F-FDG PET was 100%.

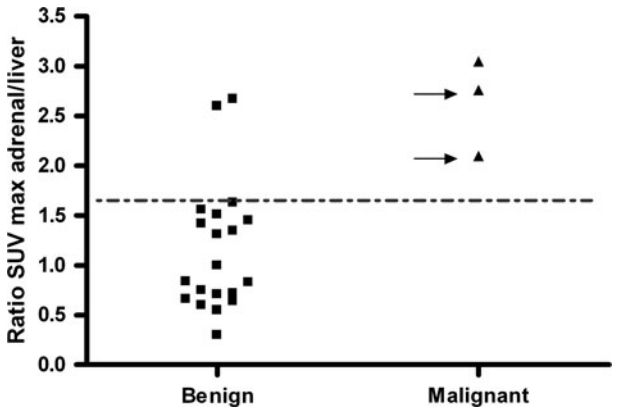

Fig. 1 Adrenal/liver maxSUV ratio in 18F-FDG PET for the 23 suspicious adrenocortical lesions on CT scan. *Arrows* indicate both adrenocortical carcinomas. The chosen cut-off at 1.6 is represented as a *dotted bar*

Discussion

Computed tomography has been proposed to distinguish adrenocortical adenomas (ACAs) from ACCs with the measurement of unenhanced attenuation values and quantification of contrast media washout. However, these measurements have a rather low specificity and have been poorly studied in the context of primary ACC justifying the study of new imaging technologies [8, 9]. One main study prospectively examined the performance of 18F-FDG PET to identify ACCs among adrenal tumors in patients without a previous history of malignancy [4, 5]. Among the 77 patients of this large series [4], only 38 had an indeterminate lesion at CT scanning, and 1 ACC (>50 mm in size) was diagnosed among these. In this subset of patients the ACC displayed an adrenal to liver maxSUV ratio >1.45, whereas 13 of the 15 ACAs had a ratio below this threshold. In the whole series of patients (including patients with obvious ACCs and ACAs at CT scanning), this threshold had a 100% sensitivity and 88% specificity to distinguish ACAs from ACCs. The negative predictive value was 100%. In a more limited series of adrenal incidentalomas with no benign feature at CT scanning and that included 3 nonsecreting ACCs and various adrenal malignancies in patients with a previous history of cancer, Tessonnier et al. [5] recommended an adrenal to liver maxSUV ratio of 1.8. This threshold provided 100% sensitivity and specificity for the differential diagnosis between ACAs and malignant tumors. However, pathological examination was not performed in a number of suspected ACAs, and the narrowness of the gap between maxSUVs of benign and malignant tumors (1.7 and 1.98, respectively) intuitively suggests that this absolute diagnostic accuracy may not be confirmed with an increased number of cases.

With the adrenal to liver maxSUV ratio, our findings confirm that ACCs display an increased uptake of the radiotracer. Interestingly, the 2 ACCs of our series were small in size (<5 cm), a condition that has seldom been published in TEP series (2 cases in the series of Maurea et al. [6]). Thus, 18F-FDG-PET may be useful to identify ACCs in this rare challenging diagnostic situation. However, as found by others [4, 7], we confirm that false positive uptake may occur in apparently benign adrenal adenomas. This intriguing finding does not seem to be correlated with tumoral endocrine secretion [4]. Although the limited specificity of 18F-FDG PET for adrenal tumors must be kept in mind, the main concordant finding between studies is its excellent negative predictive value [4–7, 10]. It is striking that the discriminant threshold for the adrenal to liver maxSUV ratio found in our study is very close to those found by of Groussin et al. [4] and Tessonnier et al. [5] (1.6, 1.45, and 1.8, respectively). Complementary studies involving a larger number of "small" ACCs are needed to refine these criteria and determine an ideal threshold usable across centers as has been done for CT unenhanced density at CT scanning [8, 9].

Despite a detrimental effect on the specificity, it is probably safe to recommend actually the use the lowest published threshold (1.45) to exclude a malignant tumor.

Conclusions

Because of its excellent negative predictive value, 18F-FDG-PET may be of help in avoiding unnecessary surgery in patients with nonsecreting equivocal tumors at CT scanning and low 18F-FGD uptake. Alternatively, 18F-FGD PET may favor surgical removal with no delay in tumors with elevated uptake and no biological evidence of pheochromocytoma. The pathological signification of ACAs that display an uptake equivalent to that of ACCs remains to be understood. Long-term follow-up of patients with these tumors may be useful to determine an unexpected rate of recurrence.

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