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Preoperative 18F-FDG Uptake is Strongly Correlated with Malignancy, Weiss Score, and Molecular Markers of Aggressiveness in Adrenal Cortical Tumors

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Abstract

Background Adrenal incidentaloma are frequent in the general population. It can be difficult to diagnose adrenocortical carcinomas among them, even with the progress of imaging techniques. We studied the results of PET-FDG in the diagnosis of such tumours.

Methods We studied patients referred to the Department of Endocrine Surgery at La Timone Hospital, Marseilles, France, between June 2006 and October 2010 for adrenal tumours. All patients underwent a complete work-up (biological tests and imagery), completed with PET-FDG. We compared the results of PET-FDG and molecular analysis with Weiss score and clinical follow-up. We calculated correlations with the Pearson test.

Results A total of 51 patients were studied. We found that PET-FDG had a sensitivity of 95% and specificity of 97% for the diagnosis of adrenocortical carcinoma. The correlation between PET-FDG and Weiss score was 77% ($P \leq 0.0001$). Molecular analyses were correlated as well with Weiss score and malignancy ($P < 0.05$).

Conclusions The nature of atypical adrenal masses can be difficult to define during preoperative investigations. For undetermined tumours smaller than 6 cm, characterization with PET-FDG can be one more diagnostic argument pointing to malignancy. It could potentially change the therapeutic strategy and surgical management. In our experience, molecular analyses are available after surgery and have less impact on the therapeutic strategy than PET-FDG. Preoperative PET-FDG can be an asset in the management of adrenal incidentaloma and adrenocortical carcinoma.

Introduction

Adrenal incidentaloma are frequent in the general population [1–3]. In contrast, with a prevalence of one to two per million populations, adrenocortical carcinomas (ACC), however, are uncommon but have a very poor prognosis [4].

To improve the management of adrenal tumours, several diagnostic tools can be used.

Pheochromocytoma can be excluded with meta- and nor-metanephrine assays. For cortical tumours, a computed tomography (CT) scan is mandatory in the imaging work-up in order to characterize them. It is an efficient investigative tool for the diagnosis of adrenal adenomas (AA). Magnetic resonance imaging (MRI), with shift of phase sequence can also diagnose AA accurately [3, 5, 6]. The most frequent malignant tumours are metastases. In most cases they are suspected on the basis of a patient's history. Lymphoma and sarcoma can be identified by their specific morphologic and biological characteristics.

Adrenocortical carcinomas can be diagnosed fortuitously or after an abdominal exploration if symptomatic

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(functional tumours, mass syndrome). The definitive diagnosis is supported by histopathological examination, clinical follow-up and molecular analysis. After the initial work-up (biological assessment, CT scan more or less completed with MRI), some cortical adrenal tumours remain indeterminate. Positron emission tomography-fluorodeoxy-D-glucose (PET-FDG) is an investigative tool that gives information on the metabolism of tumours. It is used in lung cancer to characterize the initial lesion and perform the extension work-up [7–9].

The goal of the present study was to assess the accuracy of PET-FDG for ACC diagnosis. We compared the results of this preoperative examination with Weiss score and clinical follow-up.

Materials and methods

We reviewed retrospectively patients referred to the Department of Endocrine Surgery of the University Hospital La Timone, for surgical management of adrenal tumours between June 2006 and October 2010. All patients underwent a complete work-up for an adrenal tumour and were initially treated in the Department of Endocrine Surgery either because the tumour was suspicious or because it was functional.

The initial work-up consisted of a complete hormonal assessment as recommended by the European network for the study of adrenal tumours. Glucocorticoid excess was explored with assays of basal cortisol (serum sample), basal ACTH (plasma sample), and excretion of free urinary cortisol (24 h urine sample). Sexual steroids and steroid precursors (DHEA-S, 17-OH-progesterone, androstenedione, testosterone, 17β-estradiol), as well as mineralocorticoid, were tested (kalemia, aldosterone/renin ratio). Meta- and nor-metanephrine were tested in order to exclude pheochromocytoma.

The imaging work-up consisted of a CT scan exploring the characteristics of the primary tumour: size, homogeneity, attenuation value less than or greater than ten Hounsfield units, enhancement, and washout when possible. Local invasion, lymph node involvement, and distant metastases were studied as well. When needed, the imaging investigations were completed with MRI.

All patients underwent a PET-FDG study. Patients fasted for at least 6 h before the tracer injection (4 MBq/kg), and scanning began at 60 min post-injection. Three-dimensional images were acquired from the skull base to the upper thigh in a GE Discovery ST PET/CT hybrid scanner (General Electric Medical System). Computed tomography was performed first, from the head to the upper thigh, with 140 kV, 80 mA, and a 5 mm section thickness, which matched the PET section thickness. Immediately

after CT, a PET emission scan was obtained that covered the identical transverse field of view. Acquisition time was 3 min per table position. PET image data sets were reconstructed iteratively (OSEM algorithm), with CT data used for attenuation correction. Co-registered images were displayed on a workstation (Xeleris; GE Healthcare), with 3D representation and axial, coronal, and sagittal slices. All PET/CT scan interpretations were performed independently by two experienced nuclear medicine physicians. The physicians were blinded to the reports of other imaging studies, including nuclear and conventional morphologic imaging. Adrenal tumour uptake was evaluated by visual analysis and by quantitative analysis with tumour SUV_{max} and a ratio of SUV_{max} tumor on SUV_{max} liver [10]. A ratio ≥ 1.7 was considered as probably malignant and <1.7 as probably benign.

After operation, a histopathological examination was performed by an expert. Weiss score was given for all patients [11]. Malignancy was confirmed on the basis of both clinical and imaging follow-up and Weiss score. Tumours were considered benign when Weiss score was equal to or less than 2 and they were suspected of being an ACC if Weiss score was greater than or equal to three. During our study no tumour classified as an adenoma proved to be malignant.

Molecular analyses were performed, with the following results: Loss of heterozygosity (LOH) 17p13 loci 1 and 3 of tumour-suppressor-gene TP53, and overexpression of IGF-2 ARNm above 50 copies were tested. These results have been described as predictive of ACC [12, 13].

Statistical tests

All statistical analyses were performed with Statistica 7.1 for Windows (StatSoft Inc., Tulsa, OK). Correlations were assessed with a Pearson test and independence of the diagnostic test was assessed with a chi-squared test.

Results

Fifty-one patients underwent surgery for a functional and/or suspicious adrenal mass between June 2006 and October 2010. The mean age of those patients was 54 years (range: 27–80 years). Mean size of the tumours was 63.7 mm (range: 15–210 mm). Twenty-one of the tumours were functional; 30 non-functional.

For 22 patients we concluded that the tumour was an ACC, on the basis of a Weiss score $\geq$ 3. The median Weiss value was 6 (range: 3–9). Twenty-nine tumours were considered benign on the basis of pathological exam and follow-up. The median Weiss value was 0 (range: 0–2). In the chi squared analysis, both PET-FDG and molecular

Table 1 Chi squared test showing that the independence hypothesis between the tests is rejected

	PET-FDG	IGF-2	LOH 17p13	Weiss score $\geq$ 3
PET-FDG		$P < 0.0001$	$P = 0.002$	$P < 0.0001$
IGF-2	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$
LOH 17p13	$P = 0.002$	$P < 0.0001$		$P = 0.009$
Weiss score $\geq$ 3	$P < 0.0001$	$P < 0.0001$	$P = 0.009$	

All the tests are correlated with each other

PET-FDG positron emission tomography-fluorodeoxyglucose scan; *LOH* loss of heterozygosity

analysis were found to be linked with Weiss score (Table 1).

PET-FDG

For 21 patients out of 22 with a final diagnosis of ACC, the SUV ratio was $\geq$1.7. The mean value of the ratio was 3.7 (range: 1.7–10.2). The adrenal SUV_{max} mean value was 7.3 mg/ml (range: 4–21.8 mg/ml).

One patient had a 38 mm tumor, with suspicious indications on CT scan. The Weiss score was 5, and the PET ratio was 1.3 (the adrenal SUV_{max} was 4.7 mg/ml). Overexpression of IGF-2 ARNm was found, but there was no indication of LOH in 17p13. After a follow-up of 15 months, this male patient did not experience relapse.

For the 29 patients with a final diagnosis of a benign pathology, 28 had a PET ratio lower than 1.7 (mean: 0.9; range: 0–1.6). One patient had a non-functional adrenal lesion measuring 38 mm that was associated with a suspicious presentation on CT. The preoperative PET ratio was 2 (adrenal SUV_{max} 6.4 mg/ml). But the final pathological examination as well as the molecular analysis concluded that the lesion was an adenoma. (Weiss score 0; no molecular mutation). Overall, in our study PET-FDG had a sensitivity of 95% (21/22) and specificity of 97% (28/29) to diagnose ACC (Table 2).

Finally we studied the correlation between the different tests. That analysis shows that there is a correlation of 77% ($P < 0.0001$) between the preoperative PET-FDG ratio, with a cut-off ratio of 1.7. In addition, the results of the definitive pathological examination are concordant with clinical follow-up (Table 3).

Table 3 Correlation factor (Pearson test, $P < 0.05$)

	PET-FDG (%)	IGF-2 (%)	LOH 17p13 (%)	Weiss score $\geq$ 3 (%)
PET-FDG				
IGF-2	32			
LOH 17p13	27	50		
Weiss score $\geq$ 3	77	34	18	
Malignancy	77	34	18	100

The results, expressed as percentages, show the strength of the correlation between the different tests

Molecular analysis

Of the 51 patients in the present study, results of the molecular analysis were available for 38. In the group of ACC ($n = 22$), such results were available for 18 patients. Twelve of the 18 had overexpression of IGF-2 ARNm. Among these 12, 10 also had a LOH of 17p13. Finally six patients, one third of the group, did not have any molecular mutations on the tests performed.

For the group of patients with AA ($n = 29$), molecular results were available for 20 patients. Four patients had molecular mutations; one patient had a mutation of IGF-2, two had a LOH 17p13, and one had both mutations (Table 4).

Overall, LOH 17p13 presented a sensitivity of 56% (10/18) and a specificity of 85% (17/20) in our study, whereas overexpression of IGF-2 had a sensitivity of 67% (12/18) and specificity of 90% (18/20).

Table 2 Results of PET-FDG and Weiss score

	PET > 1.7	PET < 1.7	Total
Weiss score > 3	21	1	22
Weiss score < 3	1	28	29
	22	29	51

Table 4 Characteristics of patients presenting adenomas and molecular mutations

	IGF-2	LOH 17p13	Tumor size (mm)	Weiss score	Ratio PET-FDG
1	+	−	43	0	0.9
2	−	+	32	0	1.2
3	−	+	34	2	1.5
4	+	+	35	2	1

Discussion

Adrenal tumours are common in the general population; most are benign and discovered incidentally. Depending on the series 3–9% of the general population have an adrenal tumour [1–3].

Pheochromocytoma should be easily diagnosed with a simple hormonal work-up. Cortical tumours, however, can be a real diagnostic challenge for the physician. Most of them are AA, and among them most are not functional. About 10% of clinically unapparent adrenal masses are ACC, though the proportion is dependent on the initial size of the tumour [3]. ACC represent a therapeutic challenge for the clinician because of their associated very poor prognosis, with an overall 5 year survival less than 40% depending on the series [14–16]. The only potentially curative treatment is surgery, and an appropriate one achieving complete resection. When surgery is not possible, the prognosis gets worse, with a median survival of 12 months [17].

To improve the medical management of adrenal tumours, different imaging techniques have been developed. Computed tomography has improved and can often diagnose benign adenomas: small, homogeneous, well-defined lesions with clear margins, attenuation less than 10 HU on conventional CT scans. About 30% of adenomas, lipid poor, are not characterized with these criteria but the study of IV contrast washout improves the diagnostic efficiency of CT scans [3–6, 17]. By comparison, suspected or clearly malignant tumours are easily diagnosed on conventional imaging: size greater than 6 cm, presence of necrosis or calcifications, irregular margins, extension to nearby organs, lymph node or distant metastasis, attenuation value higher than 50 HU.

Even with these tools, indeterminate tumours persist, and further investigations are needed for the differential diagnosis. For this purpose, PET-FDG is widely used in other cancer work-ups, in particular in lung cancer investigations [7–9, 18]. It has been used for several years for the characterization of adrenal lesions [4, 6].

PET-FDG is useful for detection of metastasis or local relapse in known ACC [19, 20], but there is no consensus in the literature for either its place in the preoperative work-up when malignancy is not proven, or the interpretation the results should be given.

The present study shows that PET-FDG, using the ratio SUV_{max} adrenal gland/ SUV_{max} liver, is strongly predictive of a malignant tumour for a ratio ≥ 1.7 and of adenomas when ≤ 1.7. In other series similar results have been found [21–23], though the ratio was not the same and bias can be found.

Definitive diagnosis of ACC is usually made with clinical follow-up and histopathological examination. But the information gained from those evaluations is only available after surgery. On the other hand, PET-FDG is a preoperative investigation, with potential consequences for the management of indeterminate adrenal tumours. Instead of waiting 3–6 months to perform a CT scan or an MRI to control an indeterminate tumor, a PET-FDG exam can help the clinician chose between surgery (high ratio) or usual follow-up if the results favor of a benign tumour.

For indeterminate lesions, knowledge of malignancy, or at least strong arguments in favour of ACC, should help to achieve the best surgical result. The ultimate goal is to detect ACC at an early stage of the disease, as it is often the only way to cure the patient or at least improve the prognosis of this disease [4, 13–17]. It has been reported that ENSAT stage 1 and 2 is associated with better survival [16]. For suspicious adrenal lesions smaller than 4 cm, identification by preoperative PET-FDG could lead to removal of the suspicious mass instead of choosing a "wait and see" strategy.

There is no consensus in the literature for taking either an open approach or a laparoscopic approach in the treatment of ACC [4, 17, 24–27]. Most of the studies, however, are biased, because for large tumours suspected to be malignant, open resection is chosen by most surgeons. In contrast, for small tumours, the laparoscopic approach is usually selected. This choice of technique remains mostly for indeterminate tumours. Preoperative PET-FDG suggestive of ACC could change both the strategy and the surgical approach. For example, resection extended to nearby organs could be chosen preoperatively if malignancy is indicated, whereas when the imaging work-up, including PET-FDG, suggests a benign tumour, a more limited surgical resection could be legitimate. Ultimately the choice of surgical approach should rely strongly on the experience of the surgeon, as long as carcinologic resection is achieved. With a preoperative PET-FDG study that strongly favours a malignant lesion; the surgical strategy could be more easily changed during the procedure, switching from a laparoscopic to an open approach.

Thus, it is an asset for the surgeon to know if the tumour is likely to be malignant. This diagnosis could also help provide the patient and the surgeon with optimal information with which to plan the surgery, and, finally, complete the procedure with the best outcome.

Weiss score can be limited to determine malignancy for adrenal tumours when a basic number of criteria are met (Weiss score: 2–4). In addition, molecular analyses have been developed to improve the diagnosis of ACC and ultimately their management. In the present study we have compared the diagnostic efficiency of two mutations— overexpression of IGF-2 and LOH of 17p13. We acknowledge that our results must be considered carefully. We have a small number of patients, only a few for who results of the molecular analyses were available.

Nevertheless, from a clinical point of view, in our department those results are available only after the initial surgery, whereas PET-FDG provides information preoperatively. Because the molecular analyses are run for groups of patients, they can be done only a limited number of times a year. As a result, it may be several weeks before the findings are available. When a tumour has already been classified as benign or malignant, follow-up and further treatment, such as mitotane or chemotherapy, can be planned without delay.

Thus, in our experience, PET-FDG was more readily available and had a greater impact on the management of patients suspected of having an ACC.

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