Fluorodesoxyglucose uptake in the remaining adrenal glands during the follow-up of patients with adrenocortical carcinoma: do not consider it as malignancy

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Abstract

Objective: To make the specificity of fluorodesoxyglucose (\textsuperscript{18}FDG) positron emission tomography (PET) precise, in the follow-up of patients with adrenal cancer. Design: This single centre retrospective study assessed the frequency and outcome of \textsuperscript{18}FDG uptake in the remaining adrenal glands after adrenalectomy for adrenocortical carcinoma (ACC) or malignant phaeochromocytoma (PH). Results: Two hundred and ten \textsuperscript{18}FDG PET scans in 62 ACC patients, all under 1,ortho-1,para\textsuperscript{0}-dichloro-diphenyl-dichloro-ethane (o,p\textsuperscript{0}-DDD) treatment, and 30 \textsuperscript{18}FDG PET scans in 8 PH patients were reviewed. Abnormal \textsuperscript{18}FDG uptake in the remaining adrenal glands was found in 19 (8\%) \textsuperscript{18}FDG PET scans, in 10 (16\%) ACC patients and in none of the PH patients. \textsuperscript{18}FDG uptake was found in 4\% of the patients before the onset of o,p\textsuperscript{0}-DDD, in 29\% of the patients 0–6 months after the onset of o,p\textsuperscript{0}-DDD (\(P=0.05\)), in 26\% of the patients 6–12 months (\(P=0.072\)) after the onset of o,p\textsuperscript{0}-DDD and in 14\% of the patients 12–24 months after the onset of o,p\textsuperscript{0}-DDD. It was never found later than 24 months after the onset of o,p\textsuperscript{0}-DDD. Adrenal glands with \textsuperscript{18}FDG uptake were normal on computed tomography scans with i.v. contrast agent in all cases. \textsuperscript{18}FDG uptake in the remaining adrenal glands decreased and disappeared on subsequent FDG PET imaging in eight of the patients with follow-up available. Conclusions: \textsuperscript{18}FDG uptake in the remaining adrenal glands occurred in 14–29\% of the patients followed for ACC within 24 months after adrenalectomy and onset of o,p\textsuperscript{0}-DDD. This uptake is transient and should not be considered as suspicious for malignancy.

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Introduction

Fluorodesoxyglucose (\textsuperscript{18}FDG) positron emission tomography (PET) is now widely used in oncology. In patients with an adrenal mass, it can be useful for the preoperative prediction of malignancy (1, 2). In malignant adrenocortical carcinoma (ACC), we previously reported that it was complementary to conventional imaging, essentially for the diagnosis of local relapse (3). Finally, in malignant phaeochromocytoma (PH), it was shown to be the most sensitive scintigraphic imaging method (4). FDG PET is therefore widely used in the follow-up of patients with ACC and malignant PH.

Normal adrenal glands can disclose FDG uptake. This uptake is, however, usually not intense and lower than the uptake of the liver (5, 6).

Following a clinical case, described in the result section of this manuscript, of a patient who underwent adrenalectomy of the remaining left adrenal glands based on the occurrence of FDG uptake 2 months after right adrenalectomy for an ACC and onset of 1,ortho-1, para\textsuperscript{0}-dichloro-diphenyl-dichloro-ethane (o,p\textsuperscript{0}-DDD) treatment, we decided to retrospectively review all FDG PET/computed tomography (CT) imaging performed in our centre in the follow-up of patients with ACC or malignant PH. The aims of the study are to describe the incidence and outcome of FDG uptake of the remaining adrenal glands.

Patients and methods

Patients

Approval from our Institutional Review Board was obtained for the study. Files of all patients between November 2003 and April 2009 were reviewed. Inclusion criteria were as follows: i) patients with...
a confirmed pathological diagnosis of malignant ACC (defined with a Weiss score of 3 or more) or a diagnosis of malignant PH (defined by the presence of loco-regional unresectable disease or distant metastasis) and ii) at least one postoperative FDG PET/CT imaging.

The following parameters were recorded in all patients: age, gender, Weiss score (7), secretory status, ENSAT stage for ACC patients (8), o,p'-DDD plasma level for ACC patients and succinate dehydrogenase (SDH) gene status for malignant PH patients. At initial diagnosis, clinically functioning tumours were confirmed by appropriate hormonal tests including plasma and/or urinary excretion of cortisol, plasma testosterone and/or androstenedione and/or DHEA sulphate in ACC patients and chromogranin A and urinary metanephrines and normetanephrines in PH patients (9).

**Imaging techniques**

**FDG PET/CT** Imaging and data acquisitions were performed on an integrated PET/CT Biograph LSO system (Siemens Medical Solutions, Erlangen, Germany). PET/CT scanning was performed after an i.v. injection of 4–5 MBq/kg $^{18}$FDG, followed by a 55–80 min uptake phase. All patients had fasted for 6 h at least. During the image acquisition, patients maintained their arms above their head, and no specific breathing instructions were given. The PET elements of the system are based on a full-ring tomography (Biograph, Siemens Medical Solutions). Emission data were acquired for 4 min at each bed position from the top of the head to the midthigh. Three-dimensional mode was used for PET image acquisition. PET data were reconstructed on a 128×128 matrix using an iterative algorithm (FORE and AWOSEM) with two iterations, eight subsets and a 5 mm FWHM Gaussian postfilter. Reconstruction data were acquired with a single slice spiral CT (Somatom Emotion, Siemens Medical Solutions) without i.v. contrast agent. CT parameters were set to 80 mA and 110 kV, slice thickness of 5 mm and pitch 1.5. CT data were reconstructed using filtered back projection with a smooth filter on a 512×512 matrix. Maximum standardized uptake value (SUV$_{\text{max}}$) was automatically extracted using e.Soft tools (Siemens Medical Solutions) dedicated to image analyses.

To determine adrenal single pixel SUV$_{\text{max}}$, a region of interest encompassing the entire adrenal with FDG uptake without encompassing adjacent organs was drawn on the PET/CT-fused images.

To determine mean liver SUV, a 2 cm round region of interest distant from liver vessels was drawn on normal liver on three adjacent axial PET slices. The mean value of the three slices was taken into account. The ratio of adrenal FDG uptake to liver FDG uptake was obtained by dividing adrenal SUV$_{\text{max}}$ by liver mean SUV. Area of brown fat FDG uptake was cautiously looked for in the whole body scan.

**Image analysis**

FDG PET/CT examinations were reviewed by an independent senior nuclear medicine specialist (D D), unaware of patients’ clinical or biological findings. Discrepancies with the routine FDG PET/CT reports were resolved by consensus reviewing with a second nuclear medicine physician (S L). Any adrenal uptake detected on the examination with a SUV$_{\text{max}}$ above mean SUV of the liver (ratio of adrenal SUV$_{\text{max}}$/liver SUV$_{\text{mean}}$ above 1.0) was considered abnormal. In cases of abnormal adrenal uptake, adrenals were morphologically

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**Figure 1** A remaining adrenal gland with FDG uptake on the FDG PET/CT-fused images (A); normal on CT scan (B) and on pathology (C).
characterized by a CT scan with i.v. injection of iodinated contrast material performed within a month of FDG PET/CT by a specialist radiologist (F B), and the width perpendicular to the long axis of the body of the gland was measured at mid length of the largest limb.

**Statistical analysis**

The frequency of FDG uptake of the remaining adrenal glands occurring before the start of o,p'-DDD and 0–6 months or 6–12 months or 12–24 months or more than 24 months after the start of o,p'-DDD was compared using the Fisher’s exact test. The significance level was 0.05.

**Results**

**Clinical case**

A 43-year-old woman was referred to our institution for follow-up after bilateral adrenalectomy for a malignant ACC. She disclosed left adrenal FDG uptake 2 months after right adrenalectomy and onset of adjuvant o,p'-DDD treatment for a 8.5 cm secreting right ACC with a Weiss score of 8. The SUV\textsubscript{max} was equal to 4.8 with an adrenal SUV\textsubscript{max}/liver SUV\textsubscript{mean} ratio of 2 (Fig. 1A). Preoperative FDG PET scan had not shown any FDG uptake in the left adrenal, and the CT of the left adrenal was normal (Fig. 1B). Because of the left adrenal uptake, she underwent a left adrenalectomy with pathological report showing a normal left adrenal gland (Fig. 1C).

**Patients**

Seventy-nine patients with adrenal cancer were seen at our institution between 2003 and 2008 including 70 ACC patients and 9 malignant PH.

Among the ACC patients, eight patients were excluded because of the absence of available FDG PET/CT scans. Sixty-two patients (35 females and 27 males; mean age at ACC diagnosis: 51 years, range: 23–75) were included, and form the basis of this study. Patients were classified at initial diagnosis as stage I in 2 cases, stage II in 32 cases, stage III in 7 cases, stage IV in 19 cases and unknown stage in 2 cases (unknown size of ACC and no distant metastases). Functioning tumours were identified in 33 patients (53%), among whom 16 patients disclosed mixed hormone productions. o,p'-DDD was given in all patients under study either as an adjuvant therapy because of a high risk of recurrence or as first-line chemotherapy in patients with unresectable disease. The median interval of time between adrenalectomy and the start of o,p'-DDD was 1.4 months (range: −0.6 to 131; mean 8.0).

Among patients with malignant PH, one was excluded because of the absence of available FDG PET/CT scan. Eight patients (three females and five males; median age
FDG PET/CT scans

Two hundred and ten FDG PET/CT scans performed on 62 patients with ACC were reviewed, with a median number of FDG PET/CT scan per patient of 3 (range 1–11). A consensus reviewing of PET/CT scans was necessary because of liver FDG uptake adjacent to the remaining adrenal glands in one case and because of low FDG uptake of the remaining adrenal glands less intense than mean SUV of the liver in two cases. After consensus reviewing, these three cases were considered as normal.

Ten patients (16%) disclosed an abnormal adrenal uptake with a $S_{\text{U}}V_{\text{max}}$ above mean $S_{\text{U}}V_{\text{of}}$ the liver on at least one scan (Table 1). Adrenal uptake with a $S_{\text{U}}V_{\text{max}}$ above mean $S_{\text{U}}V_{\text{of}}$ the liver was recorded on 19 (9%) FDG PET/CT scans. Mean adrenal $S_{\text{U}}V_{\text{max}}$ was 3.7 (range: 1.4–6.5; median: 3.5). Characteristics of adrenal uptake including $S_{\text{U}}V_{\text{max}}$, adrenal to liver $S_{\text{U}}V$ ratio, interval of time between first occurrence of FDG adrenal uptake and start of 0.0-0DDD treatment and results of plasma 0.0-0DDD level at the time of FDG PET/CT scans are reported in Table 1. CT scan with i.v. injection of iodinated contrast material performed 0–49 days (median 7 days) after the FDG PET/CT scan showed that adrenal glands with FDG uptake were morphologically normal in all cases with a median size of 9 mm (range: 5–12).

Outcome of FDG adrenal uptake with an $S_{\text{U}}V_{\text{max}}$ above mean $S_{\text{U}}V_{\text{of}}$ the liver is shown in Fig. 2. $S_{\text{U}}V_{\text{max}}$ decreased with time and FDG uptake disappeared in all patients within 24 months except two in whom follow-up was not available. Furthermore, in five patients, the normalization of FDG PET/CT scan was confirmed by at least one other FDG PET/CT scan performed 5–47 months after the first abnormal FDG PET/CT scan.

Percentage of FDG PET/CT scans and of patients with adrenal uptake according to the interval of time between surgery and FDG PET/CT scanning and according to the interval of time between the start of 0.0-0DDD and FDG PET/CT scans is reported in Table 2A and B. Briefly, only one patient (4%) demonstrated an adrenal uptake before 0.0-0DDD treatment onset, whereas 29% of the patients demonstrated adrenal uptake 0–6 months after the onset of 0.0-0DDD treatment. 26% of the patients 6–12 months after the start of 0.0-0DDD and 14% of the patients 12–24 months after the onset of 0.0-0DDD. None disclosed FDG uptake after 24 months.

The frequency (4%) of abnormal FDG uptake of the remaining adrenal glands occurring before the start of 0.0-0DDD was statistically different from the frequency (29%) of FDG uptake of the adrenal glands occurring 0–6 months after the start of 0.0-0DDD ($P=0.048$). Furthermore, there was a trend towards a difference between FDG uptake before the start of 0.0-0DDD and FDG uptake 6–12 months after the start of 0.0-0DDD ($P=0.072$).

Thirty FDG PET/CT scans performed among the eight patients with malignant PH were reviewed, with a median number of FDG PET/CT scan per patient of 4 (range 1–9). None of the FDG PET/CT scans disclosed abnormal adrenal uptake. FDG PET/CT scans were performed 0–6 months after adrenalectomy in two cases, 6–12 months after adrenalectomy in six cases,

<table>
<thead>
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<th>Table 2</th>
<th>Incidence of adrenal FDG uptake in patients with ACC according to the interval of time between surgery and FDG PET/CT scans (A) or according to the interval of time between the start of 0.0-0DDD treatment and FDG PET/CT scans (B).</th>
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<tr>
<td><strong>A Surgery</strong></td>
<td><strong>Before treatment</strong></td>
</tr>
<tr>
<td>No. with adrenal uptake/total no. of patients</td>
<td>0/1</td>
</tr>
<tr>
<td>No. with FDG PET/CT scans/total no. of patients</td>
<td>0/1</td>
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<td><strong>B 0.0-0DDD</strong></td>
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<tr>
<td>No. with adrenal uptake/total no. of patients</td>
<td>1/24 (4%)</td>
</tr>
<tr>
<td>No. with FDG PET/CT scans/total no. of patients</td>
<td>1/24 (4%)</td>
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12–24 months after adrenalectomy in ten cases, 24–36 months after adrenalectomy in six cases, 36–48 months after adrenalectomy in two cases and more than 48 months after adrenalectomy in four cases.

Discussion

Our study demonstrates for the first time that FDG uptake in the remaining adrenal glands can be found in 14–29% of ACC patients following adrenalectomy and the onset of o,p′-DDD treatment. This FDG uptake is transient: it disappears within 24 months. Furthermore, it is not accompanied by abnormal morphological characteristics on the CT scan. This uptake should therefore be considered as a non tumour-related event.

Normal adrenal glands can disclose FDG uptake, but the level of this uptake is usually low. One study reported a mean SUVmax of normal adrenal glands of 1.7 ± 0.49 (6). A second study reported SUVmax ranging from 0.95 to 2.46 (5). In fact, FDG uptake of adrenal glands with SUVmax under the mean SUV of the liver is considered as non-relevant (5). We used this criterion in our study and only considered adrenal uptake with SUVmax above the mean SUV of the liver as abnormal. Taking this criterion, the SUVmax of patients with abnormal adrenal uptake was higher than 2.46 in all cases except one, demonstrating that the intensity of FDG uptake reported in our study is clearly above the threshold considered as normal for adrenal uptake.

The mechanism of the increased FDG uptake of the remaining adrenal glands remains unknown. Different hypothesis can be raised. First, a compensatory adrenal growth and hypertrophy of the remaining adrenal glands have been shown to occur shortly after adrenalectomy in rats, but to our knowledge, there is no such data in humans (10, 11). In our study, the remaining adrenal glands of the ten ACC patients with FDG uptake all presented normal size on the CT scan (12). Furthermore, we did not observe FDG uptake in any patient who had undergone adrenalectomy for malignant PH, which does not favour the hypothesis of a compensatory adrenal growth linked to adrenalectomy only. It can only be pointed out that an increase in 111I-6β-iodomethyl-19-norcholesterol uptake of the remaining adrenal glands has been previously reported in patients after unilateral adrenalectomy (13). However, in this study, the remaining adrenal glands were nodular in most cases.

Secondly, brown fat FDG uptake in the adrenal region can mimic adrenal uptake and was previously described (14, 15). However, review of the FDG PET/CT scans was not hampered by brown fat. Furthermore, there is no reason for the brown fat artefacts to mainly occur within the first 24 months after adrenalectomy and/or the start of o,p′-DDD.

Thirdly, the hypothesis of contralateral metastases of ACC in the remaining adrenal glands is unlikely. In our study, the remaining adrenal glands with FDG uptake were not nodular and disclosed a normal size, and FDG uptake decreased until it disappeared. Furthermore, bilateral ACC is rarely reported in clinical studies with an incidence of 1.1% among the national American cohort of 3982 ACC patients reported by Bilimoria et al. (9, 16–20).

The final hypothesis concerns an involvement of o,p′-DDD treatment upon FDG uptake of the remaining adrenal glands. The absence of FDG uptake in the PH group is in favour of this last hypothesis. o,p′-DDD therapy plays a dual role in ACC. It is a cytotoxic drug with a delayed action and also an inhibitor of steroid secretion (21). This last effect is the basis for its use for Cushing’s syndrome due to ectopic ACTH secretion (22). Hormonal adrenal replacement therapy is given to patients treated with o,p′-DDD in order to prevent adrenal insufficiency. It is associated in ACC patients with various ACTH levels, which is known to stimulate both adrenal steroidogenesis and adrenal growth (23, 24). The increase in FDG uptake might therefore be linked to a trophic role of ACTH on the remaining glands. Clinical case reports of ectopic Cushing’s syndrome showing bilateral abnormal FDG uptake with SUVmax ranging from 5.9 to 8 with hypertrophic adrenal glands are in favour of this hypothesis (25, 26). The transient characteristics of the FDG uptake in ACC patients under o,p′-DDD treatment might be due to the delayed cytotoxicity of the drug.

In the end, it can be pointed out that a link has been recently identified between mitochondria and GLUT 3 receptor expression in inherited PHs (27) and that o,p′-DDD has been demonstrated to target mitochondrial proteins (28). To our knowledge, no data are available in the literature regarding the effect of o,p′-DDD on glucose metabolism or on GLUT receptors.

In conclusion, we observed FDG uptake in the remaining adrenal glands in 14–29% of the patients followed up for ACC within 24 months of adrenalectomy and onset of o,p′-DDD treatment. This uptake is transient and should not be considered as suspicious of malignancy. o,p′-DDD treatment might be responsible for this metabolic activation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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