

# High $^{18}\text{F}$ -FDG uptake by the remaining adrenal gland four months after surgery and initiation of mitotane treatment in two patients with adrenocortical carcinoma

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## Abstract

Two men, one 42 and the other 35 years old were both subjected to adrenalectomy for adrenocortical carcinoma (ACC). Adjuvant treatment with mitotane [o,p'-dichloro-diphenyl-dichloroethane, (o,p'-DDD)], was initiated following surgery. Mitotane is the only agent available at present for treatment in ACC because of a late-onset specific adrenocortical cell toxicity. Both patients underwent a  $^{18}\text{F}$ -FDG-PET/CT scan, which revealed 4 months after starting treatment with mitotane significantly high  $^{18}\text{F}$ -FDG uptake in the contralateral adrenal gland. Both patients underwent magnetic resonance imaging, while one had a laparotomy, because of an abscess at the site of previous adrenalectomy. No metastasis or size increase of the remaining adrenal glands were found suggesting that their hypermetabolic state could be attributed to mitotane treatment. Beside its cytotoxic delayed-effect, mitotane has an early -onset effect on steroid metabolism. *In conclusion*, an abnormal high  $^{18}\text{F}$ -FDG uptake was observed in the contralateral adrenal gland in both our adrenalectomized ACC patients, 4 months after starting mitotane treatment, probably related to mitotane's effect on steroid metabolism, not yet fully understood.

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## Introduction

Although adrenal adenomas are relatively common benign tumors with an 8% incidence at autopsy [1] adrenocortical carcinoma (ACC) is a rare malignancy with a yearly incidence of 1-2 new cases per million and a generally poor prognosis [2-4]. About 60% [3] of ACC cases are functional tumors, leading to hypercortisolism and/or virilisation secondary to tumoral hormonal secretion [2-4]. Non functioning ACC, are usually diagnosed during evaluation for abdominal pain or by incidental detection of an adrenal mass [5].

Hormonal work-up is always mandatory in the presence of an adrenal lesion [3] to exclude pheochromocytoma and for post-surgical follow up [6, 7]. Computed tomography (CT) and magnetic resonance imaging (MRI) constitute the main diagnostic imaging procedures in evaluating adrenal tumors, as biopsy has limited diagnostic value in differentiating adrenal lesions. The pathological diagnosis may be difficult even for an expert pathologist, due to the lack of clear-cut morphologic cell characteristics for benign and malignant adrenocortical lesions [3]. Tumor weight more than 100gr with tumor size larger than 6cm, hemorrhage and breached capsule are the most important diagnostic markers for malignancy [6, 7].

Chemical-shift MRI [8, 9], Hounsfield unit measurements and analysis of contrast medium wash-out on CT [10-12] can demonstrate the nature of an adrenal lesion. Contrast medium CT shows most ACC to be inhomogeneous, with irregular enhancement of solid components and delayed wash-out. In case of ambiguity, fluorine-18-fluoro deoxyglucose-positron emission tomography ( $^{18}\text{F}$ -FDG-PET) imaging identifies adenomas as having normal metabolic activity and/or the intensity of uptake of the tracer is equal or less than that in the liver, while pheochromocytomas and metastases show increased  $^{18}\text{F}$ -FDG uptake [13-16]. Others suggest that  $^{18}\text{F}$ -FDG-PET should be included in the work-up for initial staging and follow-up of ACC [3, 17-20].

We present two cases of surgically treated patients with ACC who had a  $^{18}\text{F}$ -FDG-PET/CT test at 4 months after starting mitotane [o,p'-dichloro-diphenyl-dichloroethane (o,p'-DDD)] treatment, which revealed a consistently high  $^{18}\text{F}$ -FDG uptake by the contralateral adrenal glands. Mitotane is the only adrenal specific agent available at present for the treatment in ACC [21-25]. The reason for this increased uptake is discussed.

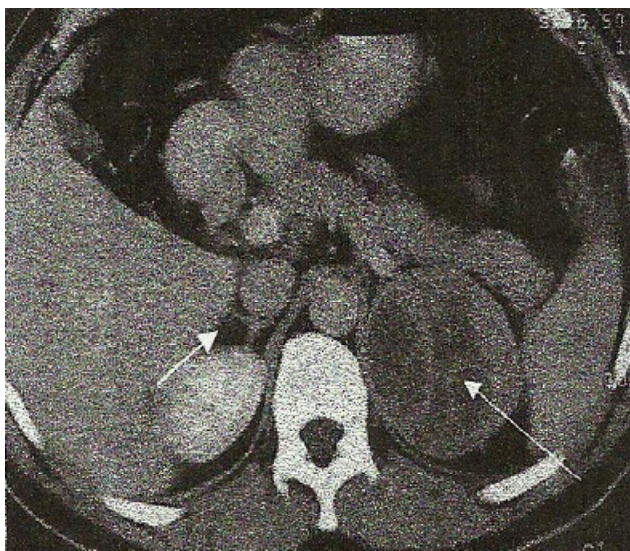
## Image acquisition and processing of PET/CT

The patients were imaged on an integrated PET/CT Siemens Biograph 6 system, USA. After an overnight fast, both patients were injected with ~370MBq  $^{18}\text{F}$ -FDG, adjusted to body weight, followed by a 60min uptake phase. Capillary glycemia was checked prior to the  $^{18}\text{F}$ -FDG ad-

ministration. First a low dose spiral CT was performed to be used for attenuation correction of the PET images. Parameters of CT were set to 30mA, 130kV, slice thickness of 5mm, and pitch 1.5. The PET emission scan was obtained immediately after the CT acquisition, without changing the patient's position. Emission data were acquired for 4min at each bed position from head to midhigh. Images were reconstructed using an iterative technique (4 iterations, 8 subjects) on a 164x164 matrix, applying a 5mm Gaussian postfilter. Maximum standardized uptake value (SUVmax) was automatically extracted using e.soft tools (Siemens Medical Solutions, USA) dedicated to image analyses. In particular, all images were corrected for body weight, dose and radioactive decay and displayed on a software tool provided by the manufacturer.

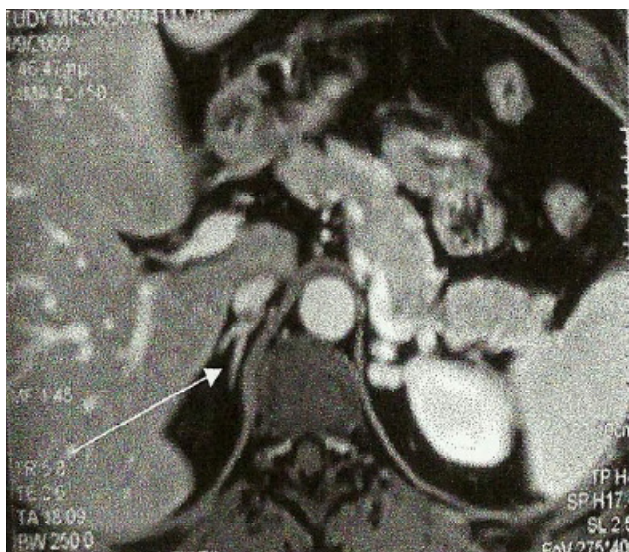
### Case 1

A 42 years old man presented with a two months history of hypertension accompanied by headaches and "flushing" episodes. His blood pressure was 170/100mmHg and the remaining clinical examination was unremarkable; he had no palpitations or diaphoresis. Abdominal ultrasonography revealed a 7.5x5.7cm left adrenal lesion with multilobular margins and areas of cystic degeneration. Endocrine investigation by 24h urinary catecholamine and free-cortisol excretion, serum basal-cortisol, DHEA-S, 17-OH-progesterone, 17 $\beta$ -oestradiol, adrostenedione, testosterone and potassium showed no evidence of excessive catecholamine secretion. A subsequent CT scan of the abdomen revealed an inhomogeneous 7.5x6cm left adrenal lesion, which showed mild contrast enhancement, multiple cystic areas and necrosis. There were no abnormal lymph nodes (Fig. 1).

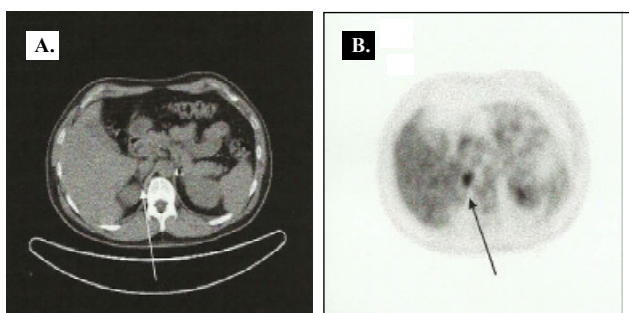


**Figure 1.** A pre-operative CT scan demonstrating a mass in the left adrenal gland (arrow) and physiologic right adrenal gland (small arrow).

The patient underwent an uneventful laparoscopic left adrenalectomy and histology was indicative of stage II [T2 (localized tumor >5cm), No, Mo] ACC. Adjuvant treatment with mitotane was administered as to achieve and maintain its levels by blood tests, within the accepted therapeutic range (14-20mg/L). Four months after mitotane treatment we started an abdominal MRI showed no pathological findings (Fig. 2) and a  $^{18}\text{F}$ -FDG-PET scan showed significantly high uptake of  $^{18}\text{F}$ -FDG (SUV=6.9) at the right adrenal gland (Fig. 3). Another MRI three months later was normal.



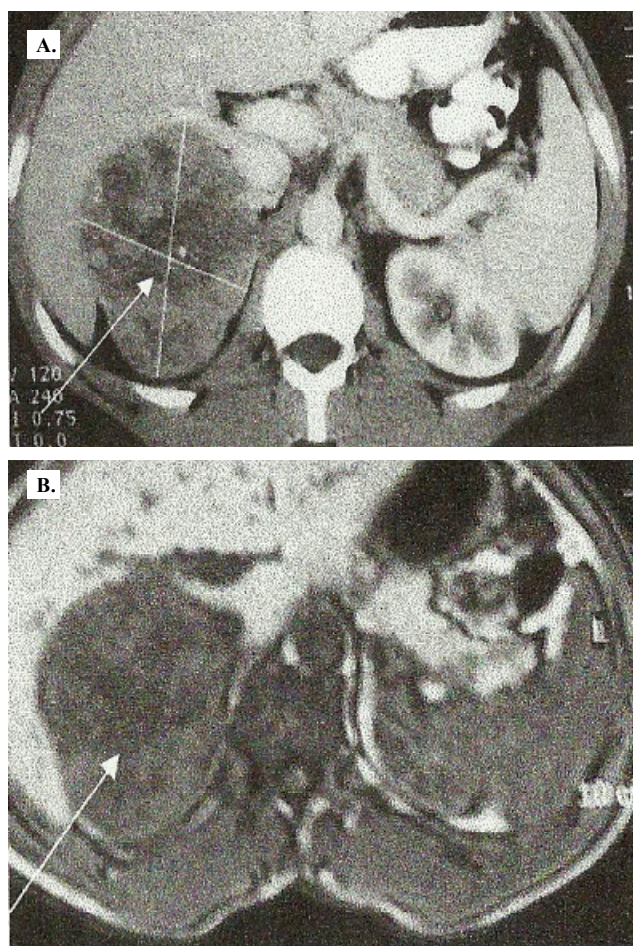
**Figure 2.** A follow-up MRI scan, 3 months after surgery, demonstrating post-surgical changes with no evidence of abnormal tissue and physiologic right adrenal gland (arrow).



**Figure 3.** Follow-up  $^{18}\text{F}$ -FDG-PET/CT scan 4 months after surgery. CT (A) and PET (B) images demonstrating significantly increased tracer uptake in the right adrenal gland (arrows)

### Case 2

The second patient was a 35 years old man with a history of dyslipidemia. Abdominal ultrasonography revealed a solid lesion with calcifications and peripheral vascularity in contact with the upper pole of the right kidney. Abdominal CT and MR imaging revealed a 10x8x8cm lesion with cystic and hemorrhagic elements and inhomogeneous contrast enhancement, of the right adrenal gland (Fig. 4). The patient was asymptomatic. Physical examination and endocrine investigation by 24h urinary catecholamine and free-cortisol excretion, serum basal-cortisol, DHEA-S, 17-OH-progesterone, 17 $\beta$ -oestradiol, adrostenedione, testosterone and potassium was normal. Resection of the right adrenal gland through an open laparotomy was performed. Histology showed a 10.5cm ACC. Adjuvant treatment with mitotane was administered immediately after surgery and the patient was followed-up with frequent o,p'-DDD level measurements aiming at a therapeutic target of 14-20mg/L. Four months after surgery the patient underwent a MRI scan that revealed an abscess at the site of surgery, which was resected together with the right hepatic lobe, the gallbladder and the right kidney (Fig. 5). A subsequent  $^{18}\text{F}$ -FDG-PET scan revealed increased uptake of the left adrenal gland with SUVmax=6.8 (Fig. 6). Another MRI, two months later, confirmed the absence of disease at the surgery area and a normal in size and image density left adrenal gland.

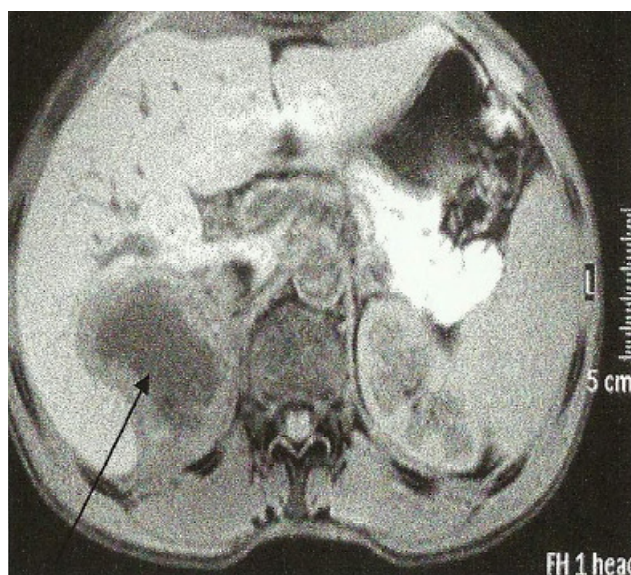


**Figure 4.** Pre-operative CT (A) and MRI (B) scan demonstrating a mass in the right adrenal gland (arrows).

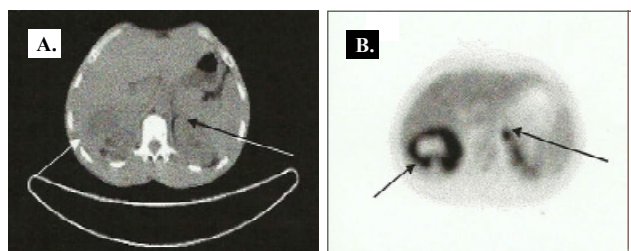
### Discussion

CT and MRI are both useful in assessing local tumor extension in ACC. MR imaging is particularly useful for detecting vascular invasion [9]. Accurate preoperative evaluation maximizes the opportunity for the patient to undergo a complete margin-negative resection, which is the most powerful prognostic variable for long term survival [26]. Although laparoscopic adrenalectomy should not be regarded as the standard of care, radical ACC resections have been successfully performed even laparoscopically [27]. Because surgical removal is a valid therapeutic option, not only for primary ACC malignancy, but also for local relapse or metastases, CT and MRI are mandatory every 3 months for the first 2 years [3]. Furthermore, it has been shown that <sup>18</sup>F-FDG-PET is able to detect local recurrent disease, even when CT was inconclusive [18-20]. Fluorine-18-FDG-PET is less reliable for diagnosing metastatic disease because occasional small metastatic lesions in the lung, liver or the peritoneum, may not accumulate enough tracer [20]. Therefore, imaging procedures are used complementarily during ACC follow-up.

Mitotane treatment is used in patients with adrenalectomy for ACC, because of the high recurrence rate, [21, 26] despite its frequent and serious side effects [28, 29]. Mitotane's primary effect is on steroid metabolism. Mitotane inhibits steroidogenic enzymes on adrenal cortex (mainly hydroxylases) [30, 31], induces increased hepatic production of cortisol-



**Figure 5.** Follow up MRI scan 4 months after surgery demonstrating the abscess at the resection site (arrow)



**Figure 6.** Follow-up <sup>18</sup>F-FDG-PET/CT scan 4 months after surgery. CT (A) and PET (B) images demonstrating significantly increased tracer uptake in the left adrenal gland (arrows) as well as significantly increased uptake in the periphery of the abscess in the anatomic bed of the right adrenal gland (small arrows).

binding globulin (CBG) resulting in decrease of cortisol-free hormone. It also induces markedly increased cortisol plasma turn-over, probably due to accelerated hepatic clearance [21, 26]. Consequently, because of mitotane-induced adrenal suppression, administration of replacement treatment may be necessary to prevent adrenal insufficiency, soon after the beginning of treatment [3]. Mitotane exerts its specific late-onset adrenal cell toxicity at concentrations of 14-20mg/L, usually achieved after three-six months of treatment [23]. Mitotane's acyl-chloride metabolite binds to macromolecules in adrenal cell mitochondria, leading to mitochondrial injury. When adrenal cell is no longer able to recover damage, autolysis or apoptosis occurs. Oxidative damage through production of free radicals may also contribute to the toxic effect of therapeutic doses of mitotane [21, 26].

In both our patients, there was a significantly high <sup>18</sup>F-FDG uptake by the contralateral adrenal gland. Higher SUVmax numbers correspond to greater metabolic activity [32-35]. A cut off of 2.5 or greater of SUVmax is widely suggested to differentiate between benign and malignant nodules in many kinds of tumors. Inflamed tissue may also take up <sup>18</sup>F-FDG as cancerous tissue does [35, 36].

The consistently high <sup>18</sup>F-FDG uptake in our cases, according to others [37], is not consistent with metastatic involvement or compensatory hyperplasia of the remaining adrenal gland [38-42]. After unilateral adrenalectomy, a brief and faint proliferative stimulus on adrenal cells of contralat-

eral gland may be neurally-mediated by both afferent and efferent sympathetic nerves but not by ACTH, as it would be reasonably assumed [43-45]. Indeed, while ACTH has a well-established role in adrenal cell metabolism, representing the main stimulating factor of steroidogenesis, its role in adrenocortical mitogenesis and hyperplasia is paradoxically suppressive [46, 47]. If a neurally-mediated hyperplastic response takes place, it is expected to be transient and negligible since it has not been described yet any size and/or morphology changes of the remaining adrenal gland.

Patients receiving mitotane are supported with high-dose corticosteroid treatment because of an early onset adrenal insufficiency, which is not easy to define. Maximum doses of replacement treatment, equivalent to the doubling and tripling of those used in Addison's disease are necessary to avoid the risk of severe hypocortisolism [3]. The increased metabolic clearance rate of glucocorticoids and the remarkable increment in CBG induced by mitotane, may contribute to the increased demand for steroid supplements [29]. Because of the increased CBG, measurements of plasma ACTH seem to be more reliable than serum cortisol, in monitoring steroid status of these patients and in adjusting cortisol replacement dose [29]. The treatment target is to achieve therapeutic levels of mitotane and normal range ACTH levels [48]. Modification of glucocorticoid replacement doses is also based on clinical assessment because it is difficult to diagnose adrenal insufficiency in these patients, even after using ACTH level for guidance [3, 29]. Despite high replacement treatment, patients maintain a state of relative hypocortisolism, usually documented by relatively increased ACTH levels, which remain at the high-normal range or slightly above normal range [3, 26]. Despite inhibited adrenal cortisol production, adrenal cortical cell becomes avid to  $^{18}\text{F}$ -FDG, probably due to ACTH stimulus. A limitation of our study is that we did not perform a second  $^{18}\text{F}$ -FDG PET scan after the first 4 months. A recent report demonstrated that mitotane in many cases may induce high  $^{18}\text{F}$ -FDG uptake by the adrenal glands early after the onset of treatment and which is transient [37].

*In conclusion*,  $^{18}\text{F}$ -FDG PET scanning in 2 ACC adrenalectomized patients demonstrated an increased SUVmax higher than 2.5 in the physiologic contralateral adrenal gland 4 months after initiating mitotane adjuvant treatment.

*The authors declare that they have no conflicts of interest*

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