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Characterization of adrenocortical tumors by $^{18}$F-FDG PET/CT: does steroid hormone hypersecretion status modify the uptake pattern?

Author’s Contributions and affiliations

Nunzia Cinzia Paladino$^a$, Carole Guérin$^b$, Aoife Lowery$^b$, Andrea Attard$^a$, Wassim Essamet$^c$, Eveline Slotema$^a$, Isabelle Morange$^d$, Frédéric Castinetti$^d$, Thierry Brue$^d$, Anderson Loundou$^e$, David Taïeb$^f$, Frédéric Sebag$^a$

$^a$ Department of General Endocrine and Metabolic Surgery, Conception University Hospital, Aix-Marseille University, 147, Boulevard Baille, 13005, Marseille, France;

$^b$ Department of Surgery, Graduate Entry Medical School, University of Limerick, Limerick, Ireland;

$^c$ Department of Neuropathology, La Timone University Hospital, Aix-Marseille University, 264, rue Saint Pierre, 13385, Marseille, France;

$^d$ Department of Endocrinology, Conception University Hospital, Aix-Marseille University, 147, Boulevard Baille, 13005, Marseille, France;

$^e$ Department of Research and Innovation, Support Unit for clinical research and economic evaluation, Aix-Marseille University, Marseille, France;

$^f$ Department of Nuclear Medicine, La Timone University Hospital, Aix-Marseille University, Marseille, 264, rue Saint Pierre, 13385, France;

Corresponding Author:

Nunzia Cinzia Paladino

MD, PhD

Department of General Endocrine and Metabolic Surgery, Conception Hospital, Aix-Marseille University, 147, Boulevard Baille, Marseille, France

Nunzia.paladino@ap-hm.fr
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Abstract

Background: adrenal tumor-to-liver uptake value (Tmx:Lmx) on $^{18}$F-FDG PET/CT is an accurate and reproducible PET parameter in the distinction between benign and malignant adrenal masses. The potential impact of steroid hormone secretion on $^{18}$F-FDG uptake is still debatable. The aim of this study was to evaluate this relationship.

Methods: 2010-2015: 73 patients who underwent adrenalectomy for adrenocortical tumors [49 secreting/(SA) and 24 non-secreting/(NSA)] were retrospectively included in the study. Fourteen were malignant. All patients underwent hormonal evaluation, functional and anatomical imaging, Weiss scoring and Ki 67 evaluation.

Results: malignant tumors exhibit higher SUVmax than benign tumors (median 7.75 vs 3.06 respectively, $p<0.001$) and Tmx:Lmx was 2.7 vs 1.17 for benign tumors, $p<0.001$.

Tmx:Lmx was positively correlated to Weiss score ($p<0.001$).

No significant difference was observed for Tmx:Lmx between SA and NSA overall ($p=0.851$), regardless of the subgroup of tumors analyzed. Tmx:Lmx was not correlated to tumor size ($p<0.508$) or 24h free urinary cortisol level ($p<0.522$).

Conclusions: no correlation was observed between Tmx:Lmx and hormonal status, however the correlation between ratio, malignancy and Weiss score confirm the utility of $^{18}$F-FDG PET/CT for the differentiation of
benign from malignant adrenal lesions, irrespective of the hormone secretory status of the tumor. $^{18}$F-FDG PET/CT is a useful biomarker in the diagnosis of adrenal tumors, regardless of the secretion status.

**Introduction**

The characterization of adrenal masses by imaging is a critical step to determine appropriate treatment and optimize prognosis. Adrenocortical carcinoma (ACC) is a rare and aggressive tumor for which comprehensive surgical resection presents the only curative option [1].

Radioclinical presentation of adrenocortical masses can be very variable. The evaluation of adrenal masses requires, firstly, a complete clinical evaluation in addition to relevant biochemical and hormonal investigation. The presence of a steroid hypersecretion pattern (ACTH-independent Cushing syndrome, hyperaldosteronism and/or hyperandrogenism) enables the diagnosis of an adrenocortical tumor, which when associated with multiple secretion patterns and/or rapid clinical progression is highly suspicious for malignancy. In large tumors ≥4 cm and/or those with an unenhanced density ≥10UH, adrenal washout CT and/or adrenal MRI with chemical shift play a central role in the characterization of adrenal masses [2,3]. In recent years, $^{18}$F-Flurodeoxyglucose positron emission tomography ($^{18}$F-FDG PET/CT) was found to provide additional information to anatomical imaging especially for patients with indeterminate masses on adrenal washout CT [2, 4, 5, 6, 7, 8, 9,10, 11].

A recent prospective study has shown that the use of Tmx:Lmx was a reliable parameter in the evaluation of adrenal masses [12]. The molecular mechanisms involved in glucose uptake of ACC are currently unknown. Although the use of a cutoff value for Tmx:Lmx >1.5 is of high clinical value, ACC and sarcomas may exhibit lower uptake ratio and inversely benign lesions can be hypermetabolic [4, 5, 13, 14, 15, 16 ]. A recent study from Patel et al. has evaluated the role of $^{18}$F-FDG PET/CT in the differentiation between nonfunctioning adrenal masses, aldosterone and cortisol secretion tumors. They showed that tumor uptake was higher in cortisol-secreting adrenal masses than in nonfunctioning adrenal masses and aldosterone-secreting tumors. They suggested that $^{18}$F-FDG PET/CT may be used for identifying cortisol-secreting adrenal masses and proposed to use $^{18}$F-FDG PET/CT for lateralization of secretion in cases with bilateral adrenal tumors [17]. The aim of this study was to evaluate the correlation between $^{18}$F-FDG (Tmx:Lmx) and hormonal secretion in patients with adrenocortical masses.
Materials and Methods

A cohort study was conducted in our Institution (Department of General Endocrine and Bariatric Surgery, La Conception University Hospital, Aix-Marseille University). Seventy-three patients that underwent adrenalectomy for benign and malignant adrenocortical masses [secreting (SA) and non-secreting (NSA) tumors] were retrospectively included from April 2010 to November 2015. All patients included had preoperative $^{18}$F-FDG PET/CT for further tumor characterization (in the absence of typical features of adrenocortical adenoma on standard imaging with CT or MRI).

Aldosterone-secreting adenomas (Conn adenoma) and pheochromocytomas were excluded from the analysis.

Preoperative hormonal work-up

All patients were investigated with biochemical tests (plasma ACTH-Cortisol cycle, free urinary cortisol/24h urine sample, serum dehydroepiandrosterone sulfate (DHEAS), serum 17-hydroxyprogesterone (17-HP), serum total testosterone, plasma and urinary metanephrines and normetanephrines, chromogranin A, plasma renin and aldosterone concentration) and conventional imaging (CT and/or MRI). Patients with an abnormal circadian cortisol rhythm or elevated urinary free-cortisol level or undetectable ACTH level, were evaluated by 1 mg dexamethasone and standard dexamethasone suppression tests (0.5 mg every six hours for 2 days).

$^{18}$F-FDG PET/CT protocol

$^{18}$F-FDG (4 MBq/Kg) was administered intravenously after fasting for 6 hours and acquisition of imaging data was performed at approximately 60 minutes post-injection. Blood glucose test was performed prior to scanning to confirm that all patients were normoglycemic.

Attenuation correction was obtained by transmission imaging with computed tomography. Reconstructions in the transaxial, coronal and sagittal planes were performed. A region of interest (ROI) was drawn on the primary tumor and on the VIII hepatic segment. Activity counts in the ROIs were normalized to injection doses per kilogram of patient body weight (maximum standardized uptake value: SUVmax). The SUVmax in the ROI on PET images was measured [12, 18, 19]. Tmx/Lmx was measured for all patients.
Gold standard

Histology was considered the gold standard for the diagnosis of benign and malignant tumors. For adrenocortical tumors, the distinction between benign and malignant tumors was based on the Weiss score, adrenocortical carcinoma being defined by a Weiss score $\geq 3$ [20, 21, 22, 23].

For oncocytomas, tumors were classified according to the Bisceglia scoring system. [21, 24].

In addition to pathological analysis, molecular status for LOH 17p13 status and expression of IGFII mRNA was obtained [22] and K67 was evaluated.

Statistical Analysis

Comparison of different quantitative parameters between benign and malignant masses were performed using Mann-Whitney U test. Correlation studies were evaluated with Spearman and Pearson correlation. For comparison between continuous and ordinal qualitative variables the Jonckheere-Terpstra test was used.

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM SPSS Inc. Chicago, IL, USA).

Results

Overall results

Of 73 patients included in our data analysis 18 were male and 55 were female with a mean age of 52 years (15-74 years) at the time of surgery.

Forty-nine masses were SA (67.1%) and 24 NSA (32.9%). Fifty-nine were benign (80.8%) and 14 malignant were masses (19.2%). Of the benign masses, 20 were non-secreting (27.39%) and the remaining 39 were secreting (53.42%). Of the malignant masses 4 were non-secreting (5.47%) and 10 were secreting (13.69%) [tab.1].

There was no significant difference in Tmx:Lmx between the SA and NSA (median of 1.26 for NSA (range 17.68 - 0.5) and 1.23 for SA (range 5.40 - 0.6), p=0.948, Mann-Whitney U test [Fig.1].
On subgroup analysis, the median ratio of benign non-secreting tumors (BNSA) was 1.2 (range 5 - 0.5) with no difference when compared with benign secreting tumors (BSA): median ratio 1.17 (range 2.7 - 0.6), (p=0.901).

The median ratio was 2.7 for both malignant subgroups (p=0.945): 4 malignant NSA (MNSA) (range 17.6 - 1.3) and of 10 malignant SA (MSA) (range 5.4 - 1.65).

**Determinants of $^{18}$F-FDG uptake**

There was a significant positive correlation between $Tm_x:Lm_x$ and Weiss score (correlation coefficient: 0.6; p<0.001, Jonckheere-Terpstra test) [Fig.2].

The correlation between $Tm_x$ in benign vs malignant tumors (median of 3.06 vs 7.75) and $Tm_x:Lm_x$ of this group (1.17 vs 2.7) were strongly significant (p<0.001).

There was no significant correlation between $Tm_x:Lm_x$ and tumor diameter (coefficient correlation: 0.07; p<0.508, Chi-square Pearson test); no correlation was observed between $Tm_x:Lm_x$ and free urinary cortisol/24h (coefficient correlation: 0.07; p<0.522, Spearman test) and there was no significant difference between $Tm_x$ of SA and NSA (median 3.3 for SA and 3.98 for NSA; p 0.514, Mann-Whitney test).

**Discussion**

Considering that approximately 12% of adrenal tumors cannot be adequately characterized by CT and MRI [25], $^{18}$F-FDG PET/CT may provide additional information for characterizing these indeterminate adrenal masses [26]. In the present study we failed to identify a correlation between $Tm_x:Lm_x$ and hormonal secretion. This result was observed in the subgroups of benign SA and NSA and also between malignant SA and NSA. No correlation was also observed between ratio/size, ratio/free urinary cortisol/24h urine sample and between $Tm_x$ of SA and NSA. Conversely, we found a correlation between $Tm_x:Lm_x$ and Weiss score (p<0.001) a finding which was previously described by Tessonier et al. [18].

The only reported experience relative to the relationship between adrenal masses and hormonal secretion concerns secretory status and $Tm_x$. It is reported in a recent pilot study as a potential approach for lateralization in patients with bilateral adrenal masses. In their series the authors analyzed 9 nonfunctioning adenomas, 4 Conn’ syndromes and 11 cortisol-hypersecreting adrenal masses including bilateral masses. The tumor size was greater in patients with cortisol hypersecretion (45 mm in patients with Cushing’s syndrome, 36 mm in non-
secreting adrenocortical masses and 12 mm in Conn adenomas). They identified 16 cortisol-secreting masses with a higher average SUVmax (5.9) than 11 nonfunctioning adrenocortical masses (4.2) or than 5 Conn adenomas (3.2); no correlation between tumor size and Tmx was observed [17] as in our study. The authors demonstrated that the $^{18}$F-FDG uptake in cortisol-secreting tumors is higher than in nonfunctioning adrenal masses, in contrast with our experience. This result could be encouraging in the management of bilateral functional adrenal masses and with diagnostic and therapeutic difficulties (lateralization). However, in their series Tmx alone was analyzed.

A qualitative approach to $^{18}$F-FDG PET/CT analysis has been advocated by Boland et al. in an analysis of 150 patients who underwent to $^{18}$F-FDG PET/CT to evaluate an adrenal mass. They reported that qualitative analysis (visual assessment) of $^{18}$F-FDG PET/CT images was a highly accurate way to differentiate benign from malignant adrenal masses when compared to the quantitative analysis provided by Tmx:Lmx and proposed that qualitative analysis alone could be sufficient to accurately characterize adrenal lesions [6, 7].

Certainly quantitative analysis using Tmx or Tmx:Lmx can be influenced by multiple patient and technical factors including body habitus, glycemia levels, varying times between radionuclide injection and imaging and image reconstruction methods [6, 27].

Furthermore the mean SUV may be influenced by size, shape and placement of regions of interest and maximal SUV by reconstruction method used [6].

Although the estimation of SUVmax is hampered to approximations and simplifications, it was found to be lower affected by partial volume effect compared to other PET-derived indices. In the recent years PERCIST has been proposed for assessment of response to therapies but has not been evaluated for disease characterization and head-to-head comparison with histological findings [28].

The use of more sensitive cameras and more precise SUV measurements has enhanced the role of quantitative PET analysis. Our results support the use of Tmx:Lmx with specific cut-off values for differentiating benign from malignant adrenal masses, regardless of secretion status [5, 25].

In our series, the analyzed cohort differs from previous studies. We included patients with only one unilateral adrenal mass and we excluded patients with primary hyperaldosteronism. All the patients had adrenal masses >2 cm with the exception of one that had adrenal lesion of 1.5 cm.
In contrast with Pattel et al. [17] no correlation was found between Tmx or Tmx:Lmx and hormonal status. This result could be explained by the differences in the study population.

As already mentioned we analyzed 73 patients with cortisol secreting and non-secreting masses. In their study Pattel [17] et al. analyzed 24 patients including bilateral masses.

Our data confirms the role and utility of $^{18}$F-FDG PET/CT in the distinction between benign and malignant tumors.

The conflicting data pertaining to $^{18}$F-FDG PET/CT uptake in functional/secreting adrenal lesions may relate to the presence of confounding patient or technical factors that may influence $^{18}$F-FDG metabolism.

At present the correlation between $^{18}$F-FDG PET/CT uptake and adrenal tumor cortisol secretion is not certain and it should not lead to use of $^{18}$F-FDG for definitive interpretation of the functional status of an adrenal tumor. Furthermore, to date, secretion status should not influence the interpretation of SUV ration in predicting malignancy.

In our longstanding experience in adrenal imaging and the present results, we still consider that Tmx:Lmx remains more reliable than Tmx alone for disease characterization and can be extrapolated in clinical routine to various PET camera, without standardization.

In the near future, the potential role of radiomics together with in vivo MR spectroscopy should be investigated in adrenal masses of various origin and secretory profile in order to potentially improve disease characterization in the preoperative work-up of patients. This integrative approach should provide crucial information for assessment of risk stratification that can help the surgeons towards the most appropriate (personalized) surgical approach to be performed in a given situation.

Conclusions

$^{18}$F-FDG PET/CT is a reliable imaging modality to distinguish benign from malignant adrenal masses especially by the measurement of Tmx:Lmx. Our study shows that there is no significant correlation between Tmx:Lmx on $^{18}$F-FDG PET/CT and hormonal status, regardless of the benign or malignant nature of the tumor. To date, the knowledge of the hormonal status should not modify $^{18}$F-FDG uptake interpretation and therefore management in unilateral and atypical adrenal tumors.
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Reference List


73 adrenal masses

49 secreting masses 67.1%
- 39 Benign 53.4%
- 10 Malignant 13.7%

24 non secreting masses 32.9%
- 20 Benign 27.4%
- 4 Malignant 5.5%
Highlights

- The characterization of adrenal masses by imaging is a critical step to determine appropriate treatment and optimize prognosis.

- $^{18}$F-FDG PET/CT is found to provide additional information to anatomical imaging especially for patients with indeterminate masses on adrenal washout CT but his role in the differentiation between nonfunctioning and functioning adrenal masses has recently been hypothesized.

- In our analysis $^{18}$F-FDG PET/CT is a reliable imaging modality to distinguish benign from malignant adrenal masses especially by the measurement of Tmx:Lmx (ratio).

- In our experience there was no significant difference in Tmx:Lmx between the secreting and non-secreting adrenal masses regardless of the benign or malignant nature of the tumor but a significant positive correlation between Tmx:Lmx and Weiss score has been found confirming the relationship between high ratio and aggressiveness.

- The correlation between ratio, malignancy and Weiss score confirm the utility of $^{18}$F-FDG PET/CT for the differentiation of benign from malignant adrenal lesions, irrespective of the hormone secretory status of the tumor.