Diagnostic and prognostic value of ^{18}F-FDG PET/CT in comparison with morphological imaging in primary adrenal gland malignancies - a multicenter experience

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Abstract

Objective: To evaluate the diagnostic and prognostic role of fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in comparison to morphological imaging such as computed tomography in primary adrenal malignancies. **Materials and Methods**: In this multicenter retrospective study, 68 patients with adrenal malignancy were included. All patients had histologically proven diagnosis of primary adrenal malignancy (adrenocortical carcinoma, malignant pheochromocytoma, neuroblastoma and lymphoma), one whole body ^{18}F-FDG PET/CT scan and one whole-body contrast enhancement computed tomography (CECT) scan acquired within one month and were followed clinically and by performing morphological tests for at least 12 months. **Results**: Overall sensitivity, specificity, accuracy, positive and negative predictive values for CECT and ^{18}F-FDG PET/CT were respectively, 59%, 100%, 65%, 100%, 27% and 75%, 100%, 82%, 100% and 63%. For adrenocortical carcinomas, ^{18}F-FDG PET/CT showed a better accuracy (93.4%) than CECT (75%). For neuroblastomas ^{18}F-FDG PET/CT also showed better accuracy (70.4%) than CECT (66.7%). For malignant pheochromocytomas ^{18}F-FDG PET/CT and CECT showed the same accuracy (90%). For primary adrenal lymphomas, ^{18}F-FDG PET/CT showed better accuracy (100%) than CECT (74.41%). Kaplan-Mayer curves showed that "histotypes" and "metastases at the last follow-up" were similarly detected for both disease free survival (DFS) and overall survival (OS), while "global ^{18}F-FDG PET/CT" and "presence of metastases at diagnosis" were significant for DFS. Stratifying the sample by the presence or absence of metastases at diagnosis, standardized uptake value (SUVmax) was a significant prognostic factor for DFS when metastases were absent (Wald test=7.035, P=0.008). **Conclusion**: Our multicenter study demonstrated that ^{18}F-FDG PET/CT better than CECT diagnosed adrenal malignancies achieving also a good prognostic performance. Therefore management algorithms should include ^{18}F-FDG PET/CT.

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Introduction

Adrenal gland lesions may frequently be incidentally detected both in patients with a history or without a history of tumors. Only few of these lesions are malignant and can be primary or metastatic. The most common adrenal primitive malignancies are adrenocortical carcinomas, malignant pheochromocytomas, and neuroblastomas, all characterized by poor prognosis [1-3].

Adrenal tumors are usually evaluated by morphological imaging techniques as ultrasound (US), contrast enhancement computed tomography (CECT) and magnetic resonance imaging (MRI) [1].

Contrast enhancement computed tomography allows a precise assessment of features of adrenal tumors as for their size, shape, homogeneity, and calcifications [4, 5]. Dedicated adrenal CECT protocols, which combine non-contrast, early and delayed enhancement studies were shown to be highly sensitive and specific. Magnetic resonance imaging allows for the detection of adrenal masses with a similar sensitivity as CT but is not considered quite as accurate as CT. Nevertheless, MRI may be useful if CT results are equivocal and the use of a contrast agent is contraindicated [6-8].

Fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is an important imaging modality in characterizing many malignancies, including adrenal gland lesions [9, 10]. The accuracy of ^{18}F-FDG PET/CT in characterizing adrenal lesions and its impact in clinical staging of patients with adrenal gland malignancies have been evaluated mostly by studies including a small number of patients and not from a multicenter origin [3, 11, 12].

It is important to identify parameters that can be considered prognostic, like tumor size, which measured by CECT, although in a few studies was prognostic in patients with

adrenal gland malignancies [4, 5]. On the other hand, the prognostic value of ^{18}F-FDG PET/CT is still investigated [13].

The purpose of this multicentric study was to evaluate the role of ^{18}F-FDG PET/CT in comparison to CECT in patients with primary adrenal malignancies and to correlate ^{18}F-FDG PET/CT results with prognosis.

Materials and Methods

Patients

A multicentric retrospective study was conducted including 68 patients who referred to 7 Medical Centers located in Turin (2 centers), Genova (2 centers), Bologna, Bari, and London. The including criteria were: a) Histological proven diagnosis of primary adrenal malignancy (adrenocortical carcinoma, malignant pheochromocytoma, neuroblastoma or lymphoma); b) Medical history negative for other tumors; c) Availability of at least one whole body ^{18}F-FDG PET/CT scan for the purpose of staging; d) Availability of at least one whole-body CECT acquired within one month from the ^{18}F-FDG PET/CT and e) Availability of a clinical and instrumental follow up of at least 12 months.

Each patient was submitted to a different treatment established by the clinicians' team of reference. Patients were given identification numbers and all relevant data were collected in a database template, in all centers. All patients gave their informed consent.

Imaging acquisition and data analysis

Examinations by CT were performed with equipment multidetector CT with 16 layers (TSX-101°, Aquilion 16, Toshiba Medical Systems, Tokyo, Japan). Fluorine-18-FDG PET/CT were acquired with a combined modality PET/CT Discovery LSA (GE Healthcare, Waukesha, Wisconsin, USA) that integrates a PET (advance nxl) with a 16-slice CT scanner (light speed, plus). The image acquisition was obtained 50min after the intravenous injection of 4.6MBq/kg of ^{18}F-FDG.

Whole body CECT and ^{18}F-FDG PET/CT exams were performed using procedures and methods according to the recommendation guidelines of the European Association of Radiology and the European Association of Nuclear Medicine [14, 15].

All images were sent as DICOM files and were reviewed retrospectively blindly by 2 radiologists and 2 nuclear medicine physicians having at least 8 years of experience in this field. Both maximum intensity projection (MIP) and multiplanar reconstruction (MPR) techniques were employed to analyze the acquired images.

Images of CECT were considered positive for malignancies in case of description of adrenal, lymphnodes and/or other organs lesions. Images of ^{18}F-FDG PET/CT were considered positive for malignancies in case of increased ^{18}F-FDG uptake in the adrenal glands, lymph nodes or other sites, excluding sites of normally increased uptake.

Images of ^{18}F-FDG PET/CT were also analyzed semi-quantitatively measuring the maximal standardized uptake value-SUVmax) by drawing a region of interest (ROI) around the adrenal lesions. The SUVmax was calculated with the following formula: activity (MBq/mL)xbody weight/injected dose (MBq/mL) [16].

Statistical analysis

The overall sensitivity (SS), specificity (SP), positive and negative predictive values (PPV and NPV) for ^{18}F-FDG PET/CT were calculated. The overall accuracy and the histotypes, were statistically studied both for CECT and ^{18}F-FDG PET/CT. The Kaplan-Meier method was applied to estimate overall survival (OS) and disease free survival (DFS). The Mantel-Cox Log-rank test was used to compare survival curves. The Cox Regression was also performed. P was considered significant if≤0.05. Statistical analysis was carried out using SPSS 20.0 for Mac.

Results

Patients and ^{18}F-FDG PET/CT

Patients' and lesions' characteristics are reported in Table 1. The CECT was positive for adrenal involvement in 35/68 patients (51.5%) and negative in 33/68 patients (45.5%). The ^{18}F-FDG PET/CT was positive for adrenal involvement in 36/68 patients (52.9%) and negative in 32/68 patients (47.1%). Mean SUVmax of the adrenal lesion was 3.76 (min=2.8; max=47; SD=7.296).

Global analysis of CECT, regardless of sites involved was positive in 45/68 patients (66.2%) and negative in 23/68 patients (33.8%). Global analysis of ^{18}F-FDG PET/CT was positive in 49/68 patients (72.1%) and negative in 19/68 patients (27.9%). In 68 patients with adrenal gland malignancies, 191 lesions were founded.

Diagnostic results

Overall SS, SP, accuracy, PPV and NPV for CECT and also for ^{18}F-FDG PET/CT in characterizing adrenal malignancies were respectively 59%, 100%, 65%, 100%, 27% and 75%, 100%, 82%, 100% and 63%. For adrenocortical carcinomas (Figure 1), a better accuracy was shown by ^{18}F-FDG PET/CT (93.4%) than by CECT (75%).

Furthermore, in neuroblastomas ^{18}F-FDG PET/CT showed a better accuracy (70.4%) than CECT (66.7%). In malignant pheochromocytomas ^{18}F-FDG PET/CT and CECT showed the same accuracy (90%). In evaluation of primary adrenal lymphomas (Figure 2), ^{18}F-FDG PET/CT showed a better accuracy than CECT (100% vs. 74.41%).

Prognostic results

Mantel Cox Log Rank results for OS and DFS are reported in

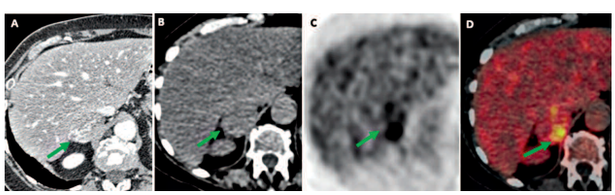

Figure 1. A 74 years old man affected by right adrenocortical carcinoma. Computed tomography transaxial image A) showed a 4.5cm solid adrenal mass characterized by an inhomogeneous enhancement after contrast enhancer injection (green arrow). Fluorine-18-FDG PET/CT axial CT, PET and fused images (B, C and D) confirmed the presence of the lesion (green arrows) with focal and intense ^{18}F-FDG uptake in the medial portion of the mass (SUVmax of 6).

Table 2. Kaplan-Mayer curves showed that global ^{18}F-FDG PET/CT showed significant DFS but not OS (Figure 3). Kaplan-Mayer curves showed that histotypes were significantly related to both DFS and OS (Figure 4). The presence of metastases at diagnosis was a significant factor for DFS, while metastases diagnosed at last follow-up were signifi-

Table 1. *Characteristics of the 68 patients.*

	Mean	SD	Min	Max
Age (years)	44.17	24.00	1.91	78.80
Metastases at diagnosis (n)	3.94	6.29	0	21
Max number of metastases	5.16	7.26	0	21
OS (months)	34.41	21.04	3	106
DFS (months)	16.81	21.94	0	92
	N			%
Sex	32			47.1
F	36			52.9
M				
Centre				
Bari	8			11.8
Bologna	9			13.2
Genova	13			19.1
London	9			13.2
Turin	29			42.6
Histotypes				
Carcinoma	38			55.9
Neuroblastoma	16			23.5
Pheocromocytoma	12			17.6
Lymphoma	2			3
3 months follow-up				
Disease free	30			44.1
Stable disease	24			35.3
Progressive disease	14			20.6
6 months follow-up				
Disease free	32			47
Stable disease	19			28
Progressive disease	17			25
12 months follow-up				
Disease free	36			53
Stable disease	12			17.6
Progressive disease	20			29.4
Outcome				
Alive	46			67.6
Dead	20			29.4
Missed	2			2.9

OS= overall survival; DFS= disease free survival

Table 2. *Mantel Cox Log Rank test results for OS and DFS.*

	OS Log Rank test	P	DFS Log Rank test	P
Global ^{18}F-FDG PET/CT (neg/pos)	3.204	0.073	3.204	0.073
^{18}F-FDG PET/CT Adrenal localization (neg/pos)	0.593	0.441	0.593	0.441
Histotypes	10.971	0.012	10.971	0.012
Metastases at diagnosis	1.422	0.233	1.422	0.233
Metastases at last follow-up	3.784	0.052	3.784	0.052

Table 3. *Cox Regression results for OS and DFS.*

	OS		DFS	
	Wald test	P	Wald test	P
Age	2.434	0.119	0.048	0.826
Metastases at diagnosis	0.031	0.861	0.451	0.502
Max number of metastases	0.571	0.450	4.857	0.028
SUVmax primary tumor	0.377	0.539	3.432	0.064
Histotypes	8.686	0.034	5.587	0.134

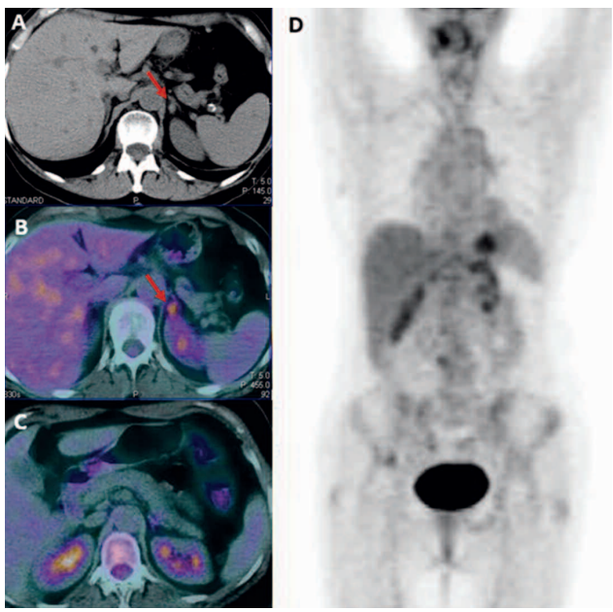

Figure 2. A 54 years old female with left primary adrenal non-Hodgkin's lymphoma. Computed tomography transaxial image A) showed a not well characterizable left adrenal lesion (red arrow). Fluorine-18-FDG PET/CT fused transaxial image B) showed ^{18}F-FDG uptake (SUVmax 4.8) in the left adrenal gland. Fluorine-18-FDG PET/CT fused transaxial C) and PET MIP D) images performed after chemotherapy, showed the resolution of the disease.

cantly correlated both for OS and for DFS.

Cox regression analysis results, about the variables analyzed for OS and DFS are reported in Table 3. Histotype was the unique variable predictive for the OS. The variable predictive for DFS was shown to be the "Max Number of Metastases", even if it did not reach statistical significance. Performing survival analysis, stratifying the sample by presence or absence of metastases at diagnosis, we observed that SUVmax was a significant prognostic factor for DFS when metastases were absent (Wald test=7.035 P=0.008).

Discussion

One of the most difficult goals of imaging is to correctly diagnose adrenal lesions and avoid unnecessary aggressive procedures. Nowadays, CECT is used to detect large, solid, irregularly shaped lesions frequently associated to heterogeneous density, due to necrosis, calcifications and hemorrhages, with accuracy of almost 100% [17-19]. Furthermore CECT provides essential information for staging adrenal malignancies. In our study the overall accuracy of CECT was lower (65%) than what is reported in the literature, but the heterogeneity of the sample should be considered in interpreting these results.

The ^{18}F-FDG PET/CT examination has become a widely used imaging tool in staging adrenal malignancies with high impact on clinical management of the patients [20, 21]. Several studies, investigating the role of ^{18}F-FDG PET/CT, demonstrated that the whole-body technique has a great potential to characterize malignant lesions and also to evaluate possible sites of secondary lesions with high detection accuracy [20].

Other studies suggested that SS, SP, PPV, NPV and accuracy of ^{18}F-FDG PET/CT in detecting adrenal malignancies were: 90%-100%, 78%-100%, 81.8%, 100% and 95.1%, respectively [22-25]. In our study, ^{18}F-FDG PET/CT showed a good performance with SS, SP, PPV, NPV and accuracy in line with the above (75.8%, 94.4%, 96.2%, 68% and 83.3% respectively). False-positive results of ^{18}F-FDG PET/CT have been reported in a variety of causes including significant ^{18}F-FDG uptake in some adrenal adenomas, in adrenal endothelial cysts, in inflammatory and in infectious lesions. False-negative findings have been seen in the presence of hemorrhage or necrosis and in small lesions [26].

To our knowledge, only a single study has compared CT to ^{18}F-FDG PET/CT for diagnosing adrenal tumors showing better results for CT [19]. The results of our multicentric study revealed a better diagnostic performance of ^{18}F-FDG PET/CT than CECT in the overall evaluation of patients with adrenal malignancies. Dome of differences between our results and those of others [19] may be due to differences in the selection of patients and in their different histotypes.

The contribution of SUVmax in characterizing adrenal lesions remains open for discussion. Boland et al. (2011) suggested that the routine use of SUVmax is problematic because it is subject to many sources of variability, including body habitus and composition, varying times between radionuclide injection and imaging, plasma glucose concentration, image reconstruction method, and partial volume effects [25]. To avoid this bias, in our study we considered only examinations performed with the same procedures.

The SUVmax of normal adrenal glands ranged from 0.95 to 2.46, but it is well known that some benign adrenal lesions can be mildly ^{18}F-FDG avid and the different types of malignancies can have different degrees of ^{18}F-FDG uptake [25, 27, 28].

High SUVmax and large extent of bone and bone marrow disease seemed to correlate with decreased survival and poor prognosis [29].

To the best of our knowledge, only the study of Leboulleux et al. (2006) showed that a high ^{18}F-FDG uptake appears to represent an independent prognostic factor. They reported that 54% of the patients with a SUVmax>10 died within 6 months after ^{18}F-FDG PET/CT examination, whereas none of the patients with a SUVmax<10 died. A high ^{18}F-FDG uptake appears to represent an additional stage-independent prognostic factor [30]. In the study of Tessonnier et al (2013) high SUVmax was not significantly associated with shortened OS and DFS [31].

In our study we observed that only when the sample was stratified by the presence/absence of metastases at diagnosis, SUVmax demonstrated a significant prognostic factor; it was predictive just for DFS, and only when metastases were absent (Wald test=7.035 P=0.008). We acknowledge that the sample size was probably too small to detect subtle differences among patients, and that no statistical adjustment could be made for potential confounding factors.

Only the maximum number of metastases was predictive for DFS. Stratifying the sample by the presence or absence of metastases at the time of diagnosis, SUVmax resulted as a significant prognostic factor for DFS when metastases were absent.

Adrenocortical carcinomas, as well as primary adrenal lymphomas, usually show moderate to intense ^{18}F-FDG uptake values and reports in the literature showed high ^{18}F-FDG PET/CT diagnostic performance for them, as well as in our study [16, 17, 32]. Neuroblastomas are ^{18}F-FDG avid, and in one study it was proposed that ^{18}F-FDG PET/CT are the only imaging modality to better assess this disease [33]. However, the exact diagnostic accuracy remains to be defined; in our study it resulted 70.4%. Malignant pheochromocytomas are rare tumors often larger than 2cm, and so easily outlined but difficult to differentiate from other adrenal tumors by CT alone, while ^{18}F-FDG PET/CT has high ^{18}F-FDG avidity for this malignancy [34]. In our study both CECT and ^{18}F-FDG PET/CT showed high diagnostic performance for these carcinomas (accuracy of 90%).

The OS and DFS are generally poor in adrenal malignancies and are influenced by many factors including histotype, presence of metastases and age. In our study, mean OS and DFS were 34.41 and 16.81 months and all histotypes were accompanied by poor prognosis. Identification of powerful predictors of prognosis could substantially improve the choice of treatment and the clinical outcome.

Our study demonstrated different OS and DFS depending on the histotypes of the tumors. Histotypes greater influenced our results. The course of the disease, the incidence of metastases and the treatment modalities in these patients varied greatly depending on the histotypes. Furthermore histotypes influenced both DFS (Log Rank test:12.738, P=0.005) and OS (Log Rank test:10.971, P=0.012). According to the evolution of known diseases, our results also showed the worst DFS and OS in neuroblastoma patients and the better ones in lymphoma patients. Furthermore, from the multivariate evaluation, histotype was the unique variable predictive of OS (Wald test=8.686 P=0.034).

The prognostic value of ^{18}F-FDG PET/CT was established in some other malignancies related with high ^{18}F-FDG uptake, but was not well established as yet in adrenal malignancies [31].

Our study demonstrated that ^{18}F-FDG PET/CT, in terms of positive or negative ^{18}F-FDG uptake in adrenal glands, influences the DFS (Log Rank test:11.743, P=0.001), but did not have any impact on OS (Log Rank test:3.204, P=0.073).

In conclusion, our study suggested that ^{18}F-FDG PET/CT was a powerful imaging tool, offering higher accuracy, in comparison to CECT, for the detection and characterization of the most common histotypes of adrenal carcinomas. Diagnostic algorithms therefore should include ^{18}F-FDG PET/CT as a step, for the diagnosis of adrenal tumors. Studies with more patients are warranted.

The authors declare that they have no conflicts of interest.

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