Adrenal Findings in FDG-PET– Analysis of a Cohort of 1021 Patients From a Cancer Center

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Abstract

Purpose: The use of FDG-PET/TC for cancer staging has been leading to the increasing diagnosis of adrenal lesions, which usually represent a clinical challenge. Our aim was to characterize the adrenal lesions found in FDG-PET of patients followed in a cancer center.

Methods: Retrospective analysis of all FDG-PET studies performed in our center in the last 10 years. Exams reporting adrenal lesions in the CT component and/or anomalous adrenal FDG uptake were selected. Cases were characterized regarding clinical, laboratorial, imaging and pathological findings.

Results: We identified 27,427 FDG-PET studies. Of those, 7.6% evidenced adrenal findings. We included 1364 exams corresponding to 1021 patients. Only 15.6% were referred to the endocrinology department and 38% of the lesions were not studied.

Malignant lesions were present in 38.9% of the studied patients: metastases in 37.5%, carcinoma in 1.2% and other malignant tumors in 0.4%. Median SUVmax of malignant lesions was significantly higher than the SUVmax of the benign findings ($p < 0.05$). We also observed a higher median SUVmax in adrenal metastases than in adenomas ($p < 0.05$). There was a tendency for higher SUVmax of adrenal carcinomas when comparing with other malignant lesions ($p = 0.066$). The median SUVmax was not different between pheochromocytomas and other tumors ($p > 0.05$).

Conclusion: Occult adrenal lesions discovered during FDG-PET/CT are common in cancer context and are frequently benign. SUVmax may be a useful tool in the workup of adrenal lesions but with several important caveats.

Introduction

The rising incidence of adrenal lesions on diagnostic imaging studies requested for indications unrelated to the adrenal gland is mainly due to the widespread use of computed tomography (CT), magnetic resonance imaging (MRI), and, more recently, positron emission tomography (PET)/CT with 2-[18F]fluoro-2deoxy-D-glucose (FDG) [1]. The evaluation of cancer patients for staging or treatment response assessment with FDG-PET/CT has been contributing to this tendency [2]. Adrenal masses incidence has also been increasing in non-adrenal cancer patients along with the number of patients living with cancer [3].

These adrenal lesions should not be ignored once these glands are common sites of metastases from several malignant tumors, and primary adrenal lesions can be malignant and /or cause adrenal dysfunction. An adrenal mass in a patient with a known malignancy has a 32–73% chance of being a metastasis [4], [5]. However, benign adrenal tumors may occur in the general population and in patients with cancer [6]. In the oncological setting, the accurate characterization of adrenal lesions may be crucial for prognostic assessment and treatment approach [7].

FDG-PET/CT is a nuclear medicine, non-invasive, whole-body imaging method that is widely used in clinical practice to differentiate malignant from benign lesions and to assess the disease stage [1]. This exam is based on the accumulation of a specific tracer (FDG) as a result of increased glucose metabolism in malignant tumors [1].

FDG-PET has a high sensitivity for detection of metabolic changes, but its spatial resolution for anatomical localization is poor. The solution is a fusion between PET and CT (PET/CT) images, allowing simultaneous acquisition of both imaging modalities [8]. Thereby, the CT data are a potentially valuable addition to FDG-PET, providing useful morphologic features of the adrenal lesions [7].

When an adrenal lesion shows FDG uptake on PET/CT imaging, the primary goal is to distinguish malignant from benign etiology. Adrenal glands are not easily accessible, and percutaneous biopsy or cytology are often contraindicated [8]. Moreover, adrenal percutaneous biopsy usually provides only limited diagnostic information in adrenocortical cancer and other malignancies [9]. Nevertheless, percutaneous adrenal biopsy can be useful, especially in cases of adrenal lymphoma, or when confirmation of adrenal infiltration by distant metastasis is key to appropriate staging and treatment of extra-adrenal cancers. There are no current guidelines regarding the management of adrenal masses with FDG uptake in patients with and without cancer history, and data addressing the need or benefit from surgery is scarce.

The objective of this study was to characterize the adrenal lesions found in FDG-PET in a group of patients with proven or suspected cancer in a single oncology center. We also intended to define a SUVmax cut-off for malignancy prediction and to study the prevalence of endocrine follow-up of these adrenal lesions.

Material And Methods

Patients

We performed a retrospective analysis of all FDG-PET and FDG-PET/CT studies acquired in our center, between January 2010 and November 2020. Exams from patients without follow-up in our center were excluded from the analysis.

Studies reporting adrenal lesions in the CT component and / or anomalous adrenal FDG uptake were selected. The corresponding clinical files of selected patients were analyzed and their adrenal lesions were characterized regarding clinical, laboratorial and imaging findings. The histology of the adrenal lesion was also collected, when available.

FDG-PET/CT

Patients fast for at least six hours (h) prior to the exam and are instructed to avoid high sugar content food or drinks, as well as caffeine rich beverages and physical exercise in the previous 24 h. Diabetic patients on regular short-acting insulin may take their insulin along with breakfast 6 h before the exam. Those receiving evening long-acting insulin are scheduled for imaging early in the morning after an overnight fast. Other types of medication are usually maintained.

Patients' glycaemia is evaluated before the exam and it is ensured that the value is below 200mg/dL. Imaging is conducted 1 h after intravenous injection of ^{18}F -FDG (3,7MBq/Kg). During this period, the patients stay at rest in a quiet and warm environment.

The tomographic images are acquired with the patient in supine position.

From 2010 until the end of 2013, the studies were FDG-PET scans and were performed on a Siemens PET ECAT ACCEL-LSO scanner. From 2014 onwards, the studies were FDG-PET/CT scans and were acquired on Philips Gemini TF or Philips Gemini 16 Power scanners. A low dose CT protocol was used, without contrast administration. The CT images were used for attenuation correction and for anatomical localization.

All scans were reviewed and reported by an experienced nuclear medicine specialist.

Findings in FDG-PET/TC

Adrenal tracer uptake was considered anomalous by the nuclear medicine physician when it was greater than the background activity in bordering tissue or if there was an asymmetric uptake in the two glands. Some lesions were only visualized on the CT component and they were considered with no significant uptake when it was equal or below to the bordering tissue.

Quantitative analysis was performed by measuring the SUVmax of the adrenal lesion. This analysis was performed by a nuclear medicine physician on a Siemens e-soft workstation from 2010 until 2013 and using Philips IntelliSpace Portal or Philips Extended Brilliance Workspace software from 2014 onwards.

For the SUVmax calculation, a region of interest (ROI) was automatically generated after its placement on the adrenal lesion, after which the threshold was adjusted by the user.

Follow-up and diagnosis of adrenal findings

In our center, the FDG-PET reports are analyzed by the physician who requested the study, usually the oncologist. This physician then decides if the patient must be referred to the Endocrinology department for characterization and follow-up.

At the Endocrinology department of our center, all patients with an adrenal finding on FDG-PET/CT are followed with physical examination and laboratorial tests. Some cases require additional imaging

workup such as CT, MRI, or [^{123}I] metaiodobenzylguanidine (MIBG) scan if a pheochromocytoma is suspected. The endocrine work-up of the adrenal function follows the international guidelines [8].

Definitive diagnosis of adrenal lesions included in this study was provided by collecting surgery or biopsy data, when these were performed, but, in most cases, was based on clinical, laboratorial and imaging behavior. Surgery was considered in the presence of hormonal hypersecretion, suspicious imaging and / or clinical findings, or rapid growth. Biopsy was proposed when the lesion was hormonally inactive and was not well characterized as benign by imaging, and if the management of the oncological disease would be altered by knowing the adrenal histology.

For this study, an adrenal lesion with proven stability in size on serial imaging studies (with at least one year of follow-up) and with imaging characteristics of adenoma in CT or MRI was classified as adenoma. An adrenal lesion evidencing stability or reduction on serial imaging after primary cancer treatment was considered as metastasis.

Throughout this paper, we included in the group of malignant tumors the adrenal cortical carcinoma, metastases from different primary tumors, neuroblastoma, and B cell lymphoma. Benign tumors included adrenal cortical adenoma, myelolipoma, schwannoma, and other benign adrenal findings (normal tissue, hyperplasia, brown adiposity). Pheochromocytoma was classified as benign or malignant based on the presence of distant metastases.

Statistical analysis

Statistical analysis was performed using SPSS 25th edition. Gaussian distribution of continuous variables was determined with Shapiro-Wilk test; non-normally variables are presented as median (minimum-maximum). Categorical variables were compared using Chi-Square test or Fisher's Exact test. Comparison of continuous variables between groups was made with Mann-Whitney and Kruskal-Wallis tests. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of SUVmax in FDG-PET/CT were determined in patients with a benign or malignant lesion, excluding those with indeterminate lesions. Receiver-operating characteristic (ROC) curves were drawn to determine the cut-off value of SUVmax that would best discriminate between benign and malignant lesions. The area under the curve was assessed, and the sensitivity and specificity were determined for an optimal cut-off of the SUVmax. The tests were considered statistically significant when $p < 0.05$.

This study was previously approved by the Ethical Committee of our center.

Results

We identified 27,427 FDG-PET/TC studies that were performed in our center in the mentioned time interval. Of those, 7.6% ($n=2082$) evidenced adrenal findings. We excluded 718 exams due to follow-up in other centers and we selected 1364 exams corresponding to 1021 patients. Figure 1 shows a general description of all lesions found in the whole cohort.

In the analyzed cohort (n=1021), 55% (n=562) of the patients were male. The majority of the patients (99.6%) presented an oncological context. The FDG-PET/TC exams were requested for diagnostic purposes (patients with suspicious lesions in any site in other exams) in 6.1% (n=62) and for disease staging or control of disease evolution in the remaining patients. Of the 62 patients who performed FDG-PET/TC for diagnostic purposes, 25 (40.3%) had previously known adrenal lesion. The median age of the patients at FDG-PET/TC was 68.3 (6.3-90.6) years old.

An anomalous FDG uptake was found in 79.2% of the patients (n=809). It was unilateral in 73.7% (n=596) and bilateral in 26.3% (n=213). The remaining 20.8% (n=212) revealed lesions in the CT component, without anomalous FDG uptake.

A malignant primary or secondary adrenal lesion was present in 398 (38.9%) patients.

Referral to the endocrinology department occurred in 159 (15.6%) patients and the remaining 862 were evaluated by their oncologist.

Cohort of patients referred to the Endocrinology department

In this group (n=159), 39.7% (n=63) were already followed in our department due to endocrine disease. The remaining 60.4% (n=96) of the patients were referred by other departments of our center due to the adrenal findings at PET-FDG/TC.

The median follow-up time in the endocrinology department was 1.6 (0.2-21.6) years.

In this group of 159 patients, 18 (11.3%) were no further investigated due to adrenal finding considered not clinically significant or due to patient poor prognostic. It was not possible to conclude a definitive diagnosis in 5.7% (n=9) of the patients. In the remaining 132 patients, the final diagnosis was established by surgery in 19.7% (n=26), biopsy in 6.8% (n=9) and by biochemical plus imaging characteristics in 73.5% (n=97).

Figure 2 details the findings of the 159 patients followed at Endocrinology department. In the group of the adenomas (n= 54), 13 (24.1%) presented inconclusive secretion study, 5 (9.3%) adrenal secreting adenomas (three secreted aldosterone and two cortisol) and the remaining 36 (66.7%) were non-secreting adenomas. The secreting adenomas (n=5) showed anomalous FDG uptake in 4 (27.7%) cases, with a median SUVmax of 5.2 (4.5-6.7), and the non-secreting adenomas (n=36) evidenced anomalous FDG uptake in 24 (15.1%) cases, with a median SUVmax of 4.5 (2.1-8.8), $p>0.05$.

Cohort of patients not referred to the Endocrinology department

The lesions of the 862 (84.4%) patients that were not followed at the endocrinology department are detailed in Table 1. In 363 (42.1%) cases, the adrenal work-up was not pursued, given that the adrenal

findings were considered irrelevant. The remaining patients (n=499) presented adrenal lesions that were classified in accordance with their imaging and behavior characteristics. The adenomas found in this group were not screened for functional secretion for reasons that were not clear in the clinical files.

Table 1
Diagnosis of the lesions found in
FDG-PET/TC from other department
's patients.

	N	%
Hyperplasia	46	5.5
Adenoma	98	11.4
Incomplete study	363	40.4.
Metastases	355	41.2
Total	862	100

Whole cohort of 1021 patients

Table 2 details the adrenal lesions found in the whole cohort.

Table 2

FDG uptake in adrenal lesions found in patients of our cohort (n=631 well-studied patients). The non-studied (n=382) and inconclusive (n=8) lesions were excluded.

¹The other malignant tumors were: sarcoma (2), lymphoma (1), malignant pheochromocytoma. One of the sarcomas didn't demonstrate anomalous FDG uptake. ²The other benign tumors are schwannoma (1), ganglioneuroma (1), adrenal necrosis (1), peri-renal brown fat (1), hemangioma (1). Schwannoma and peri-renal brown fat showed anomalous FDG uptake (with no reference to SUVmax value on the report).

Diagnoses	N	Anomalous FDG uptake		SUVmax (median)
		N	%	
Malignant lesions	398	395	99.2	7.9 (2.4-49.2)
- Metastases	382	380	99.5	7.6 (2.4-49.29)
- Adrenal Carcinoma	12	12	100	17.5 (3.0-42.0)
- Other malignant tumors ¹	4	3	75	8.8 (3.9-13.7)
Benign lesions	233	172	73.8	4.5 (2.1-14.4)
- Pheocromocytoma	6	6	100	6.5 (3.9 – 14.4)
- Adenomas	152	107	70.4	4.3 (2.1 – 9.4)
- Hyperplasia	52	45	86.5	4.7 (2.8 – 10.0)
- Other benign tumors ²	5	2	40	
- Normal adrenal gland	18	12	66.7	5.3 (4.3 – 8.3)

Of these patients, 383 (37.5%) presented adrenal metastases; most cases spread from lung carcinoma, melanoma and lymphoma (Figure 3). Bilateral involvement was seen in 25.4% (n=97), the majority of the cases with melanoma (n=25), lung carcinoma (n=24) and lymphoma (n=13). Only 2 cases (0.2%) were diagnosed with adrenal insufficiency from the group of 159 patients evaluated.

We found significant differences when comparing the median SUVmax between malignant and benign lesions [7,9 (2.4-49,2) vs. 4.5 (2.1-14.4), $p<0.005$]. The same occurred between the adenomas and adrenal metastases [4.3 (2.1 – 9.4) vs. 7.6 (2.4-49.29), $p<0.05$].

There was a tendency for higher SUVmax of adrenal cortical carcinomas when comparing with other malignant lesions [17.5 (3-42) vs. 7.6 (2.4-49.2), $p=0.066$].

The median SUVmax was not significantly different between pheochromocytomas and other benign tumors or malignant tumors [6.5 (3.9 – 14.4) vs. 4.4 (2.1-10), $p>0.05$; 6.5 (3.9 – 14.4) vs. 7.9 (2.4-49.2), $p>0.05$, respectively.].

The cut-off of 6.7 for SUVmax distinguished between malignant and benign tumors, with a sensitivity and specificity of 61.1% (95%CI, 55.6-66.5) and 90.1% (95%CI, 82.5-95.1), respectively (Figure 4). Positive predictive value, negative predictive value and accuracy are detailed in Table 3.

Table 3
Performance characteristics of FDG-PET/TC SUVmax using a cutoff value of 6.7 for the distinction between benign and malignant adrenal tumors (n =631).

	Malignant	Benign	Total
SUVmax≥ 6.7	243 True positive	11 False positive	254
SUVmax<6.7	155 False negative	222 True negative	377
Total	398	233	631

Discussion

To our knowledge, this is the largest study analyzing the adrenal findings in FDG-PET scans performed in a population with confirmed or suspected cancer. There are different reports, with smaller cohorts of cancer patients, ranging from 30 to 163 patients with adrenal lesions in PET-FDG [2], [7], [10]–[14].

The prevalence of adrenal findings varies depending on the source of data (autopsy, surgery, or radiological studies) and patient selection (from general or specialized centers). Autopsy studies suggest a prevalence of clinically unapparent adrenal masses of around 2%, which increases with age [15]. Radiological studies report a frequency of around 3% in the age of 50 years, which increases up to 10% in the elderly [16]. In our series, we observed a prevalence of adrenal findings of 7.6% in almost 30,000 exams, probably due to the older age of our patients.

The most frequent adrenal diagnosis were metastases, present in more than 1/3 of the whole cohort, and the most common primary tumors spreading to adrenals were lung carcinoma, melanoma and lymphoma. These secondary lesions evidenced a high FDG uptake [7.6 (2.4-49.29)]. Our prevalence is similar to the reported in literature (38–57%) [10], [17], [18].

Our findings demonstrate that FDG uptake does not imply malignancy, as 172 (16.9%) patients evidenced benign lesions with anomalous FDG uptake. However, we had 37.1% (n=379) of the patients with non-studied adrenal lesions and, for this reason, the percentage of benign tumors in this series is probably higher. We found a SUVmax cut-off that distinguished between benign and malignant tumors (<6.7/ ≥ 6.7, respectively) however the area under the ROC curve was only 0,825, making the method less reliable. SUVmax may be a useful tool in the routine appreciation of these patients, always in conjunction with other elements, such as clinical presentation and evolution, and CT characteristics.

We observed that SUVmax was significantly different between benign and malignant lesions. Interestingly, there was a tendency for the adrenocortical carcinomas showing a higher SUVmax than

other malignant tumors. Thus, when patients present an extremely high SUVmax clinicians must maintain a high level of suspicion of adrenocortical carcinoma, which usually portends a very poor prognosis [9]. In other hand, SUVmax was not different between pheochromocytomas and other benign or malignant tumors. In these cases, as CT alone and MRI [22], PET-FDG does not bring any additional value in the diagnosis of confined pheochromocytoma. We detected that SUVmax did not differentiate secreting from non-secreting adenomas. Because of a frequent but variable FDG uptake by functional adenomas/carcinomas or pheochromocytomas, FDG-PET/TC cannot be correctly analyzed without the results of hormonal tests [23]. Therefore, hormonal workup is crucial in the definitive diagnosis of an adrenal lesion such adenoma, hyperplasia, pheochromocytoma, carcinoma and bilateral metastases.

In our cohort, the proportion of endocrinology referral was low (15.6%), probably due to the oncological context of these patients, and to their poor prognosis. In many cases, it may be futile to pursue an endocrine workup when the objective is symptomatic control or palliative care. However, the correct investigation of an adrenal mass, in the oncological, and even in the metastatic context, may be performed as it may be prognosis-changing [8]. Furthermore, it is important to highlight that patients with bilateral adrenal lesions should always be referred to an endocrinology specialist due to the risk of adrenal insufficiency [8]. In agreement with our findings, a recent large American epidemiology study involving 1287 patients with adrenal tumors showed that sufficient hormonal workup was not performed in most patients. When all the laboratorial tests done during the study period were considered, only 47.0% of patients had some form of hormonal workup, and only 15.2% had a sufficient workup. Furthermore, patients diagnosed during cancer staging had the most incomplete workup, with only a quarter of patients with malignant tumors being investigated for any kind of hormonal secretion [24].

The reduced prevalence of endocrinology referral was, at the same time, one of our main findings, as we wanted to understand the global approach to these adrenal findings in our center, and was also a limitation of our study. Furthermore, we used follow-up data to determine the nature of the adrenal lesions, as we only obtained a histologic diagnosis in 3.4% of the cases. PET scans were acquired on the available equipment in our center, i.e., on a PET alone scanner in the first years and then on two PET/CT scanners, with different acquisition and reconstruction algorithms, which may further introduce variability in SUVmax values. The use of SUVmax may be controversial as it can be influenced by a several variables, such as body habitus and composition, time elapsed from radionuclide injection and imaging, plasma glucose concentration, image reconstruction method, and partial volume effects. Other factors, including the recovery coefficient, and the type of ROI may interfere with SUV measurement [20]. Some authors have proposed the use of adrenal to liver SUV ratio, rather than adrenal SUVmax alone, as it may improve the ability to correctly classify adrenal tumors [6], [19]–[21]. Finally, a major limitation of this work is its retrospective nature. However,, this work has major strengths, such as the large sample size, with the patients being followed at a single center; the fact that virtually all patients have a history of cancer turns this cohort homogeneous. Furthermore, we also intended to demonstrate the clinical challenge that these FDG-PET findings can represent for the endocrinologist.

In sum, adrenal findings in FDG-PET are common in cancer context and SUVmax may be useful in differentiating malignant from benign adrenal lesions but with important caveats. In cancer context, the adrenal findings are commonly metastases, however, adenomas are also frequent. All these lesions must be well characterized, especially if the workup may alter the global approach.

Declaration

Competing Interests and Funding:

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Figures

Figure 1

Description of all lesions found in this cohort. Pts, patients.

Figure 2

Diagnosis of adrenal lesions found in FDG-PET/TC from 159 patients from the Endocrinology department. Other tumors are sarcoma (n=2), malignant pheochromocytoma, lymphoma, schwannoma, ganglioneuroma, hemangioma, adrenal necrosis, peri-renal brown fat (one case for each).

Figure 3

Primary cancers with adrenal metastases.

Figure 4

ROC generated from SUVmax data. A SUVmax cut-off of 6.7 is the best compromise and provides a sensitivity of 61.1% (95 % CI, 55.6-66.5) and a specificity of 90.1% (95%CI, 82.5-95.1) for malignancy. AUC 0.825, 95% CI (0.785-0.860). Positive predictive value 95.7%. Negative predictive value 58.9%. Accuracy 73.7%