Adrenal findings in FDG-PET: analysis of a cohort of 1021 patients from a cancer center

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Received: 16 February 2022 / Accepted: 18 November 2022 / Published online: 7 December 2022
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Abstract
Purpose The use of FDG-PET for cancer staging has led to the increasing incidence of adrenal lesions, which are usually a clinical challenge. We aimed to characterize the adrenal lesions found in FDG-PET of patients followed in a cancer center.

Methods Retrospective analysis was conducted 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 by the clinical, laboratory, imaging, and pathological findings.

Results We identified 27,427 FDG-PET studies. Of those, 7.6% reported adrenal findings. We included 1364 exams corresponding to 1021 patients. Only 15.6% of the patients were referred to the Endocrinology Department and 38% of the lesions were not studied. In 38.9% of the studied patients, malignant lesions were present, including metastases in 37.5%, carcinoma in 1.2%, and other malignant tumors in 0.4%. The 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 compared 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 the cancer context and are frequently benign. SUVmax may be a useful tool in the workup of adrenal lesions but with several important caveats.

Keywords Adrenal incidentaloma · Adrenal FDG uptake · PET/CT-FDG · Adrenal adenoma · Adrenocortical carcinoma · Adrenal metastases

Introduction

The rising incidence of adrenal lesions on diagnostic imaging studies requested for indications unrelated to adrenal pathology 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 contributed to this trend [2]. Adrenal mass incidence has also increased 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 secondary deposits from several malignant tumors, and primary adrenal lesions can be malignant; in some cases, these lesions may 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 both 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 assess the disease stage [1]. This exam is based on the accumulation of FDG as a result of increased glucose metabolism in malignant tumors [1].
FDG-PET has a high sensitivity for the 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]. The CT data are thus 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 is often contraindicated [8]. Moreover, adrenal biopsy usually provides only limited diagnostic information in adrenocortical cancer and other malignancies [9]. Nevertheless, a 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 a cancer history, and data addressing the need for or benefit from surgery are 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 aimed to define a SUVmax cut-off for malignancy prediction and to study the prevalence of the 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 the selected patients were analyzed and their adrenal lesions were characterized by clinical, laboratory, and imaging findings. The histology of the adrenal lesion was also collected when available.

**FDG-PET/CT**

All the exams included in this study were performed in the Nuclear Medicine Department of our institution.

Patients fast for at least 6 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 during 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.

The patient’s glycemia is evaluated before the exam and it is ensured that the value is below 200 mg/dL. Imaging is conducted 60 min after intravenous injection of $^{18}$F-FDG (3.7 MBq/Kg). During this period, the patients stay at rest in a quiet and warm environment.

The tomographic images are acquired with the patient in the 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 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 laboratory tests. Some cases require additional imaging workup such as CT, MRI, or $^{123}$I metaiodobenzylguanidine (MIBG) scan if a pheochromocytoma is suspected. The endocrine workup of the adrenal function follows 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, laboratory, 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 clearly 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 1 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 metastasis.

Throughout this study, 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, and brown adiposity). Pheochromocytoma was classified as malignant upon the presence of distant metastases.

### Statistical analysis

Statistical analysis was performed using SPSS 25th edition. Gaussian distribution of continuous variables was determined with the Shapiro–Wilk test; non-normally variables are presented as median (minimum–maximum). Categorical variables were compared using the chi-square test or Fisher's exact test. A 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

Between 2010 and 2020, 27,427 FDG-PET/CT exams were performed in our center. Of those, 7.6% ($n = 2082$) evidenced adrenal findings. We excluded 718 exams—these patients were followed at another center; the final cohort consisted of 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. Most of the exams (99.6%) were performed in an oncological context. The FDG-PET/CT exams were requested for diagnostic purposes (patients with suspicious lesions in any site in other exams) in 6.1% ($n = 62$) and disease staging or control of disease evolution in the remaining patients. Of the 62 patients who performed FDG-PET/CT for diagnostic purposes, 25 (40.3%) had a previously known adrenal lesions. The median age of the patients at FDG-PET/CT 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 patients (38.9%).

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

### The 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 (thyroid carcinoma, adrenal tumors, and other diseases in 31, 25, and seven patients, respectively). In these 25 patients with previously known adrenal lesions, the FDG PET was performed with diagnostic purposes and in five cases it led to a diagnosis of adrenal carcinoma. The remaining 60.4% ($n = 96$) of the patients in this group were referred by other departments of our center due to the adrenal findings at PET-FDG/CT.

The median follow-up in the Endocrinology Department was 1.6 (0.2–21.6) years.

In this group of 159 patients, 18 (11.3%) were not further investigated, either due to patients’ poor prognosis or because the adrenal findings were considered not clinically relevant. It was not possible to reach 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 biochemical plus imaging characteristics in 73.5% (n = 97). The imaging modality used in these cases was non-contrast CT with measurement of Hounsfield units. Some cases also performed contrast-enhanced washout CT with a measure of contrast washout values.

Figure 2 details the findings of the 159 patients followed in the Endocrinology Department. In the group of the adenomas (n = 54), 5 (9.3%) presented adrenal-secreting adenomas (three secreted aldosterone and two cortisol) and 36 (66.7%) were non-secreting adenomas; 13 (24.1%) were inconclusive. Secreting adenomas (n = 5) showed anomalous FDG uptake in 4 (7.4%) 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 (44.4%) cases, with a median SUVmax of 4.5 (2.1–8.8), p > 0.05. Two cases (0.01%), with bilateral involvement, were diagnosed with adrenal insufficiency.
The cohort of patients not referred to the Endocrinology Department

The lesions of the 862 patients not followed by the Endocrinology Department are detailed in Table 1. In 363 (42.1%) cases, the adrenal workup was not pursued, given that the adrenal findings were considered irrelevant. The remaining patients (n = 499) presented adrenal lesions that were classified by 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.

The whole cohort of 1021 patients

Table 2 details the adrenal lesions found in the whole cohort. Of these patients, 382 (37.4%) presented adrenal metastases; most cases spread from lung carcinoma, melanoma, and lymphoma (Fig. 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).

We observed 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 (2.4–49.2), p < 0.05).

There was a tendency for higher SUVmax of adrenal cortical carcinomas when compared 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,

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Table 1 Diagnosis of the lesions found in FDG-PET from patients of other departments

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

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 as follows: sarcoma (2), lymphoma (1), and malignant pheochromocytoma. One of the sarcomas did not demonstrate anomalous FDG uptake. 2The other benign tumors are as follows: schwannoma (1), ganglioneuroma (1), adrenal necrosis (1), perirenal brown fat (1), and hemangioma (1)

| Diagnoses            | N   | SUVmax (median) | N  | %   |
|----------------------|-----|----------------|----|-----|
| Malignant lesions    |     |                |    |     |
| Metastases           | 380 | 99.5           | 7.6 (2.4–49.2) | 390 | 100  |
| Adrenal carcinoma    | 12  | 70.4           | 4.3 (2.1–9.4)  | 100 | 100  |
| Other malignant tumors1 | 4  | 4.7           | 4.7 (2.8–10.0) | 45  | 100  |
| Benign lesions       |     |                |    |     |
| Pheochromocytoma     | 6   | 4.3           | 4.3 (2.1–9.4)  | 6   | 100  |
| Adenomas             | 152 | 100           | 4.7 (2.8–10.0) | 107 | 70.4 |
| Hyperplasia          | 52  | 4.7           | 4.7 (2.8–10.0) | 52  | 100  |
| Other benign tumors2 | 5   | 4.5           | 4.5 (2.3–9.6)  | 2   | 100  |
| Normal adrenal gland | 18  | 66.7          | 5.3 (4.3–8.3)  | 12  | 100  |

Fig. 3 Primary cancers with adrenal metastases
Discussion

To our knowledge, this is the largest study analyzing adrenal findings in FDG-PET scan 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 with 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 the 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 the literature (38–57%) [10, 17, 18].

Our findings demonstrate that FDG uptake does not imply malignancy, as 172 patients (16.9%) evidenced benign lesions with anomalous FDG uptake. However, we had 37.3% (n = 381) 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 SUV-max 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.

Nevertheless, we observed that SUVmax was significantly different between benign and malignant lesions. Interestingly, there was a tendency for the adrenocortical carcinomas to show a higher SUVmax than other malignant tumors. Thus, when patients present extremely high SUVmax, clinicians must maintain a high level of suspicion of adrenocortical carcinoma, which usually portends a very poor prognosis [9]. On other hand, SUVmax was not different between pheochromocytomas and other benign or malignant tumors. In these cases, as CT alone and MRI [19], PET-FDG does not bring any additional value in the diagnosis of confined pheochromocytoma. We also observed 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 [20]. Therefore, a hormonal workup is crucial in the definitive diagnosis of an adrenal lesion such as 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

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   |
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 laboratory 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 [21].

The reduced prevalence of endocrinology referral was, at the same time, one of our main findings, as we sought 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 adrenal lesions, as we obtained a histologic diagnosis in only 3.4% of the cases. PET scans were acquired using 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. Moreover, the use of SUVmax may be controversial as it can be influenced by several variables, such as body habitus and composition, the 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 Snt [19]. Some authors have proposed the use of the adrenal-to-liver SUV ratio, rather than adrenal SUVmax alone, as it may improve the ability to correctly classify [6, 22–24]. Finally, a major limitation of this work is its retrospective nature.

Nevertheless, this work has major strengths when compared with the published literature. The large sample size, being the biggest reported to date, with patients followed at a single center, allowed us to draw a number of conclusions, including the following. Adrenal findings in FDG-PET are common in the cancer context, and lung carcinoma, melanoma, and lymphoma are the most common primary tumors spreading to the adrenals. FDG uptake does not imply malignancy and it has a role in the differential diagnoses of these lesions. For the diagnosis of pheochromocytoma, FDG seems to have no additional value. The fact that virtually all patients have a history of cancer renders this cohort homogeneous, thus enabling confirmation that the prevalence of studied adrenal lesions in the cancer context is low. We also observed that in the oncological setting, adrenal findings commonly correspond to metastases, although adenomas are also frequent. Furthermore, we also demonstrate the clinical challenge that these FDG-PET findings can represent for the endocrinologist.

Declarations

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

Informed consent Informed consent was not mandatory by our Ethics Committee as this was a retrospective analysis of anonymous data.

Competing interests The authors declare no competing interests.

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