

Research paper**Clinical utility of FDG-PET for diagnosis of adrenal mass: a large single-center experience**

Allison Pitts,¹ Grace Ih,² Meng Wei,³ Deepti Dhall,⁴ Nicholas N. Nissen,⁵
Alan Waxman,⁶ Run Yu¹

¹Division of Endocrinology, ²Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, ³Clinical Analytics, Cedars-Sinai Medical Care Foundation, Beverly Hills, ⁴Department of Pathology, ⁵Department of Surgery, ⁶Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, California, USA

ABSTRACT

OBJECTIVE: To examine the clinical utility of ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) for diagnosing whether an adrenal mass is malignant, in contemporary clinical practice. **DESIGN:** Retrospective medical record review of patients from 2 databases at a large hospital. The first database consisted of patients who underwent FDG-PET between the years 2009 to 2011 while the second database included patients who had histological diagnosis of adrenal mass between the years 1997 to 2011. **RESULTS:** 3.4% of 2921 patients had adrenal FDG uptake. Approximately 43% of them did not exhibit corresponding adrenal mass. FDG-PET performance parameters were better if a cutoff of SUV (standardized uptake value) ≥ 3 was used to define positivity. The imaging characteristics of malignant adrenal masses and pheochromocytoma were similar but differed remarkably compared to those of benign tumors. Serial imaging revealed that the malignant adrenal masses consistently exhibited high CT attenuation, while more than half of them initially exhibited SUV < 3 and in some cases FDG uptake indistinguishable from the background. The FDG-PET results were confirmatory in 87% of patients, contributory in 11%, but definitely misleading in 2%. **CONCLUSIONS:** FDG-PET is not required for adrenal mass diagnosis in most patients in contemporary practice but may help clinical decision making in specific situations.

Key words: FDG-PET, Adrenal mass, Clinical utility

INTRODUCTION

Adrenal mass is a common clinical entity occurring in 1-5% of adult patients.^{1,2} After establishing whether

an adrenal mass is hormonally active, the other critical question is whether it is benign or malignant.³⁻⁵ Small tumor size and anatomical imaging characteristics such as unenhanced CT attenuation < 10 HU (Hounsfield units) and drop of signal on out-of-phase MRI imaging are highly predictive of the benign nature of an adrenal mass.⁶⁻⁹ A fair number of patients in clinical practice, however, can have adrenal tumors with conflicting clinical and imaging features such

Address for correspondence:

Run Yu, MD, PhD, Division of Endocrinology, Cedars-Sinai Medical Center, B-131, 8700 Beverly Blvd, Los Angeles, CA 90048, USA, Tel.: 310-423-4774, Fax: 310-423-0440, e-mail: run.yu@cshs.org

Received 26-11-2012, Accepted 01-04-2013

as small tumor size and high CT attenuation. ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) has been shown to be excellent in differentiating malignant from benign adrenal tumors.¹⁰⁻¹⁵ It is not clear, though, whether FDG-PET provides independent information on whether an adrenal mass is malignant besides that already provided by clinical data and anatomical imaging. Guidelines from professional societies and authoritative reviews offer various and inconsistent opinions on the clinical utility of FDG-PET in adrenal mass diagnosis.^{3,4,16-19} Some advocate FDG-PET as an effective modality for adrenal mass diagnosis, while others discourage its use due to lack of supportive evidence.

A large number of patients undergo FDG-PET and adrenalectomy at our institution. To study the clinical utility of FDG-PET for diagnosing whether an adrenal mass is malignant, we retrospectively reviewed our institutional experience in using FDG-PET in identifying and characterizing adrenal masses.

SUBJECTS AND METHODOLOGY

Data retrieval

This study was approved by the Cedars-Sinai Institutional Review Board. The list of patients who received injection of ^{18}F -FDG at Cedars-Sinai Medical Center from October, 2009 to October, 2011 was obtained from a database at the Nuclear Medicine Department (Group 1) (Figure 1). The list of patients who underwent adrenalectomy or adrenal biopsy at Cedars-Sinai Medical Center from 1997 to 2011 was derived from a database at the Pathology Department (Group 2). Electronic or paper medical records of the patients from each group were reviewed and clinical history, imaging studies, biochemical test results, and pathological reports analyzed.

FDG-PET

Most patients underwent combined PET/CT. Prior to the procedure, patients were required to fast for >6 hours before injection of 10-15 millicuries of

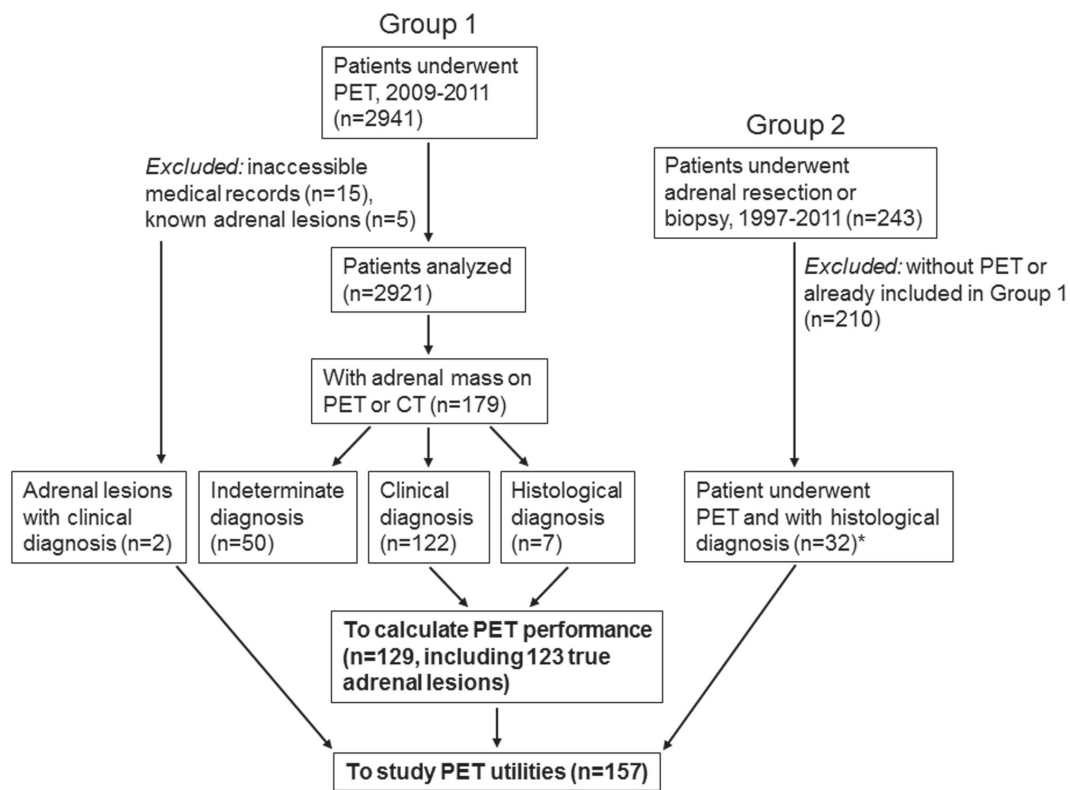


Figure 1. Two groups of patients analyzed. See text for details. *Group 2 included 6 patients with non-functioning adenoma, 2 with ectopic Cushing's syndrome, 10 with pheochromocytoma, and 14 with adrenal malignancy.

¹⁸F-FDG. Finger stick blood glucose levels ranged 65-120 mg/dL. Patients were scanned 90 minutes post injection with images obtained from the base of the brain through the mid-thigh region. CT was used for attenuation correction and localization in most cases. PET/CT images were interpreted by board-certified, experienced, nuclear medicine physicians and radiologists. Reports of CT or MRI performed within 3 months of FDG-PET were also reviewed to collect additional imaging characteristics on the adrenal masses. If multiple PETs were performed, the highest SUV (standard uptake value) of the adrenal mass was used in calculating PET performance.

Diagnostic criteria

The diagnosis of adrenal masses was made clinically in most patients and histologically in some. The clinical criteria for malignant adrenal mass were one or more of the following: explosive growth, response to chemotherapy, new lesions, and large masses with local invasion.⁸⁻¹⁵ The criteria for benign adrenal mass were one or more of the following: no significant growth (<1 mm/year) in 1 year or a longer time, Hounsfield units (HU) less than 10 on CT, and drop of signal on out-of-phase imaging on MRI. The mean and median follow-up duration for the benign adrenal masses were 18.0 and 12.1 months (range 0, 120), respectively. If sufficient clinical or imaging information regarding the adrenal mass was unavailable, the diagnosis was deemed indeterminate; patients with indeterminate diagnosis were excluded from calculation of PET performance or evaluation of PET utility. Among the 179 patients with PET- or CT-identified adrenal mass, the nature of the adrenal mass was determined by imaging follow-up in 63 patients (including 6 likely adjacent but non-adrenal lesions), by imaging criteria in 59, and by histology in 7, and deemed indeterminate in 50; their diagnoses were used to calculate the PET performance (Figure 1). The pathology database identified an additional 32 patients with histological diagnosis of the adrenal mass, and 2 of the 5 patients with known adrenal mass who were excluded from PET performance calculation in the first database also had clinical diagnosis of their adrenal masses. All the patients with clinical or histological diagnosis were used for studying imaging characteristics, dynamic changes of imaging characteristics, and impact of FDG-PET on clinical decision making.

Statistical analysis

The Student t test was used to compare the continuous values between 2 groups and the Fisher's exact test used to compare rates of discrete values from 2 groups. Linear regression was used to model the dependency of SUV on tumor size. Sensitivity, specificity, positive and negative predictive values were expressed as percentage and 95% confidence interval.²⁰ A p-value less than 0.05 was considered statistically significant. Microsoft Excel and GraphPad were used for the statistical analyses.

RESULTS

Patients and indications

In the two years from October, 2009 to October, 2011, 2941 patients (1767 female, 1173 male, and 1 unknown) underwent a total of 4445 FDG-PETs (Group 1). Patients from this database were used to study the frequency of positive adrenal findings on FDG-PET and to calculate FDG-PET performance in adrenal mass diagnosis (Figure 1). The most common indication was staging malignancies of lungs, breast, gastrointestinal tract, and hematopoietic or lymph systems, which accounted for 71.3% of patients and 73.2% of PETs. Other indications were staging less common malignancies, finding primary malignancies in patients with metastatic cancer of unknown origin, and identifying occult infections. The average age of patients was 62.6 years (range 6, 97). After exclusion of 15 patients whose medical records could not be accessed, 2926 patients were analyzed.

PET and CT findings

To assess the frequency of positive adrenal findings on FDG-PET, we excluded 5 patients who underwent PET for suspicion of adrenal malignancy. Of the remaining 2921 patients, 99 patients were found to have positive adrenal findings on PET (PET+, 3.4%) and 139 on CT (CT+, 4.8%) (Table 1). More than half of the PET+ patients (55/99) had confirmed or suspected lung malignancies; conversely, patients with lung malignancies also had a much higher rate of positive adrenal findings (8.3%) than those with other indications (1.9%) ($p < 0.001$). Seven of the 99 patients had no anatomical or clinical information, 52 had corresponding adrenal mass detected by CT

Table 1. Clinical and imaging characteristics of patients with adrenal FDG uptake (PET+), with adrenal mass on anatomical imaging (mostly CT, CT+), with both (PET+/CT+), with adrenal mass on anatomical imaging but without adrenal FDG uptake (PET-/CT+), or with adrenal FDG uptake but without adrenal mass on anatomical imaging (PET+/CT-).

	PET+, all	CT+, all	PET+/CT+	PET-/CT+	PET+/CT-	PET+/CT-, non-adrenal lesions excluded
n	99*	139	52	87	40	34
Age, mean (range), yr	69.0 (37, 96)	68.7 (20, 91)	68.9 (40, 90)	68.6 (20, 91)	68.8 (37, 96)	69.5 (37, 96)
F/M, n	41/58	71/68	21/31	50/37	18/22	15/19
Indications, lung/breast/GI/lymphoma	55/2/16/8	54/20/20/11	25/1/9/7	29/19/11/4	26/1/5/1	22/1/4/1
Unilateral/bilateral	75/24	115/24	40/12	75/12	30/10	24/10
SUV, mean (range)	6.2 (1.2, 38.3)	NA	7.7 (1.2, 30)**	NA	4.6 (1.5, 38.3)**	4.4 (1.5, 38.3)
Tumor size, mean (range), cm	NA	2.0 (0.5, 5.8)	2.7 (0.5, 8.5)	1.7 (0.7, 4.4)	NA	NA
Clinical diagnosis, malignant/benign/indeterminate	36/22/34	26/88/25	26/17/9	0/71/16	10/5/25	4/5/25
PET+ if SUV ≥ 3 Clinical diagnosis, malignant/benign/indeterminate	35/8/14	26/88/24	26/7/4	0/81/20	9/1/10	3/1/10

*Seven patients have no anatomical imaging or detailed clinical information. ** $p=0.021$.

or MRI (PET+/CT+), and surprisingly, 40 did not have an identifiable adrenal mass (PET+/CT-). Of the 139 CT+ patients, 52 were PET+ and 87 were PET-. The demographics of the PET+/CT+ and the PET+/CT- groups were not different. Similarly, lung malignancies were the PET indications in about half the patients. Seven patients in the PET+/CT+ group underwent adrenalectomy and pathology demonstrated metastatic lesions in 6 and nodular cortical hyperplasia in 1. The remaining 45 patients likely had metastatic malignant adrenal mass (n=20), benign adrenal tumor (n=16), or adrenal tumor of indeterminate nature (n=9). The average SUV of the PET+/CT- group was significantly lower than that of the PET+/CT+ group. On detailed re-examination of the PET and CT or MRI images, 6 "adrenal" lesions identified on PET were actually enlarged lymph nodes or diaphragmatic tumor implantation. Most (n=20) of the 34 PET+/CT- patients with true adrenal PET+ lesions had SUV lower than 3. The clinical diagnosis of most of the 34 patients could not be established as the patients either died shortly after the PET or did not go through further imaging; 4 of the remaining 9

patients had clinical diagnosis of adrenal malignancy and 5 benign adrenal tumors (Figure 2). None of the 34 patients had clinical evidence of Cushing's syndrome. Random serum cortisol levels were measured in only 3 patients; one of them had normal and 2 elevated cortisol levels.

PET Performance in adrenal mass diagnosis

The performance of PET was assessed based on 2 cutoffs: any adrenal FDG uptake as described in the nuclear medicine report and SUV ≥ 3 (Table 2). Using the first criterion, the sensitivity of PET to detect malignant adrenal mass is 100.0 \pm 4.0% (36/36), specificity 76.3 \pm 9.1% (71/93), positive predictive value 62.1 \pm 13.1% (36/58), negative predictive value 100.0 \pm 2.1% (71/71), positive likelihood ratio 4.22, and negative likelihood ratio 0. Using the second criterion, the sensitivity (35/35), negative predictive value (81/81), and negative likelihood ratio did not change, while the specificity increased to 91.0 \pm 6.5% (81/89), positive predictive value to 81.4 \pm 12.5% (35/43), and positive likelihood ratio to 11.1. Thus, using an SUV cutoff of 3 to define PET positivity

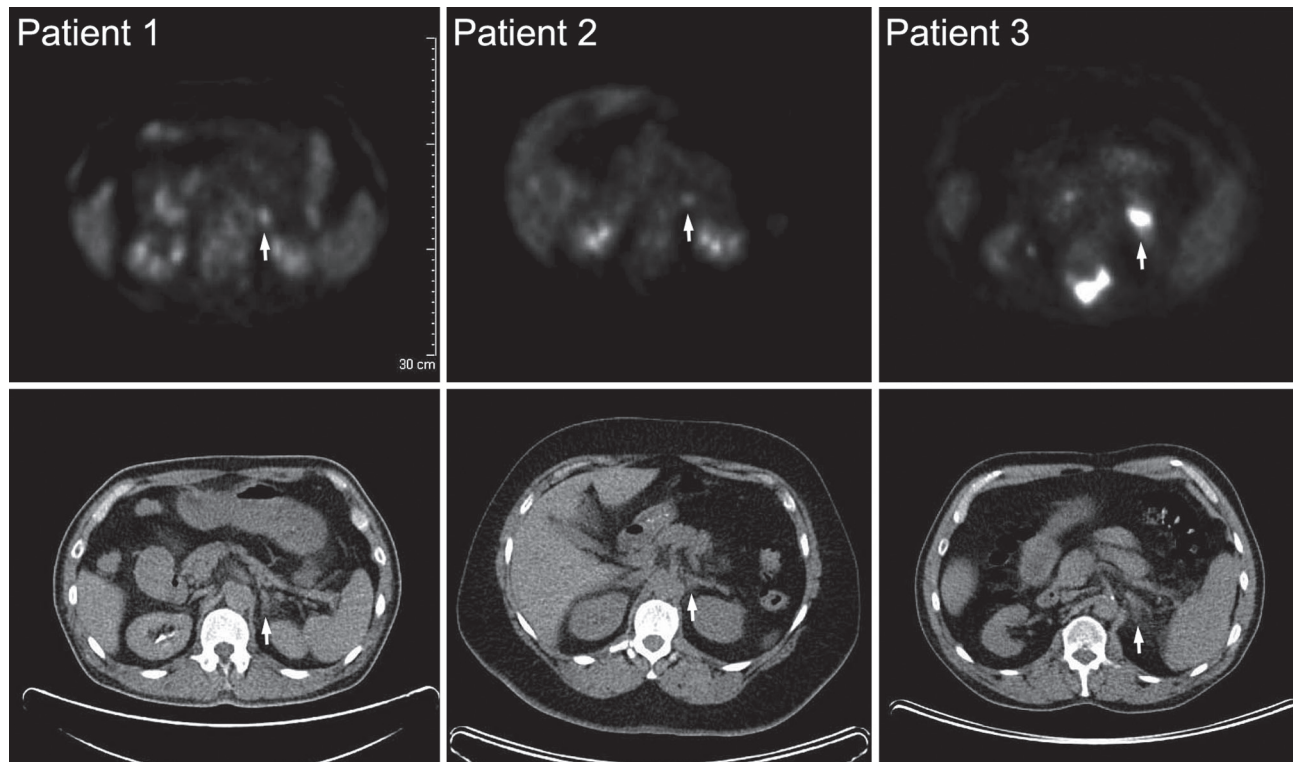


Figure 2. FDG-PET-positive adrenal lesions without corresponding CT abnormalities. Upper panels are axial PET images showing left adrenal FDG uptake, and in lower panels are the corresponding CT images. Patient 1 was a 59-year-old male with small cell lung cancer. The left adrenal FDG uptake disappeared after chemotherapy. Patient 2 was a 59-year-old female with non-small cell lung cancer. The left adrenal was monitored by imaging for 2 years without mass development. Patient 3 was a 72-year-old male with non-small cell lung cancer. He died within a month of the PET examination without further study of the adrenal gland. Arrow, left adrenal gland.

Table 2. FDG-PET performance in identifying malignant adrenal mass. The first numbers in the cells were based on data that consider any adrenal FDG uptake as positive. The numbers in parentheses were derived from data that only consider adrenal FDG uptake with $SUV \geq 3$ as positive.

	PET+	PET-	Total
Malignant	36 (35)*	0 (0)	36 (35)
Benign	22 (8)	71 (81)	93 (89)
Total	58 (43)	71 (81)	129 (124)

*Including 6 adjacent but non-adrenal lesions.

appears to be more beneficial than considering any SUV values as positive.

PET and CT imaging characteristics of adrenal lesions

All patients with clinical or histological adrenal mass diagnosis from the first database and 32 ad-

ditional patients (6 with benign non-functioning adenoma, 2 with bilateral adrenal hyperplasia, 10 with pheochromocytoma, and 14 with malignancy) from the pathology database (Group 2) were used to study imaging characteristics, dynamic changes of imaging characteristics, and impact of FDG-PET on clinical decision making (Figure 1). Altogether, 157 patients (39 with histological diagnosis and 118 with clinical diagnosis) were identified, including 100 with benign adenoma, 2 with bilateral hyperplasia, 10 with pheochromocytoma, and 45 with malignant adrenal mass (Table 3). The demographics of patients with adenoma, pheochromocytoma, or malignancy were similar. The average size of malignant tumors (3.5 cm) was significantly larger than that of adenomas (2.0 cm) but similar to that of pheochromocytomas (3.3 cm). The average tumor SUV, the relative numbers of tumors with $SUV > \text{liver SUV}$, and the unenhanced CT attenuation of malignant adrenal masses were

Table 3. Clinical and imaging characteristics of patients with diagnosed adrenal lesions who underwent both FDG-PET and CT. The SUV of background adrenal FDG uptake is arbitrarily assigned a value of 1.

	Benign adrenal mass	Ectopic Cushing's syndrome	Pheochromocytoma	Malignant adrenal mass
n	100	2	10	45
Age, mean (range), yr	69.0 (41, 91)	58/47	62.0 (46, 81)	66.9 (37, 89)
F/M, n	54/46	1/1	4/6	18/27
Tumor size, mean (range), cm	2.0 (0.5, 5.8)	NA	3.3 (1.8, 5.3)	3.5 (1.0, 8.5)*
SUV, mean (range)	1.6 (1, 23.4)**	3.2/1	4.2 (1.7, 6.3)	10.3 (1.5, 30)*
SUV, >liver/≤liver, n	7/93	2/2	6/4	42/3*
Unenhanced CT attenuation, HU	2.9 (-74, 36.5)	NA	32.5 (20.2, 42)	29.3 (13.3, 51)*

* $p < 0.0001$ comparing the parameters between the benign and malignant groups. HU, Hounsfield unit.

**A 66-year-old male had a 4.5-cm left adrenal mass exhibiting an unenhanced CT attenuation of 27 HU and an SUV of 23.4, and similar lesions in the spine. All the lesions were stable over 7 years. Biopsy of the adrenal and spinal lesions did not find malignant cells. The patient declined surgical resection.

all much higher than those of adenomas. There was a poor correlation between tumor SUV and tumor size for both benign and malignant adrenal masses. Pheochromocytomas had similar unenhanced CT attenuations but lower SUV than malignancies (Table 3). Both patients with bilateral adrenal hyperplasia had Cushing's syndrome due to ectopic ACTH production; the one with higher cortisol production (24-hour urine free cortisol levels 2170.5 μg) had moderate bilateral FDG uptake but the other with lower cortisol production (1359.4 μg) did not exhibit significant FDG uptake.

Dynamic changes in PET and CT imaging characteristics over time

Ten patients with benign adrenal masses (1 tumor per patient) that had some FDG uptake and 12 patients with malignant ones (13 tumors as 1 patient had bilateral adrenal masses) underwent more than one PET. The median duration between the first and last PETs for the benign adrenal masses was 5.1 months (range 1.5, 71.2). None of the benign tumors exhibited noticeable growth between the PETs and the SUV of the adrenal mass fluctuated slightly but remained mostly below 3 (Figure 3). The median duration

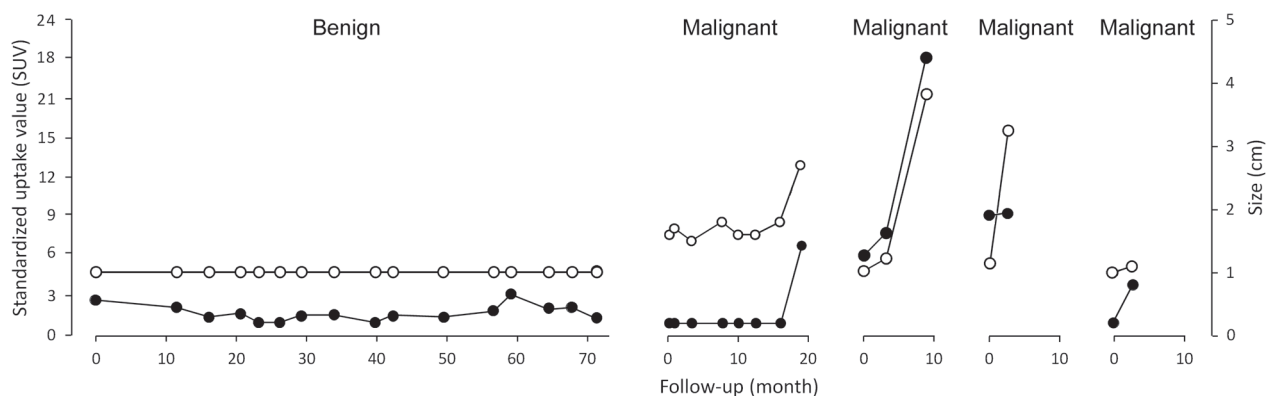


Figure 3. FDG-PET SUV and tumor size changes over time in 5 patients. Solid symbols represent SUV and hollow ones tumor size. The patient with the benign adrenal tumor was a 59-year-old male with colon cancer. The four patients with metastatic adrenal mass were, from left to right, 49-, 68-, and 85-year-old male, all with non-small cell lung cancer, and 62-year-old male with colorectal cancer, respectively. Normal PET findings in the adrenal areas were assigned an SUV of 1.

between the first and last PETs for the malignant adrenal masses was 4.9 months (range 2.6, 56.0). Most of the malignant tumors grew significantly between the PETs and the SUV of the adrenal masses exhibited 3 patterns of increase over time: 1) SUV increases with the growth of adrenal mass (in 10 patients); 2) SUV remains high regardless of tumor growth (in 1 patient); and 3) SUV increases with little tumor growth (in 1 patient) (Figure 3). Although the SUV of 5 malignant tumors was always ≥ 3 , remarkably, the SUV of 8 others (4 non-small cell lung cancers, 3 colorectal cancers, and 1 renal cell cancer) from 7 patients was initially < 3 , even completely normal in 7 of the 8 tumors, and only became elevated after significant tumor growth. The median size of those 8 malignant tumors was 1.25 cm (range 0.5-2.5) at the time of the first PET. If the initial SUVs had been used to calculate the performance of PET, the sensitivity would have been reduced to $88.6 \pm 11.8\%$ (31/35), and specificity to $95.3 \pm 5.2\%$ (81/85). The unenhanced CT attenuation measured by Hounsfield units (HU) was relatively stable for pheochromocytomas and adrenal malignancies (Figure 4). For example, the unenhanced HU of all pheochromocytomas and malignancies was consistently > 10 , and usually > 20 . Only two patients with benign adrenal adenomas had serial follow-up of unenhanced HU which remained largely stable. The MRI imaging characteristics of 1 pheochromocytoma and 1 renal cell cancer metastasized to the adrenal

also did not change. Figure 5 shows a metastatic adrenal mass which grew significantly in 3.5 years; the mass had similar imaging characteristics on CT and MRI over time, but exhibited initially normal SUV.

Impact of PET on clinical decision making

To analyze the clinical utility of PET, we reviewed the cases of the 157 patients with histological or clinical diagnosis of the adrenal mass to determine whether the PET results would have influenced the clinical decision making. In most patients (87.3%), the PET results confirmed the clinical diagnoses which were made solidly without the PET results (Table 4). In 20 patients (12.7%), the PET results significantly influenced clinical decision making. Low FDG uptake contributed to the correct diagnosis of benign mass in 6 patients with medium-sized adrenal masses with high CT attenuation, but high FDG uptake contributed to the incorrect diagnosis of adrenal malignancy in 3 patients with benign adrenal masses. Strong FDG uptake contributed to the correct diagnosis of malignant adrenal mass in 10 patients with small-to-medium-sized adrenal masses. Overall, 17 patients (10.8%) significantly benefited from PET, but the diagnosis of 3 (1.9%) was misled by PET.

DISCUSSION

In this study, the clinical utility of FDG-PET for

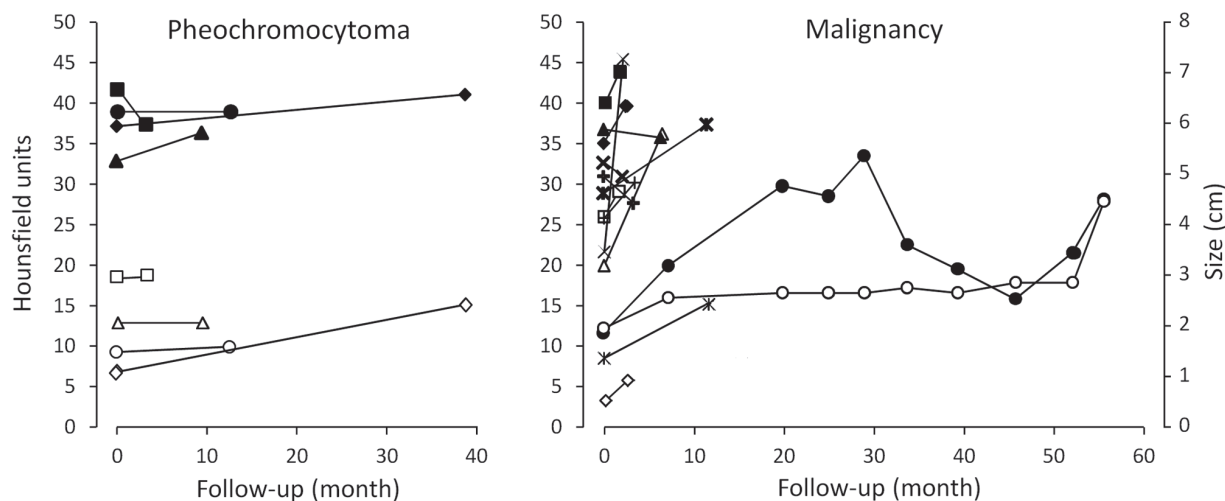


Figure 4. Unenhanced CT attenuation and tumor size changes over time in patients with pheochromocytoma (n=4) or malignant adrenal mass (n=7). Solid or bold symbols represent Hounsfield units (HU) and hollow or regular ones tumor size.

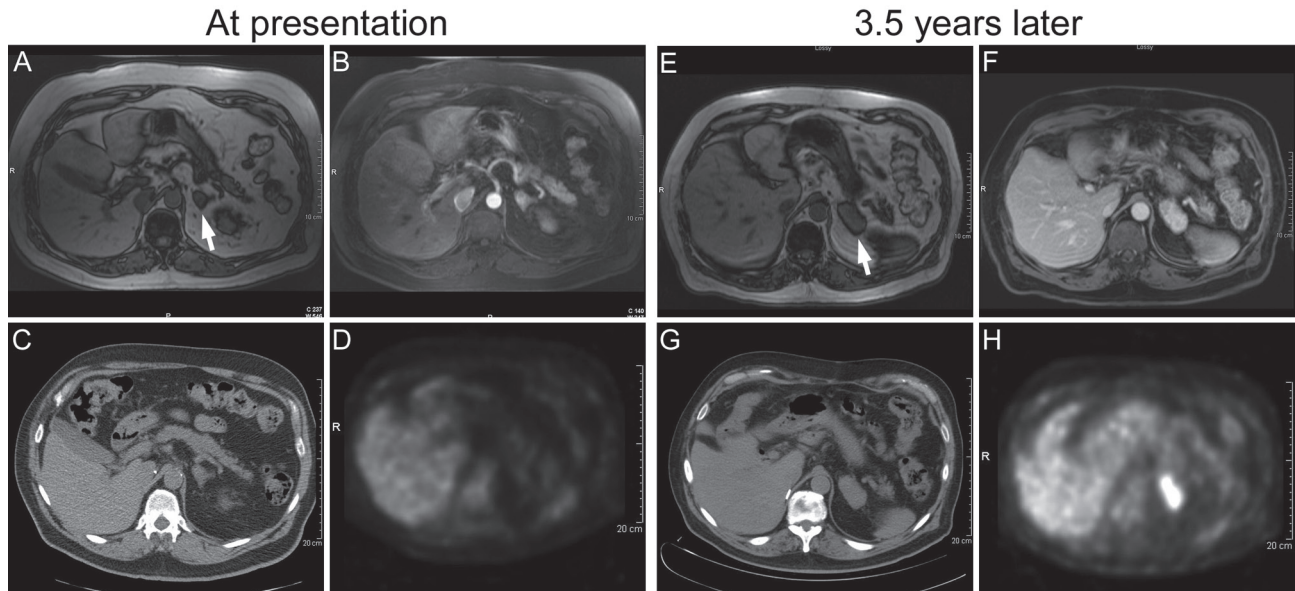


Figure 5. MRI, CT, and FDG-PET axial images of the same left adrenal mass 3.5 years apart. The adrenal mass was from a 71-year-old male with renal cell carcinoma metastasis. A and E, out-of-phase MRI showing similar no drop of signal; B and F, enhancement after gadolinium on T1 MRI showing similar enhancement; C and G, pre-contrast CT with Hounsfield units of 25 and 29, respectively; and D and H, FDG-PET with SUV of 1.2 and 5.2, respectively.

Table 4. Impact of FDG-PET on clinical decision making. All cases of diagnosed adrenal masses were reviewed. The FDG-PET results were evaluated and their contribution to clinical decision making determined.

	Benign adrenal mass	Ectopic Cushing's syndrome	Pheochromocytoma	Malignant adrenal mass
n	100	2	10	45
Insignificant FDG-PET contribution, n	91	2	9	35
Significant FDG-PET contribution, n	9	0	1	10
Correct FDG- PET contribution, n	6	0	1	10
Incorrect FDG-PET contribution, n	3	0	0	0

adrenal mass diagnosis at a large general hospital was examined. To our knowledge, this is the first study to comprehensively analyze the FDG-PET findings, performance, and effectiveness regarding the adrenal gland in an unselected patient population based on routine clinical practice. Our study clearly indicates that although FDG-PET, when used alone, is effective in differentiating malignant from benign adrenal mass, it only adds limited additional information on the nature of adrenal mass in modern-day routine clinical practice.

We describe, for the first time, the prevalence (3.4%) of adrenal FDG uptake in patients undergo-

ing FDG-PET for cancer staging or diagnosis. As the prevalence of adrenal FDG uptake in patients with lung cancer in our study (8.3%) is very similar to the 10.6% calculated from a previous report with large number of patients,²¹ the overall prevalence described in our study probably reflects the prevalence of adrenal FDG uptake in general practice. We demonstrate that the PET+ and CT+ adrenal lesions belong to two overlapping but different groups, and most of the former are malignant but most of the latter are benign. We further demonstrate that more than half of the PET+ patients had corresponding adrenal mass on anatomical imaging, but interestingly, 43% of them did not. The nature of the PET+/CT- lesions

is intriguing and still not entirely clear. Misreading of adjacent, non-adrenal lesions only explains several cases, while the majority of them had unknown diagnosis because the PET+/CT- patients often died too soon to allow a definitive clinical diagnosis or had too advanced cancer to warrant resection. As metastasis in a morphologically normal adrenal gland is not uncommon,^{22,23} it is possible that PET+/CT- lesions are adrenal glands with microscopic metastatic tumors which accumulate enough FDG. The PET+/CT- adrenal lesions are unlikely to have been caused by ectopic ACTH production. As shown in this study and another,²⁴ only patients with ectopic Cushing's syndrome who have very high cortisol levels exhibit significant adrenal FDG uptake. Absence of clinical Cushing's syndrome in the PET+/CT- patients implies that it is unlikely that they had ectopic Cushing's syndrome.

Our data confirm that FDG-PET performs very well in differentiating malignant from benign adrenal mass,¹⁰⁻¹⁵ but with several important caveats. In our study, FDG-PET indeed is highly sensitive in detecting malignant adrenal mass and negative findings rule out malignant adrenal mass. The calculations of sensitivity and negative predictive value, however, were based on the highest SUV if the patients had undergone serial PETs. More than half of the malignant adrenal masses were initially completely negative on FDG-PET. One may argue that metastasis was not present on the initial PET and only occurred later, after which the PET results became positive. We cannot completely disprove that argument but we suggest that it is implausible based on the following considerations. All the adrenal masses exhibited CT or MRI features inconsistent with benign adenomas at the very beginning of discovery by CT or MRI. There was also no heterogeneity in imaging characteristics after the tumors grew bigger. Finally, histological examination of the resected adrenal tumors showed homogeneous malignancy and did not find a benign tumor component. The malignant adrenal masses that are initially negative on FDG-PET are not necessarily very small. Although it is well recognized that malignant adrenal masses less than 1 cm may exhibit negative FDG-PET findings,¹⁵ we show here that malignant adrenal masses up to 2.5 cm may not be detected by FDG-PET and there is

a poor correlation between tumor SUV and size in general. Thus, negative FDG-PET findings on small adrenal masses need to be interpreted very cautiously. In contrast to the evolving SUV on FDG-PET, the imaging characteristics of malignant adrenal tumors (and pheochromocytomas) on CT or MRI are remarkably stable so that they are more useful to exclude malignancy than FDG-PET for small adrenal tumors. In agreement with previous reports,¹⁰⁻¹⁵ we also show that specificity and positive predictive value of FDG-PET can be increased by using a cutoff SUV of 3 or > that of liver. Even with the cutoff, 1 in five patients with positive adrenal FDG-PET finding still has benign adrenal mass which does not require resection. As pheochromocytoma and malignant adrenal mass have rather similar FDG-PET and anatomical imaging characteristics, pheochromocytoma needs to be tested in patients with an adrenal mass that are positive on FDG-PET.

No matter how FDG-PET performs in differentiating malignant from benign adrenal mass, our data clearly indicate that it adds little additional clinical utility to diagnose adrenal mass besides what the clinical information and anatomical imaging characteristics already provide. In modern clinical practice, barely any patients would undergo FDG-PET as the initial and only imaging modality to study the adrenal mass. The adrenal gland is covered by both thoracic and abdominal CT or MRI. Most commonly, adrenal masses are identified incidentally by CT or MRI for non-adrenal indications such as abdominal pain or cancer staging.^{1,2} The imaging characteristics of the adrenal masses are already known to some extent. We show that against this background, FDG-PET only confirms the pre-PET diagnosis in the vast majority of patients. In about 10% of patients, the FDG-PET does add new information. Those patients either have small adrenal masses with high CT attenuation, large adrenal masses with low or borderline CT attenuation, or incomplete anatomical imaging such as CT of the abdomen without the unenhanced protocol. Even for those patients, it is not clear if the negative FDG-PET results can be interpreted with confidence when the adrenal masses are small because malignant adrenal masses may not exhibit significant FDG uptake if the masses are <2.5 cm, discussed previously. In a few patients, significant FDG uptake prompted surgical

resection or recommendation of surgical resection of benign adrenal masses, which is not unreasonable considering the 80% positive predictive value, but the uncertainty needs to be explained to patients. We thus do not recommend FDG-PET for adrenal mass diagnosis in general, with perhaps one exception: FDG-PET may benefit patients with a large, non-pheochromocytoma, adrenal mass of unknown growth speed by suggesting whether this tumor is likely malignant and whether metastasis has already occurred so that the appropriate treatment strategy can be formulated. If FDG-PET is indicated anyway for staging of non-adrenal malignancies, the “free” additional information on the adrenal mass provided by PET is welcome but should be interpreted with all the caveats we have discussed. Finally, we wish to emphasize that a patient’s clinical background, including the nature of preexisting malignancy and the extent of metastasis, gives “free” but important information on the nature of an adrenal mass.

This study has a few limitations. First, the data were from a single institution. Second, only 22% of patients had histological diagnosis of their adrenal masses. Third, the adrenal mass diagnosis was indeterminate in 27% of patients. Third, as some evidence suggests that pheochromocytomas and benign adenomas may grow at a similar speed,²⁵ the clinical diagnosis criteria could classify pheochromocytoma as benign, which is not incorrect but oversimplifies the diagnosis. Last, most patients in our study had preexisting or suspected malignancy of other organs, so that it is not clear if the results in this study can be extrapolated to guide the diagnosis of adrenal mass in the general population.

In summary, this study demonstrates that although FDG-PET performs very well in differentiating malignant from benign adrenal mass in patients with preexisting or suspected malignancy of other organs, it is not required for adrenal mass diagnosis per se in most patients in contemporary clinical practice. Several caveats in interpreting adrenal FDG-PET findings are suggested, including evolving tumor SUV, SUV cutoff, and correlation of FDG-PET findings with the more consistent anatomical imaging characteristics. In a few specific situations, FDG-PET may help clinical decision making on adrenal mass diagnosis and treatment.

REFERENCES

1. Bovio S, Cataldi A, Reimondo G, et al, 2006 Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *J Endocrinol Invest* 29: 298-302.
2. Davenport C, Liew A, Doherty B, et al, 2011 The prevalence of adrenal incidentaloma in routine clinical practice. *Endocrine* 40: 80-83.
3. Young WF Jr, 2007 The incidentally discovered adrenal mass. *N Engl J Med* 356: 601-610.
4. Anagnostis P, Karagiannis A, Tziomalos K, Kakafika AI, Athyros VG, Mikhailidis DP, 2009 Adrenal incidentaloma: a diagnostic challenge. *Hormones (Athens)* 8:163-184.
5. Nieman LK, 2010 Approach to the patient with an adrenal incidentaloma. *J Clin Endocrinol Metab* 95: 4106-4113.
6. Mantero F, Terzolo M, Arnaldi G, et al, 2000 A survey on adrenal incidentaloma in Italy. *J Clin Endocrinol Metab* 85: 637-644.
7. Wang TS, Cheung K, Roman SA, Sosa JA, 2012 A cost-effectiveness analysis of adrenalectomy for nonfunctional adrenal incidentalomas: Is there a size threshold for resection? *Surgery* 152: 1125-1132.
8. Hamrahian AH, Ioachimescu AG, Remer EM, 2005 Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. *J Clin Endocrinol Metab* 90: 871-877.
9. Israel GM, Korobkin M, Wang C, Hecht EN, Krinsky GA, 2004 Comparison of unenhanced CT and chemical shift MRI in evaluating lipid-rich adrenal adenomas. *AJR Am J Roentgenol* 183: 215-219.
10. Yun M, Kim W, Alnafisi N, Lacorte L, Jang S, Alavi A, 2001 18F-FDG PET in characterizing adrenal lesions detected on CT or MRI. *J Nucl Med* 42: 1795-1799.
11. Metser U, Miller E, Lerman H, Lievshitz G, Avital S, Even-Sapir E, 2006 18F-FDG PET/CT in the evaluation of adrenal masses. *J Nucl Med* 47: 32-37.
12. Caoili EM, Korobkin M, Brown RK, Mackie G, Shulkin BL, 2007 Differentiating adrenal adenomas from non-adenomas using (18)F-FDG PET/CT: quantitative and qualitative evaluation. *Acad Radiol* 14: 468-475.
13. Han SJ, Kim TS, Jeon SW, et al, 2007 Analysis of adrenal masses by 18F-FDG positron emission tomography scanning. *Int J Clin Pract* 61: 802-809.
14. Okada M, Shimono T, Komeya Y, et al, 2009 Adrenal masses: the value of additional fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in differentiating between benign and malignant lesions. *Ann Nucl Med* 23: 349-354.
15. Boland GW, Dwamena BA, Jagtiani Sangwaiya M, et al, 2011 Characterization of adrenal masses by using FDG PET: a systematic review and meta-analysis of diagnostic test performance. *Radiology* 259: 117-126.
16. Zeiger MA, Thompson GB, Duh QY, et al, 2009 The

- American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. *Endocr Pract* 15: Suppl 1: 1-20.
17. Terzolo M, Stigliano A, Chiodini I, et al, 2011 AME position statement on adrenal incidentaloma. *Eur J Endocrinol* 164: 851-870.
 18. Terzolo M, Bovio S, Pia A, Reimondo G, Angeli A, 2009 Management of adrenal incidentaloma. *Best Pract Res Clin Endocrinol Metab* 23: 233-243.
 19. Harrison B, 2012 The indeterminate adrenal mass. *Langenbecks Arch Surg* 397: 147-154.
 20. Browner WS, Newman TB, 1987 Are all significant P values created equal? The analogy between diagnostic tests and clinical research. *JAMA* 257: 2459-2463.
 21. Brady MJ, Thomas J, Wong TZ, Franklin KM, Ho LM, Paulson EK, 2009 Adrenal nodules at FDG PET/CT in patients known to have or suspected of having lung cancer: a proposal for an efficient diagnostic algorithm. *Radiology* 250: 523-530.
 22. Pagani JJ, 1983 Normal adrenal glands in small cell lung carcinoma: CT-guided biopsy. *AJR Am J Roentgenol* 140: 949-951.
 23. Gupta NC, Graeber GM, Tamim WJ, Rogers JS, Irisari L, Bishop HA, 2001 Clinical utility of PET-FDG imaging in differentiation of benign from malignant adrenal masses in lung cancer. *Clin Lung Cancer* 3: 59-64.
 24. Pruthi A, Basu S, Ramani SK, Arya S, 2010 Bilateral symmetrical adrenal hypermetabolism on FDG PET in paraneoplastic Cushing syndrome in breast carcinoma: correlation with contrast-enhanced computed tomography. *Clin Nucl Med* 35: 960-961.
 25. Yu R, Phillips E, 2012 Growth speed of sporadic pheochromocytoma. *Clin Endocrinol (Oxf)* 77: 331-332.