

# Does Side Matter?: A Retrospective Study Exploring the Side Preference of Abnormal Hypermetabolic Adrenal Activity

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**Abstract:** Hypermetabolic adrenal activity can be seen on F-18 FDG positron emission tomography (F-18 FDG PET) in patients undergoing evaluation for malignancy. The adrenal glands are bilateral organs that are anatomically similar to each other with no differences to arterial supply. They are also a common site of metastases. A retrospective study of 1135 patients with tumors at a veteran hospital was performed to see if hypermetabolic adrenal activity was more common on the left or right. Chi-square analysis demonstrated a significant side preference, with hypermetabolic activity occurring significantly more often in the left adrenal gland.

**Keywords:** Adrenal, PET/CT, incidentaloma, F18-FDG.

## INTRODUCTION

F-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) is a functional imaging modality which uses a radioactive glucose analog to allow visualization of cellular metabolism which is reflected by F-18 FDG activity. As such FDG activity can be quantitatively described by a standard uptake value (SUV). This type of imaging has found its role in clinical practice in the monitoring and evaluation of disease, as many pathological processes increase cellular metabolic activity. Even though PET has proven to be very useful in the evaluation of malignancy, it does have its shortcomings as inflammatory or infectious process may present increased FDG uptake. In order to minimize these shortcomings, PET is now usually combined with computed tomography (CT). This combination allows for fusion of the anatomic images with the functional images thus allowing for better tissue activity localization. Additionally, CT fusion allows for attenuation correction which greatly improves image quality. Though this combination of modalities has greatly improved PET imaging, problems still arise. One such problem, is that of the unexpected "incidental finding", which includes unexpected adrenal lesions on CT, ultrasound (US), or magnetic resonance imaging (MRI) as well as unknown adrenal metabolic activity on PET. Though "incidentalomas" present a diagnostic dilemma in any modality, it is especially true in patients undergoing PET/CT as 38-57% of "incidentalomas" in this population were associated with extra-adrenal primary malignancy [1].

The adrenal glands are suprarenal structures with a cortex and a medulla, both of which provide endocrinological support for the body. While both adrenal glands function similarly it is well known and established that the adrenal glands are anatomically similar to one another. Though the arterial supplies of the right and left adrenal gland are generally similar, there is a difference with regards to venous drainage and lymphatics [2, 3]. On the right, the suprarenal vein drains directly into the inferior vena cava while on the left, it drains directly into the left renal vein. With regards to the lymphatics, both left and right adrenal lymphatics drain towards aortic lymph nodes, drainage towards hepatic lymphatics is often seen on the right.

With advent of cross sectional imaging, adrenal "incidentalomas" are seen in up to 5% of the population [4]. While the majority of these adrenal abnormalities tend to be benign, up to 21-50% have been found to harbor malignancy in patients with cancer [4, 5]. Since those who were imaged with PET/CT usually have a history of a cancer, incidental findings involving the adrenal gland tends to be more worrisome and of greater clinical significance. Utilizing PET imaging, previous authors have formulated methods to differentiate malignant from benign lesions, using both qualitative (visually) and quantitative (SUV) methods [6, 7]. Although these studies have progressed the evaluation of adrenal "incidentalomas" on PET, using somewhat complex metabolic characteristics/calculations, simple characteristics such as anatomic sidedness of abnormal hypermetabolic adrenal activity has not been evaluated.

Upon the author's observation, it has been noticed that hypermetabolic adrenal lesions on PET tend to be more common on the left than on the right. It is

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therefore hypothesized that there is a difference between the frequency of involvement of the right and left adrenal gland with regards to the presence of hypermetabolic activity. The purpose of this study is to evaluate the presence of the hypothesized difference and discuss the potential implications of such a difference.

## MATERIALS AND METHODS

### Subjects

After the institution review board approved this retrospective HIPPA complaint study and waived informed consent, data were obtained by chart/image review without the need for patient informed consent. Subjects in this study included all patients, both male and female, who had undergone PET imaging between January 2012 and March 2016. A total of 1135 patients, with 1097 males and 38 females, were included in the study with each patient only contributing one data entry point. The average patient age was 68.1 years.

Non-contrast-enhanced 18F-FDG PET/CT images were obtained using Biograph Molecular PET/CT, Siemens. All patients referred for PET/CT fasted for 8 hours prior to injection of F18-FDG except for glucose-free oral hydration before the PET/CT examination. Blood glucose level were measured and met the service requirement of no more than 150 mg/dl prior to 18F-FDG injection. Intravenous injection of 370-555 MBq (10-15 mCi) of 18F-FDG was subsequently administered. The non-enhanced CT scan was performed from the skull base through the mid-thigh on 64-slice CT scanner using the following parameters: 120 kVp; 58 mAs; 0.5 second gantry rotation time; 1.0 pitch beam width; 5 mm reconstruction thickness. Each patient's images were reviewed by a nuclear medicine attending physician for the presence of hyper-metabolic activity in the adrenal glands. PET findings were interpreted as positive if FDG activity in the adrenal lesion is greater than that in the liver and as negative if lesion uptake is equal to or less than that in the liver [1].

The patients indication for the PET/CT imaging was to evaluate malignancy or to follow up the malignancy. The exams were then reviewed for the presence of hypermetabolic activity centered within the adrenal gland. If present, the sidedness of the hypermetabolic foci was recorded as neither, bilateral, left or right.

## Statistics

A Pearson Chi Square test was used to evaluate whether an adrenal hypermetabolic focus was significantly more common on the left, right, or bilaterally. A  $P < 0.05$  was considered statistically significant. The Independent – samples Kruskal-Wallis Test was used to evaluate whether age and SUV value, separately, vary between sidedness. All tests were two sided and considered to be statistically significant at an alpha level of 0.05.

## RESULTS

Of the total 1135 patients, 60 were found to have adrenal hyper-metabolic activity with 41/60 in the left adrenal gland, 9/60 in the right adrenal gland and 10/60 in bilateral glands (Table 1 and Figure 1). For 60 cases with hypermetabolic foci in the adrenal gland, lung cancer is the most common malignancy, followed by head and neck cancer, gastrointestinal cancer, melanoma, prostate cancer, lymphoma, unknown, neuroendocrine tumor, pancreatic tumor, thymoma and renal cell carcinoma (Table 2). There is no relationship between SUV value or the patient's age and the side of the hypermetabolic adrenal activity (Figures 2, 3).

Table 1: Side of Adrenal Hypermetabolic Activity

Side	Total (of 1135)	Percentage %
Left	41	3.6
Right	9	0.08
Bilateral	10	0.09

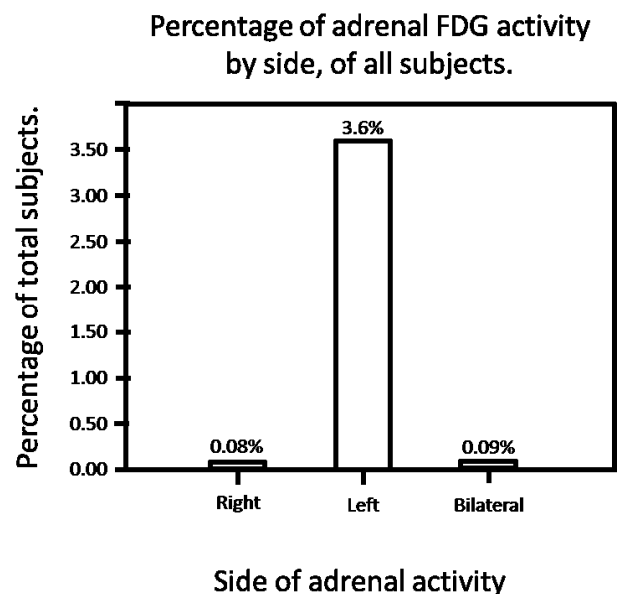
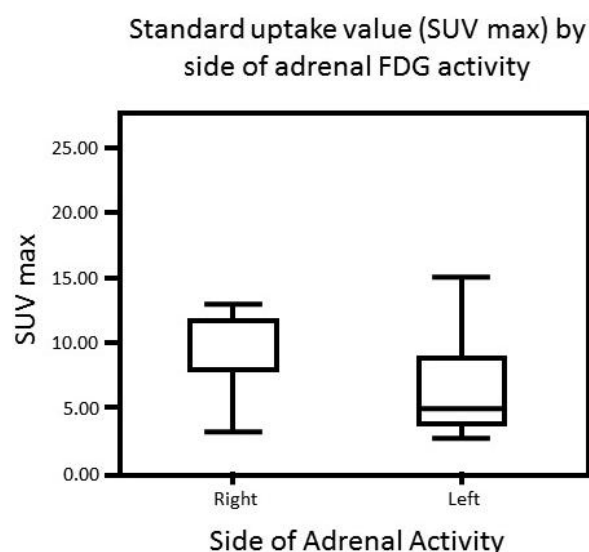
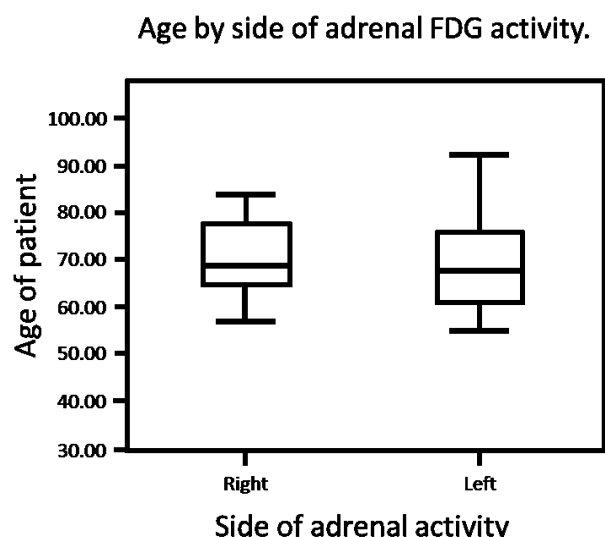


Figure 1:

**Table 2: Site of Primary Malignancy**

Malignancy Site	Cases (out of 60)
Lung	38
Head and Neck	5
Gastrointestinal	4
Melanoma	3
Prostate	2
Lymphoma	2
Unknown	2
Neuroendocrine	1
Pancreatic	1
Thymoma	1
Renal	1

**Figure 2:****Figure 3:**

A chi-square and fisher's exact test found that adrenal hypermetabolic activity was found significantly more frequently on the left, than the right or bilaterally  $\chi^2$  (2, N=1135) = 35.32,  $p$  = <.001 (Figure 1).

An independent Kruskal-Wallis t-test found no relationship between sidedness and the SUV ( $p$  = .167) (Figure 2) or sidedness and age ( $p$  = .693) (Figure 3).

## DISCUSSION

In effort to evaluate adrenal hypermetabolic activity, a retrospective case review was performed demonstrating a significant anatomic preference for the left adrenal gland. No relationship was found between SUV value or the patient's age and the side of the hypermetabolic adrenal activity.

Although left side preference with regards to hypermetabolic activity has been demonstrated, it is unclear why this preference exists though it may be related to the anatomical differences. While these findings may not instantly impact patient management or change the practice of radiographic evaluation, it does provide direction for future research consideration.

Though no prior studies have been performed specifically evaluating the sidedness of hypermetabolic adrenal activity there have been multiple studies which have progressed the methods used to evaluate hypermetabolic activity in the adrenal gland as either benign or malignant [8]. These studies, including a meta-analysis performed by Boland *et al.*, have described two main evaluation methods: qualitative and quantitative. The qualitative method depends on visual analysis, where the metabolic activity of the liver is compared to that of the adrenal gland. If the adrenal metabolic activity is greater than the metabolic activity of the liver, then the activity is more likely to be classified as hypermetabolic. The quantitative method uses either an absolute cut off value (based on the maximum adrenal SUV) or an adrenal to liver SUV ratio [4]. However, these methods are not flawless as Vikram *et al.*, using a quantitative method, demonstrated the presence for potential false positives and negatives. Utilizing follow up data and biopsy results, of the 37 "PET positive" lesions evaluated 12 were found to be benign, and of the 75 "PET negative" lesions, five were found to be malignant [9]. Multiple other methods of evaluation have been described in the literature, including the use of other modalities such as MRI and contrast enhanced CT both of which come

with their own shortcomings. While these described methods are efficient in the evaluation of benign versus metastatic adrenal lesions, simple anatomic sidedness was not taken into accounts.

The results of our study describe an interesting finding that there is more hypermetabolic foci in the left adrenal gland than the right gland or bilateral glands. Using hypermetabolic activity as a pathology marker, correlating the hypermetabolic adrenal activity with or without underlying adrenal lesions found on CT, could provide useful clinical information in early detection of metastases in the adrenal glands. Though this study has demonstrated an anatomic side preference between the right and left adrenal gland with regards to hypermetabolic activity, it is unclear if side preference is related to the anatomic differences between the two adrenal glands, the individual disease processes, or a combination of the two. Additionally, this study did not take into accounts underlying adrenal pathologies such as an adrenal adenoma, myolipoma, or adrenal hemorrhage all of which can result in false positives as they have the potential for producing hypermetabolic activity. Finally, the patient population used in this study may limit the external validity of the results. Since data for this study was acquired at a Veterans Affairs hospital, which has a mostly male population with different risk factors than the general population, it is unknown how these findings apply to the general population. Additionally, because children were excluded from this study, a large subset of adrenal pathology (such as neuroblastoma), was not included.

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