Adrenal lesions: Common findings and pitfalls on ^{18}F-FDG PET/CT

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ABSTRACT

Adrenal lesions are commonly observed during ^{18}F-FDG PET/CT studies. Although, most of these lesions are considered benign, an important consideration in oncologic patients is metastasis. Benign lesions, such as adenomas usually present with low ^{18}F-FDG uptake, although overlap with malignant lesions exist and clear SUV cut-off for distinguishing adrenal adenomas has not been established. Different criteria have been proposed to further characterize adrenal lesions, as benign or metastatic. Conventional imaging modalities have additional value when the degree of uptake is equivocal. In this review, we go through some of the common adrenal lesions, as well as discerning features that favor either benign or malignant etiology.

Key words: Adrenal; Metastasis; Adenoma; PET/CT; Cancer

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INTRODUCTION

Adrenal gland is a common site for development of primary benign or malignant lesions, the distinction between benign and malignant etiologies is of clinical significance as benign lesions do not require further treatment, primary malignant lesions are treated surgically, and metastatic lesions are more commonly treated palliatively [1, 2]. In recent studies, it has been demonstrated that when extra-adrenal tumoral involvement is limited, improved survival by resection of adrenal metastases has been achieved [1, 3].

Adrenal lesions are frequently discovered in PET/CT studies of patients referred for oncologic evaluation and less commonly to characterize a known adrenal mass. Although, a frequent pathology is an adrenal adenoma, a wide range of other diagnoses, especially metastasis in oncologic patients, should be ruled out [4].

On a non-contrast CT scan, observation of a low-density lesion in adrenal gland, can help to suggest a lipid rich adenoma; however, the lipid poor lesions remain as a diagnostic challenge [5]. Another helpful but not adequate measure is the size of the adrenal mass. It has been reported that lesions larger than 5 cm are more likely to be malignant [5]. A follow-up study can also be helpful by demonstrating disease progression, which favors metastatic involvement. Correlative CT and MRI imaging are suggested to further characterize these lesions; however, lipid poor adenomas cannot be adequately distinguished by MRI, mainly due to lack of signal loss on out of phase images. Also lack of characteristic findings in some lesions such as a benign pheochromocytoma which do not have the washout pattern of a benign lesion may lead to uncertain diagnosis [5]. Thus, these techniques may lack sufficient specificity and leading to many unnecessarily interventions [6]. It is reported that, in the patients with documented extraadrenal malignancy, less than half of the adrenal masses are found to be malignant on biopsy [7]. Several studies have been performed to further evaluate the potential role of ^{18}F-FDG PET/CT to differentiate malignant from benign lesions, which has been shown a valuable additional modality to further characterize adrenal lesions [8].

Adrenal lesions can be divided into benign and malignant categories. Benign lesions include cysts, hemorrhage, myelolipoma, adenomas (functional and non-functional) and benign pheochromocytomas. Malignant lesions include metastatic lesions, lymphomas and, adrenal carcinoma. Some of the lesions are readily recognized on conventional imaging, including cysts and lipid rich adenomas; however, there are certain lesions that are considered indeterminate, usually requiring percutaneous biopsy for definite evaluation [7]. Conventional imaging indices such as HU can be helpful diagnostic parameters. Boland et al. demonstrated that a 2HU can characterize lesions as benign with high specificity of 100% low sensitivity of 47% while a 20HU lead to specificity 84% of and sensitivity of 88% [9]. Characteristics of a few benign lesions are described in the following section.

Adrenal hematomas

Attenuation in hematomas depend on the age of the bleeding. Acute bleeding results in high attenuation of 50-90HU [10]. On ^{18}F-FDG PET/CT hemorrhage, whether acute or chronic, can present with increased ^{18}F-FDG uptake. Repko et al. reported a case of resolving bilateral adrenal hematomas due to anticoagulation consumption presenting with intense ^{18}F-FDG uptake in the adrenal gland [11]. In another report, SUV of 3.4 and 4.8 were noted in the left and right adrenal glands respectively, due extensive adrenal hemorrhage [12]. Hemorrhage can also be as a result of an oncologic condition. In fact, enhancing lesions with increased ^{18}F-FDG uptake and calcification are in favor of neoplastic etiologies. Calcification is helpful in cases where acute hemorrhage is suspected but not useful in chronic condition [4].

Adenoma

Adenoma is a benign adrenal tumor. On CT scan, they are recognized as a round or oval soft-tissue density with a well-defined, smooth margin [10]. Adenomas are typically slow growing tumors [13]. Attenuation of less than 10HU is used to characterize lipid rich adenomas [4, 9]. Attenuation greater than 10HU can be an adenoma or other pathologies [13]. Relative and absolute washout at 10 minutes of more than 40% and 60%, respectively, are other strong indicators for characterization on enhanced MRI images [5]. On chemical shift MRI images, loss of signal on out of phase gradient echo (GRE) images will distinguish lipid rich adenomas, however, this cannot characterize lipid poor lesions [5, 14]. In the study by Metser et al. SUV cut off of 3.1 showed a high sensitivity of 98.5% and specificity of 92% for distinguishing adenomas from malignant lesions, CT characteristics were also considered in this study and this SUV cut-off alone would have misclassified 9 of the cases [15]. In another study SUVmax of 3.1 and 3.6 were reported in two adrenal adenomas [16]. In the study by Metser et al. ^{18}F-FDG uptake was not able to different between lipid rich and lipid poor adenomas [15]. The cut off of 3.1 must be used with caution as it can produce false negative results, especially in cases of small adrenal metastases [8].

Adenomas usually present with low SUV values, most commonly presenting with less ^{18}F-FDG uptake than the liver. Despite this, in 3% of cases they can present

with moderately increased ^{18}F-FDG uptake [17]. Among adenomas, functional as well as black adenomas (lipofuscin containing adrenal lesions) can produce false-positive results [4, 18, 19]. In the study by Akkuş et al. on incidental adrenal lesions which underwent surgery, functional adrenal lesions were found to have higher ^{18}F-FDG uptake than nonfunctional lesions [20]. Cortisol secreting adrenal adenomas had the highest SUVmax. A cut-off of 4.135 was able to distinguish cortisol secreting adrenal mass with a sensitivity of 84.6% and specificity of 75.6%. In this study, there was no correlation between SUVmax and mass size (p=0.28). In the study by Patel et al., higher SUVmax was noted when adrenal secreting adenomas were compared to nonfunctioning adenomas [21]. When comparing attenuation in these lesions, lower values were noted in aldosterone producing adenoma (mean HU: 1.8 ± 9.9 HU), as compared to Cushing's syndrome (mean HU: 27.6 ± 12) and pheochromocytoma (mean HU: 35.9±9.8) [22].

Myelolipomas

Myelolipomas are found incidentally as unilateral benign masses in the adrenal glands. In up to 20% of cases, calcification may be visualized. Although it is commonly noted as a well-defined encapsulated fat-rich mass (with attenuation of -30 to -115HU, significantly lower than adenomas). Its composition can range from fat-dominant to completely non-fatty structures. The soft-tissue component shows variable post-contrast enhancement [10]. On MR images, they are visualized as high signal intensity lesions on non-fat-suppressed T1-weighted images, showing signal loss within the fatty component after suppression. On T2-weitghted images, they typically show moderate to high signal intensity. Signal intensity varies depending on the composite, i.e., fat and myeloid elements [14]. On ^{18}F-FDG -PET images, myelolipoma have typically lower ^{18}F-FDG uptake than the liver [23]. However, rare cases of hypermetabolic myelolipoma have been reported [24, 25].

Ganglioneuroma

Ganglioneuroma of adrenal gland a rare tumor of neural fiber including ganglions and with accompanying stroma usually presenting in early adulthood as an independent entity or as a result of differentiation of ganglioneuoroblastoma. They are treated surgically, with low risk of recurrence [26]. Ganglioneuroma can present as distinct oval masses in adrenal gland and usually present with low density on unenhanced CT. This low density correlates with the amount of myxoid stroma. They are not enhanced on early phases of CT scan and show increasing enhancement on delayed images [27]. On MRI, they are inhomogeneously hyperintense on T2WI and show

increasing enhancement of postcontrast phase of the study [27]. In a few documented cases of ganglioneuroma, mild ^{18}F-FDG uptake was noted in the adrenal gland (Figure 1) [28, 29].
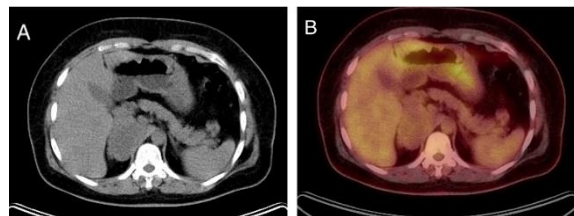

Fig 1. Ganglioneuroma. Pseudo-lesion of adrenal region on ^{18}F-FDG PET/CT demonstrated in a 39-year-old-woman (CT (A) and fused PET/CT (B) images). The ^{18}F-FDG PET/CT image shows a mass lesion without significant ^{18}F-FDG uptake at the anatomical site of right adrenal gland. The patient underwent surgery, which was compatible with a paravertebral, retrocaval ganglioneuroma.

Pheochromocytomas

Pheochromocytomas are mostly small solid lesions. Larger lesions; however, can be cystic or hemorrhagic (30). On non-contrast CT they are well-defined and similar in attenuation to that of the muscle (30-40 HU) (22). These lesions are hypervascular and enhance after intravenous contrast injection (Figure 2).
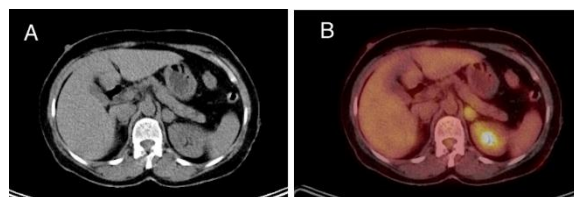

Fig 2. Pheochromocytoma. ^{18}F-FDG PET/CT findings in a 54-your-old woman with neurofibromatosis and pathologically confirmed pheochromocytoma (PASS score: 3) (CT (A) and corresponding PET/CT (B) images). The ^{18}F-FDG PET/CT image reveals a hypermetabolic nodule in the left adrenal gland (measuring about 18 mm x 14 mm, SUVmax= 3.41, average HU= 40).

Although Pheochromocytomas can have similar characteristics to adenomas, demonstrating low HU (10 HU) and more than 60% wash out of contrast on delayed images [31], Szolar et al. reported significant lower washout for pheochromocytoma, more similar to metastases when compared to lipid rich adenomas [32]. Intravenous administration of nonionic contrast does not have alpha blocking effect; thus, it is considered safe in pheochromocytoma patients [33]. There are some studies that suggest higher ^{18}F-FDG uptake may indicate malignancy in pheochromocytomas [34, 35]. In a study by Akkuş et al., three benign pheochromocytomas had SUVmax of 8.7±2.7 [20]. In this study patients with pheochromocytoma showed moderate to high SUVmax compared to nonfunctional adenomas

(p<0.005). In the study by Shulkin et al. higher number of malignant pheochromocytomas accumulated ^{18}F-FDG; however, SUV values in benign pheochromocytoma were from 2.6 to 13.4 (mean: 7.1 ± 4.1) and in malignant pheochromocytoma ranged from 1.6 to 13.3 (mean: 6.6 ± 3.4) [36]. It should be noted, that another PET tracer, ^{68}Ga-Dotatate/Dotatoc/Dotanoc have shown great efficacy in detecting neuroendocrine tumors, including pheochromoctyomas [37, 38].

Malignant vs benign lesions

Although a solitary adrenal lesion in a patient with known malignancy is more likely benign, a substantial number of these lesions are malignant and should undergo further evaluation [7].

Farrugia et al. indicated that an increase in size usually signifies malignancy. On follow-up studies, no change in size implies benignity. If the size is more than 4 cm, the malignancy risk increases to 70%. Heterogenicity and homogeneity can be seen in both benign and metastatic lesions. Although, irregular margin and a heterogenous density accompanied by thick enhancing rim imply malignancy, smooth margin and homogeneous density are a shared feature between benign and malignant lesions [30]. On MRI, malignant lesions demonstrate higher attenuation on T2 weighted images and more delayed wash out, however, overlap exits [39]. In the study by Krestin et al. nine patients were classified as indeterminate on precontrast MRI, five of which lesions could be further classified as adenoma or malignant lesion by contrast enhanced MRI [39].

^{18}F-FDG PET/CT can be helpful in evaluating adrenal lesions. In a study by Boland et al. when evaluating 150 patients with known adrenal lesions and primary known malignancy, absolute SUV value of 2.31 showed a sensitivity of 100% and specificity of 94% and the adrenal to liver ratio >1 showed sensitivity of 100% and specificity of 97% to characterize metastatic lesions [17]. In the study by Kim et al. total lesion glycolysis (TLG) was shown as the best indicator to recognize intermediate to high-risk adrenal incidentalomas [40].

Perri et al. evaluated the effect of size, mean attenuation value, percentage of negative pixels at histogram analysis, SUVmax and average SUV for 117 adrenal lesions [41]. Malignant lesions showed higher SUVmax in comparison with background liver (SUV ratio of 1.6), spleen (SUV ratio of 1.77) and aorta (SUV ratio of 1.85) as well as SUVmax> 2.8 were noted in all malignant lesions. Negative pixels percentage higher than 10% was associated with benignity.

In the study by kunikowska et al. in 85 patients who underwent FDG PET/CT, Tumor to liver SUVmax ratio>1.53 and SUVmax>5.2 demonstrated high sensitivity and specificity in differentiating malignant lesions [42]. Different tumor to liver SUVmax ratios have been introduced by other studies, Gratz et al. suggested a cut off of 1 for differentiating benign and malignant lesions [43] and Watanabe et al. asserted the cut off of 1.37 had a sensitivity of 96% and specificity of 100% for differentiating metastases and adenomas [44].

In the study by Guerin et al. 87 adrenal masses were evaluated, fifteen adrenal masses where characterized as malignant based on their histopathologic results and follow-up studies, these masses had higher HU and lower relative washout and higher FDG uptake [45]. Tumor to liver SUVmax ratio> 1.5 showed a sensitivity of 86.7% and specificity of 86.1% to distinguish malignant masses. They recommended that FDG PET/CT is valuable as an additional modality to evaluate large or indeterminate adrenal masses.

Although these studies indicate that quantitative measures are helpful in distinguishing malignant from benign lesions, Jana et al. indicated that visual analysis and SUV has comparable accuracy (15). Boland et al. [17] and Caoili et al. [46] demonstrated that qualitative measure, as to the intensity of adrenal lesion in comparison with that of liver, was superior to SUVmax and SUV ratio data in distinguishing benign from malignant lesions. In the study by Caoili et al. SUVmax could not differentiate malignant and benign lesions [46]. A previous report indicated that, that lesions with markedly increased FDG uptake are most likely malignant. There is some controversy regarding mild and moderate FDG uptake, necrotic lesions and non FDG avid metastases have been reported. In these cases, differentiating malignant from benign lesions may require further imaging modalities or biopsy [47].

Symmetrical increased FDG uptake may be a sign of adrenal metastasis, mainly in case of lymphoma (Figure 3). In patients with early-stage lymphoma and involvement of adrenal glands, enlargement of adrenal glands with preservation of its triangular shape simulating adrenal hyperplasia may be noted, unlike adrenal hyperplasia the adrenal function is normal, and treatment of lymphoma returns the metabolic activity to normal level [4]. Bilateral adrenal FDG uptake my also signify adrenal hyperplasia, which could be due to a paraneoplastic syndrome. Fard-Esfahani et al. reported a case of Cushing's syndrome, presenting with bilateral adrenal hypertrophy on CT, in a patient with lung cancer [48]. Pruthi et al. reported a case of bilateral symmetrical adrenal hypermetabolism, with enlarged adrenal limbs on CT in a patient with breast cancer due to paraneoplastic Cushing's syndrome [49].
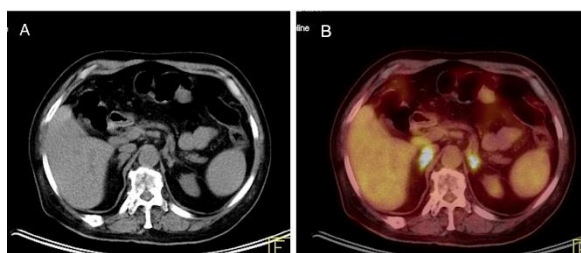
Fig 3. Adrenal lymphoma. A 65-year-old man with diffuse large B-Cell lymphoma presenting for ^{18}F-FDG PET/CT evaluation of treatment response (CT (A) and corresponding fused PET/CT (B)). ^{18}F-FDG PET/CT shows bilateral symmetrical adrenal involvement.

Adrenal carcinoma

Adrenal cancer can present as large masses, either functioning or nonfunctioning. Functioning carcinomas are usually smaller. Large masses present on noncontrast CT as an inhomogeneous mass displacing the nearby organs (Figure 4).

Calcification may be noted in these lesions. Intravenous contrast results in inhomogeneous enhancement more prominent in the periphery. On T1 weighted MR they are hypointense to liver signal and on T2 weighted images, the signal intensity is increased. Vascular invasion is an important consideration in these patients, which can be evaluated with GRE MR sequences [7].

^{18}F-FDG PET/CT has high diagnostic performance in staging and restaging of these tumors. It has also demonstrated higher positive likelihood ratio for recurrence detection, compared to conventional imaging modalities [50]. SUVmax of more than 10 is reported to have prognostic implications [51].
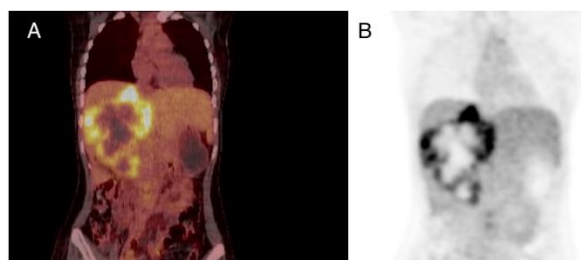

Fig 4. Adrenal Cancer. A17-year-old woman with right adrenal cancer presenting for staging with ^{18}F-FDG PET/CT. Hybrid PET/CT (A) and corresponding CT (B) images demonstrate large metabolically active tumoral lesion with necrotic center between liver and right kidney likely originating from right adrenal.

Most common causes of adrenal metastases are melanoma, lung (Figure 5) and breast cancers. Adrenal metastases are usually heterogeneously enhanced on CT with intravenous contrast, calcification in these lesions is not common and areas of necrosis can result in irregular cystic appearance in larger lesions. Hemorrhage has been reported with adrenal metastasis

with malignant melanoma and carcinoma of lung origin. On MRI, the lesions are isointense or slightly less intense than the liver on T1 images. The signal intensity on T2 images is notably increased due to the increased water content of the lesions [7]. When evaluating the ^{18}F-FDG uptake, Caoili et al. demonstrated that metastases demonstrate the same intensity of ^{18}F-FDG uptake as the original cancer and adenomas reveal less uptake [44]. In the retrospective study by Zhang et al. 13 patients with adrenal lesions, ^{18}F-FDG PET/CT was able to distinguish primary tumor in the presence of metastatic adrenal lesions; however, it was limited in differentiating between different metastatic adrenal lesions due to different malignancies [52].
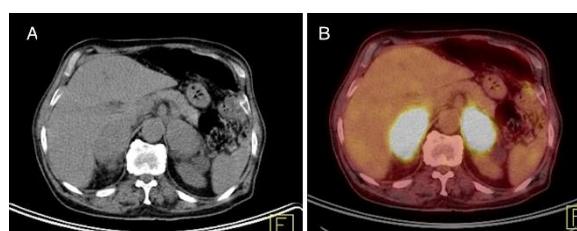

Fig 5. Adrenal Metastases. A 70-year-old-man presenting for staging due to a poorly differentiated adenocarcinoma of lung. (CT (A) and corresponding PET/CT (B) reveal bilateral huge metabolically active adrenal metastases.

Even in the case of metastases, there are a number of adrenal lesions that can lead to false negative results, including metastases from pulmonary carcinoma with bronchoalveolar component, carcinoid tumor as well as tumors with necrosis and hemorrhage. Size is also a critical component when evaluating PET/CT studies, size ≤ 1 cm is more likely to show less ^{18}F-FDG uptake than the liver (8). Also, sources of false positive result mainly infections/ inflammations such as tuberculosis or sarcoidosis should be considered [42, 53].

Another important issue when evaluating adrenal lesions is recognizing the so-called pseudo lesions. The anatomic location of these lesion, can be misinterpreted as adrenal lesions. The main differential diagnosis includes tumors of adjacent organs, sarcomas, reteroperitoneal lymphadenopathies and other malformations. As some of these lesions can present with increased ^{18}F-FDG uptake, awareness of this potential pitfall is important when evaluating ^{18}F-FDG PET/CT studies [54] (Figure 1).

CONCLUSION

Both ^{18}F-FDG PET/CT and conventional imaging findings are complementary in characterizing malignant from benign lesions. Several approaches to characterize indeterminate ^{18}F-FDG uptake on PET/CT studies has been proposed. If there is mild to moderate ^{18}F-FDG uptake more than liver, it is

reasonable to evaluate the noncontrast CT and if characterization is not possible, relative and absolute washout on MRI gradient echo images might be helpful, and finally, if a diagnosis cannot be made, percutaneous biopsy is recommended [17, 47].

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