



## The Addition of <sup>18</sup>F-FDG PET/CT in the Assessment of Indeterminate Adrenal Incidentalomas

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### Abstract

Adrenal masses are common and their management has been the subject of some scrutiny. Initial workup consists of history and physical examination, biochemical evaluation, and imaging, typically using CT or MRI. Some lesions are convincingly benign-appearing on initial imaging and their management typically consists of routine follow-up or laparoscopic resection if the lesion is functional. Others possess imaging characteristics concerning for adrenal cortical carcinoma, such as size >4 cm, heterogeneity, central necrosis or calcifications. For lesions with one or more of these characteristics, the use of <sup>18</sup>F-FDG PET/CT is currently unclear in the literature. We propose a novel algorithm utilizing PET/CT for the assessment of indeterminate adrenal masses. We recommend using PET/CT to distinguish lesions that can be followed from those that can be resected endoscopically and those for which an open surgical approach should be used.

### Introduction

Adrenal masses represent one of the most common incidental findings. The incidence of clinically unapparent adrenal masses is estimated to be 2.0% on autopsy studies [1]. With the widespread use of cross-sectional imaging, these lesions are found frequently, and are found with a prevalence of 3-10% of imaging done for non-adrenal causes [1,2]. The differential diagnosis for adrenal masses is broad, but most lesions (75%) are found to be non-functioning adenomas [1]. Other causes include functioning cortical adenomas that secrete cortisol or aldosterone, pheochromocytomas, myelolipomas, cysts, ganglioneuromas, metastases and rarely adrenal cortical carcinomas.

Adrenal Cortical Carcinoma (ACC) is a rare clinical entity with an estimated prevalence of 4-12 per million adults [3]. The prevalence for ACC is size-dependent, as only 2% of adrenal lesions less than 4 cm are ACC, 6% of lesions between 4.1-6 cm are ACC, and ACC is found in 25% of adrenal lesions greater than 6 cm [4]. A broad spectrum of age ranges is affected by this disease but the average age at presentation in the adult population is 40 to 50 years [5]. Females are affected more than males, at 58.6% vs. 41.4% [6].

A number of algorithms and approaches to incidental adrenal masses and adrenal cortical carcinoma have been proposed, including guidelines from the National Institutes of Health, the European Society for Medical Oncology, the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons, the American College of Radiology, the European Society of Endocrinology, and others [1,4,7-11]. For patients with a history of known malignancy, Positron Emission Tomography (PET) or PET/CT using the radiopharmaceutical 2-deoxy-2-[fluorine-18]fluoro-D-glucose (<sup>18</sup>F-FDG) is typically recommended to distinguish between benign lesions and metastases [1,4,8-12]. The role of <sup>18</sup>F-FDG PET/CT in patients without a history of malignancy is currently unclear in the literature. Recommendations range from avoiding its use to considering it a useful tool for distinguishing benign from malignant disease for radiographically indeterminate lesions [1,8,10,11,13]. Recent experience at our center with three complex incidentalomas has provided us with some insight into the value of PET/CT in the surgical planning of these lesions. We propose a novel algorithm for the workup of incidental adrenal masses that uses <sup>18</sup>F-FDG PET/CT to confidently classify otherwise indeterminate lesions, allowing the surgeon to appropriately select the surgical approach, and for the non-operative management of benign tumors that may otherwise have been resected.

### Evaluation

The initial evaluation of a patient with an adrenal mass begins with a detailed history and physical

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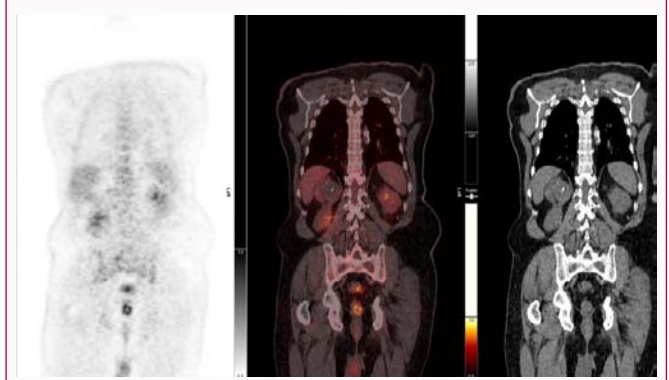
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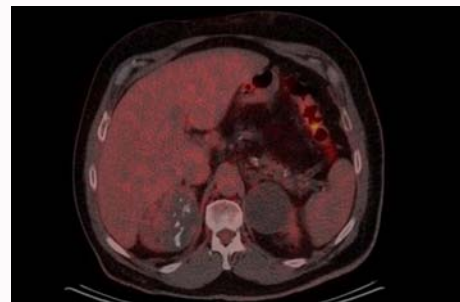
**Figure 1:** Axial contrast-enhanced CT image of Patient A, who was found to have an incidental 8.3 x 7.9 cm mass arising from the right adrenal gland with heterogeneity and calcifications.



**Figure 2:** Coronal contrast-enhanced CT image of Patient A, who was found to have an incidental 8 x 8 cm mass arising from the right adrenal gland with heterogeneity and calcifications.



**Figure 3:** Coronal <sup>18</sup>F-FDG PET, PET/CT, and CT of Patient A's right adrenal mass. Note the metabolic activity within the mass less than background liver activity.



**Figure 4:** Axial <sup>18</sup>F-FDG PET/CT of Patient A's right adrenal mass. Note the metabolic activity within the mass less than background liver activity.

examination. Symptoms and signs stemming from the hypersecretion of adrenal hormones should be elicited, as should those of mass effect. A personal or family history of cancer is another crucial component of the initial history. Cross-sectional imaging such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) should be performed. Cysts and myelolipomas can be readily characterized on CT or MRI scans. On CT, a mass measuring less than 10 Hounsfield units of attenuation is suggestive of a benign cortical adenoma due to their high intracellular lipid content. Using a cut-off value of 10 Hounsfield units, the sensitivity of identifying adenomas on CT was found to be 71% and the specificity was found to be 98% in a pooled analysis of the literature performed by Boland, et al. [14]. CT with intravenous contrast can also be performed to measure washout as benign lesions typically demonstrate greater than 50% washout. On MRI, chemical shift imaging can be used to diagnose lipid-rich adrenal cortical adenomas. Features of adrenal cortical carcinomas on imaging include large size (90% are >4 cm, heterogeneity, invasion of surrounding structures, growth ≥0.8 cm on follow up CT (72%), central necrosis (73%), and calcifications (30%) [15-18].

Unfortunately, not all adrenal lesions are readily characterized on cross-sectional imaging. There exists a subset of indeterminate lesions which can be defined as all adrenal masses with some but not all of the above features of ACC on both CT and MRI. For these lesions, the recommendation is predominantly interval imaging, with consideration of additional imaging with another modality or immediate surgery after multidisciplinary consideration [4,7,9,10].

All incidental adrenal masses require biochemical evaluation, as functioning lesions should be removed regardless of their appearance. Subclinical Cushing's syndrome can be found in 5-20% of patients with incidental adrenal masses, and so even in the absence of symptoms or signs, screening should be performed [19]. A low-dose

1 mg dexamethasone overnight suppression test, late night salivary cortisol, or 24-hour urinary cortisol testing are all appropriate screening tests for hypercortisolism. Pheochromocytomas make up approximately 10% of incidental adrenal masses [20]. Either plasma or 24-hour urinary metanephrines should be obtained even without obvious symptoms of catecholamine excess. Hypertensive patients should be screened for primary hyperaldosteronism, with a plasma aldosterone to renin ratio.

**Cases**

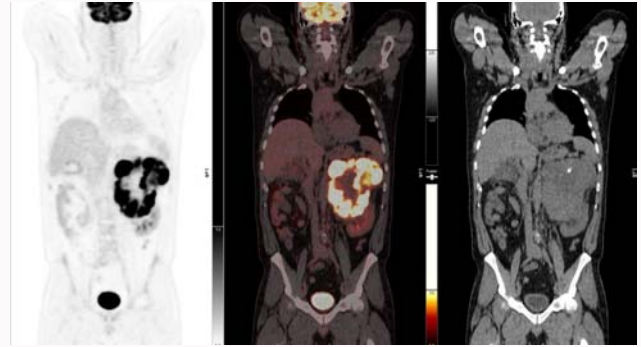
Recent experiences at our centre have prompted the question of whether to expand the role of PET/CT in evaluating incidental adrenal masses. Below are three representative cases.

**Patient A**

Patient A is a 67-year-old male who was found to have a 9.7 cm right adrenal mass on ultrasound performed as part of the evaluation for a new diagnosis of congestive heart failure. This prompted a CT scan which revealed an 8.3 x 7.9 cm mass arising from the right adrenal gland and in close proximity to the liver and IVC (Figure 1,2). The lesion was a heterogeneously enhancing mass with central cystic changes and calcification. There was no definite macroscopic fat. Clinically, the patient had morbid central obesity and was hypertensive, on two antihypertensive agents. Biochemical evaluation revealed an elevated 24-hour urinary cortisol and a lack of suppression found on overnight dexamethasone suppression testing. The findings were concerning for an ACC. An <sup>18</sup>F-FDG PET/CT was obtained to clinically stage the patient prior to surgical resection of this mass. The mass was found to have low grade metabolic activity less than liver background activity (Figures 3,4) which favoured a benign pathology.



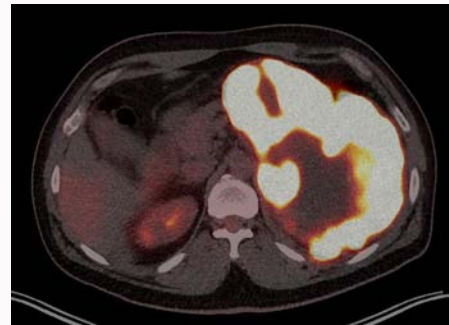
**Figure 5:** Axial contrast-enhanced CT of Patient B, who was found to have an incidental left adrenal mass. The mass is 20 x 15 x 13 cm and heterogeneous with central hypoattenuation and calcification.



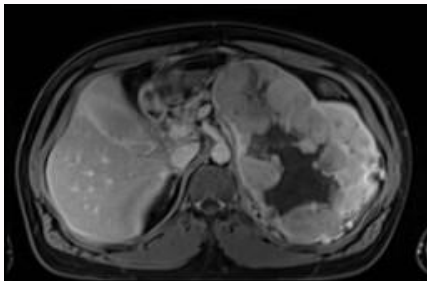
**Figure 8:** Coronal <sup>18</sup>F-FDG PET, PET/CT, and CT of Patient B's left adrenal mass. Note the intense FDG avidity greater than liver background.



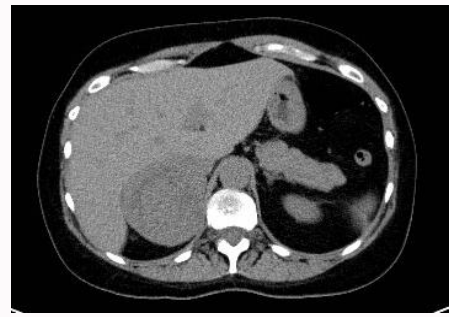
**Figure 6:** Coronal CT of Patient B, who was found to have an incidental left adrenal mass. The mass is 20 x 15 x 13 cm and heterogeneous.



**Figure 9:** Axial <sup>18</sup>F-FDG PET/CT of Patient B's left adrenal mass. Note the intense FDG avidity greater than liver background.



**Figure 7:** Axial MRI T1-weighted post gadolinium image of Patient B, who was found to have an incidental left adrenal mass. The mass is 20 x 15 x 13 cm and has heterogeneous enhancement with central cystic change. No evidence of macroscopic or microscopic fat on other MRI sequences (not shown).



**Figure 10:** Axial unenhanced CT image of Patient C, who was found to have a mass arising from the right adrenal gland with heterogeneity on CT performed for abdominal discomfort and bloating. The density of this mass measured greater than 20 HU.

Given the secretory nature of the tumor, resection was warranted, and an open adrenalectomy was pursued given the size and features on imaging that were suspicious for ACC. The final pathology demonstrated a benign adrenocortical adenoma with areas of old hemorrhage and cystic degeneration.

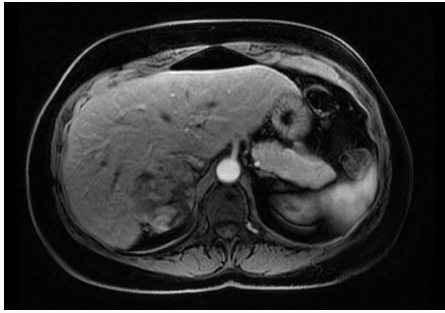
**Patient B**

Patient B is a 43-year-old man who was found to have an incidental 14 cm left upper quadrant mass found on ultrasound performed to investigate for biliary colic. Subsequent CT scan revealed a 20 x 15 x 13 cm mass arising from the left adrenal gland (Figures 5,6). This lesion was heterogeneous in density and enhanced with irregular borders and areas of calcification. On MRI, the mass enhanced heterogeneously with no evidence of intracellular lipid or macroscopic fat (Figure 7). The patient was asymptomatic with

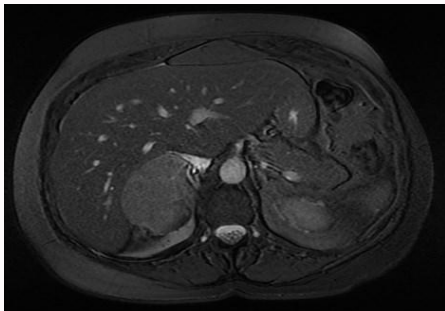
no features suggestive of hormonal excess and his only physical examination findings were a palpable left upper quadrant mass and some mild right upper quadrant tenderness. Biochemical evaluation revealed a lack of suppression on overnight dexamethasone suppression testing despite a normal 24-hour urinary cortisol level, as well as an elevated DHEA-S level. Once again, a PET/CT was obtained to look for evidence of distant metastatic disease prior to surgical intervention. Unlike the first patient, this mass was intensely FDG avid greater than liver background on the <sup>18</sup>F-FDG PET/CT highly suggestive of ACC (Figures 8,9).

An open en-bloc left adrenalectomy, nephrectomy and resection of the retroperitoneal lymph nodes was performed. Final pathology demonstrated adrenal cortical carcinoma with a Ki67 of 2%, few mitoses and negative lymph nodes. Lymphovascular invasion and microscopic extension into adjacent adipose tissue was found.

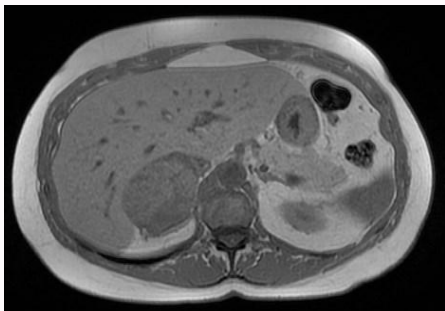




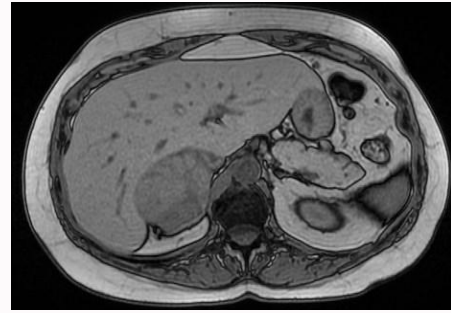
**Figure 11:** Axial post-gadolinium T1-weighted MRI image of patient C, showing large heterogeneously enhancing right adrenal mass.



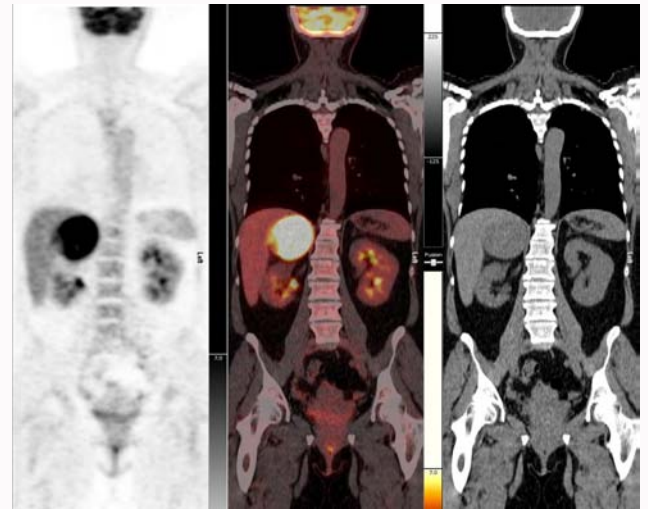
**Figure 12:** Axial T2-weighted MRI image of patient C, showing large right adrenal mass with heterogeneous signal intensity and no macroscopic fat.



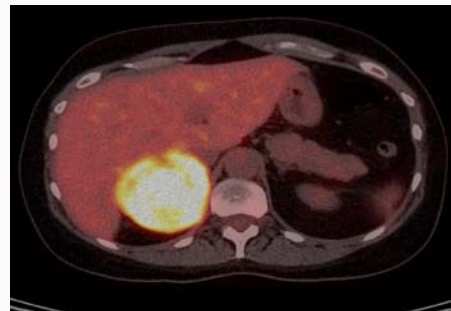
**Figure 13:** Axial MRI in-phase image of patient C, showing large right adrenal mass.



**Figure 14:** Axial MRI out-of-phase image of patient C, showing no loss of signal to confirm intracellular fat in right adrenal mass.



**Figure 15:** Coronal  $^{18}\text{F}$ -FDG PET, PET/CT, and CT of Patient C's right adrenal mass. Note the intense FDG avidity greater than liver background.



**Figure 16:** Axial  $^{18}\text{F}$ -FDG PET, PET/CT, and CT of Patient C's right adrenal mass. Note the intense FDG avidity greater than liver background.

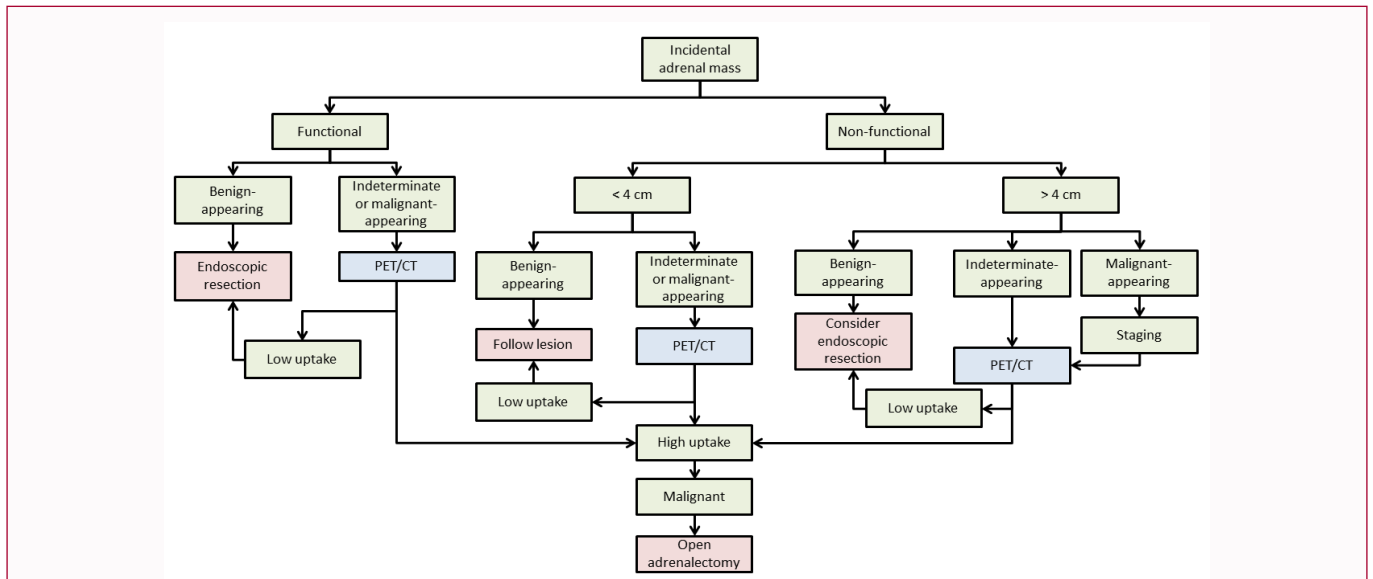
### Patient C

Patient C is a 50-year-old female who was found to have a 6 cm right adrenal mass on a CT scan performed for abdominal discomfort and bloating. There were no other symptoms aside from a weight gain of 8-10 lbs over one year. The lesion measured greater than 20 Hounsfield units on a non-contrast CT and enhanced heterogeneously on a contrast CT (Figure 10). The patient's 24-hour urine cortisol was elevated, and overnight dexamethasone suppression testing revealed a lack of suppression. DHEA-S level was also elevated. On MRI, the mass was heterogeneous and did not have evidence for microscopic or macroscopic fat to confirm a benign etiology and was therefore indeterminate (Figures 11-14). To help further define this intermediate lesion, a PET/CT was obtained. The mass showed intense metabolic activity on  $^{18}\text{F}$ -FDG PET/CT greater than liver background level, suggestive of ACC (Figures 15,16).

Although this lesion was amenable to a laparoscopic resection, the PET/CT was concerning for ACC, so an open adrenalectomy was performed. Final pathology revealed a 15 cm ACC, with tumor

extension into the margins of the specimen including the adrenal vein and the kidney margin. Within the tumor, multifocal necrosis and 24 mitoses per 50 high power fields were found.

Given the similarity of all three cases with respect to imaging findings using conventional modalities, the utilization of PET/CT could have helped to guide the surgical approach. A case can be made for the utilization of PET/CT in differentiating benign from malignant adrenal masses. The exclusion of malignancy could have allowed for the utilization of a laparoscopic approach in the first case; appropriately staged and solidified the aggressive open approach in the second case, and helped focus to select the appropriate resection of a very aggressive ACC in the third patient. It is also conceivable



**Figure 17:** Algorithm for the management of patients with indeterminate adrenal masses. Indeterminate masses include those with any of: > 10 Hounsfield units on CT, lack of changes to suggest lipid rich adenoma on CT or MRI, contrast agent washout less than 50% on CT, heterogeneity, calcifications, or irregular borders.

**Table 1:** Benign v/s indeterminate/malignant features on various imaging modalities.

	Benign Features	Indeterminate / Malignant Features
<b>Non-contrast CT</b>	<ul style="list-style-type: none"> <li>• Macroscopic fat</li> <li>• Smooth contours</li> <li>• Stable size</li> <li>• &lt;10 HU density</li> </ul>	<ul style="list-style-type: none"> <li>• &gt;4 cm</li> <li>• &gt;10 HU density</li> <li>• Heterogeneous</li> <li>• Necrosis</li> <li>• Calcification</li> <li>• Irregular margins</li> <li>• Growth</li> <li>• Invasion</li> </ul>
<b>CT Washout (15 min delays)</b>	<ul style="list-style-type: none"> <li>• &gt;60% absolute washout</li> <li>• &gt;40% relative washout</li> </ul>	
<b>MRI</b>	<ul style="list-style-type: none"> <li>• Uniform enhancement</li> <li>• Chemical shift imaging with loss of signal on out of phase imaging</li> <li>• Macroscopic fat</li> </ul>	

to consider a non-operative approach in small non-functional indeterminate adrenal lesions that are shown to be benign on PET/CT.

**<sup>18</sup>F-FDG PET/CT**

Positron Emission Tomography (PET) using 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG) is an imaging modality that leverages the uptake of fluoride-tagged glucose molecules as a surrogate of metabolic activity. It is thus an excellent marker for identifying areas of intense hypermetabolism such as metastases in highly metabolically active cancers. Potential pitfalls of PET include its inability to pick up small lesions (less than 1 cm), cancers with a low metabolic rate, and cancers where nearby physiologic uptake such as the brain or the bladder will obfuscate results [21]. It is frequently combined with synchronous computed tomography, improving its anatomic localization (PET/CT). There is a five percent false positive rate with increased FDG uptake present in certain processes such as sarcoidosis, infection, some adrenal adenomas and adrenal cortical hyperplasia [22]. The use of <sup>18</sup>F-FDG PET/CT in the evaluation of incidental adrenal masses is evolving. In the setting of patients with a prior history of cancer, <sup>18</sup>F-FDG PET/CT is relatively well-established as a method for identifying metastases, including in the adrenals [1,4,8-12,21]. Conversely, the use of <sup>18</sup>F-FDG PET/CT in evaluating adrenal masses in patients without a history of cancer is less clear.

There have been several prospective studies attempting to clarify

this issue. In studies using histopathology as a gold standard, the sensitivity of <sup>18</sup>F-FDG PET/CT ranges from 97% to 100%, with a specificity of 83% to 93% [13,17,23,24]. These values, however, reflect cut-off values selected for the maximal standardized uptake value of the lesion (SUV<sub>max</sub>) or the adrenal to liver SUV<sub>max</sub> ratio. Area under the curve for receiver operator curves (ROC) for these values range from 0.91 to 0.99 for both values [17,25]. Qualitative analysis is also frequently used in current practice, and in a meta-analysis of the use of <sup>18</sup>F-FDG PET/CT for all adrenal masses, its performance was also found to be excellent with a sensitivity of 96% and a specificity of 91% [25]. In this same study, however, the adrenal to liver SUV<sub>max</sub> ratio was a better discriminator, with a sensitivity of 100% and a specificity of 92% [25].

**Clinical Application**

Currently, the recommendation for adrenal lesions suspicious for ACC is an open en-bloc resection as opposed to endoscopic adrenalectomy [4,7,8,10,11]. For benign adrenal lesions endoscopic adrenalectomy is recommended given the reduced morbidity and hospital length of stay. [26-29]. When there is a strong suspicion for ACC or metastatic cancer, <sup>18</sup>F-FDG PET/CT should be performed to appropriately stage the patient prior to any surgical intervention. We propose however the selective use of PET/CT for indeterminate adrenal lesions (Figure 17).

The utility of PET/CT must however be balanced with its cost

and its accessibility. At our institution, the approximate cost of an  $^{18}\text{F}$ -FDG PET/CT is \$1400-1600 CAD. For comparison, an MRI for an adrenal mass is approximately \$700 CAD for an enhanced study, and a CT for an adrenal mass is \$250 for a non-contrast scan. Because of this discrepancy in cost and accessibility of some of these modalities throughout the world, the judicious use of PET/CT in situations where it can positively affect patient care and when it can result in cost and resource savings elsewhere is important. Even lesions with concerning features on imaging (size >4 cm, heterogeneity, calcifications, and irregular borders) but low FDG uptake are much less likely to be malignant, and as such an endoscopic resection could be considered. Therefore, the decision to use PET/CT should be a multidisciplinary decision and only undertaken when it may change the surgical approach or the decision to operate at all.

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