European Journal of Radiology 81 (2012) 441–450

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Evaluation of incidentally discovered adrenal masses with PET and PET/CT

Ka Kit Wong[a,b,**], Mohammad Arabi[a,b], Wessam Bou-Assaly[a,b], Maria Cristina Marzola[c], Domenico Rubello[c,*], Milton D. Gross[a,b]

[a] Department of Nuclear Medicine, Veterans Affairs Hospital, Ann Arbor, MI, USA
[b] University of Michigan Health System, Department of Radiology, Division of Nuclear Medicine, Ann Arbor, MI, USA
[c] Department of Nuclear Medicine, PET/CT Centre, Radiology, Medical Physics, Santa Maria della Misericordia Hospital, Via Tre Martiri 150, 45100 Rovigo, Italy

ARTICLE INFO

Article history:
Received 13 December 2010
Accepted 23 December 2010

Keywords:
Adrenal mass
Adrenal incidentaloma
Adrenal adenoma
Adrenocortical cancer
Positron emission tomography
Pheochromocytoma

ABSTRACT

Background and purpose: Incidentally discovered adrenal masses are commonly seen with high resolution diagnostic imaging performed for indications other than adrenal disease. Although the majority of these masses are benign and non-secretory, their unexpected discovery prompts further biochemical and often repeated imaging evaluations, sufficient to identify hormonally active adrenal masses and/or primary or metastatic neoplasms to the adrenal(s). In the present paper we investigate the role of PET and PET/CT for the detection of adrenal incidentalomas in comparison with CT and MRI.
Materials and methods: a systematic revision of the papers published in PubMed/Medline until September 2010 was done.
Results: The diagnostic imaging approach to incidentally discovered adrenal masses includes computed tomography (CT), magnetic resonance imaging (MRI) and more recently positron emission tomography (PET) with radiopharmaceuticals designed to exploit mechanisms of cellular metabolism, adrenal substrate precursor uptake, or receptor binding.
Conclusion: The functional maps created by PET imaging agents and the anatomic information provided by near-simultaneously acquired, co-registered CT facilitates localization and diagnosis of adrenal dysfunction, distinguishes unilateral from bilateral disease, and aids in characterizing malignant primary and metastatic adrenal disease.

1. Introduction

Adrenal masses are often detected with high resolution diagnostic imaging performed for indications other than adrenal disease. Computed tomography (CT) is the imaging modality that most often identifies these so-called 'adrenal incidentalomas' with an incidence between 0.4 and 4.5% [1–3]. Adrenal masses occur with increasing frequency after the age of 30 years, and in patients without a history of cancer the majority (70–94%) are benign, non-hormonally active adenomas, however unsuspected adrenal malignancy can occur in up to 21% of masses detected in this group [3]. In patients with a prior history of cancer, the incidence of adrenal incidentaloma ranges between 7% and 68% and a higher proportion (32–73%) of these adrenal masses represent metastatic spread to the adrenals [1–3]. Table 1 summarizes the most common etiologies of incidentally discovered adrenal masses.

Once an adrenal mass has been detected, CT can be used to distinguish benign from malignant etiologies [4–10]. When these masses are small (<4 cm), well-defined, with homogenous low density (Hounsfield units < 10) on unenhanced CT, they are usually benign and further anatomic imaging is not required [9,11,12]. Similarly magnetic resonance imaging (MRI) can be used to evaluate the lipid content of adrenal masses with a diagnostic accuracy similar to CT [4–6,9,12]. When chemical-shift MR identifies high intracellular lipid content with lesion intensity similar to liver on T2-weighted images, benign etiology is confirmed [4–6,9,12]. However, lipid-poor adenomas, which represent 30% of adrenal cortical adenomas, will often remain indeterminately characterized using either (or both) these anatomical imaging techniques.

The last decade has seen an increasing number of studies reporting the utility of co-registered PET/CT imaging for evaluation of adrenal masses, using radiopharmaceuticals targeted to various characteristics of adrenocortical and medulla function. PET/CT combines anatomic cross-sectional information with functional, tomographic maps and has demonstrated potential for distinguishing benign from malignant adrenal masses, characterizing adrenal lesions as adrenocortical or non-adrenal in origin, and for staging

* Corresponding author. Tel.: +39 0425 39 4431; fax: +39 0425 39 4434.
** Corresponding author at: Department of Radiology, Division of Nuclear Medicine, University of Michigan Medical Center, 1500 E Medical Center Dr., B1G505G, Ann Arbor, MI 48105, USA. Tel.: +1 734 936 5388; fax: +1 734 936 8182.
E-mail addresses: domenico.rubello@libero.it, rubello.domenico@azisanrovigo.it (D. Rubello), kakitw@hotmail.com (M.D. Gross).

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doi:10.1016/j.ejrad.2010.12.060

Table 1
Incidentally discovered adrenal masses.

Etiology	Frequency
Adrenal cortex	
Adenoma	
Non-oncology and non-selected series	36–94%
Oncology patients	7–68%
Nodular hyperplasia	7–17%
Carcinoma	0–25%
Ganglioneuroma	0–6%
Pheochromocytoma	0–11%
Neuroblastoma (rare beyond early childhood)	0–11%
Metastases	
Non-oncology and non-selected series	0–21%
Oncology patients	32–73%
Pseudo and other adrenal masses	
Cysts	4–22%
Parasitic	0–1%
Pseudocyst	2–9%
Hematoma/hemorrhage	0–4%
Lipoma	0–11%
Myelolipoma	7–15%

Modified with permission from Kloos RT, et al. Incidentally discovered adrenal masses. Endocr Rev 1995;16:460–84.

of primary adrenocortical cancer, neuroendocrine tumors of chromaffin origin, and other malignancies with respect to the presence of to the adrenal(s) [13–17].

2. Positron emitting radiopharmaceuticals

2.1. PET adrenocortical imaging agents

In the early 1970s ^{131}I-19-iodocholesterol was used to successfully image the adrenal cortex in Cushing's disease, and many cholesterol analogues labeled with a variety of radioisotopes have since been offered as alternative agents for adrenocortical scintigraphy [18,19]. The 6β nor-derivative, ^{131}I- or ^{75}Se-labeled 6β-iodomethyl-19-norcholesterol, has been shown to display the greatest avidity for the adrenal cortex and to date represents the standard radiopharmaceutical imaging the adrenal cortex [14,20]. More recently, ^{18}fluorine labeled cholesteryl-*p*-^{18}fluorobenzoate has been used for PET imaging of the adrenal glands in animal models, but not yet in humans [21]. Alternative agents to radio-labeled cholesterol for imaging the adrenal cortex are inhibitors of enzymes of steroid hormone biosynthesis. Imaging with radioiodine-labeled metyrapone was attempted in the late 1970s, but success has only recently been achieved with ^{11}C-labeled metomidate (MTO). This selective inhibitor of 11β-hydroxylase, an enzyme involved in adrenocorticotrophin-regulated biosynthesis of cortisol and aldosterone, allows PET imaging of tumors of adrenocortical origin in humans [22–24].

Other substrates of cellular metabolism not specific for the adrenal cortex, include ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a radiolabeled glucose analog accumulated via cellular glucose transport mechanisms and trapped by intracellular phosphorylation, widely used to image primary adrenocortical cancer and detect adrenal metastases, ^{11}C-acetate, an intermediate of lipid metabolism, and either ^{11}carbon or ^{18}fluorine-labeled choline, a phospholipid precursor, which have been reported to image adrenal adenomas [13,14].

2.2. PET sympathomedulla imaging agents

The development of imaging radiopharmaceuticals specific for the adrenal medulla began with [14] C-dopamine which was demonstrated to accumulate in human adrenal medulla, neuroblastoma and pheochromocytoma, but follow-on studies with radioiodinated dopamine were not successful [25–27]. Although other agents were investigated, it was not until the development of the radioiodinated meta-isomer of iodobenzylguanidine (mIBG), which demonstrated high levels of uptake in adrenal medulla and in neoplasms of sympathoadrenomedullary origin, that clinical imaging could be routinely performed [28–32]. More recently catecholamine precursors radio-labeled with positron emitters have been used to image tissues of sympathomedulla origin in humans. ^{11}Carbon-labeled hydroxyephedrine (HED), an analog of norepinephrine (NE) is accumulated by NE transporters into adrenergic nerve terminals and can be used to image pheochromocytomas [16,17,33,34]. It was the first in a group of PET radiopharmaceuticals targeting catecholamine precursor synthesis and/or reuptake pathways that now also includes ^{11}C-epinephrine, ^{11}C-hydroxytryptophan, ^{18}F-fluorodopamine (DA), and ^{18}F-fluorodihydroxyphenylalanine (DOPA) [15–17,35–37].

Alternative receptor-mediated pathways have been exploited for adrenal imaging. Somatostatin receptors (SSTR) are expressed by neoplasms of neural crest origin and somatostatin analogues including ^{68}gallium -DOTA-Tyr-3-octreotide (DOTATOC), ^{68}gallium-DOTA-NaI-octreotide (DOTANOC) and ^{68}gallium-DOTA-octreotate (DOTATATE) have been used for PET imaging of neuroendocrine tumors in humans [38–42]. These somatostatin analogues vary with respect to affinity for SSTR subtypes I–V, although they are unlikely to have significantly different imaging performance. Furthermore, ^{18}F-FDG has also been used to depict and stage benign and malignant sympathomedullary tumors [16,43–47]. A list of PET radiopharmaceuticals for adrenal PET imaging are summarized in Table 2.

3. PET imaging of incidentally discovered adrenal masses

3.1. ^{18}F-FDG PET and PET/CT evaluation of adrenal incidentaloma

Incidentally discovered adrenal masses are most commonly detected with CT performed for indications other than adrenal disease, but with the widespread utilization of ^{18}F-FDG PET/CT for

Table 2
Radiopharmaceuticals for adrenal PET imaging.

Radiopharmaceutical	Metabolic activity	Target(s)/mechanism(s)
^{11}C-acetate	TCA intermediate[a]	Metabolic intermediate
^{11}C or ^{18}F-choline	Amino acid	Phospholipid membrane component
^{11}C or ^{18}F-metomidate (MTO)	Enzyme inhibitor	Adrenal cortical enzyme inhibitor
^{11}C-epinephrine	Catecholamine	Neuroendocrine via active transport into
^{11}C-hydroxyephedrine (HED)	Catecholamine analog	neurosecretory granules
^{18}F-dopamine (DA)	Catecholamine	↓
^{18}F-dihydroxyphenylalanine (DOPA)	↓	↓
^{68}Ga-DOTA-tyr3-octreotide (DOTATOC)	Somatostatin analog	Neuroendocrine via somatostatin-receptor
^{18}F-fluorodeoxyglucose (FDG)	Glucose analog	Glucose transport/metabolic intermediate

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[a] Tricarboxcylic acid cycle intermediate.