^{11}C-metomidate PET-CT scanning can identify aldosterone-producing adenomas after unsuccessful lateralisation with CT/MRI and adrenal venous sampling.

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Running title: **^{11}C-metomidate PET-CT scanning in primary hyperaldosteronism**

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Overview

Primary hyperaldosteronism, characterised by hypertension and hypokalaemia, is a syndrome caused by aldosterone excess most commonly from either a unilateral aldosterone-producing adenoma or bilateral adrenal hyperplasia. Sub-type classification can be challenging with cross-sectional imaging and even with interventional radiological techniques such as adrenal venous sampling. Imaging with ^{11}C-metomidate PET-CT is an emerging tool that facilitates functional characterisation and potentially successful surgical intervention of aldosterone-producing adenomas. This technique has highlighted that although unilateral adenomas and bilateral hyperplasia represent opposite ends of the disease spectrum, a relatively common intermediate phenotype exists of unilateral/bilateral multinodular disease.

A 44 year old female presented to a tertiary endocrine clinic with a blood pressure of 188/114 mmHg, managed with several anti-hypertensive drugs including spironolactone 50 mg o.d., having been previously investigated for secondary hypertension. Biochemically her baseline investigations were consistent with primary hyperaldosteronism with an aldosterone:renin ratio of 2125 prior to drug treatment. A high-resolution adrenal CT scan had suggested a bulky left adrenal gland, and possible right adrenal nodule; however, subsequent adrenal magnetic resonance imaging reported normal adrenal glands bilaterally. Adrenal venous sampling (AVS) was attempted on two occasions, but was technically unsuccessful. Thus, in the absence of an exact sub-type of primary aldosteronism (PA), medical management with mineralocorticoid receptor antagonists was preferred with spironolactone titrated up to 100 mg b.d. The patient was intolerant of medication and sought referral to a supraregional neuroendocrine tumour multi-disciplinary team (NET MDT).

Application of serial cross-sectional imaging and AVS had failed to localise the source of aldosterone excess so an ^{11}C-metomidate PET-CT scan was performed at Addenbrooke's Hospital, Cambridge. Dexamethasone 0.5 mg q.d.s. was administered for 72 hours prior to the scan with the final dose being administered on the morning of the scan with the aim of suppressing ^{11}C-metomidate uptake into background normal adrenal tissue, thereby facilitating identification of the functionally active nodules.

The medial limb of the right adrenal gland was noted to be thickened proximally, with an apparent 9.5 x 7.0 mm nodule at this site, which showed focal tracer uptake (SUVmax 27.2) (Figure 1A-C). A smaller 5.0 x 7.1 mm nodule was suspected in the body/proximal medial limb of the left adrenal gland, corresponding to a site of less intense tracer uptake (SUVmax 23.8) (Figure 1A-C). The difference in maximal tracer uptake between the two sides (SUVmax ratio = 1.14) did not reach the value (1.25) reported previously to discriminate between unilateral and bilateral causes of PA. However, taken together, the cross-sectional and ^{11}C-metomidate PET findings indicated that the right adrenal nodule was likely to be a significant contributor to excess aldosterone secretion in our patient. These findings were discussed with the patient, and she was offered a unilateral right adrenalectomy, but on the clear premise that although an improvement in blood pressure would be anticipated, it was possible that she would be left with residual disease, requiring ongoing medical therapy, following surgery.

A retroperitoneoscopic right adrenalectomy was performed uneventfully with discharge 48 hours post-surgery. Macroscopic examination of the adrenal gland revealed a 6mm well-demarcated and unencapsulated nodule, which microscopically was composed of lipid rich cells showing eosinophilic cytoplasm with many cells containing concentrically laminated eosinophilic 'spironolactone bodies' consistent with an adrenal cortical adenoma (Figure 1 D/E). Immediately post-operatively, and throughout clinic follow-up during the last 12

months, her blood pressure has been consistently normal (around 130/80 mmHg) without anti-hypertensive medication, with normal renal profile and a normal aldosterone:renin ratio (aldosterone 106 pmmol/l; plasma renin activity 1.2 ng/ml/h) excluding residual PA.

Primary aldosteronism (PA) is a syndrome characterised by hypertension, with hypokalaemia in a proportion of patients, caused by excess aldosterone secretion, most commonly attributable to a unilateral aldosterone producing adenoma (APA) or bilateral adrenal hyperplasia (idiopathic hyperaldosteronism, IH)[1]. However, increasingly an intermediate phenotype of unilateral or bilateral multinodular disease is emerging[2].

Subsequent to a biochemical diagnosis of PA, the next stage of management is sub-type classification with lateralisation of the source of the excess aldosterone to distinguish between an APA, treated with unilateral adrenalectomy and IHA, treated with lifelong mineralocorticoid receptor antagonists (using spirinoloactone or eplerenone). The initial recommended imaging modality is an adrenal CT, useful for detecting larger adrenal masses particularly those with malignant potential. However, the poor sensitivity and specificity of adrenal CT scanning for detection of microadenomas and distinguishing between a non-functioning and an aldosterone-producing adenoma is well recognised, leading to consensus guidelines recommending AVS to lateralise when surgical intervention is practical and desired by the patient[3]. Lateralisation is confirmed in the presence of a 3-4 fold difference, between adrenal veins, in the aldosterone to cortisol ratios.

Despite these recommendations AVS is technically challenging and is not widely available, hence there is a need for less invasive, functional imaging modalities to manage patients with PA. ^{11}C-metomidate, a potent inhibitor of the adrenocortical steroidogenic enzymes, 11ß-hydroxylase and aldosterone synthase, has been developed as a novel tracer for positron-emission tomography (PET) scanning. In a case series of 173 patients with adrenal tumours, Hennings *et. al* demonstrated sensitivity of 0.89 and specificity of 0.96 in proving the

adrenocortical origin of adrenal lesions *i.e.* adrenocortical adenomas or hyperplasias and adrenocortical cancers (ACCs), with phaeochromocytomas, adrenal metastases and non-adrenal masses all MTO negative[4]. PET measurements using standardised uptake values (SUV) differentiated aldosterone-producing adenomas from normal and contralateral adrenal glands[4]. Burton *et. al.* subsequently demonstrated the sensitivity and specificity of MTO-PET, compared with the current gold standard of AVS, and found it able to detect even the smallest microadenomas without the need for withdrawal from spironolactone or other anti-hypertensive drugs[5]. A 25% excess SUVmax between sides was reported to be diagnostic in this cohort. Although this patient's adenoma represented a predominant component of bilateral nodular disease, rather than pure unilateral disease, it has been suggested that even "removal of one randomly selected nodular adrenal might improve blood pressure and serum potassium concentrations in nearly 100% of patients"[2].

As the cost of 11C-metomidate PET-CT is less than that of AVS in most centres, this imaging modality represents a cost-effective alternative for lateralisation in PA. We recognise however, that at present only a few sites are able to offer functional imaging, although it is anticipated that wider rollout of this tracer, or of next generation compounds (including ^{18}F-labelled), will allow for greater access comparable to AVS.

In summary, we highlight what we believe to be a relatively common clinical scenario in patients with PA, whereby the limitations and challenges of adrenal cross-sectional imaging (CT/MRI) and interventional radiological techniques (AVS) preclude optimal management and outcomes. In our patient, successful surgical intervention for an aldosterone-producing adenoma was based on the identification of a right-sided micronodule as the site of greatest ^{11}C-metomidate uptake. Results of further studies may potentially guide clinicians to wider use of ^{11}C-metomidate PET-CT in preference to AVS.

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Figure 1

^{11}C- metomidate PET-CT scan.

(A) CT demonstrates subtle thickening/nodular change in the body/proximal medial limb of both adrenal glands.

(B) Raw PET findings suggest maximal tracer uptake bilaterally in the same locations, but with greater uptake on the right.

(C) Merged PET-CT image confirming co-localisation of cross-sectional and functional imaging findings.

Histology of the specimen

D) Low power image of the well-demarcated, unencapsulated nodule. The arrows indicate the junction between the nodule and normal medullary tissue (haematoxylin and eosin).

E) High power image of the nodule showing lipid rich adrenal cortical cells with pale, foamy cytoplasm. Several cells contain rounded, laminated eosinophilic 'spironolactone' bodies (arrows) (haematoyxlin and eosin).

Figure 1

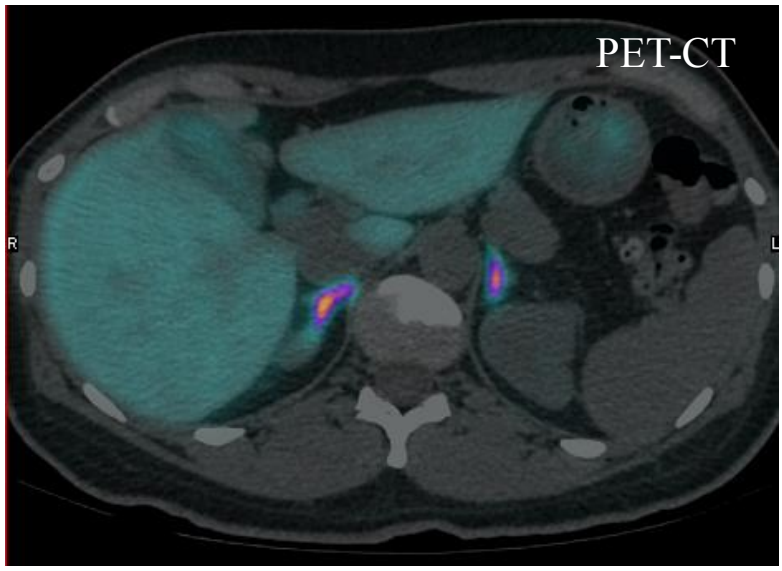
A

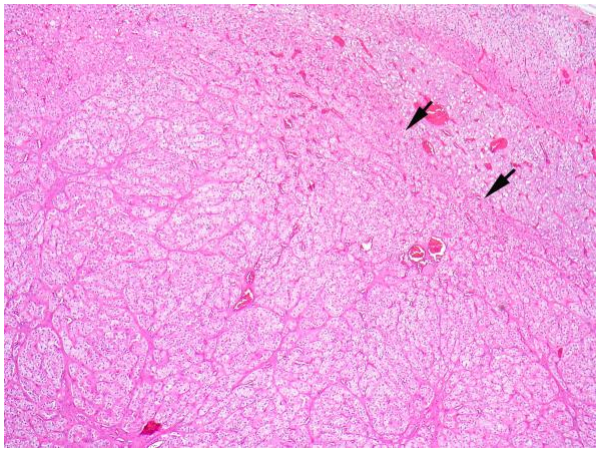
B

Right SUV_{max} = 27.2 Left SUV_{max} = 23.8

Ratio = 1.14

C





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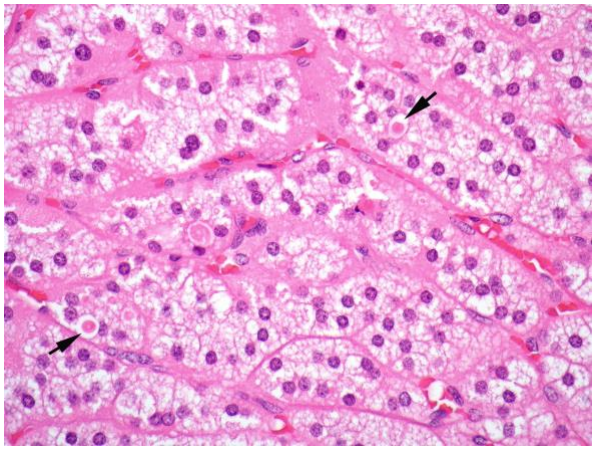

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