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EDITORIAL

EANM position on positron emission tomography in suspected functional pituitary neuroendocrine tumours

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Pituitary neuroendocrine tumours (PitNET) [1] are, after meningioma, the most frequent intracranial tumours. They are classified according to their size (micro < 10 mm, macro ≥ 10 mm and giant ≥ 40 mm), their hormonal secretion pattern and molecular expression profile. Although most PitNET are benign, they can cause significant morbidity due to local compression and associated hormonal syndromes. Clinical management is multidisciplinary, and treatment consists of surgical resection, radiotherapy, pharmacotherapy or a combination. Magnetic resonance imaging (MRI) is the primary diagnostic method, and dedicated protocols include dynamic contrast-enhanced imaging [2]. Ultra-high field MRI (7T) has shown to increase detection, particularly in small micro-PitNET [3]. However, there remain some unmet diagnostic needs. Some functional micro-PitNET (including 30–40% of corticotroph adenomas) are not readily visualized on standard pituitary MRI even when including a dynamic contrast enhanced sequences [4]. Further, even in patients with Cushing's disease who have a micro-PitNET detected on MRI, guidelines suggest to confirm localization of the tumour within the pituitary gland through bilateral inferior petrosal sinus sampling (IPSS) [5]. This technique is considered the gold standard to confirm origin of adrenocorticotrope hormone hypersecretion. However, this invasive procedure has a risk of non-negligible complications and even neurologic damage. Similarly, following transsphenoidal surgery, sites of residual or recurrent disease may not be evident or readily distinguished from posttreatment changes [6], complicating redo surgery or adjuvant radiotherapy. Therefore, despite advancements in MR imaging modalities, more accurate imaging methods providing further information on activity and localization would prove beneficial for patients. Also, from another perspective, evaluation of metabolic characteristics of pituitary neuroendocrine tumours has potential to advance diagnostics. For instance, hormonal functionality of a pituitary

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incidentaloma is not always easy to confirm and MRI-based imaging provides primarily structural information, but little functional information, e.g. prognostic information on growth potential of the tumour. As, such molecular imaging could be of complementary value.

Due to the increased resolution and sensitivity of new digital PET systems, small structures such as the pituitary can now be accurately measured. This leads to an increased scientific interest of PET imaging in pituitary neuroendocrine tumours. Although 2-[^{18}F]fluoro-deoxy-D-glucose ([^{18}F]FDG) PET is widely available, its performance in suspected functional PitNET is limited due to a high rate of false negatives and insensitivity to the functional status of the PitNET [7]. Similarly, interpretation using [^{68}Ga]Gallium-DOTA-Tyr3-Octreotate ([^{68}Ga]DOTATATE)/ [^{68}Ga]Gallium-DOTA-D-Phe1-Tyr3-Octreotide ([^{68}Ga]DOTATOC)/ [^{68}Ga]Gallium-DOTA-1-Nal3-Octreotide ([^{68}Ga]DOTANOC) is challenging due to physiological uptake in pituitary tissue and variable uptake in PitNET [8, 9]. Increasing evidence indicates that PET with amino acid radioligands may be advantageous in this setting [10]. Specifically, PET with O-(2'[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) and [^{11}C]-L-methionine ([^{11}C]MET) has been suggested as an auxiliary tool to confirm and localize functional pituitary neuroendocrine tumours [11–14]. Of note, a good quality of registration between PET and MRI images (or, if available, a PET/MRI scan) is required for appropriate localization and differentiation between the nearby vascular structures (Fig. 1). Hybrid PET/MRI scans facilitate good quality registration, especially as dedicated pituitary sequences only encompass part of the brain. In case no hybrid PET/MRI scanner is available, additional whole brain sequences, fi 3DT1, are needed for correct registration.

Although most evidence is available for [^{11}C]MET, [^{18}F]FET-PET seems to have at least similar accuracy as [^{11}C]MET-PET to detect a functional pituitary neuroendocrine tumour [11, 15]. Also, its 18F-labeling makes it more practical in use. For 6-[^{18}F]fluoro-L-3,4,-dihydroxy-phenylalanin ([^{18}F]FDOPA) only case reports are available which suggest a potential role in prolactinoma [16, 17].

The value of PET using radiolabeled amino acids has been mainly investigated in Cushing's disease. Slagboom et al. proposed to add PET scans in the diagnostic work-up of patients with persistent biochemical or clinical Cushing's syndrome with negative or inconclusive imaging results and contraindications to IPSS [18]. In the other functional

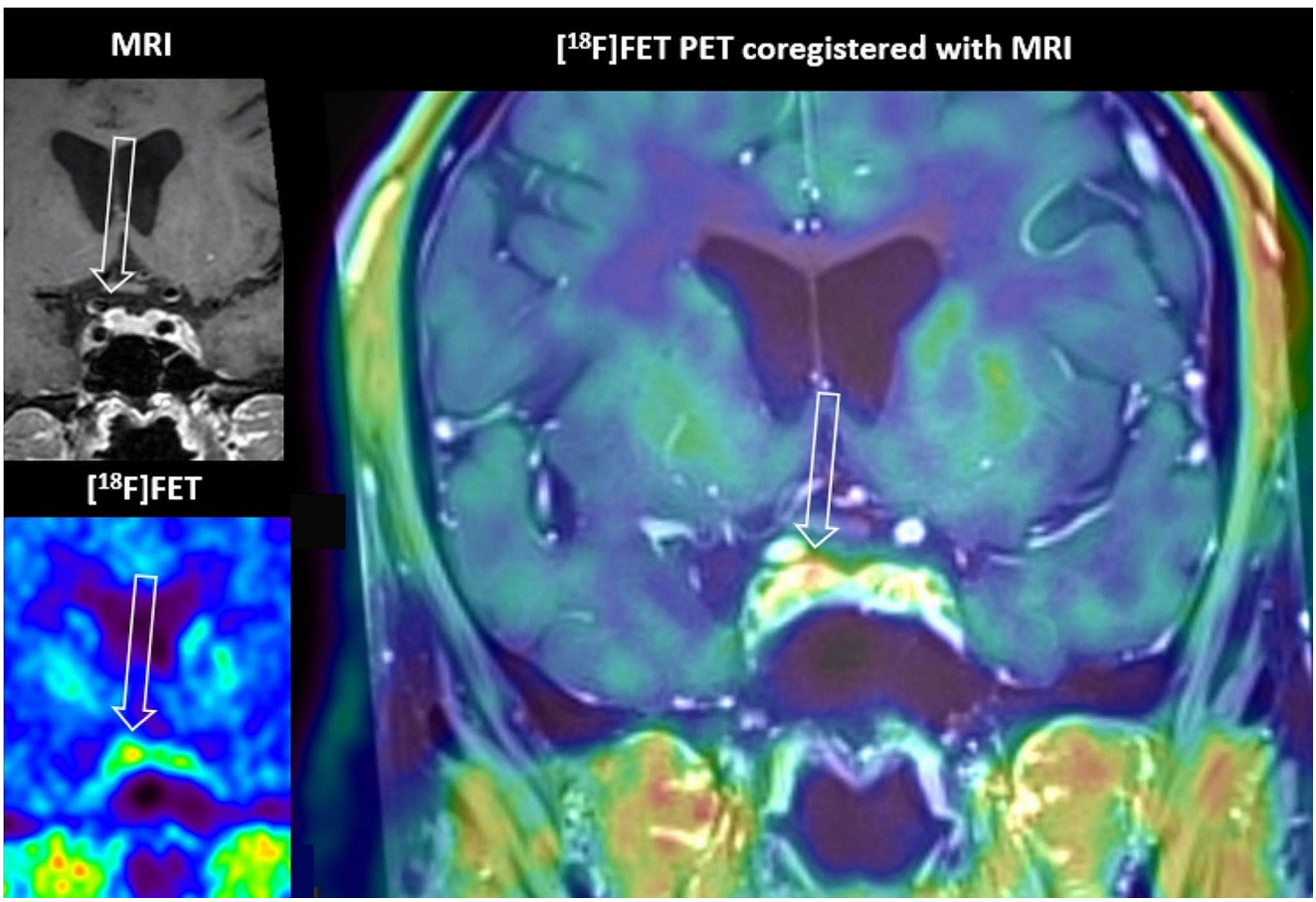

Fig. 1 Example of functional pituitary neuroendocrine tumour on [^{18}F]FET PET with a negative MRI in a patient with Cushing's disease

pituitary adenoma, such as prolactinoma, acromegaly and TSHoma only small case series have been documented [16, 17, 13–22], requiring further investigations in these entities.

Although still limited, published data suggest that in selected cases with negative or equivocal structural imaging and with persistent biochemical hormone excess, amino acid imaging could be useful. Interpretation should be made using visual assessment (uptake higher than background pituitary) after proper PET alignment and fusion with MRI, as currently no cut-off value for semi-quantitative analysis has been determined. Moreover, revision of the MRI pre- and postsurgery should be integrated with the functional information.

Larger studies in real-life clinical setting are needed to define the accuracy and clinical indications of PET using radiolabeled amino acids scans. Moreover, the optimal cut-off for semi-quantitative assessment should be examined and validated by post-surgery follow-up (biochemical remission, neuropathology results).

In conclusion, PET using radiolabeled amino acids [^{11}C]MET and [^{18}F]FET might be a promising diagnostic tool in functional PitNET, especially corticotrope adenomas, with clinical challenges. It is a rapid developing field, however still in early stages as data is mainly based on retrospective studies. Therefore, longitudinal prospective trials including patients with both functional and non-PitNET are required: firstly to determine the accuracy to discriminate between functional and non-functional neuroendocrine tumours and secondly to determine the added clinical value.

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest DVW received research support from General Electric and reader honoraria from Life Molecular Imaging. HB received research support from Life Molecular Imaging and Positrigo, consulting/speaker honoraria from Hermes Medical Solutions, IBA, Lilly, Eisai and Novartis/AAA, reader honoraria from Life Molecular Imaging, and dosing committee honoraria from Pharmtrace. MB received consulting/speaker honoraria from Life Molecular Imaging, GE healthcare, and Roche, and reader honoraria from Life Molecular Imaging. AV received consulting/speaker honoraria from GE healthcare, Novartis and Curium. IY received speaker honoraria from Piramal and consultant fees from ABX-CRO, Blue Earth Diagnostics, and Pentixapharm.

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Informed consent Not applicable.

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