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Original Research

Real-world experience with 11C-methionine positron emission tomography in the management of acromegaly

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Abstract

Background: L-[methyl-11C]-methionine-positron emission tomography (Met-PET) is a potentially important imaging adjunct in the diagnostic workup of pituitary adenomas, including somatotroph tumors. Met-PET can identify residual or occult disease and make definitive therapies accessible to a subgroup of patients who would otherwise require lifelong medical therapy. However, existing data on its use are still limited to small case series. Here, we report the largest single-center experience ($n = 61$) in acromegaly.

Methods: A total of 189 cases of acromegaly were referred to our national Met-PET service in the last 12 years. For this analysis, we have reviewed outcomes in those 61 patients managed exclusively by our multidisciplinary team (single center, single surgeon). Referral indications were as follows: indeterminate magnetic resonance imaging (MRI; $n = 38$, 62.3%), occult residual ($n = 14$, 23.0%), (radio-)surgical planning ($n = 6$, 9.8%), and occult de novo tumor ($n = 3$, 4.9%).

Results: A total of 33/61 patients (54.1%) underwent PET-guided surgery. Twenty-four of 33 patients (72.7%) achieved complete biochemical remission following (re-)surgery. Insulin-like growth factor 1 levels were reduced to <2 × upper limit of normal (ULN) in 6 of the remaining 9 cases, 3 of whom achieved levels of <1.1 × ULN compared with mean preoperative levels of 2.4 × ULN (SD 0.8) for $n = 9$. Only 3 patients developed single new hormonal deficits (gonadotropic/thyrotropic insufficiency). There were no neurovascular complications after surgery.

Conclusion: In patients with persistent/recurrent acromegaly or occult tumors, Met-PET can facilitate further targeted intervention (surgery/radiosurgery). This led to complete remission in most cases (24/33) or significant improvement with comparatively low risk of complications. L-[methyl-11C]-methionine-positron emission tomography should therefore be considered in all patients who are potential candidates for further surgical intervention but present no clear target on MRI.

Keywords: acromegaly, growth hormone–secreting pituitary adenoma, magnetic resonance imaging, positron emission tomography

Significance

Disease remission can be achieved in most patients with acromegaly but may require life-long medical therapy with its attendant costs and potential adverse effects. Such treatments are typically recommended when there is persistent disease following primary transsphenoidal surgery. Although repeat surgery is considered in some patients, there are several challenges, including difficulty in distinguishing postoperative tissue remodeling from sites of residual tumor on magnetic resonance imaging, and a risk of increased morbidity (especially hypopituitarism). Here, we show that molecular imaging with ^{11}C-methionine PET can guide focused transsphenoidal surgery for residual/recurrent or primary occult tumors to attain disease remission in a significant proportion of patients previously deemed unsuitable for surgery. Importantly, this was achieved with minimal risk to remaining pituitary function.

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Introduction

Acromegaly is a rare disorder characterized by an excess of growth hormone (GH), leading to increased morbidity and mortality. Most cases of acromegaly are caused by a somatotroph pituitary adenoma (or somatotroph pituitary neuroendocrine tumor).[1] The most effective treatment to achieve biochemical remission remains neurosurgery.[2] However, as most somatotroph tumors are macroadenomas, gross total resection can only be achieved when surgical planning is supported by adequate imaging.[3] The gold-standard imaging modality remains magnetic resonance imaging (MRI), with higher field strengths and modern sequences improving sensitivity.[4] However, cases of residual/recurrent disease and occult adenomas can be challenging to identify on anatomical imaging alone.

Recently, the incorporation of molecular (functional) imaging including positron emission tomography (PET) into diagnostic algorithms has proven to be a promising approach.[5] Specifically, L-[methyl-11C]-methionine-PET (Met-PET) has been shown to be effective in locating residual tumor, with a sensitivity of 86% and specificity of 100% reported for Met-PET coregistered with volumetric magnetic resonance (MR) sequences (Met-PET/MR^{CR}).[6,7] Somatotroph tumors exhibit a particularly high tracer uptake, rendering Met-PET especially effective in acromegaly diagnostics. In 2016, Koulouri *et al.*[5] reported detection of a residual tumor in 25/26 patients with residual acromegaly using Met-PET, facilitating revision/further surgery in 14 patients, achieving gross total resection in 7 patients. This indicates that Met-PET can enable further targeted intervention in patients otherwise requiring lifelong medical therapy. However, this diagnostic method is currently still not widely available, and larger studies on its clinical impact are awaited.

In the last 12 years, 189 cases of acromegaly were referred to our national Met-PET service. In this study, we retrospectively analyze real-world data of 61 patients treated exclusively by our multidisciplinary team (MDT). Here, we present the largest single-center study of Met-PET in acromegaly and report indications for the initial referral and concordance with MRI, as well as treatment outcomes in the subgroup proceeding to PET-guided neurosurgery.

Methods

Patients

Between December 2010 and November 2022, 189 patients were referred to our national Met-PET service. Of these 189 patients, 61 were exclusively treated by our specialist pituitary MDT. Fourteen of these 61 patients have been reported previously.[5] All patients had confirmed biochemical acromegaly with elevated insulin-like growth factor 1 (IGF-1, above the age- and sex-matched upper limit of normal [ULN]) and failure to suppress GH during an oral glucose tolerance test (nadir GH >0.4 µg/L after a 75-g oral glucose load). The study received Institutional approval (Cambridge University Hospitals Service Evaluation: 2803), and all patients provided written informed consent for PET-guided revision surgery. All protocols were in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Biochemical measurements

Biochemical measurements were analyzed at the time of scan as well as 6 months (±2 months) after surgery, if applicable. All analytes were measured in a UK Accreditation Service (UKAS)-accredited laboratory and had been verified and accredited according to UKAS standards. Serum GH concentration was measured using a solid-phase 2-site sequential chemiluminescent immunometric assay using mouse monoclonal antibodies (Siemens Immulite2000—Siemens Medical Solutions Diagnostics Ltd., Llanberis, Gwynedd, UK) calibrated to IS 98/574 (analytical sensitivity 0.1 ng/mL, interassay coefficient of variation <5% across the range of 0.1-40 ng/mL). Serum samples giving GH higher than this were diluted using a pool of patient serum with a GH result <0.05 ng/mL. Serum IGF-1 was measured using a solid-phase chemiluminescent immunoassay. (Liaison—Diasorin, Italy or Siemens Immulite2000—Siemens Medical Solutions Diagnostics Ltd., Llanberis, Gwynedd, UK). Both assays were calibrated to the first WHO international standard for IGF-1 NIBSC code 02/254 (analytical sensitivity 3 nmol/L, interassay coefficient of variation <11% across the range of 3-195 [Diasorin] or 3-130 [Immulite] nmol/L).

Clinical care

All patients were managed in accordance with local and international clinical guidelines,[8-10] and all patients provided informed consent for Met-PET and 3D gradient echo MRI. In each case, a consensus on treatment was reached through discussion at a specialist pituitary MDT (East of England) as recommended by the Pituitary Tumor Centre of Excellence (PTCOE) Initiative.[11] Any further treatment was undertaken at our center. Transsphenoidal endoscopic surgery was performed by a team including a single dedicated pituitary neurosurgeon and an ENT surgeon.

Synthesis of 11C-methionine

The PET tracer, l-[methyl-11C]-methionine, was synthesized in compliance with good manufacturing practice using a captive solvent in loop methylation method without preparative high-performance liquid chromatography (HPLC), adapted from methods published previously.[12-14] Briefly, [11C]CO_2 was produced using a PET-trace cyclotron (GE Medical Systems, Milwaukee, WI, USA) via the 14N(p,α)11C reaction before conversion to [11C]MeI in the MeI MicroLab (GE Medical Systems). This was then transferred to the HPLC loop of a modified TRACERlab FXC (GE Medical Systems) synthesizer containing l-homocysteine precursor solution (0.5 M aqueous NaOH solution in ethanol). 11C-methionine was produced in yields up to 15 GBq with a radiochemical purity of >96% and specific activity between 32.2 and 1564 GBq/µmol (average 205.5 GBq/µmol).

Met-PET imaging

Scans between December 2010 and April 2022 were acquired on a GE Discovery 690 PET-CT scanner (GE Medical Systems). Scans after April 2022 were acquired on a GE Discovery MI-2. The study was performed 20 min after intravenous administration of 300-400 MBq of l-[methyl-11C]-methionine. A low-dose computed tomography (CT) (140 kV, 220 mA, 0.5 s rotation, and 0.984 mm pitch) was acquired for attenuation correction followed by a single bed position PET study of the head. Time-of-flight (ToF) PET data were acquired for a total acquisition time of 20 min. Positron emission tomography images were reconstructed

with CT attenuation correction using fully 3D iterative reconstruction algorithms (3 iterations, 24 subsets, and 2 mm Gaussian postfilter) incorporating ToF and resolution recovery software (VUE Point FX and Sharp IR) to a 3.27-mm slice thickness. The CT images were reconstructed at 1.25-mm slice thickness. L-[methyl-11C]-methionine-positron emission tomography studies were reviewed by experienced nuclear medicine physicians as well as other members of the pituitary MDT.

Standard and 3D gradient echo MRI

Imaging was performed on either a 1.5-T or a 3-T superconducting unit (GE Signa, Milwaukee, WI, USA) using a circularly polarized head coil. For standard clinical MRI, sagittal and coronal T1-weighted spin echo images were obtained before and after intravenous injection of 0.1 mmol/kg gadopentetate dimeglumine. Coronal T_2-weighted imaging was also performed in more recent cases. Subsequently, T_1-weighted fast spoiled gradient echo images were acquired (repetition time 11.5 ms, echo time 4.2 ms, isotropic voxel spacing of 1 mm × 1 mm [256 × 256 matrix size] ×1 mm [slice thickness]). The absence or presence of cavernous sinus invasion was defined according to Knosp criteria.[15] Magnetic resonance imaging scans were reviewed by 2 experienced neuroradiologists as core members of the pituitary MDT.

Coregistration of Met-PET and MRI

Positron emission tomography images were reconstructed using ordered subset expectation maximization algorithms (attenuation compensation, time of flight [ToF], point spread functions, 3 iterations, 24 subsets, and Gaussian postfilter [2011: 3.2 mm; 2020/2021: 2 mm]). Coregistration was performed with 3D Slicer (free open-source software for visualization, processing, segmentation, and registration and analysis of medical, biomedical, and other 3D images and meshes [https://www.slicer.org]).

Assessment of reports and concordance

We assessed the concordance between MRI and Met-PET. If the molecular imaging findings mapped onto a corresponding suspicious area identified on MRI, the reports were noted as concordant. If MRI and Met-PET suggested different targets or one of the 2 modalities identified no target, the reports were registered as discordant.

Results

Cohort characteristics

The mean age at the time of scan was 51 years (range 23-74 years). The cohort included more men than women (25 women, 36 men). At initial diagnosis, 77.1% of the cohort ($n = 47$) presented with a macroadenoma and 16.4% with a microadenoma ($n = 10$). There were 3 cases of occult tumor and 1 case of a mesoadenoma. Baseline characteristics including biochemical assessments for acromegaly are reported in Table 1.

The majority of patients (82.0%, $n = 50$) were referred to Met-PET following primary treatment, with most having received combined surgical and medical therapy (39.3%, $n = 24$). Seventeen patients had undergone surgery alone, and 6 patients had undergone medical therapy. Two patients had received surgery, medical therapy, and radiotherapy, while 1 patient had undergone surgery and radiotherapy without medical treatment. These results are illustrated in Figure 1.

Table 1. Baseline characteristics.

Characteristic	Entire cohort		Neurosurgery subgroup	
	n	Value	*n*	Value
Age (years)	61	51.2 (SD 12.5)	33	49.7 (SD 12.4)
Sex				
Female	25	41.0%	15	45.5%
Male	36	59.0%	18	54.5%
Initial tumor size				
Macro	47	77.1%	25	75.8%
Meso	1	1.6%	1	3.0%
Micro	10	16.4%	6	18.2%
Occult	3	4.9%	1	3.0%
Biochemistry[a]				
IGF-1 (nmol/L)	57	58.08 (SD 32.9)	33	71.11 (SD 34.0)
IGF-1 (×ULN)	57	1.84 (SD 0.9)	33	2.19 (SD 0.8)
GH nadir (µg/L)	42	1.94 (SD 2.4)	23	2.75 (SD 3.0)

[a]At the time of the scan.
Abbreviations: GH, growth hormone; IGF, insulin-like growth factor 1.

For the patients receiving adjunctive medical therapy, discontinuation of depot somatostatin analog therapy was recommended for a minimum of 12 weeks (4 weeks for dopamine agonist therapy) prior to undergoing Met-PET to avoid tumor suppression and thereby maximize the likelihood of detecting the target lesion.

Indications for molecular imaging

In the majority of cases (62.3%, $n = 38$), molecular imaging was requested after the MRI had been deemed indeterminate following review by a specialist pituitary MDT in the referring center. Fourteen patients (23%) were referred despite initial postoperative remission/normalization of disease activity because of biochemical recurrence of acromegaly and an occult residual. Six patients were referred for surgical planning, and 3 patients because of occult de novo acromegaly. Illustrative case examples for each indication are provided in Figures S1-S4.

Reporting and concordance with MRI

L-[methyl-11C]-methionine-positron emission tomography identified site(s) of suspected disease in 52 of the 61 cases (85.2%), while MRI suggested a lesion in 42 (68.9%). No differences in disease activity or initial tumor size were observed in 9 patients in whom Met-PET did not identify the site of residual disease when compared with those with a positive scan. L-[methyl-11C]-methionine-positron emission tomography was able to localize sites of residual disease in a small number of patients where conventional imaging was negative. At the other end of the spectrum, the largest tumor residuum identified in the current study had a diameter of 26 mm. Detection rates for the different indications are shown in Figure 2.

All 3 occult de novo tumors could be identified on Met-PET. Of the 14 cases with occult residual tumor, 12 (85.7%) could be identified on Met-PET. Notably, in 4 cases, the MDT identified a suspicious lesion on the MRI not reported on the previously available external imaging, which was then concordant with the Met-PET. This resulted in an overall concordance between MRI and Met-PET of 42.9% ($n = 6/14$).

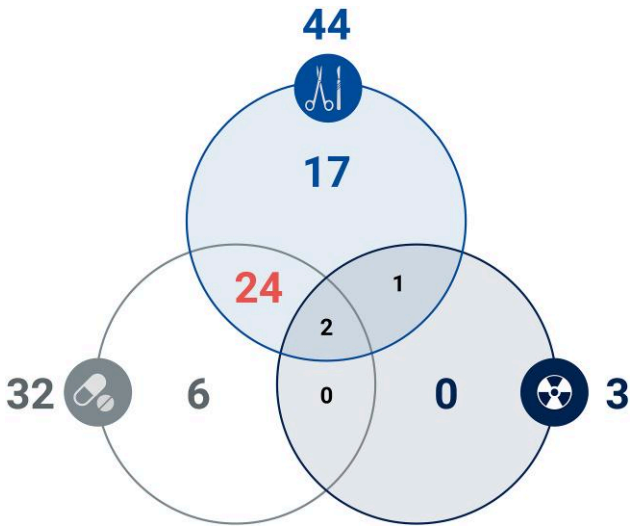

Figure 1. Previous treatments. Venn diagram of the pretreated patients ($n = 50$). The top circle represents surgery, the right circle radiotherapy, and the left circle medical therapy. The intersecting areas represent patients receiving multiple or all therapy modalities. The largest subgroup ($n = 24$) received surgical and medical treatment. Figure created with BioRender.com.

Figure 2. Met-PET findings. The 4 bars depict the different indications for referral for Met-PET. Targets were identified in 52/61 cases. Met-PET, L-[methyl-11C]-methionine-positron emission tomography.

Of the cases referred with an indeterminate MRI, Met-PET found a target in 31 of 38 cases (81.6%), while finding no target in the remaining 7 cases. In 26 of these 31 cases, the target corresponded to a suspected lesion on the MRI. In the other 5 cases, functional imaging suggested a different site of disease. This results in a concordance of 68.4% ($n = 26/38$).

In 5 of the 6 cases (83.3%) referred for surgical planning, MRI and Met-PET were concordant. In the 1 discordant case, Met-PET placed the target in a different anatomical location.

Clinical and biochemical outcomes

Of the 52 patients with a target identified on PET, 14 cases were referred for medical therapy or radiotherapy in line with a MDT recommendation. This was based on a risk–benefit analysis, mostly because of the tumor being identified in a location difficult or impossible to reach for even an experienced pituitary neurosurgeon. In 5 additional cases, the patient decided against further surgery.

Thirty-three patients proceeded to (further) surgery, which resulted in biochemical remission 6 months after intervention in 24 patients (72.7%). Insulin-like growth factor 1 levels were reduced to $<2 \times$ ULN in 6 of the remaining 9 cases, 3 of whom achieved levels of $<1.1 \times$ ULN compared with mean preoperative levels of $2.4 \times$ ULN (SD 0.8) for $n = 9$.

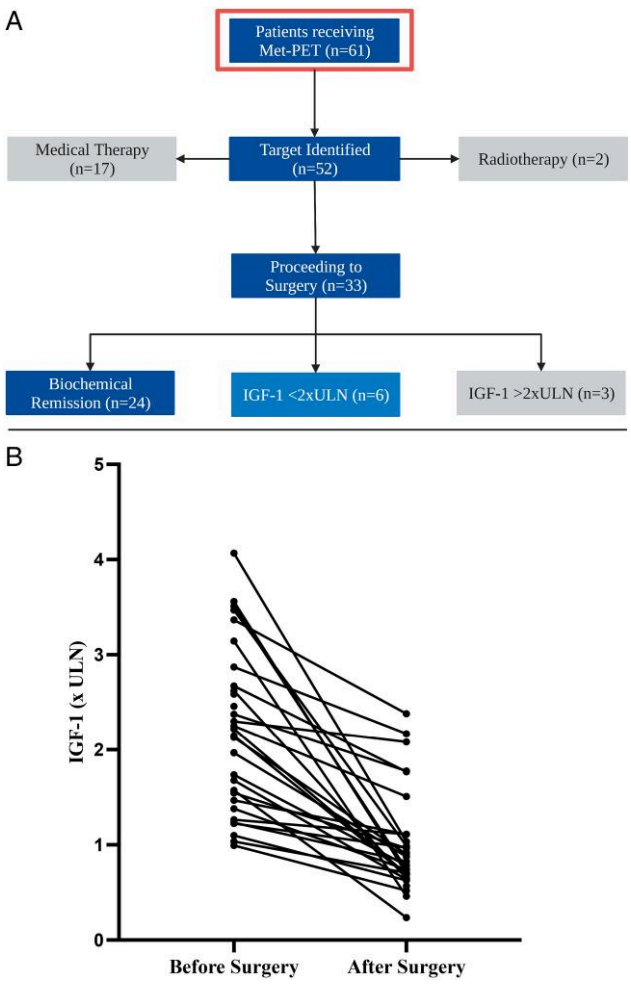

Figure 3. Treatment and biochemical outcomes after Met-PET and surgery. A) A flowchart of the patient pathway after Met-PET. B) A dot plot of the IGF-1 values of the 33 subjects undergoing additional surgery after Met-PET. Each dot represents a single subject. IGF-1, insulin-like growth factor 1; Met-PET, L-[methyl-11C]-methionine-positron emission tomography.

Four of the 9 patients who did not achieve remission proceeded to a second Met-PET. This recommendation followed careful consideration at the pituitary MDT, taking into account each patient's preference for definitive therapy. On the basis of the second Met-PET, 2 patients were considered candidates for further surgical exploration. Although disease burden improved in 1 patient (IGF-1 $3.3 \times$ ULN decreased to $1.3 \times$ ULN), residual disease activity was unchanged in the other despite histopathological confirmation of an atypical sparsely granulated somatotroph adenoma at the site identified on both PET scans (IGF-1 of $2.6 \times$ ULN before to $2.4 \times$ ULN after resurgery).

Notably, new pituitary deficits only occurred in 3 of 33 patients (receiving 35 operations) and included 2 cases of gonadotropic insufficiency and 1 case of thyrotropic insufficiency. There were no neurovascular complications following neurosurgery.

The patient pathway is depicted in Figure 3A. A dot plot of the IGF-1 levels before and after surgery is shown in Figure 3B.

Discussion

In this study, we present the largest series to date of patients with acromegaly who have undergone Met-PET. In patients

with persistent/recurrent acromegaly or occult tumors, Met-PET enabled our center to perform additional targeted neurosurgery in 33 patients. This in turn led to complete remission in the majority of cases (72.7%) or significant improvement in disease burden with a low complication rate despite many patients having undergone previous surgery.

Limitations

As a real-word experience, this study retrospectively reports routinely collected clinical data. However, to ensure consistent data acquisition, interpretation, and clinical decision-making, we elected to report only single-center, single-surgeon outcomes from a national referral center.

As there is no control group, it remains unclear how much of the biochemical improvement after surgery is due to Met-PET guidance. The encouraging results could theoretically be attributed to neurosurgical performance alone. However, although a causal relation cannot be established, the additional information provided by Met-PET led to adjunctive definitive therapy in patients who would otherwise not have been offered neurosurgical intervention.

Biochemical and surgical outcomes

Considering that a majority of patients had already undergone previous surgery in specialist pituitary centers, the observed remission rate of 72.7% after (re-)surgery represents an encouraging result. Reported cure rates for somatotroph adenomas in primary surgery, even for experienced pituitary surgeons, are 80%-90% in microadenomas and 50%-60% in macroadenomas.[3] The median remission rate of somatotroph macroadenomas in the 9 centers of excellence participating in the PTCOE validation study was reported as 49%.[16]

Even in patients not achieving complete biochemical remission, a significant reduction in biochemical/clinical disease burden was observed. As shown in Figure 3B, there was a reduction of IGF-1 levels in all patients following neurosurgery. It should be noted that patients were required to stop any pituitary-targeted medical treatment in advance of the Met-PET scan, and therefore, a benefit over medical therapy may be assumed but cannot be clearly assessed. However, a dose reduction or increased injection interval of somatostatin receptor ligand (SRL) therapy could be considered for patients achieving a significant reduction of IGF-1 following surgery.

Three patients in this cohort attained an IGF-1 of $<1.1\times$ ULN after surgery and would have been identified as in biochemical remission using criteria employed in a 2014 study on combined medical therapy.[17] However, noting inadequate GH suppression following glucose challenge in all 3 subjects, these patients still classified as persistent acromegaly, although medical therapy might not be indicated.[12,13]

Of the 3 patients who had radiotherapy prior to Met-PET, 2 were not initially considered suitable for further surgery and received medical therapy. In the third patient, radiotherapy had occurred >20 years prior to Met-PET, and although surgery was performed, no biochemical improvement was observed (IGF-1 $>2\times$ ULN).

In 4 patients receiving repeat Met-PET, 2 additional operations were performed. However, no additional biochemical remission was observed, although 1 patient achieved a clinically relevant reduction in IGF-1. This might suggest that if no clinically relevant improvement is achieved by the first Met-PET–directed intervention, further functional imaging is unlikely to facilitate surgical remission.

Only 3 single additional endocrine deficits (2 gonadotropic, 1 thyrotropic insufficiency) occurred despite previous interventions in the majority of patients, and indeed the rate of new complications after surgery was lower than the median reported by the PTCOE criteria validation study.[16] Again, this low complication rate might reflect neurosurgical performance. However, additional Met-PET guidance allows for a more targeted approach compared with explorative surgery.

Imaging in acromegaly

While this cohort represents a particularly challenging subgroup of cases requiring further imaging, MRI with fine sections through the sella remains the gold standard in most patients with acromegaly.[14] At initial diagnosis, 77.1% of the patients in our cohort presented with macroadenomas, which can be easily identified on MRI, which also allows for a robust analysis of extrasellar expansion and specifically cavernous sinus invasion. The MRI-based Knosp classification is an important prognostic factor and provides insight as to the likelihood of gross total resection and biochemical remission.[15,18] Magnetic resonance imaging is named as primary imaging for somatotroph adenomas across guidelines.[8-10,19] However, as highlighted above, gross total resection rates of somatotroph macroadenomas are only around 50%-60% as reported from globally leading centers.[3] Differentiating residual tumor from postoperative change, such as scar tissue, and from residual normal gland can be challenging, especially if the MRI was not acquired optimized for pituitary imaging.

The role of Met-PET

Functional imaging is emerging as a relevant adjunct part of the diagnostic workup of pituitary tumors, including somatotroph adenomas.[5,20,21] While other tracers such as 18F-fluoro-ethyl-tyrosine have shown promising results,[22] Met-PET has so far been the most extensively studied. It has been reported to have particular value in localizing residual tumor,[6] with a sensitivity of 86% and specificity of 100% compared with a sensitivity of 28% for 18F-fluorodeoxyglucose-PET in a head-to-head comparative study.[7] A previous report from this group, aggregating 26 patients treated in multiple centers, localized residual tumor in 25 of 26 patients, with PET-directed transsphenoidal surgery (TSS) performed in 14 individuals, 7 of whom achieved biochemical remission.[5]

The results in the present study further support the additional value of Met-PET imaging in acromegaly. In addition, it is potentially applicable to other pituitary tumor subtypes, as we and others have previously reported.[23-26] Still, its availability is limited by the short half-life of the tracer requiring an on-site cyclotron facility.[23] We suggest that while Met-PET should be considered in cases in whom optimal MRI imaging has not demonstrated a candidate lesion, its use may be limited to specialized PTCOEs. In these centers, an experienced MDT including a neurosurgeon familiar with Met-PET imaging can provide optimal outcome using this imaging modality.

It should be noted that while Met-PET is particularly effective in detecting somatotroph adenomas, which demonstrate avid uptake of the tracer, concomitant treatment with SRLs or dopamine agonists can reduce this through suppression of tumor activity. We therefore recommend a washout period (12 weeks for SRLs, 4 weeks for dopamine agonists) before

proceeding to Met-PET imaging.[5] However, an additional Met-PET scan can be performed after (re-)starting treatment with SRLs to further increase confidence in localizing the lesion via subtraction imaging. Figure S4 illustrates such a case in a treatment-naive patient with an occult adenoma.

Conclusion and outlook

With the encouraging results reported in the present study, we propose that Met-PET should be considered in all patients with acromegaly who are potential candidates for further neurosurgery but present no clear target on dedicated pituitary MRI. Further optimization and increased availability of this imaging modality will make definitive treatment available to patients with acromegaly otherwise dependent on lifelong medical therapy.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Conflict of interest: The authors have nothing to disclose.

Authors' contributions

Linus Haberbosch (conceptualization [supporting], formal analysis [lead], methodology [equal], visualization [lead], writing—original draft [lead], writing—review and editing [equal]), James MacFarlane (conceptualization [supporting], data curation [equal], formal analysis [supporting], investigation [equal], methodology [equal], validation [equal], writing—review and editing [equal]), Olympia Koulouri (conceptualization [equal], formal analysis [supporting], investigation [equal], methodology [equal], supervision [supporting], writing—review and editing [equal]), Daniel Gillett (conceptualization [supporting], data curation [equal], formal analysis [equal], methodology [supporting], software [lead], visualization [equal], writing—review and editing [equal]), Andrew Powlson (methodology [supporting], validation [supporting], writing—review and editing [equal]), Susan Oddy (methodology [equal], validation [supporting], writing—review and editing [equal]), David Halsall (methodology [equal], validation [supporting], writing—review and editing [equal]), Kevin A. Huynh (data curation [supporting], validation [supporting], writing—review and editing [equal]), Jonathan Jones (methodology [supporting], validation [supporting], writing—review and editing [equal]), Heok K. Cheow (methodology [supporting], validation [supporting], writing—review and editing [equal]), Joachim Spranger (resources [equal], writing—review and editing [equal]), Knut Mai (supervision [supporting], validation [supporting], writing—review and editing [equal]), Christian Strasburger (methodology [supporting], project administration [supporting], supervision [equal], validation [supporting], writing—original draft [supporting], writing—review and editing [equal]), Richard J. Mannion (investigation [equal], project administration [supporting], validation [supporting], writing—review and editing [equal]), Mark Gurnell (conceptualization [lead], data curation [supporting], formal analysis [equal], funding acquisition [lead], investigation [equal], methodology [equal], project administration [lead], resources [equal], supervision [lead], validation [lead], visualization [supporting], writing—original, and draft [equal], writing—review and editing [lead])

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