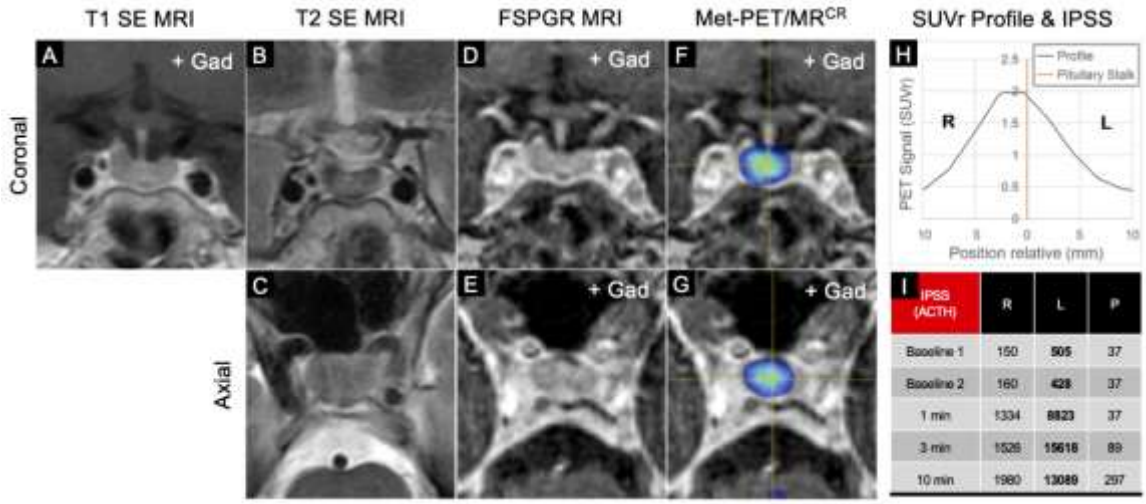
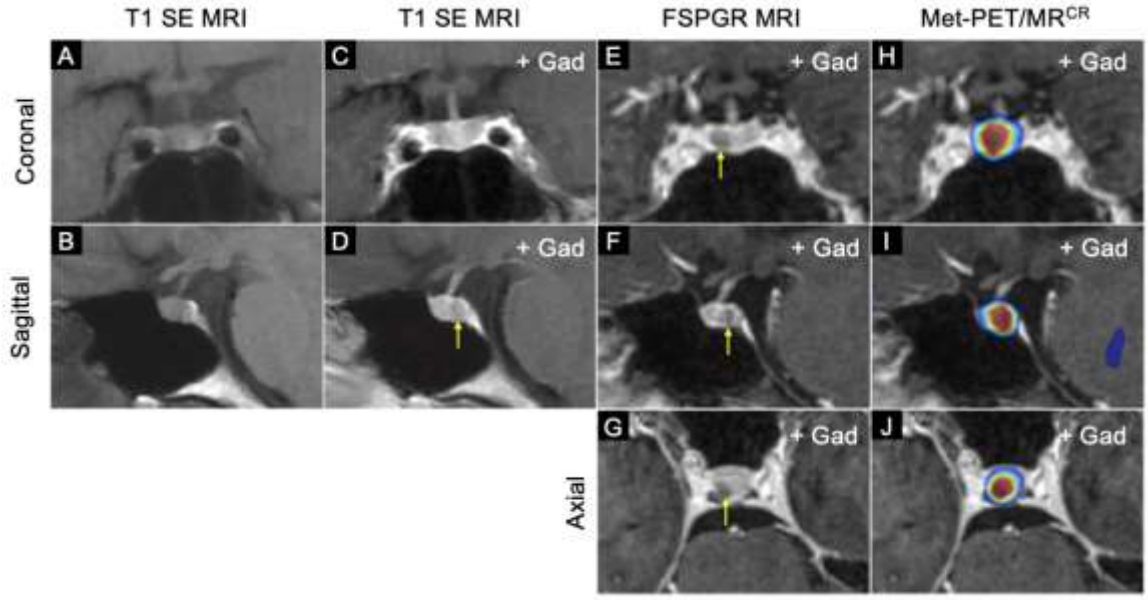
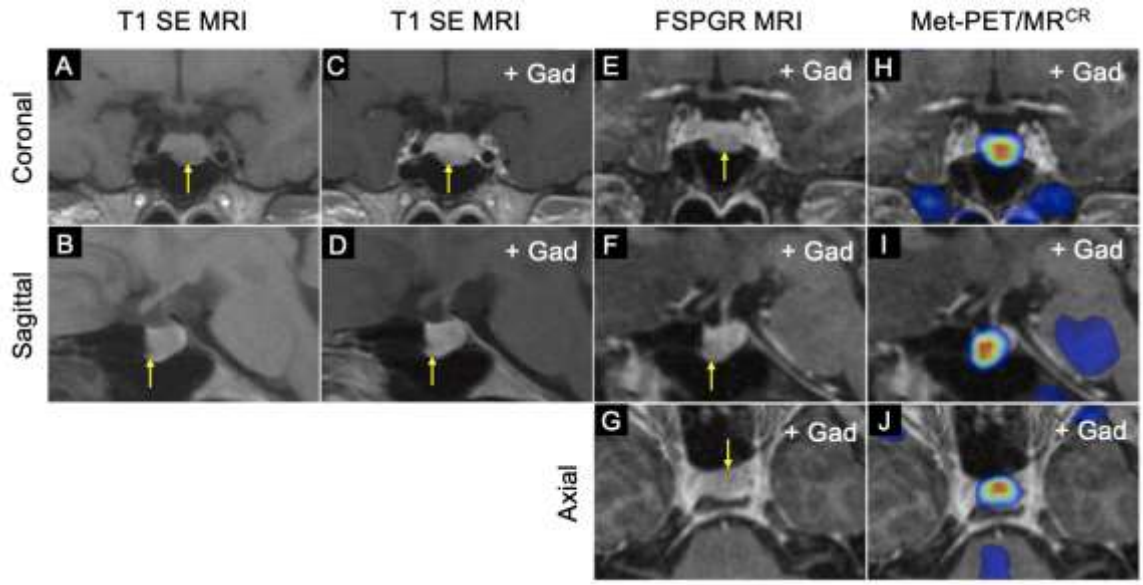


IPSS (ACTH)	R	L	P
Baseline 1	150	505	37
Baseline 2	160	428	37
1 min	1334	8823	37
3 min	1526	15618	89
10 min	1980	13089	297

Supplemental Fig. 1 Profiling of ^{11}C-methionine sellar uptake in a middle-aged man with Cushing Disease. **A-C** Preoperative coronal T1 (**A**), coronal T2 (**B**) and axial T2 (**C**) SE MRI do not reliably identify a pituitary adenoma; note the central position of the infundibulum, with slight gland asymmetry (right>left). **D, E** FSPGR MRI demonstrates similar appearances with no clear lesion visualised. **F-H** Met-PET/MR^{CR} shows predominantly central tracer uptake, but with minor asymmetry relative to the infundibulum (right>left), which is confirmed on the SUVr profile (**H**). **I** In contrast, bilateral IPSS, demonstrates a pituitary source, but with apparent left-sided dominance. However, at TSS a small microadenoma was resected from the right side of the gland, with subsequent complete clinical and biochemical remission. ***Key:*** *FSPGR, fast spoiled gradient recalled echo; Gad, gadolinium; IPSS, inferior petrosal sinus sampling; L, left; Met-PET/MR^{CR}, ^{11}C-methionine PET/CT coregistered with FSPGR MRI; P, peripheral; R, right; SE, spin echo; SUVr, Standardised uptake value ratio (relative to cerebellum). TSS, transsphenoidal surgery.*



Supplemental Fig. 2 Confirmation of the site of a microprolactinoma in a young woman with dopamine agonist intolerance. A-D Coronal and sagittal SE MRI pre-and post-gadolinium demonstrates equivocal appearances, with a possible abnormal area posteriorly (yellow arrow) (**D**). **E-G** Coronal, sagittal and axial FSPGR MRI identifies a poorly enhancing lesion posteriorly on the right (yellow arrows). **H-J** Met-PET/MR^{CR} shows intense focal tracer uptake at this site, confirming the location of the microprolactinoma. ***Key:*** *FSPGR, fast spoiled gradient recalled echo; Gad, gadolinium; Met-PET/MR^{CR}, ^{11}C-methionine PET/CT coregistered with FSPGR MRI; SE, spin echo.*



Supplemental Fig. 3 Confirmation of the site of a thyrotropinoma in a young woman with secondary hyperthyroidism. A-D Coronal and sagittal SE MRI pre-and post-gadolinium demonstrates equivocal appearances, with a possible abnormal area anteriorly/inferiorly (yellow arrows). **E-G** Coronal, sagittal and axial FSPGR MRI also raises the possibility of a poorly enhancing lesion in this area (yellow arrows). **H-J** Met-PET/MR^{CR} shows intense focal tracer uptake at this site, confirming the location of the microthyrotropinoma. ***Key:*** *FSPGR, fast spoiled gradient recalled echo; Gad, gadolinium; Met-PET/MR^{CR}, ^{11}C-methionine PET/CT coregistered with FSPGR MRI; SE, spin echo.*

Supplemental Table 1: Key findings in studies targeting somatostatin receptor expression for pituitary imaging

Ligand	Studies*	Tumour subtypes (number of subjects)	Key findings
^{123}I-Tyr3-octreotide	Faglia et al, 1991(*1*)	GH (3), NFPA (8), PRL (3)	3/3 GH-secreting PA, 2/8 NFPA and 0/3 macroprolactinoma demonstrated tracer uptake
	Ur et al, 1992(*2*)	GH (15)	Positive correlation between tracer uptake and biochemical response in 8/15 subjects with acromegaly who also underwent an acute GH suppression test with octreotide
^{111}In-pentetreotide	de Bruin et al, 1992(*3*)	NFPA (7)	6/7 NFPA demonstrated uptake; correlated with tumoral SSTR expression; but no correlation with tumour shrinkage in response to octreotide therapy
	Scheidhauer et al, 1993(*4*)	Different CNS tumors (45)	Tracer uptake demonstrated in 50% of PAs (independent of endocrine status)
	Boni et al, 1995(*5*)	GH (13), NFPA (12), TSH (3)	Positive scans more commonly observed with GH- (12/13) and TSH- (2/3) secreting pituitary PA, and less frequently in NFPA (2/12)
	Maini et al, 1995(*6*)	GH (7), NFPA (8), PRL (5)	Variable uptake across CNS tumour subtypes: modest in pituitary adenomas; intense in meningiomas
	Tumiati et al, 1995(*7*)	na (21)	Uptake predominantly in GH-secreting macroadenomas
	Colao et al, 1996(*8*)	GH (23)	Positive correlation between degree of tracer uptake and reduction of GH and IGF-1 levels in patients with acromegaly treated with short-acting octreotide
	Luyken et al, 1996(*9*)	na (18)	Tracer uptake observed in 50% of PA (regardless of endocrine secretory state)
	van Royen et al, 1996(*10*)	NFPA (2), PRL (1), TSH (2), ACTH (1)	Tracer uptake more accurately determined using a fixed ROI (without background correction)
	Borson-Chazot et al, 1997(*11*)	GH (19), NFPA (29)	In patients with acromegaly (n=19), positive SSTR scintigraphy predicted biochemical response to octreotide therapy (but with low negative predictive value); in patients with NFPA (n=29), negative SSTR scintigraphy correlated with an absence of visual improvement during octreotide therapy.
	Losa et al, 1997(*12*)	TSH (5)	Tracer uptake observed in a small cohort of TSH-secreting PA, with a trend for the degree of uptake to correlate with extent of TSH suppression in response to an octreotide test dose
	Plockinger et al, 1997(*13*)	GH (25), NFPA (24)	Poor correlation between tracer uptake and tumour volume in both GH-secreting PA and NFPA; no correlation with biochemical status; unable to identify postoperative tumour remnants not already visible on MRI
	Rieger et al, 1997(*14*)	GH (11), NFPA (25), PRL (6)	Tracer uptake not predictive of biochemical or structural responses to octreotide therapy in different subtypes of PA
	Legovini at al, 1997(*15*)	GH (12)	Tracer uptake not predictive of response to octreotide therapy in acromegaly
	Gorges et al, 1997(*16*)	GH (22)	Poor ability to discriminate between normal pituitary gland and GH-secreting PA
	Lauriero et al, 1998(*17*)	GH (10), NFPA (1), PRL (10)	Detection of PA remnants enhanced when MRI is combined with ^{111}In-pentetreotide SPECT
	Oppizzi et al, 1998(*18*)	GH (17), NFPA (22)	Variable tracer uptake in GH-secreting and non-functioning PA
	Schmidt et al, 1998(*19*)	GH (8), NFPA (14), PRL (2)	Positive scans in 9 of 24 (37.5%) PA (2/8 GH-secreting; 6/14 NFPA; 1/2 prolactinomas)
	Duet et al, 1999(*20*)	GH (11), NFPA (17), TSH (4)	Tracer uptake not predictive of response to octreotide therapy across PA subtypes
	Colao et al, 1999(*21*)	GH (24), GH/PRL (4), NFPA (9)	Tracer uptake not predictive of response to octreotide therapy in acromegaly, mixed GH/PRL-secreting PA or NFPA
	Nielsen et al, 2001(*22*)	GH (7), NFPA (11), PRL (2), ACTH (1)	Tracer uptake not significantly different between GH-secreting and NFPA
	Socin et al, 2003(*23*)	TSH (7)	Positive scan in 3 of 7 TSH-secreting PA
	Acosta-Gomez et al, 2005(*24*)	GH (7), NFPA (10), PRL (6), ACTH (8), FSH (2), LH (1)	Able to differentiate scar tissue from recurrent PA post-operatively (sensitivity = 79%) when combined with MRI
	de Herder et al, 2005(*25*)	GH (10)	No correlation between tracer uptake and GH response to octreotide in 10 patients with acromegaly
99mTc P829	Chiewvit et al, 1999(*26*)	na (11)	Tracer uptake demonstrated in in 3 of 8 PA
99mTc-HYNIC-TOC	Vukomanovic et al, 2019(*27*)	GH (3), NFPA (20), PRL (8), ACTH (2)	Sella uptake demonstrated in 30 of 33 patients (3 negative NFPAs in a population of 8 macroadenomas and 25 microadenomas); however, tracer uptake also observed in 8 of 37 control subjects without PA.
^{68}Ga DOTATATE	Zhao et al, 2014(*28*)	GH (14), GH/PRL (1), NFPA (10), ACTH (9)	Higher ^{68}Ga-DOTATATE uptake observed in normal pituitary tissue; ^{18}F-FDG uptake greater in recurrent/remnant PA
	Wang et al, 2018(*29*)	GH (3), TSH (1), ACTH (33)	Combination of ^{18}F-FDG PET and ^{68}Ga-DOTATATE PET aids differentiation of microadenomas from normal pituitary tissue
^{68}Ga DOTATOC	Tjornstrand et al, 2019(*30*)	NFPA (9)	Lower tracer uptake in clinically non-functioning PA (7 SF-1 and 2 T-Pit staining tumours) when compared with normal pituitary gland.

Key: *CNS, central nervous system; DOTATATE, DOTA-Tyr3-octreotate; DOTATOC, DOTA-Tyr3-octreotide; FDG, fluorodeoxyglucose; Ga, gallium; GH, growth hormone; HYNIC-TOC, hydrazinonicotinyl-Tyr3-octreotide; MRI, magnetic resonance imaging; na, not available; NFPA, non-functioning pituitary adenoma; P829, peptide 829 (a low molecular weight SSTR ligand); PA, pituitary adenoma; PET, positron emission tomography; ROI, region of interest; SF-1, steroidogenic factor 1; SPECT, single photon emission computed tomography; SSTR, somatostatin receptor(s); T-Pit, corticotroph lineage transcription factor; Tc, technetium; TSH, thyroid stimulating hormone (thyrotropin).*

*Only studies reporting ≥5 subjects are shown

Supplemental Table 2: Key findings in studies targeting dopamine receptor expression for pituitary imaging

Ligand	Studies*	Tumour subtypes (number of subjects)	Key findings
^{11}C-N-methylspiperone	Muhr et al, 1986(*31*)	na (26)	Good correlation between degree of tracer uptake and biochemical and radiological responses to bromocriptine in prolactinomas; in contrast, minimal tracer uptake in NFPAs in keeping with limited response to bromocriptine therapy.
^{11}C-*raclopride*	Muhr et al, 1986(*31*)	na (26)	
	Muhr et al, 2006(*32*)	na (165)	Tracer uptake in prolactinomas and D2R-expressing GH-secreting tumours predicted response to dopamine agonist therapy
^{18}F-FESP	Lucignani et al, 1997(*33*)	NFPA (8)	Tracer uptake 2-3-fold higher in NFPAs compared with meningioma and craniopharyngioma.
^{123}I-iodobenzamide	Pirker et al, 1994(*34*)	GH (2), NFPA (4), PRL (8), ACTH (1)	Low sensitivity for visualisation of prolactinomas and GH-secreting PA
	de Herder et al, 1996(*35*)	GH (12), NFPA (17), MacroPRL (5), MicroPRL (2) TSH (1)	Variable positivity in macroprolactinomas; negative scans in microprolactinomas (n=2), TSH-secreting PA (n=1) and GH-secreting PA (n=12)
	Ferone et al, 1998(*36*)	GH (4), NFPA (6), PRL (4)	Positive correlation between SPECT uptake and biochemical and structural responses to quinagolide and cabergoline in prolactinomas and NFPAs
	Colao et al, 2000(*37*)	NFPA (10), PRL (10)	
^{123}I-epidepride	Pirker et al, 1996(*38*)	GH (4), NFPA (4), PRL (9), ACTH (2)	Tracer uptake (using SPECT) demonstrated in prolactinoma (8/9), NFPA (4/4) and GH-secreting PA (2/4); no uptake shown in ACTH-secreting PA (2/2)
	de Herder et al, 1999(*39*)	NFPA (15), PRL (4)	SPECT uptake using ^{123}I-epidepride superior to ^{123}I-iodobenzamide in dopamine receptor-positive adenomas; uptake seen in 60% of NFPA cases (9/15).
	de Herder et al, 2006(*40*)	na (85)	Limited clinical utility in predicting clinical efficacy of DA therapy in selected patients with NFPAs

Key: *ACTH, adrenocorticotropic hormone; D2R, dopamine receptor subtype 2; FESP, fluoroethylspiperone; GH, growth hormone; NFPA, non-functioning pituitary adenoma. SRS, somatostatin receptor scintigraphy; MRI, magnetic resonance imaging; na, not available; PA, pituitary adenoma; PET, positron emission tomography; SPECT, single photon emission computed tomography.*

*Only studies reporting ≥5 subjects are shown

Supplemental Table 3: Key findings in studies using ^{18}F-FDG for the detection of pituitary adenomas

Ligand	Studies*	Tumour subtypes (number of subjects)	Key findings
^{18}F-FDG	Francavilla et al, 1991(*41*)	na (24)	Highest tracer uptake in NFPAs compared with other PAs (with TSH-secreting PA exhibiting lowest uptake); findings in recurrent macroadenomas comparable to non-operated cases; lower tracer uptake observed in previously irradiated PA
	Alzahrani et al, 2009(*42*)	ACTH (12)	Tracer uptake in 7 of 12 ACTH-secreting PA (7 *de novo* and 5 postsurgical cases); in 4 patients with 'negative' MRI scans, ^{18}F-FDG PET positive in one case; in 5 patients with 'negative' PET scans, MRI positive in 2 subjects
	Ikeda et al, 2010(*43*)	ACTH (12)	^{18}F-FDG PET less sensitive (8/12) than ^{11}C-methionine PET (11/11) for the detection of ACTH-secreting PA
	Seok et al, 2013(*44*)	GH (5), NFPA (14), PRL (2), ACTH (2), TSH (1)	Tracer uptake observed in all 14 macroadenomas (8 NFPA, 3 GH-secreting, 1 Prolactin-secreting, 1 ACTH-secreting, 1 TSH-secreting) and 5 of 10 microadenomas (3/6 NFPA, 1/2 GH-secreting, 1/1 Prolactin-secreting, 0/1 ACTH-secreting); positive scan in only 1 of 7 Rathke's cleft cysts
	Zhao et al, 2014(*28*)	GH (14), GH/PRL (1), NFPA (10), ACTH (9)	^{18}F-FDG PET, in combination with ^{68}Ga DOTATATE PET, permitted improved distinction between residual/recurrent PA and normal pituitary gland
	Chittiboina et al, 2015(*45*)	ACTH (10)	^{18}F-FDG PET more sensitive than SE MRI, but less sensitive than FSPGR MRI, for detection of microadenomas in *de novo* Cushing Disease
	Feng et al, 2016(*46*)	GH (16), PRL (12), ACTH (15)	Comparison of ^{18}F-FDG PET (n=43) and ^{11}C-methionine PET (n=39) in surgically-confirmed PA (16 acromegaly, 15 Cushing's Disease, 12 prolactinomas); ^{18}F-FDG PET positive in 29 of 43 patients; ^{11}C-methionine PET positive in 37 of 39 cases (2 false positive scans); 12 patients positive on ^{11}C-methionine PET but with negative ^{18}F-FDG PET; in 9 patients with a recurrent microadenoma, ^{11}C-methionine PET positive in all instances, but ^{18}F-FDG PET ^{18}F-FDG PET positive in only 2 cases
	Tosaka et al, 2017(*47*)	GH (8), NFPA (14)	Higher tracer uptake in NFPA (n=14) than GH-secreting PA (n= 8).
	Wang et al, 2018(*48*)	GH (3), ACTH (33), TSH (1)	Combination of ^{18}F-FDG PET and ^{68}Ga-DOTATATE PET aids differentiation of microadenomas from normal pituitary tissue
	Boyle et al, 2019(*49*)	ACTH (27)	Ability of ^{18}F-FDG PET to detect ACTH-secreting PA enhanced by CRH stimulation

Key: *ACTH, adrenocorticotropic hormone; CD, Cushing Disease; CRH, corticotropin releasing hormone; DOTATATE, DOTA-Tyr3-octreotate; FDG, fluorodeoxyglucose; Ga, gallium; GH, growth hormone; MRI, magnetic resonance imaging; na, not available; PA, pituitary adenoma; PET, positron emission tomography; NFPA, non-functioning pituitary adenoma; SE, spin echo; SPGR, spoiled gradient recalled.*

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